2.5 CLINICAL OVERVIEW

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES 5
LIST OF IN-TEXT FIGURES 9
ABBREVIATIONS 10
2.5. CLINICAL OVERVIEW 12
2.5.1. Product Development Rationale 14
2.5.1.1. Therapeutic Context 14
2.5.1.1.1. Disease or Condition 14
2.5.1.1.2. Clinical Features and Epidemiology of COVID-19 14
2.5.1.2. Vaccine Clinical Development Program 15
2.5.1.2.1. Rationale for Development 15
2.5.1.2.2. Vaccine Product Information 15
2.5.1.2.3. Vaccine Development Program 15
2.5.1.2.4. Proposed Indication 17
2.5.1.2.5. Rationale for Candidate and Dose Selection 17
2.5.1.3. Regulatory Status 18
2.5.1.4. Ethical Considerations 20
2.5.2. Overview of Biopharmaceutics 20
2.5.2.1. Formulation Development 20
2.5.2.2. Biopharmaceutical Studies 20
2.5.2.3. Bioanalytical and Analytical Methods Used in Human Studies 20
2.5.3. Overview of Clinical Pharmacology 21
2.5.4. Overview of Efficacy (Including Immunogenicity) 21
2.5.4.1. Efficacy Endpoints and Analysis Methods 21
2.5.4.1.1. Efficacy Endpoints 21
2.5.4.1.2. Efficacy Analysis Methods 23
2.5.4.2. Immunogenicity Endpoints and Analysis Methods 23
2.5.4.2.1. Immunogenicity Endpoints 23
2.5.4.2.2. Immunogenicity Analysis Methods 23
2.5.4.3. Efficacy Results 24
2.5.4.3.1. Updated Analysis of Efficacy – Adolescents 12-15 Years of Age 24

2.5.4.4. Immunogenicity Results 36
2.5.4.4.1. Immunogenicity Populations....36
2.5.4.4.2. Noninferiority Between 12-15 Years of Age and 16-25 Years of Age Groups 37
2.5.4.4.3. Immunogenicity Conclusions....37
2.5.5. Overview of Safety....38
2.5.5.1. Safety Endpoints and Analysis Methods 38
2.5.5.1.1. Safety Endpoints 38
2.5.5.1.2. Safety Analysis Methods....39
2.5.5.2. Safety Results 40
2.5.5.2.1. Safety Populations....40
2.5.5.2.2. Reactogenicity....47
2.5.5.2.3. Adverse Events....47
2.5.5.2.4. Deaths....98
2.5.5.2.5. Serious Adverse Events....98
2.5.5.2.6. Adverse Events Leading to Withdrawal....111
2.5.5.2.7. Other Significant Adverse Events – Phase 3....112
2.5.5.3. Other Safety Assessments....119
2.5.5.3.1. Severe COVID-19 Illness....119
2.5.5.3.2. Pregnancies....120
2.5.5.3.3. Adverse Drug Reactions....120
2.5.5.4. Safety in Special Groups and Situations....120
2.5.5.4.1. Geriatric Use 120
2.5.5.4.2. Pediatric Use 120
2.5.5.4.3. Use During Pregnancy and Lactation....120
2.5.5.4.4. Use in Immunocompromised Individuals 121
2.5.5.4.5. Other Safety Considerations....121
2.5.5.5. Post-Authorization Safety Summary 121
2.5.5.6. Safety Conclusions 122
2.5.6. Benefits and Risks Conclusions 122
2.5.6.1. Benefits 123
2.5.6.2. Risks 123

2.5.6.3. Supportive Real World and Post-Authorization Data Following Use of BNT162b2 in Children 12-15 Years of Age 125
2.5.6.4. Benefit-Risk Conclusions 126
2.5.7. References 128

LIST OF IN-TEXT TABLES

Table 1. Efficacy Populations – Subjects 12 Through 15 Years of Age – Blinded Placebo-Controlled Follow-up Period 26

Table 2. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population 28

Table 3. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population 29

Table 4. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age – Dose 1 All-Available Efficacy Population 31

Table 5. Summary of SARS-CoV-2 Variants for the First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population 34

Table 6. Summary of SARS-CoV-2 Variants of Concern or Variants of Interest for the First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population 35

Table 7. Safety Population – Phase 2/3 Subjects 12 Through 15 Years of Age 40

Table 8. Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 41

Table 9. Follow-up Time After Dose 1 of BNT162b2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received Placebo) – Safety Population 42

Table 10. Disposition of All Randomized Subjects – Phase 2/3 Subjects 12 Through 15 Years of Age 43

Table 11. Demographic Characteristics – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 46

Table 12. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 50

Table 13. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 53

Table 14. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 61

Table 15. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 62

Table 16. Number (%) of Subjects Reporting at Least 1 New Severe Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 66

Table 17. Incidence Rates of at Least 1 Adverse Event From Unblinding Date to Data Cutoff Date (02SEP2021) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2 – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 68

Table 18. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2 – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 71

Table 19. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 72

Table 20. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 74

Table 21. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 78

Table 22. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2 – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 82

Table 23. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 84

Table 24. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 85

Table 25. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population 88

Table 26. Incidence Rates of at Least 1 Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 92

Table 27. Incidence Rates of at Least 1 Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021), by System Organ Class and Preferred Term – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 93

Table 28. Incidence Rates of at Least 1 Serious Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population....101

Table 29. Number (%) of Subjects Reporting at Least 1 New Serious Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population....103

Table 30. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population....105

Table 31. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population....106

Table 32. Number (%) of Subjects Reporting at Least 1 New Serious Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population....108

Table 33. Number (%) of Subjects Reporting at Least 1 New Serious Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population....109

Table 34. Incidence Rates of at Least 1 Serious Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021), by System Organ Class and Preferred Term – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population....111

Table 35. Subjects Reporting an Adverse Event of Lymphadenopathy – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population....114

Table 36. Incidence Rates of at Least 1 Adverse Event of Special Interest From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 116

Table 37. Subjects Reporting an Adverse Event of Arthralgia – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 118

Table 38. Number (%) of Subjects Reporting at Least 1 New Adverse Event of Special Interest After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population 119

LIST OF IN-TEXT FIGURES

Figure 1. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Subjects 12 Through 15 Years of Age – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population 32

Figure 2. Phase 2/3 Safety Analyses of Adolescent Participants: Time Periods and Analysis Groups 49

ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
BLA	(US FDA) Biologics License Application
BMI	body mass index
CBER	(US FDA) Center for Biologics Evaluation and Research
CDC	(US) Centers for Disease Control and Prevention
CFR	case fatality rate
CI	confidence interval
CO	Clinical Overview
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DART	developmental and reproductive toxicity
ECMO	extracorporeal membrane oxygenation
EKG	electrocardiogram
EMA	European Medicines Agency
ER	emergency room
EU	European Union
EUA	Emergency Use Application
FDA	(US) Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean-fold rise
GMR	geometric mean ratio
GMT/GMC	geometric mean titer/concentration
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
ICU	intensive care unit
IM	intramuscular(ly)
IND	Investigational New Drug application
iPSP	initial Pediatric Study Plan
IQR	interquartile range
IR	incidence rate
LNP	lipid nanoparticle
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification testing
NHP	non-human primate
NI	noninferiority
PDCO	Paediatric Committee

Abbreviation	Definition
PCR	polymerase chain reaction
PIP	Paediatric Investigational Plan
PSP	Pediatric Study Plan
PT	Preferred Term
PY	person-years
RNA	ribonucleic acid
RNA-LNP	RNA lipid nanoparticle
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
SMQ	Standardized MedDRA query
SOC	System Organ Class
TME	targeted medical event
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	Variant of Concern
VOI	Variant of Interest
WHO	World Health Organization

2.5. CLINICAL OVERVIEW

This Clinical Overview (CO) describes the clinical data for a prophylactic, RNA-based SARS-CoV-2 vaccine developed by BioNTech and Pfizer. Evidence is summarized in this CO for the updated efficacy and safety and tolerability of the vaccine administered to healthy adolescent participants 12-15 years of age. Additional safety and efficacy details are presented in Module 5.3.5.1 C4591001 Adolescent 6-Month Update Interim CSR.

The pivotal data are derived from a single registrational study, Phase 1/2/3 Study C4591001, conducted under a United States (US) Investigational New Drug (IND) Application. The clinical experience reflected in this CO represents 2260 study participants 12-15 years of age.

The proposed indication and dosing administration for BNT162b2 (30 µg) are:

Proposed indication: Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals ≥12 years of age

Dosing administration: single 0.3 mL intramuscular (IM) dose followed by a second 0.3 mL dose 3 weeks later

Study C4591001, an ongoing Phase 1/2/3 study, is the registrational and pivotal study of the prophylactic BNT162b2 vaccine candidate against COVID-19 in healthy individuals ≥12 years of age that was initiated in April 2020.

This ongoing study has demonstrated the safety, tolerability, immunogenicity, and efficacy of BNT162b2 when administered as 2 doses of 30 µg given approximately 21 days apart, which was the basis of the current authorizations and approvals. Study C4591001 data supporting authorization or licensure for the 2-dose series in participants ≥12 years of age are summarized below:

- Phase 1 evaluated safety and immunogenicity results in healthy adult participants across dose levels of 2 vaccine candidates, BNT162b1 and BNT162b2. The Phase 1 reactogenicity and immunogenicity profiles, combined with available nonclinical animal study data, led to the selection of BNT162b2 at the 30-µg dose level to advance to Phase 2/3 evaluation.

- Phase 2/3 evaluated efficacy of BNT162b2 30 µg, and provided additional safety, efficacy, and immunogenicity data in a larger population. Prespecified efficacy (event driven) in participants ≥12 years of age and ongoing safety data in participants ≥16 years of age with a median of at least 2 months of follow-up after Dose 2 and up to a data cutoff date of 14 November 2020 were previously reported in the C4591001 Final Analysis Interim Clinical Study Report (CSR), dated 03 December 2020 (Module 5.3.5.1 C4591001 Final Analysis Interim CSR). On 11 December 2020, the US FDA issued an EUA for use of BNT162b2 at 30 µg in individuals ≥16 years of age.

- For adolescents (12 through 15 years of age), immunobridging and safety (median ≥2 months follow-up) were compared with young adults 16 through 25 years of age

were reported in the adolescent interim CSR, dated 14 April 2021 (Module 5.3.5.1 C4591001 Adolescent Interim CSR). Immunogenicity data from adolescent (and young adult) participants showed robust neutralizing GMTs after vaccination with 2 doses of BNT162b2 at 30 µg. In addition, descriptive efficacy analyses during blinded placebo-controlled follow-up period conducted on all confirmed COVID-19 cases accrued up to the data cutoff date of 13 March 2021 for adolescents (12 through 15 years of age) showed estimated vaccine efficacy (VE) was 100.0% for cases reported from at least 7 days after Dose 2 in individuals without and with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen. On 10 May 2021, the US FDA issued an EUA for use in individuals 12 to 15 years of age. At present, there are currently no licensed vaccines in the US to immunize against COVID-19 for individuals 12 to 15 years of age.

- Follow-up to 6 months after Dose 2 was provided in the C4591001 6-Month Update Interim CSR, dated 29 April 2021 (Module 5.3.5.1 C4591001 6-Month Update Interim CSR), and provided up to 6 months of additional safety, efficacy, and immunogenicity follow-up data. The report included analysis of safety during the blinded and post-unblinding (open-label) periods through 6 months post-Dose 2 for participants ≥16 years of age, and updated efficacy analysis based on all confirmed COVID-19 cases in participants ≥12 years of age that accrued in blinded follow-up to a data cutoff date of 13 March 2021. On 23 August 2021, the US FDA granted licensure of COMIRNATY (BNT162b2) for individuals ≥16 years of age.

Based on a data cutoff date of 02 September 2021, this CO for adolescent participants 12 --15 years of age summarizes updated descriptive efficacy analyses from 7 days after Dose 2 during blinded placebo-controlled follow-up (Section 2.5.4.3.1) and the following safety data, as ordered:

- Blinded placebo-controlled follow-up period from Dose 1 to the date of unblinding for BNT162b2 and placebo participants, including new AEs that were reported after the EUA snapshot date (based on events on or after the data cutoff date of 13 March 2021) (Section 2.5.5.2.3.1)

- Open-label observational follow-up period of original BNT162b2 recipients from the date of unblinding to the data cutoff date (Section 2.5.5.2.3.2)

- Cumulative safety from Dose 1 to at least 6 months after Dose 2, inclusive of blinded data and open label- data for original BNT162b2 recipients, including new AEs that were reported after the EUA snapshot date (Section 2.5.5.2.3.3)

- Open-label observational follow-up period for original placebo recipients who then received BNT162b2 from the first dose of BNT162b2 to the data cutoff date (Section 2.5.5.2.3.4)

2.5.1. Product Development Rationale

2.5.1.1. Therapeutic Context

2.5.1.1.1. Disease or Condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission.

At the time of this submission, the ongoing pandemic remains a significant challenge to public health and economic stability worldwide, for which for a licensed prophylactic vaccine is a necessary and critical mitigation across all age groups.

2.5.1.1.2. Clinical Features and Epidemiology of COVID-19

COVID-19 presentation is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing.[1] However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death.[1]

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhea, headache, weakness, and rhinorrhea.[1] Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.[1]

The US Centers for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:[2] fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting, fatigue, headache, nasal congestion or runny nose, or nausea.

All ages may present with the disease, with case fatality rates (CFR) elevated in persons >60 years of age.[3] Comorbidities are associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease.[4] Healthcare workers are over-represented among COVID-19 patients due to occupational exposure to infected patients.[4]

With the widespread availability of COVID-19 vaccines in the United States, the disease burden has shifted to increasingly impact younger age groups, particularly pediatric and adolescent populations who remain largely unvaccinated.[5] As of the week ending October 16, 2021, the age groups 5-11, 12-15, and 16-17 years had among the highest weekly case rates per 100,000 population (164.1, 154.0, and 163.8 per 100,000, respectively).[6] Although the hospitalization rate among those 12-17 years of age is low relative to other age groups (1.6/100,000 or lower since October 2021)[7], among those who are hospitalized, the risk of progression to severe disease (requiring ICU admission, invasive mechanical ventilation, or in-hospital death) in this age group is approximately 30-34%.[8,9,10]

2.5.1.2. Vaccine Clinical Development Program

2.5.1.2.1. Rationale for Development

2.5.1.2.1.1. Current Therapies

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations.[1,11] Monoclonal antibody therapies help prevent hospitalization and reduce viral load and severe symptoms.[12] While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus during the ongoing pandemic.

2.5.1.2.1.2. BNT162b2 Development

Pfizer and BioNTech developed an investigational vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a first-in-human (FIH) study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study. Additional information on Study C4591001 is provided in Section 2.5.1.2.3.2.1.

The vaccine is based on SARS-CoV-2 spike glycoprotein (S) antigens encoded in RNA formulated in lipid nanoparticles (LNPs) and is referred to as BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048). The structural elements of the vector backbones of BNT162 vaccines are optimized for prolonged and strong translation of the antigen-encoding RNA. The potency of RNA vaccines is further optimized by encapsulation of the RNA into LNPs, which protect the RNA from degradation by RNAses and enable transfection of host cells after IM delivery.

2.5.1.2.2. Vaccine Product Information

BioNTech has developed multiple RNA lipid nanoparticle (RNA-LNP) platforms, including nucleoside-modified RNA (modRNA) which has blunted innate immune sensor activating capacity and thus augmented antigen expression. The current vaccine formulation is described in Section 2.5.2.1.

2.5.1.2.3. Vaccine Development Program

2.5.1.2.3.1. Nonclinical Studies

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

These data supported the clinical development of BNT162b2 and were previously submitted. Additional details of nonclinical studies were provided in Module 2.4 Nonclinical Overview.

2.5.1.2.3.2. Clinical Studies

2.5.1.2.3.2.1. Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 registration study. The study design, eligibility criteria, endpoints and analysis methods are detailed in the C4591001 Protocol and Statistical Analysis Plan and have been described in prior submissions.

Data from C4591001 participants in all phases and all age groups have been previously submitted. All ongoing C4591001 participants remain in study follow-up for up to approximately 2 years after Dose 2 of randomized study intervention, except for those who enrolled into Study C4591031 for a booster evaluation.

Study Eligibility Criteria

In Phase 2/3, participants were enrolled with stratification of younger adults (18 to 55 years of age) and older adults (>55 years of age) to achieve approximately 40% enrollment in the older adult group. Additional adolescents were added later by a protocol amendment: older adolescents 16 to 17 years of age are included in the younger adult stratum (ie, 16 to 55 years of age), and younger adolescents 12 to 15 years of age were analyzed as a separate age stratum. Eligibility in Phase 2/3 included higher risk for acquiring COVID-19 in the investigator's judgment, due to medical conditions or exposure, such as:

- Chronic condition (eg, hypertension; diabetes; asthma; pulmonary, liver, or kidney disease)
- Autoimmune disease requiring therapeutic intervention (or history of)
- Chronic HIV, HCV, or HBV infection that is stable and controlled
- Vaping or smoking (or history of smoking within the prior year)
- Resident in a long-term facility
- Occupation with high risk of SARS-CoV-2 exposure (eg, healthcare, emergency response)

Phase 3 (which is ongoing) included planned interim analyses of the first primary efficacy endpoint, ongoing efficacy and safety evaluations including reactogenicity assessment in a subset of participants, and exploratory vaccine immunogenicity evaluation in a subset of participants. Phase 3 is being conducted at sites in the US, Brazil, Argentina, Turkey, South Africa, and Germany. Participants were stratified by age group as previously described. The final efficacy analysis was conducted when at least the prespecified total number of 164 efficacy events accrued. Safety and long-term persistence of efficacy follow-up will continue for at least 2 years and/or end of study. Safety and efficacy analyses included the 360 participants who were analyzed for Phase 2.

Unblinding Considerations

Unblinding to randomized treatment assignment has completed for participants 12-15 years of age in the study, with respect to the participants, Sponsor, and site personnel. This is

subsequent to authorizations/approvals granted in the US and other regions in this age group starting in May 2021 (refer to Section 2.5.1.3).

Individuals 12-15 years of age or older have been unblinded at such time that they become locally eligible and wish to know their treatment assignment to confirm prior vaccination with BNT162b2 (if randomized to this group), or to receive BNT162b2 (if randomized to placebo). Unblinded recipients originally randomized to BNT162b2 continue to be followed in an open-label (ie, observational) manner. Unblinded recipients originally randomized to placebo are offered BNT162b2 vaccination and thereafter followed in an open-label manner.

Participants randomized to placebo who became eligible for vaccination with BNT162b2 (or another COVID-19 vaccine) had the opportunity to receive BNT162b2 in a phased manner as part of the study (no later than at the approximate time participants in Phase 2/3 reach Visit 4). The investigator ensured the participant met at least one of the recommendation criteria. Any participant who originally received placebo and subsequently received BNT162b2 was moved to a new visit schedule to receive both doses of BNT162b2 at each of two additional vaccination visits (Visits 101 and 102).

Sponsor and site personnel who are responsible for the ongoing conduct of the study remain blinded to the data from participants whose treatment assignment has not been disclosed in the ongoing study (ie, not unblinded), with regard to individual participants' randomization. Safety evaluation for these participants by the study team remains blinded until a decision is made to unblind the entire study. A separate (from study conduct) unblinded submissions team is responsible for regulatory submissions.

All participants continue to be expected to remain in study follow-up for a maximum of approximately 2 years after Dose 2 of randomized study intervention.

2.5.1.2.3.2.2. Planned Studies

Further studies (or additional groups/analyses from ongoing studies) are planned or ongoing, including pediatric populations, maternal immunization, concomitant use with adult pneumococcal and influenza vaccines, and obtaining blood samples for potential evaluation for subclinical myocarditis.

2.5.1.2.4. Proposed Indication

The proposed indication for BNT162b2 (30 µg) is:

- Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals ≥12 years of age.

2.5.1.2.5. Rationale for Candidate and Dose Selection

The final candidate and dose level (BNT162b2 at 30 µg) was selected following review of immunogenicity and safety data from the dose-finding Phase 1 portion of Study C4591001 and review of nonclinical data. BNT162b2 at 30 µg proceeded into the Phase 2/3 portion of Study C4591001 because this dose and construct provided the optimum combination of a favorable reactogenicity profile and a robust immune response to afford protection against

COVID-19 in younger and older age groups (see Section 2.5.1.3 for a summary of regulatory submissions, authorizations, and approvals).

2.5.1.3. Regulatory Status

As of December 2021, BNT162b2 30-µg has received temporary authorization for emergency use, conditional marketing authorization approval, or full approval in >90 countries globally. The name of the product supplied under emergency/temporary use authorization for all applicable regions is Pfizer-BioNTech COVID-19 Vaccine. The tradename of the product for all applicable regions is COMIRNATY.

United States

In the US, the vaccine is in clinical development under an IND application, BB-IND 19,736. Fast Track Designation was granted on 07 July 2020 for individuals ≥18 years of age. The initial Pediatric Study Plan (iPSP) was submitted to the FDA on 17 September 2020 and FDA agreed with the final agreed PSP on 23 April 2021.

A summary regarding emergency use authorization status is provided below.

- An EUA application was filed to the FDA on 20 November 2020 and the product was authorized for emergency use in the US on 11 December 2020 as a primary series of BNT162b2 30 µg for individuals ≥16 years of age (EUA 27034).

- Authorization was granted on 10 May 2021 to expand use to individuals ≥12 years of age.

- Authorization was granted on 13 August 2021 for a third dose to be administered ≥28 days following the second dose in individuals ≥12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

- A single booster dose was authorized on 22 September 2021 to be administered ≥6 months after completing the primary series in individuals ≥65 years of age or 18 to 64 years of age at high risk of severe COVID-19 or with frequent institutional or occupational exposure to SARS-CoV-2. On 20 October 2021 authorization was granted for the use of a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine (based on booster eligibility criteria associated with the primary series vaccine received).

- Authorization was granted on 29 October 2021 to expand use to individuals 5 through 11 years of age and for a manufacturing change to include an additional formulation of the vaccine that uses Tris buffer instead of PBS.

- On 19 November 2021, the eligible population for the homologous and heterologous booster doses was expanded to individuals 18 years of age and older.

- On 9 December 2021, the eligible population for the homologous and heterologous booster doses was expanded to individuals 16 years of age and older.

A summary regarding licensure status in the US is provided below.

- The initial BLA for the 30-µg formulation was submitted to US FDA on 18 May 2021 and approved on 23 August 2021 for individuals ≥16 years of age.

European Union

A rolling review for a Marketing Authorisation Application (MAA) was initiated on 05 October 2020 with nonclinical data followed by Module 3 documents submitted on 05 November 2020 and completed with submission of clinical modules on 07 December 2020. A Paediatric Investigational Plan (PIP) was submitted to the Paediatric Committee (PDCO) on 21 September 2020 and a decision on the agreement of the PIP was received 27 November 2020.

A summary regarding conditional approval status in the EU is provided below.

- Conditional marketing approval was granted by the European Medicines Agency (EMA) on 21 December 2020 for administration of the primary series of BNT162b2 30 µg to individuals ≥16 years of age and was later expanded to include use in individuals ≥12 years of age on 28 May 2021.

- A booster dose (third dose) of BNT162b2 30 µg administered at least 6 months after the second dose to individuals ≥18 years of age was approved in the EU on 05 October 2021; on the same day, a third dose was approved in the EU to be administered at least 28 days after the second dose to individuals who are severely immunocompromised.

- An extension was approved on 26 November 2021 for administration of a primary series of BNT162b2 10 µg to individuals 5 to 11 years of age, including a third dose in severely immunocompromised individuals 5 years and older.

Rest of World

- Marketing Authorization Applications were initiated beginning in October 2020 and Conditional Marketing Authorizations have been granted in many countries globally including Switzerland, Japan, Australia, New Zealand, and Brazil. Requests for temporary authorization for emergency supply have also been filed and approved in many countries globally under emergency or temporary use authorization procedures or special import procedures beginning in November 2020. The World Health Organization (WHO) issued a positive opinion on the Emergency Use Listing of COMIRNATY on 31 December 2020. In addition to the approval of the US BLA on 23 August 2021, other countries are also beginning to grant full approval for COMIRNATY, including Canada on 16 September 2021 and Israel on 19 September 2021.

2.5.1.4. Ethical Considerations

All studies in the clinical development program were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. They were designed, performed, and analyzed in accordance with all applicable regulations, laws, and guidelines in effect at the time they were conducted from the US FDA, EU Directive 2001/20/EC, and local regulatory agencies in countries where the study was conducted. The study design reflects recommendations from local review boards/committees, and other local regulatory authorities.

The pivotal Phase 1/2/3 Study C4591001 was conducted at sites in the US, Brazil, Argentina, Turkey, South Africa, and Germany; the majority of participants were enrolled at sites in the US. The supporting Phase 1/2 Study BNT162-01 was conducted at sites in Germany. Pediatric Study C4591007 was conducted at sites in the US, Finland, Poland, and Spain.

2.5.2. Overview of Biopharmaceutics

2.5.2.1. Formulation Development

Two vaccine formulations are currently authorized.

PBS/Sucrose vaccine product: supplied as a preservative-free, sterile dispersion of LNPs in aqueous cryoprotectant buffer formulated at 0.5 mg/mL in phosphate-buffered saline and 300 mM sucrose at pH 7.4 to be diluted for IM administration. The presentation is diluted with sterile 0.9% sodium chloride solution prior to use and delivers a 30 µg RNA dose for individuals ≥12 years of age.

Tris/Sucrose vaccine product: supplied as a preservative-free, sterile dispersion of LNPs in aqueous cryoprotectant buffer for IM administration formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4. The presentation of the vaccine is:

- 30 µg RNA dose for individuals ≥12 years of age, not for dilution (0.3 mL administration)
- 10 µg RNA dose for individuals 5 through 11 years of age, requires dilution (0.2 mL administration).

Details of formulation development and storage conditions are provided in Module 3.

2.5.2.2. Biopharmaceutical Studies

Not applicable.

2.5.2.3. Bioanalytical and Analytical Methods Used in Human Studies

Information on assays used to assess SARS-CoV-2 infection is in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

2.5.3. Overview of Clinical Pharmacology

Not applicable.

2.5.4. Overview of Efficacy (Including Immunogenicity)

The methods and statistical analyses for efficacy evaluation are summarized in Section 2.5.4.1.1 and Section 2.5.4.1.2, respectively, and results are in Section 2.5.4.3.

Details of efficacy analysis methods in Study C4591001 are provided in the Module 5.3.5.1 C4591001 Protocol and statistical analysis plan (SAP).

2.5.4.1. Efficacy Endpoints and Analysis Methods

2.5.4.1.1. Efficacy Endpoints

Study C4591001 is the pivotal efficacy study for BNT162b2. Efficacy was assessed based on confirmed cases of COVID-19 in the efficacy populations. Results from the protocol specified interim analysis conducted on an accrued 94 cases (data cutoff date: 04 November 2020) and the final analysis conducted on an accrued 170 cases (data cutoff date: 14 November 2020) were previously submitted. These analyses included data from all participants in Phase 3 age groups (12-15, 16-55, and >55 years of age) at the time of the analyses. Prespecified primary and secondary efficacy endpoint analyses were completed per protocol as of 14 November 2020. At the time of the final analysis, there were relatively few participants 12-15 years of age enrolled in the study and no COVID-19 cases in this age group accrued at that time (14 November 2020). Updated efficacy analyses were presented for adolescent participants 12-15 years of age in the adolescent interim CSR dated 14 April 2021 (through data cutoff date of 13 March 2021), and for participants ≥12 years of age in the 6-month update interim CSR dated 29 April 2021 (through data cutoff date of 13 March 2021). Further updated efficacy analyses in this CO include cases in the 12-15 years of age group accrued in blinded follow-up to a data cutoff date of 02 September 2021 (see Section 2.5.4.1.2).

2.5.4.1.1.1. Efficacy Endpoints

The updated efficacy described and reported for adolescents 12-15 years of age in this CO include the following endpoint:

- COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT.

2.5.4.1.1.2. COVID-19 Case Determination

COVID-19 case determination methodology has not changed since the initial report of vaccine efficacy for BNT162b2. Briefly, participants who developed any potential COVID-19 symptoms listed in the protocol were to contact the site immediately and if confirmed to participate in an in-person or telehealth visit as soon as possible (optimally within 3 days of symptom onset, and at the latest 4 days after symptom resolution). At the visit (or prior to the visit, if a participant utilized a self-swab as permitted per protocol), investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis.

Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; EUA200047/A001) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local NAAT result was only acceptable if it met protocol-specified criteria and if a central laboratory result was not available. Participants with and without evidence of prior infection were determined by virological testing via NAAT on mid-turbinate swab and serological testing for SARS-CoV-2 N-binding antibodies.

COVID-19 cases (defined per FDA guidance)[13] were based on SARS-CoV-2 positive test result per central laboratory or local testing facility (using an acceptable test per protocol and if no central laboratory result was available) and presence of at least 1 of the following:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhea
- Vomiting.

Severe COVID-19 cases (defined per FDA guidance)[13] included presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness:
    - respiratory rate ≥30 breaths per minute
    - heart rate ≥125 beats per minute
    - SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2 <300 mm Hg

- Respiratory failure:
    - needing high-flow oxygen
    - noninvasive ventilation
    - mechanical ventilation
    - extracorporeal membrane oxygenation (ECMO)

- Evidence of shock:
    - systolic blood pressure <90 mm Hg
    - diastolic blood pressure <60 mm Hg
    - requiring vasopressors

- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit
- Death.

In addition to the above specified definition of severe COVID-19, an efficacy analysis for severe COVID-19 cases was conducted using the CDC definition of severe COVID-19 (hospitalization, admission to the ICU, intubation or mechanical ventilation, or death).[14]

2.5.4.1.2. Efficacy Analysis Methods

The statistical analyses of efficacy data presented in this CO are from Study C4591001 and were based on the evaluable efficacy and all-available populations.

Updated efficacy analyses were conducted for efficacy endpoints using statistical methods described in the study statistical analysis plan (Module 5.3.5.1 C4591001 SAP). The point estimate of VE and associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time were provided as a descriptive summary. Updated analyses in this CO include COVID-19 cases accrued in blinded follow-up in adolescents 12-15 years of age to the data cutoff date (02 September 2021).

2.5.4.2. Immunogenicity Endpoints and Analysis Methods

Assay methods and qualification/validation reports for immunoassays are provided in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods. Details of immunogenicity analyses are summarized below. Statistical analysis methods are provided in Section 2.5.4.2.2.

2.5.4.2.1. Immunogenicity Endpoints

In Phase 3, an immunogenicity objective was to demonstrate noninferiority (NI) of the immune response to prophylactic BNT162b2 in participants 12-15 years of age compared to participants 16-25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. This NI analysis of neutralizing titers was performed to provide immunobridging between these younger adolescents and young adults 16-25 years of age. Only a validated SARS-CoV-2 neutralization assay was used.

Immunogenicity endpoints were analyzed for SARS-CoV-2 serum neutralizing titers including:

- geometric mean titers (GMT) in each age group and GMR of 12-15 years group to 16-25 years group at 1 month after Dose 2
- geometric mean-fold rise (GMFR) from before vaccination to 1 month after Dose 2 in each age group
- percentage of participants with a ≥4-fold rise in neutralizing titers (seroresponse) from before vaccination to 1 month after Dose 2 in each age group.

2.5.4.2.2. Immunogenicity Analysis Methods

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations.

Immunogenicity analyses of neutralizing titers were conducted with the statistical methods described in the study SAP (Module 5.3.5.1 C4591001 SAP).

NI was assessed based on the geometric mean ratio (GMR) of SARS-CoV-2 neutralizing titers at 1 month after Dose 2 using a 1.5-fold margin. The GMR and its 2-sided 95% CI were derived by calculating differences in means and CIs on the natural log scale of titers based on Student's t-distribution, then exponentiating the results. The difference in means on the natural log scale was calculated as: (12-15 years of age) – (16-25 years of age). NI was declared if the lower bound of the 2-sided 95% CI for the GMR was >0.67.

2.5.4.3. Efficacy Results

2.5.4.3.1. Updated Analysis of Efficacy – Adolescents 12-15 Years of Age

Updated efficacy data for the Phase 3 portion of Study C4591001 were analyzed for all participants 12-15 years of age who met the protocol-specified criteria for efficacy evaluation. Data are summarized for the efficacy populations.

COVID-19 case evaluation for primary and secondary efficacy endpoints is discussed in Section 2.5.4.1. Efficacy endpoints evaluated confirmed COVID-19 cases in participants either without or with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen.

Efficacy population characteristics in the updated analysis are presented in Section 2.5.4.3.1.1, and results of the updated analysis are presented in Section 2.5.4.3.1.2 (VE against COVID-19), and Section 2.5.4.3.1.3 (VE against severe disease).

2.5.4.3.1.1. Efficacy Populations – Updated Analysis

In the efficacy analyses, adolescents in the efficacy populations included:

Evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2: N=1057 in the BNT162b2 group and N=1030 in the placebo group.

Evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2: N=1119 in the BNT162b2 group and N=1109 in the placebo group.

Dose 1 all-available efficacy population: N=1131 in the BNT162b2 group and N=1129 in the placebo group.

The proportions of participants included in the updated efficacy populations were similar in the BNT162b2 and placebo groups (Table 1). There were 36 participants (15 [1.3%] in the BNT162b2 group and 21 [1.9%] in the placebo group) were excluded from the evaluable efficacy (7 days) population mostly because they did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1).

Demographics of participants (including sex, race, ethnicity, country, comorbidities, obesity status, and age at vaccination) in the evaluable efficacy (7 days) population for adolescent participants without evidence of infection prior to 7 days after Dose 2 were similar in the BNT162b2 and placebo groups. Note that all adolescent participants 12-15 years of age were

from the US. This analysis population had generally similar demographics compared to the safety population (Section 2.5.5.2.1).

Demographic characteristics for the Dose 1 all-available efficacy population and for participants with or without evidence of infection prior to 7 days after Dose 2 (evaluable efficacy [7 days] population) were similar to those in the evaluable efficacy (7 days) population.

Table 1. Efficacy Populations – Subjects 12 Through 15 Years of Age – Blinded Placebo-Controlled Follow-up Period

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	1134 (100.0)	1130 (100.0)	2264 (100.0)
Dose 1 all-available efficacy population	1131 (99.7)	1129 (99.9)	2260 (99.8)
Subjects without evidence of infection before Dose 1	1083 (95.5)	1078 (95.4)	2161 (95.5)
Subjects excluded from Dose 1 all-available efficacy population	3 (0.3)	1 (0.1)	4 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	3 (0.3)	1 (0.1)	4 (0.2)
Dose 2 all-available efficacy population	1123 (99.0)	1117 (98.8)	2240 (98.9)
Subjects without evidence of infection prior to 7 days after Dose 2	1061 (93.6)	1037 (91.8)	2098 (92.7)
Subjects excluded from Dose 2 all-available efficacy population	11 (1.0)	13 (1.2)	24 (1.1)
Reason for exclusion[c]			
Did not receive 2 vaccinations	10 (0.9)	13 (1.2)	23 (1.0)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)
Evaluable efficacy (7 days) population	1119 (98.7)	1109 (98.1)	2228 (98.4)
Subjects without evidence of infection prior to 7 days after Dose 2	1057 (93.2)	1030 (91.2)	2087 (92.2)
Subjects excluded from evaluable efficacy (7 days) population	15 (1.3)	21 (1.9)	36 (1.6)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	1 (0.1)	1 (0.1)	2 (0.1)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	14 (1.2)	19 (1.7)	33 (1.5)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)
Had other important protocol deviations on or prior to 7 days after Dose 2	0	3 (0.3)	3 (0.1)

a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.

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2.5.4.3.1.2. Vaccine Efficacy Against COVID-19 – Updated Analysis

2.5.4.3.1.2.1. Vaccine Efficacy From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-Up Period

2.5.4.3.1.2.1.1. Participants Without Evidence of Infection Before and During Vaccination Regimen

Among adolescent participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0% (2-sided 95% CI: 86.8%, 100.0%), with 0 and 28 cases in the BNT162b2 and placebo groups, respectively (Table 2).

The VE of BNT162b2 for the same efficacy endpoint based on the Dose 2 all available efficacy population was 100.0% (2-sided 95% CI: 87.2%, 100.0%), with 0 and 29 cases in the BNT162b2 and placebo group, respectively.

Table 2. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1057)		Placebo (N[a]=1030)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2	0	0.343 (1043)	28	0.322 (1019)	100.0	(86.8, 100.0)
≥7 days after Dose 2 to <2 Months after Dose 2	0	0.138 (1043)	15	0.133 (1019)	100.0	(73.2, 100.0)
≥2 Months after Dose 2 to <4 Months after Dose 2	0	0.148 (1008)	10	0.139 (957)	100.0	(58.0, 100.0)
≥4 Months after Dose 2	0	0.057 (723)	3	0.050 (682)	100.0	(-112.1, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2) were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period for the overall row and from start to the end of the range stated for each time interval.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
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2.5.4.3.1.2.1.2. Participants With or Without Evidence of Infection Before and During Vaccination Regimen

Among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen, estimated VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0% (2-sided 95% CI: 87.5%, 100.0%), with 0 and 30 cases in the BNT162b2 and placebo groups, respectively (Table 3). For the 2 additional cases in adolescent participants with evidence of SARS-CoV-2 infection (as compared with those without evidence of infection from Table 2), both participants were SARS-CoV-2 negative at baseline.

Table 3. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1119)		Placebo (N[a]=1109)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2	0	0.362 (1098)	30	0.345 (1088)	100.0	(87.5, 100.0)
≥7 days after Dose 2 to <2 Months after Dose 2	0	0.146 (1098)	17	0.142 (1088)	100.0	(76.4, 100.0)
≥2 Months after Dose 2 to <4 Months after Dose 2	0	0.155 (1061)	10	0.148 (1022)	100.0	(57.4, 100.0)
≥4 Months after Dose 2	0	0.061 (767)	3	0.055 (726)	100.0	(-117.8, 100.0)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period for the overall row and from start to the end of the range stated for each time interval.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
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(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adc19ef_ve_cov_7pd2_peds_eval

2.5.4.3.1.2.1.3. Subgroup Analyses (Vaccine Efficacy From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-Up Period)

In the evaluable efficacy (7 days) population, among participants without and with or without evidence of SARS CoV-2 infection before and during the vaccination regimen, the estimated VE was 100.0% for all subgroups by sex, race, ethnicity, country, comorbidities, and obesity status. Due to the small number of participants, the data must be interpreted with caution.

2.5.4.3.1.2.2. All Confirmed Cases of COVID-19 After Dose 1 – All-Available Efficacy Population

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in (Table 4), which provides a summary of VE for all adolescent participants in the Dose 1 all-available efficacy (modified intention-to-treat) population adjusted for exposure, regardless of evidence of infection before or during the vaccination regimen. Among these participants, the estimated VE against confirmed COVID-19 occurring after Dose 1 was 94.0% (2-sided 95% CI: 81.3%, 98.8%), with 3 and 48 cases of COVID-19 in the BNT162b2 and placebo groups, respectively. All 3 cases in the BNT162b2 group occurred <11 days after Dose 1 and in

participants who had baseline SARS-CoV-2 negative status, and represented all cases reported in this group at any time.

The observed VE for BNT162b2 in adolescents in the Dose 1 all-available efficacy population was 100.0% (ie, all cases were confined to the placebo group) for all time intervals starting from ≥11 days after Dose 1 to before Dose 2 through ≥4 months after Dose 2.

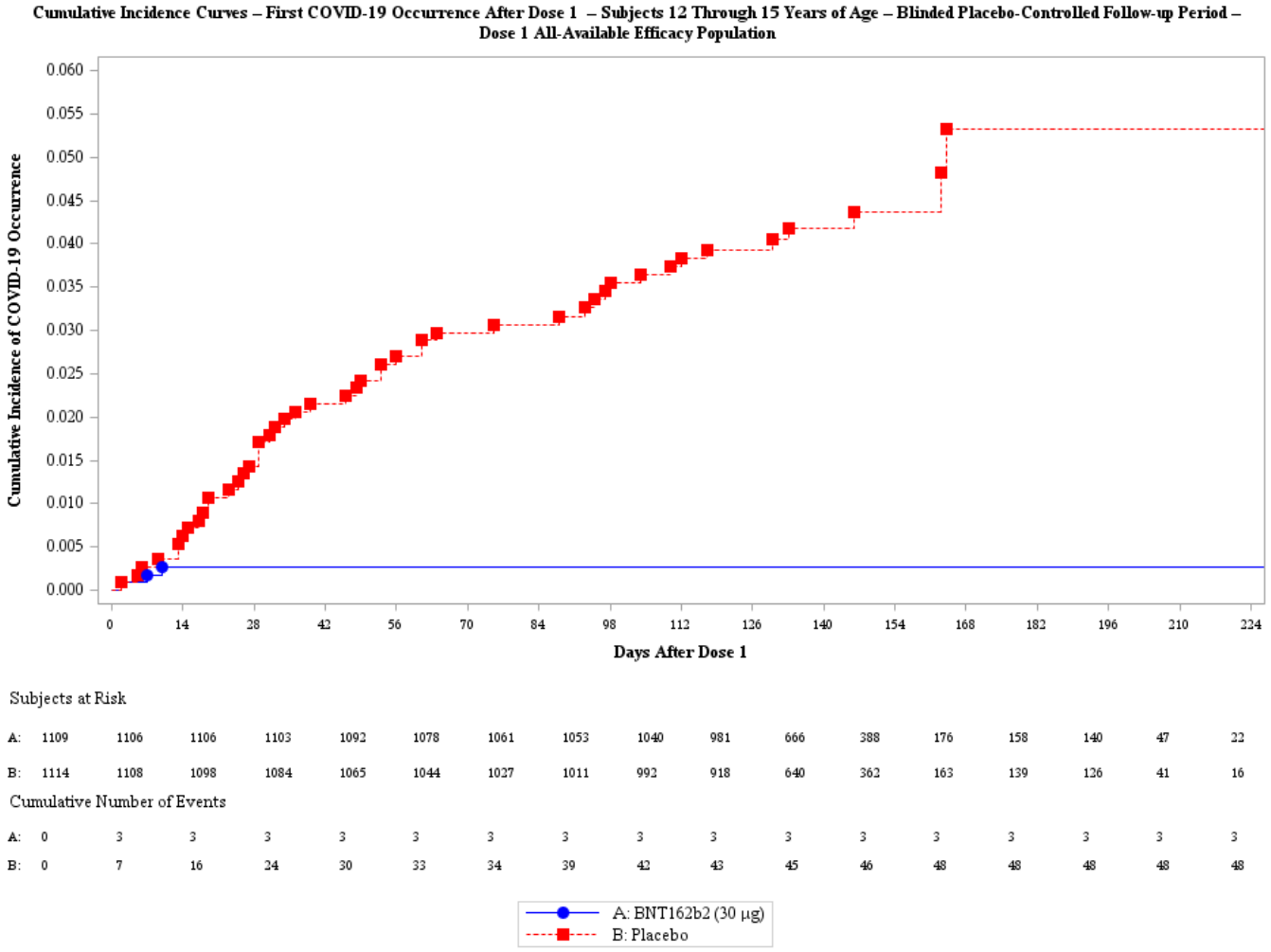
The early onset of protection is readily apparent in Figure 1, which displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until approximately 11 days after Dose 1 (consistent with the data shown in Table 4), at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining flat with no more cases in the BNT162b2 group.

Table 4. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1131)		Placebo (N[a]=1129)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	3	0.450 (1109)	48	0.434 (1114)	94.0	(81.3, 98.8)
After Dose 1 to before Dose 2	3	0.065 (1109)	12	0.065 (1114)	75.1	(7.6, 95.5)
After Dose 1 to <11 days after Dose 1	3	0.033 (1109)	4	0.033 (1114)	24.7	(-345.0, 89.0)
≥11 Days after Dose 1 to before Dose 2	0	0.032 (1106)	8	0.031 (1110)	100.0	(42.0, 100.0)
Dose 2 to 7 days after Dose 2	0	0.021 (1103)	5	0.021 (1100)	100.0	(-8.7, 100.0)
≥7 Days after Dose 2	0	0.364 (1102)	31	0.348 (1095)	100.0	(87.9, 100.0)
≥7 days after Dose 2 to <2 Months after Dose 2	0	0.146 (1102)	17	0.143 (1095)	100.0	(76.3, 100.0)
≥2 Months after Dose 2 to <4 Months after Dose 2	0	0.156 (1065)	10	0.149 (1029)	100.0	(57.3, 100.0)
≥4 Months after Dose 2	0	0.062 (770)	4	0.056 (732)	100.0	(-37.7, 100.0)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of the range stated for each time interval.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adc19ef Table Generation: 03NOV2021 (11:38)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adc19ef_ve_cov_pd1_st_peds_aai

Figure 1. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Subjects 12 Through 15 Years of Age – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population



PFIZER CONFIDENTIAL SDTM Creation: 30SEP2021 (10:35) Source Data: adc19ef Table Generation: 08NOV2021 (15:26)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adc19ef_f001_km_d1_peds_aai

2.5.4.3.1.2.2.1. Subgroup Analyses (All Confirmed Cases of COVID-19 After Dose 1 – All-Available Efficacy Population)

Additionally, in subgroup analyses for VE by sex, race, ethnicity, country, comorbidities, and obesity status, the observed subgroup VEs based on the Dose 1 all-available efficacy (modified intent-to-treat) population were generally similar to those based on the evaluable efficacy population except for a few subgroups that the number of participants and cases were too small to provide robust estimates. The observed VEs for all subgroups were ≥88.7% except for one subgroup (race, all others) with 1 case in each group: American Indian or Alaska native in placebo and Asian in BNT162b2. Due to the small number of participants, the data must be interpreted with caution.

2.5.4.3.1.3. Vaccine Efficacy Against Severe COVID-19 – Updated Analysis

No severe COVID-19 cases (per protocol definition or CDC criteria) were reported in participants 12 15 years of age as of the data cutoff date (02 September 2021).

2.5.4.3.1.4. Variants of Concern

Among the 30 placebo participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen and had COVID-19 cases, most variants sequenced were neither VOI nor VOC except for the B.1.1.7 (Alpha) (Table 6), which was found in 23.3% of placebo participants (Table 5). There were no cases belonging to the Beta, Gamma, Delta, Lambda, or Mu variants (Table 6). Importantly, all of the cases in the efficacy analyses occurred between 02 November 2020 to 19 May 2021, which is before the Delta surge in the US.

Table 5. Summary of SARS-CoV-2 Variants for the First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)		
SARS-CoV-2 Lineage[b] (WHO Classification)	BNT162b2 (30 µg) (N[a]=0) n[c](%)	Placebo (N[a]=30) n[c](%)	Total (N[a]=30) n[c](%)
B.1	0	1 (3.3)	1 (3.3)
B.1.1.222	0	1 (3.3)	1 (3.3)
B.1.1.29	0	1 (3.3)	1 (3.3)
B.1.1.519	0	1 (3.3)	1 (3.3)
B.1.1.7 (Alpha)	0	7 (23.3)	7 (23.3)
B.1.142	0	1 (3.3)	1 (3.3)
B.1.2	0	10 (33.3)	10 (33.3)
B.1.243	0	1 (3.3)	1 (3.3)
B.1.361	0	1 (3.3)	1 (3.3)
B.1.369	0	1 (3.3)	1 (3.3)
B.1.400	0	1 (3.3)	1 (3.3)
B.1.427	0	2 (6.7)	2 (6.7)
B.1.526	0	1 (3.3)	1 (3.3)
Unknown[d]	0	1 (3.3)	1 (3.3)

Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of subjects with first COVID-19 occurrence. This value is the denominator for the percentage calculations.
b. Based on PANGO lineages (cov-lineages.org).
c. n = Number of subjects with the specified characteristic.
d. Include indeterminate result and not quantifiable (QNS) samples.
PFIZER CONFIDENTIAL SDTM Creation: 02NOV2021 (15:56) Source Data: adxb Table Generation: 04NOV2021 (14:59)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adxb_seq_var_cov_7pd2_peds_eval

Table 6. Summary of SARS-CoV-2 Variants of Concern or Variants of Interest for the First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)		
SARS-CoV-2 Lineage[b] (WHO Classification)	BNT162b2 (30 µg) (N[a]=0) n[c](%)	Placebo (N[a]=30) n[c](%)	Total (N[a]=30) n[c](%)
B.1.1.7 (Alpha)	0	7 (23.3)	7 (23.3)
B.1.351 (Beta)	0	0	0
P.1 (Gamma)	0	0	0
B.1.617.2 (Delta)	0	0	0
C.37 (Lambda)	0	0	0
B.1.621 (Mu)	0	0	0
Other	0	22 (73.3)	22 (73.3)
Unknown[d]	0	1 (3.3)	1 (3.3)

Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of subjects with first COVID-19 occurrence. This value is the denominator for the percentage calculations.
b. Based on PANGO lineages (cov-lineages.org).
c. n = Number of subjects with the specified characteristic.
d. Include indeterminate result and not quantifiable (QNS) samples.
PFIZER CONFIDENTIAL SDTM Creation: 02NOV2021 (15:56) Source Data: adxb Table Generation: 04NOV2021 (14:59)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2 unblinded/C4591001 S Peds/adxb seq cov 7pd2 peds eval

2.5.4.3.1.5. Efficacy Conclusions – Updated Analysis

Descriptive efficacy analyses were conducted for the adolescent group on cases accrued during blinded placebo-controlled follow-up period through the data cutoff date of 02 September 2021.

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

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

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

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

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

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

2.5.4.4. Immunogenicity Results

2.5.4.4.1. Immunogenicity Populations

For immunogenicity analyses, it was planned to select a random sample of 280 participants in the BNT162b2 group for each of the two age groups (12-15 and 16-25 years of age) as an immunogenicity subset for the NI assessment. To maintain blinding of the laboratory personnel, 50 participants in each placebo group were also randomly selected from each of the two age groups for serology testing.

The Dose 2 evaluable immunogenicity population for adolescents 12-15 years of age included 209 participants in the BNT162b2 group and 36 participants in the placebo group), and for young adults 16-25 years of age included 186 participants in the BNT162b2 group and 32 participants in the placebo group. The majority of participant exclusions from the evaluable immunogenicity populations were due to participants not having at least 1 valid and determinate immunogenicity result after Dose 2, mostly as the result of testing laboratory supply limitation of the qualified viral lot and were generally balanced across age and vaccine groups.

Demographics were generally similar for BNT162b2 and placebo, and between adolescents and young adults 16-25 years of age. Demographics of the evaluable immunogenicity population were similar to those in the all-available immunogenicity population and to those in the corresponding safety population.

2.5.4.4.2. Noninferiority Between 12-15 Years of Age and 16-25 Years of Age Groups

Geometric Mean Ratio (GMR) in Neutralization Titers

The immune response to BNT162b2 in adolescents 12-15 years of age was noninferior to that observed in young adults 16-25 years of age, based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2, in participants without prior evidence of SARS-COV-2 infection, and in fact greatly exceeded the response observed in young adults. The GMT ratio of adolescents to young adults was 1.76 (2-sided 95% CI: 1.47, 2.10), meeting the 1.5-fold NI criterion (ie, lower bound of the 2-sided 95% CI for GMR >0.67). Of note, the lower bound of the 2-sided 95% CI for the GMR is >1 which indicates a statistically greater response in the adolescents than that of young adults.

Seroresponse

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 of BNT162b2, high proportions (97.9% of adolescents and 100.0% of young adults) had a ≥4-fold rise (seroresponse) in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had a ≥4-fold rise between the two age groups (adolescents – young adults) was -2.1% (2-sided 95% CI: -6.0%, 0.9%)

2.5.4.4.3. Immunogenicity Conclusions

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

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

2.5.5. Overview of Safety

The methods and statistical analyses for safety evaluation are summarized in Section 2.5.5.1 and Section 2.5.5.1.2, respectively, and results as of the data cutoff date (02 September 2021) are presented in Section 2.5.5.2.

Details of safety analysis methods in Study C4591001 are provided in the Module 5.3.5.1 C4591001 Protocol and SAP.

2.5.5.1. Safety Endpoints and Analysis Methods

2.5.5.1.1. Safety Endpoints

Reactogenicity

All participants 12-15 years of age and a subset of participants ≥16 years of age (young adults 16-25 years of age and adults 16-55 years of age), were asked to record reactogenicity (referred as reactogenicity subset):[15] local reactions (pain, redness and swelling at the injection site), systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication usage for 7 days, each evening following administration of study intervention using prompts from an electronic diary (e-diary). This allowed recording of these assessments only within a fixed time window and provided an accurate representation of the participant's experience at that time. Participants were asked to assess local reactions and systemic events from Day 1 through Day 7 after each dose.

Adverse Events

Adverse events (AEs) were recorded for up to 1 month after Dose 2 and categorized by frequency, maximum severity, seriousness, and relationship to study intervention using SOC and PT according to MedDRA. Serious AEs (SAEs) will be recorded up to 6 months after Dose 2. Deaths are recorded to the end of study.

Myocarditis and pericarditis were included as pre-specified adverse events of special interest (AESIs) in Protocol Amendment 18 (07 September 2021).

Pfizer also utilizes a safety review as part of the signal detection processes that highlights specified targeted medical events (TMEs) of clinical interest. TMEs are specific AE terms reviewed on an ongoing basis by routine safety data review procedures throughout the clinical study. Although not prespecified in the protocol, TMEs are maintained in a separate list as part of the Safety Surveillance Review Plan for the vaccine program. By definition, TMEs are considered to be AESIs specific for a product or program's protocol(s). They are based on review of known pharmacology, toxicology findings, possible class effects, published literature, and potential signals arising from safety data assessments.

The list of TMEs is customized for each development program and is dynamic. For this study, the list of TMEs includes events of interest because of their association with COVID-19 and terms of interest for vaccines in general. Terms are chosen from the MedDRA dictionary and may include PTs, high level term, high level group terms, or

standardized MedDRA queries (SMQs; all evaluated as broad and narrow). Other events of clinical interest identified by the sponsor in the reported safety dataset were also reviewed and summarized (Section 2.5.5.2.7).

Prior SARS-CoV-2 infection was determined by virological testing via nucleic acid amplification test (NAAT) on mid-turbinate swab and serological testing for IgG to the SARS-CoV-2 N-antigen at baseline, and via NAAT at Dose 2. Participants were surveilled for potential COVID-19 illness from Visit 1 onwards.

Pregnancies were reported for participants in any phase of the study.

Narratives for safety events in adolescents (12-15 years of age) are located in Module 5.3.5.1 C4591001 Adolescent 6-Month Update Interim CSR Section 14 Narratives. Narratives for this age group were prepared for participants if they had the following events:

- deaths
- Related SAEs
- AEs leading to study discontinuation
- AEs of clinical interest (including anaphylaxis, appendicitis, Bell's palsy)
- pregnancy exposures
- COVID-19 (participants with a case meeting severe criteria or >1 episode of COVID-19)

2.5.5.1.2. Safety Analysis Methods

Safety data were analyzed and reported using descriptive summary statistics for the safety population for each study phase. Analyses were performed for endpoints described in Section 2.5.5.1.1.

Reactogenicity

Descriptive statistics were provided for each reactogenicity endpoint for the reactogenicity subset after each dose for each vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination are presented by severity and cumulatively across severity levels. Descriptive summary statistics included counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. Missing reactogenicity e-diary data were not imputed.

Adverse Events

Descriptive summary statistics including counts, percentages, and associated Clopper-Pearson 2-sided 95% CIs were provided for AEs for each vaccination group.

AE analyses of participants who had different durations of follow-up time due to unblinding in the study (per protocol) were summarized as incidence rates (IR) adjusted for exposure time. This was calculated as: (number of participants reporting event) / (total exposure time across all participants in the specified group). This accounts for variable exposure since unblinding began for individual participants (as described in Section 2.5.1.2.3.2.1). Two-sided 95% CIs for the IRs were provided based on Poisson distribution.

2.5.5.2. Safety Results

2.5.5.2.1. Safety Populations

The safety population included a total of 2260 participants who were 12-15 years of age: 1131 participants in the BNT162b2 group and 1129 participants in the placebo group (Table 7). Four participants were excluded from the safety population because they did not receive any study intervention.

Table 7. Safety Population – Phase 2/3 Subjects 12 Through 15 Years of Age

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) n[a]	Placebo n[a]	Total n[a] (%)
Randomized[b]			2264
Vaccinated	1131	1129	2260 (99.8)
Safety population	1131	1129	2260 (99.8)
Excluded from safety population			4 (0.2)
Reason for exclusion			
Subject did not receive study vaccine			4 (0.2)

a. n = Number of subjects with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
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(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adsl s003 saf1 ped6

2.5.5.2.1.1. Duration of Follow-Up

During the blinded placebo-controlled follow-up period, median follow-up time for adolescent participants was 4.4 months. There were 634 (56.1%) and 629 (55.7%) of participants in the BNT162b2 and placebo groups, respectively, who had follow-up time ≥4 months to <6 months after Dose 2 (Table 8). From Dose 2 to the cutoff date, 740 (65.4%) of participants in the BNT162b2 group had a total follow-up time ≥8 to <10 months, which was composed of blinded and unblinded exposure. There were few participants (18 total) with follow-up time of <6 months, as most adolescent participants 12-15 years of age should have had ≥6 months of follow-up by the data cutoff date (02 September 2021), and also corresponding with the number of participants who withdrew from the study (Table 10).

For original adolescent placebo recipients who received at least the first dose of BNT162b2, median follow-up time was 3.8 months, and 65.0% of these participants had follow-up time between ≥2 months to <4 months after Dose 1 of BNT162b2 (Table 9).

Table 8. Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Original blinded placebo-controlled follow-up period			
<2 Months	45 (4.0)	62 (5.5)	107 (4.7)
≥2-<4 Months	300 (26.5)	294 (26.0)	594 (26.3)
≥4-<6 Months	634 (56.1)	629 (55.7)	1263 (55.9)
≥6 Months	152 (13.4)	144 (12.8)	296 (13.1)
Mean (SD)	4.5 (1.24)	4.4 (1.27)	4.4 (1.26)
Median	4.4	4.4	4.4
Min, max	(0.0, 10.8)	(0.0, 9.1)	(0.0, 10.8)
Total follow-up period from Dose 2 to cutoff date			
<2 Months	8 (0.7)		
≥2-<4 Months	0		
≥4-<6 Months	10 (0.9)		
≥6-<8 Months	326 (28.8)		
≥8-<10 Months	740 (65.4)		
≥10 Months	47 (4.2)		
Mean (SD)	8.3 (1.03)		
Median	8.4		
Min, max	(0.0, 10.9)		

a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 30SEP2021 (10:35) Source Data: adsl Table Generation: 08NOV2021 (03:38)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adsl_fu_d21_ped6

Table 9. Follow-up Time After Dose 1 of BNT162b2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received Placebo) – Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=1010) n[b] (%)
Open-label follow-up period	
<2 Months	66 (6.5)
≥2-<4 Months	656 (65.0)
≥4-<6 Months	228 (22.6)
≥6 Months	60 (5.9)
Mean (SD)	3.8 (1.09)
Median	3.8
Min, max	(0.1, 8.6)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 30SEP2021 (10:35) Source Data: adsl Table Generation: 08NOV2021 (03:38)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adsl_fu_d11_ped6

2.5.5.2.1.2. Disposition

Blinded Placebo-Controlled Follow-Up Period

During the blinded placebo-controlled follow-up period, there were 3 (0.3%) participants in the BNT162b2 group and 14 (1.2%) participants in the placebo group who discontinued from the vaccination period (Dose 1 to 1 month after Dose 2) (Table 10). Most participants completed the visit at 1 month post-Dose 2 (≥97.0%). Few participants in the BNT162b2 and placebo groups were withdrawn from the study (0.4% and 1.2%, respectively), and all were because of withdrawal by the participant, withdrawal by parent/guardian, or they were lost to follow-up.

Open-Label Follow-Up Period

Individuals have been unblinded as they became locally eligible and wished to know their vaccine assignment to confirm prior vaccination with BNT162b2 (if randomized to this group), or to receive BNT162b2 (if randomized to placebo). Participants who originally received BNT162b2 continued to be followed in an open-label manner. Participants who originally received placebo were offered BNT162b2 vaccination (Doses 3 and 4 [first and second dose of BNT162b2 30 µg, respectively]) and thereafter followed in an open-label manner.

Most participants in the BNT162b2 (98.1%) and placebo (97.0%) groups completed the 1 month post-Dose 2 visit before unblinding (Table 10).

A total of 4 (0.4%) original BNT162b2 adolescent participants received Dose 1 of BNT162b2 during the blinded placebo-controlled follow-up period and then received Dose 2 of BNT162b2 30 µg during the open-label follow-up period (when they were unblinded) (Table 10). There were 45 (4.0%) participants withdrawn from the study, and most were because of other reasons (21 of 23 participants were enrolled into Study C4591031 to evaluate a booster dose of BNT162b2).

During the open-label follow-up period, most participants originally randomized to the placebo group received Doses 3 and 4 (89.4% and 87.8%, first and second dose of BNT162b2 30 µg, respectively). There were 47 (4.2%) participants who were withdrawn from the study after unblinding and before Dose 3. There were few participants in this group (who received at least the first dose of BNT162b2 30 µg) who were withdrawn from the study (0.5%), and most were because of withdrawals by the participant, or they were lost to follow-up (Table 10).

Table 10. Disposition of All Randomized Subjects – Phase 2/3 Subjects 12 Through 15 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=1134) n[b] (%)	Placebo (N[a]=1130) n[b] (%)	Total (N[a]=2264) n[b] (%)
Randomized	1134 (100.0)	1130 (100.0)	2264 (100.0)
Not vaccinated	3 (0.3)	1 (0.1)	4 (0.2)
Original blinded placebo-controlled follow-up period			
Vaccinated	1131 (99.7)	1129 (99.9)	2260 (99.8)
Dose 1	1131 (99.7)	1129 (99.9)	2260 (99.8)
Dose 2	1124 (99.1)	1117 (98.8)	2241 (99.0)
Discontinued from original blinded placebo-controlled vaccination period[c]	3 (0.3)	14 (1.2)	17 (0.8)
Reason for discontinuation			
No longer meets eligibility criteria	0	7 (0.6)	7 (0.3)
Protocol deviation	0	2 (0.2)	2 (0.1)
Adverse event	1 (0.1)	0	1 (0.0)
Physician decision	1 (0.1)	0	1 (0.0)
Withdrawal by subject	0	1 (0.1)	1 (0.0)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.0)
Other	1 (0.1)	3 (0.3)	4 (0.2)
Unblinded before 1-month post–Dose 2 visit	12 (1.1)	21 (1.9)	33 (1.5)
Completed 1-month post–Dose 2 visit	1113 (98.1)	1096 (97.0)	2209 (97.6)
Withdrawn from the study	5 (0.4)	14 (1.2)	19 (0.8)
Withdrawn after Dose 1 and before Dose 2	0	0	0

Table 10. Disposition of All Randomized Subjects – Phase 2/3 Subjects 12 Through 15 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=1134) n[b] (%)	Placebo (N[a]=1130) n[b] (%)	Total (N[a]=2264) n[b] (%)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	0	3 (0.3)	3 (0.1)
Withdrawn after 1-month post–Dose 2 visit	5 (0.4)	11 (1.0)	16 (0.7)
Reason for withdrawal from the study			
Withdrawal by subject	1 (0.1)	7 (0.6)	8 (0.4)
Withdrawal by parent/guardian	1 (0.1)	5 (0.4)	6 (0.3)
Lost to follow-up	3 (0.3)	2 (0.2)	5 (0.2)
Open-label follow-up period			
Originally randomized to BNT162b2	1107 (97.6)		
Received Dose 2/unplanned dose	4 (0.4)		
Completed 1-month post–Dose 2 visit	15 (1.3)		
Completed 6-month post–Dose 2 visit	1065 (93.9)		
Withdrawn from the study	45 (4.0)		
Withdrawn before 6-month post–Dose 2 visit	25 (2.2)		
Withdrawn after 6-month post–Dose 2 visit	20 (1.8)		
Reason for withdrawal from the study			
Withdrawal by subject	7 (0.6)		
Withdrawal by parent/guardian	7 (0.6)		
Lost to follow-up	6 (0.5)		
Protocol deviation	1 (0.1)		
No longer meets eligibility criteria	1 (0.1)		
Other	23 (2.0)		
Originally randomized to placebo		1108 (98.1)	
Withdrawn from the study after unblinding and before Dose 3		47 (4.2)	
Received Dose 3 (first dose of BNT162b2 [30 µg])		1010 (89.4)	
Received Dose 4 (second dose of BNT162b2 [30 µg])		992 (87.8)	
Discontinued from open-label vaccination period[d]		5 (0.4)	
Reason for discontinuation from open-label vaccination period			
Protocol deviation		4 (0.4)	
Withdrawal by subject		1 (0.1)	
Completed 1-month post–Dose 4 visit		933 (82.6)	
Withdrawn from the study		6 (0.5)	
Withdrawn after Dose 3 and before Dose 4		5 (0.4)	
Withdrawn after Dose 4 and before 1-month post–Dose 4 visit		0	
Withdrawn after 1-month post–Dose 4 visit		1 (0.1)	
Reason for withdrawal from the study			
Withdrawal by subject		3 (0.3)	
Lost to follow-up		2 (0.2)	
Protocol deviation		1 (0.1)	

Table 10. Disposition of All Randomized Subjects – Phase 2/3 Subjects 12 Through 15 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=1134) n[b] (%)	Placebo (N[a]=1130) n[b] (%)	Total (N[a]=2264) n[b] (%)

a. N = number of randomized subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Original blinded placebo-controlled vaccination period is defined as the time period from Dose 1 to 1-month post–Dose 2 visit.
d. Open-label vaccination period is defined as the time period from Dose 3 (first dose of BNT162b2 [30 µg]) to 1-month post–Dose 4 (second dose of BNT162b2 [30 µg]) visit.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:30) Source Data: adds Table Generation: 04NOV2021 (04:49)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adds s002 all1 ped6

2.5.5.2.1.3. Demographics

Demographic characteristics for adolescents (12-15 years of age) were similar in the BNT162b2 and placebo groups in the safety population, and all adolescents were enrolled at sites in the United States (Table 11). Most adolescent participants in the BNT162b2 group were White (85.8%), with 4.6% Black or African American participants and 6.4% Asian participants, and other racial groups were ≤2.1%. There were 11.7% Hispanic/Latino participants. The median age of adolescents in the BNT162b2 group was 14.0 years and 50.1% were male. Obese adolescents of this age group (based on age- and sex-specific BMI) made up 11.3% (placebo group) to 12.6% (BNT162b2 group).

Overall, there were 96 (4.2%) and 2161 (95.6%) participants who were baseline SARs-CoV-2 positive and negative, respectively (Table 11). Considering that the baseline positive subgroup had fewer participants than the negative subgroup overall, there were no clinically meaningful differences in demographics in the 2 vaccine groups by SARS-CoV-2 status.

Adolescent participants had a diverse medical history profile consistent with that of individuals in the general population in the same age group. For adolescents in the BNT162b2 group, conditions in the immune system disorders (399 [35.3%]; of which 241 [21.3%] were seasonal allergy); psychiatric disorders (293 [25.9%], with frequently reported PTs of attention deficit hyperactivity disorder (182 [16.1%]), anxiety (107 [9.5%]), and depression (51 [4.5%]); respiratory, thoracic, and mediastinal disorders (179 [15.8%]); and skin and subcutaneous tissue disorders (170 [15.0%]) SOCs were most frequently reported.

There were 123 (10.9%) and 136 (12.0%) participants in the BNT162b2 and placebo groups, respectively, who had any comorbidity (per the Charlson comorbidity index), which was mostly chronic pulmonary disease (119 [10.5%] and 127 [11.2%] participants, respectively).

Table 11. Demographic Characteristics – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Sex			
Male	567 (50.1)	585 (51.8)	1152 (51.0)
Female	564 (49.9)	544 (48.2)	1108 (49.0)
Race			
White	970 (85.8)	962 (85.2)	1932 (85.5)
Black or African American	52 (4.6)	57 (5.0)	109 (4.8)
All others	109 (9.6)	110 (9.7)	219 (9.7)
American Indian or Alaska Native	4 (0.4)	3 (0.3)	7 (0.3)
Asian	72 (6.4)	71 (6.3)	143 (6.3)
Native Hawaiian or other Pacific Islander	3 (0.3)	0	3 (0.1)
Multiracial	24 (2.1)	29 (2.6)	53 (2.3)
Not reported	6 (0.5)	7 (0.6)	13 (0.6)
Racial designation			
Japanese	5 (0.4)	2 (0.2)	7 (0.3)
Ethnicity			
Hispanic/Latino	132 (11.7)	130 (11.5)	262 (11.6)
Non-Hispanic/non-Latino	997 (88.2)	996 (88.2)	1993 (88.2)
Not reported	2 (0.2)	3 (0.3)	5 (0.2)
Country			
USA	1131 (100.0)	1129 (100.0)	2260 (100.0)
Baseline SARS-CoV-2 status			
Positive[c]	46 (4.1)	50 (4.4)	96 (4.2)
Negative[d]	1083 (95.8)	1078 (95.5)	2161 (95.6)
Missing	2 (0.2)	1 (0.1)	3 (0.1)
Comorbidities[e]			
Yes	249 (22.0)	242 (21.4)	491 (21.7)
No	882 (78.0)	887 (78.6)	1769 (78.3)
Obese[f]			
Yes	143 (12.6)	128 (11.3)	271 (12.0)
No	988 (87.4)	1001 (88.7)	1989 (88.0)
Age at vaccination (years)			
Mean (SD)	13.6 (1.11)	13.6 (1.11)	13.6 (1.11)
Median	14.0	14.0	14.0

Table 11. Demographic Characteristics – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Min, max	(12, 15)	(12, 15)	(12, 15)

Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
d. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
e. Number of subjects who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as subjects who had at least one of the Charlson comorbidity index category or BMI ≥95th percentile.
f. Obese is defined as BMI ≥95th percentile from the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html charts/bmiagerev htm.
PFIZER CONFIDENTIAL SDTM Creation: 30SEP2021 (10:35) Source Data: adsl Table Generation: 08NOV2021 (03:38)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adsl_s005_all1_ped6_saf

2.5.5.2.1.3.1. Participants With at Least 6 Months Follow-Up Time – BNT162b2 Group

Demographic characteristics for all original BNT162b2 recipients 12-15 years of age and having at least 6 months of follow-up time after Dose 2 were similar to demographic characteristics in the BNT162b2 group overall (Table 11).

2.5.5.2.1.3.2. Original Placebo Recipients 12 Through 15 Years of Age Who Then Received BNT162b2

Demographic characteristics for all original placebo recipients 12-15 years of age who then received BNT162b2 later during the open-label follow-up period were similar to demographic characteristics in the placebo group overall (Table 11).

2.5.5.2.2. Reactogenicity

There are no new reactogenicity data presented in this submission since the adolescent interim CSR, dated 14 April 2021.

The majority of reactogenicity events previously reported in adolescent participants were mild or moderate in severity and short-lived after dosing (ie, median onset mostly between 1-3 days after dosing and resolution within 1-3 days after onset) (full details in Sections 12.1.1 and 12.1.2 of the adolescent interim C4591001 CSR dated 14 April 2021).

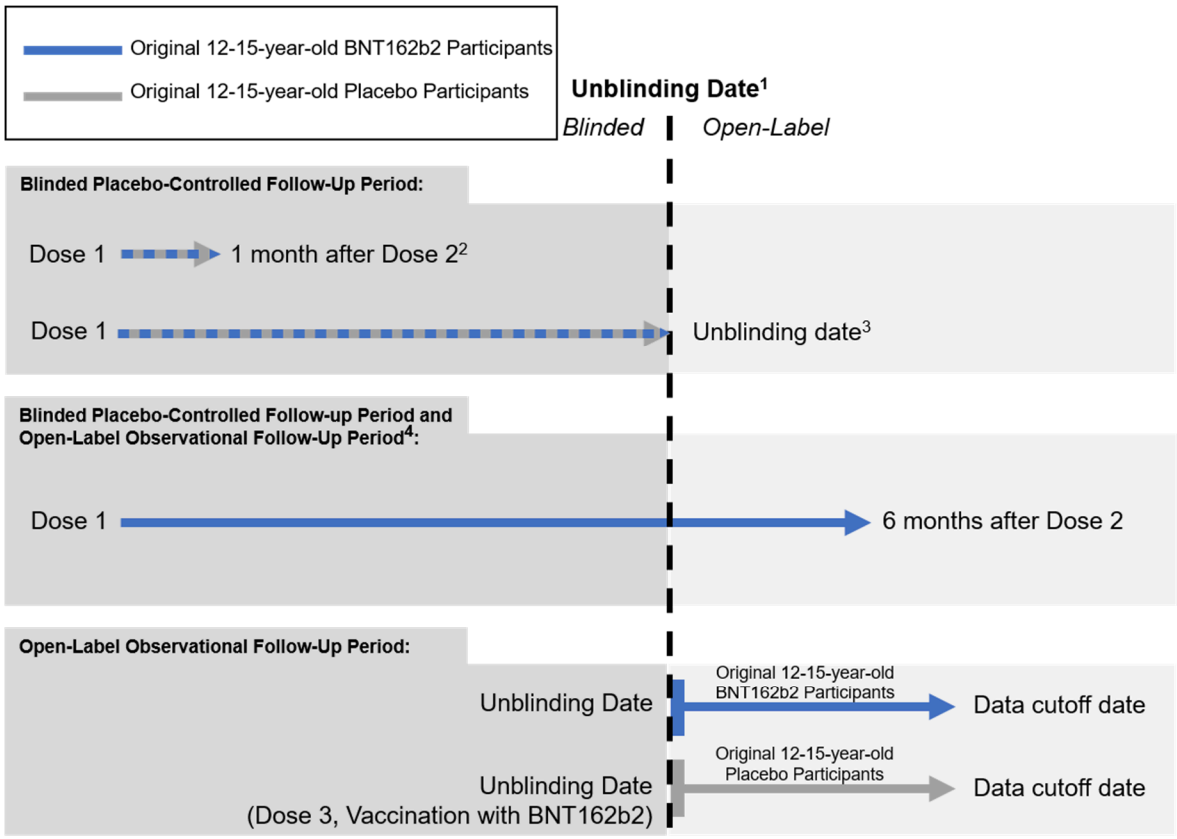
2.5.5.2.3. Adverse Events

AE safety data are from either the blinded placebo-controlled follow-up period, the open-label observational follow-up period, or both. The time periods and safety analysis

groups are presented below and in Figure 2. AEs reported from Dose 1 to 1 month after Dose 2 during the blinded placebo-controlled follow-up period were previously reported in the adolescent interim CSR, dated 14 April 2021. For each time period, overall safety will be presented in addition to new AEs that were reported since the EUA snapshot occurred (based on a data cutoff date of 13 March 2021), in the following order:

- Blinded placebo-controlled follow-up period from Dose 1 to the unblinding date, including separate summaries for new AEs that were reported after the EUA snapshot date (Section 2.5.5.2.3.1)
- Open-label follow-up period – original BNT162b2 recipients (Section 2.5.5.2.3.2)
- Blinded placebo-controlled and open-label follow-up periods from Dose 1 to 6 months after Dose 2 – original BNT162b2 participants, including separate summaries for new AEs that were reported after the EUA snapshot date (Section 2.5.5.2.3.3)
- Open-label follow-up period – original placebo recipients who then received at least 1 dose of BNT162b2 after unblinding (Section 2.5.5.2.3.4)

Figure 2. Phase 2/3 Safety Analyses of Adolescent Participants: Time Periods and Analysis Groups



[1] Will vary by participant. Adverse event data analyzed from Dose 1 to unblinding date or from unblinding date to data cutoff date are reported as incidence rates adjusted for exposure time.
[2] Data previously reported in the adolescent interim CSR dated 14 April 2021.
[3] Up to ~6 months after Dose 2.
[4] Cumulative BNT162b2 follow-up to at least 6 months after Dose 2.

2.5.5.2.3.1. Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date (Adverse Events)

2.5.5.2.3.1.1. Summary of Adverse Events (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

An overview of AE IRs adjusted for exposure time from Dose 1 to the unblinding date for adolescent participants during the blinded placebo-controlled follow-up period is presented in Table 12, and total exposure time in 100 PY was similar in the BNT162b2 and placebo groups (4.6 vs 4.5 per 100 PY, respectively). Hence, frequencies are summarized in the safety results.

The percentage of adolescent participants with any AE was similar in the BNT162b2 and placebo groups (8.4% and 10.0%, respectively). Severe AEs, SAEs, and AEs leading to withdrawal were reported by ≤1.1%, ≤0.9%, and ≤0.1%, respectively, in both groups. All reported SAEs were assessed by the investigator as not related to study intervention.

Withdrawals due to related AEs were reported in 1 adolescent participant in the BNT162b2 group (pyrexia occurring 1 day after Dose 1; previously reported in adolescent interim CSR dated 14 April 2021, Section 12.3.2.4.1), and none in the placebo group. There were no deaths.

Table 12. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)		
Adverse Event	n[c] (%)	IR[d]	(95% CI[e])	n[c] (%)	IR[d]	(95% CI[e])
Any event	95 (8.4)	20.8	(16.8, 25.4)	113 (10.0)	25.1	(20.7, 30.1)
Related[f]	36 (3.2)	7.9	(5.5, 10.9)	24 (2.1)	5.3	(3.4, 7.9)
Severe	13 (1.1)	2.8	(1.5, 4.9)	5 (0.4)	1.1	(0.4, 2.6)
Life-threatening	2 (0.2)	0.4	(0.1, 1.6)	1 (0.1)	0.2	(0.0, 1.2)
Any serious adverse event	10 (0.9)	2.2	(1.0, 4.0)	2 (0.2)	0.4	(0.1, 1.6)
Related[f]	0	0.0	(0.0, 0.8)	0	0.0	(0.0, 0.8)
Severe	7 (0.6)	1.5	(0.6, 3.2)	1 (0.1)	0.2	(0.0, 1.2)
Life-threatening	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Any nonserious adverse event	89 (7.9)	19.5	(15.6, 24.0)	111 (9.8)	24.6	(20.3, 29.6)
Related[f]	36 (3.2)	7.9	(5.5, 10.9)	24 (2.1)	5.3	(3.4, 7.9)
Severe	6 (0.5)	1.3	(0.5, 2.9)	4 (0.4)	0.9	(0.2, 2.3)
Life-threatening	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Any adverse event leading to withdrawal	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Related[f]	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Severe	0	0.0	(0.0, 0.8)	0	0.0	(0.0, 0.8)
Life-threatening	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Death	0	0.0	(0.0, 0.8)	0	0.0	(0.0, 0.8)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of the blinded follow-up period. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
f. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:22)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2 unblinded/C4591001 S Peds/adae s092 all unb1 ped6

Subgroup Analyses (Summary of Adverse Events [Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date])

Total exposure time in 100 PY was similar in the BNT162b2 and placebo groups for each subgroup analysis.

There were 4 (8.7%) and 91 (8.4%) participants who were baseline SARS-CoV-2 positive and negative in the BNT162b2 group who reported at least 1 AE, respectively, and 4 (8.0%) and 109 (10.1%) participants who were baseline SARS-CoV-2 positive and negative in the placebo group who reported at least 1 AE, respectively. The frequency of severe AEs, SAEs (all assessed as not related), or AEs leading to withdrawal in participants who were SARS-CoV-2 negative was 1.2%, 0.9%, and 0.1%, respectively, while there were no severe AEs, SAEs, or AEs leading to withdrawal in participants who were SARS-CoV-2 positive, supporting previous observations in this study that participants who are SARS-CoV-2 positive at baseline do not report AEs at a higher rate than those who are negative at baseline (previously reported in 6-month update interim CSR, dated 29 April 2021).

The frequency of at least 1 AE reported in the BNT162b2 group was 6.8% in Hispanic/Latino and 8.6% in non-Hispanic/non-Latino participants. The frequency of related AEs, severe AEs, SAEs (all not related), and AEs leading to withdrawal was similar in the Hispanic/Latino and Non-Hispanic/Non-Latino subgroups. Considering that the Hispanic/Latino subgroup (N=132) had fewer participants than the non-Hispanic/non-Latino subgroup (N=997) in the BNT162b2 group, the small numerical differences in these subgroups were not considered clinically meaningful.

The frequency of at least 1 AE reported in the BNT162b2 group was 5.8% to 8.6% across race subgroups. Related AEs were reported in the BNT162b2 group across race subgroups at frequencies of 1.9% to 5.5%. Low incidences of severe and serious AEs were reported in the BNT162b2 groups across race subgroups (≤1.9%). Considering that some race subgroups had fewer participants than others (within the BNT162b2 groups: White N=970, Black or African American N=52, and ‘All Others’ N=109), the small numerical differences in these subgroups were not considered clinically meaningful.

The frequency of at least 1 AE reported in the BNT162b2 group for males and females was 7.4% and 9.4%, respectively, and the corresponding frequency in the placebo group was 9.7% and 10.3%, respectively. In the BNT162b2 group, frequencies of at least 1 SAE in male and female participants were 0.5% and 1.2% in the BNT162b2 group and 0.3% and none in the placebo group, respectively.

2.5.5.2.3.1.2. Analysis of Adverse Events (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

Adverse Events by System Organ Class and Preferred Term (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

AEs from Dose 1 to the unblinding date during the blinded placebo-controlled follow-up period are presented in Table 13. AEs reported in adolescents were similar in the BNT162b2 and placebo groups (8.4% and 10.0%, respectively). The most frequently reported AEs in the

BNT162b2 group included lymphadenopathy (9 [0.8%]), injection site pain (8 [0.7%]), fatigue (8 [0.7%]), pyrexia (6 [0.5%]), depression (6 [0.5%])nausea (5 [0.4%]), and headache (5 [0.4%]). Most of these AEs were previously reported in the adolescent interim CSR, dated 14 April 2021.

The number of participants with psychiatric disorder AEs were comparable in the 2 groups, (17 [1.5%] in BNT162b2 group vs. 13 [1.2%] in placebo group) (Table 13). There were 4 participants who were hospitalized with the event of suicidal ideation (3 of these were new after the EUA snapshot and are discussed in Section 2.5.5.2.5.1.1; the remaining case that was previously reported in the adolescent interim CSR, dated 14 April 2021 is discussed in Section 2.5.5.2.5.1). All participants were in the BNT162b2 group and had an ongoing past medical history of depression and/or anxiety (3 diagnosed within 2020 and 1 since 2018). Of these 4 participants, 3 had been taking selective serotonin reuptake inhibitors (fluoxetine or sertraline) for their ongoing condition. The fourth participant had their concomitant medication for attention deficit hyperactivity disorder changed from methylphenidate hydrochloride to demethylphenidate hydrochloride approximately 22 days before the event of suicidal ideation occurred.

A total of 9 participants reported depression: 6 [0.5%] in the BNT162b2 group and 3 [0.3%] in the placebo group (Table 13), (6 of these were new after the EUA snapshot; 4 in the BNT162b2 group and 2 in the placebo group [Table 15]). Of the 6 participants in the BNT162b2 group 3 participants had a known past medical history of ongoing depression, and of the 4 newly diagnosed cases in the BNT162b2 group, 3 participants had an ongoing past medical history of attention deficit hyperactivity disorder and the depression for the remaining participant in this group was reported to be due to social events. Within the placebo group, 2 of the 3 participants were newly diagnosed with depression (Table 13 and Table 15, respectively).

The event of conversion disorder (BNT162b2 group) has been previously reported in the adolescent interim CSR dated 14 April 2021 Section 12.4.2.1.1 as an SAE of neuralgia and had been extensively investigated. Further follow-up since the adolescent interim CSR: the participant was continuing with physical therapy and had undergone further neurological examination and investigations including an MRI brain scan with and without contrast that was normal. There has been little change in her symptoms, and she continues to require treatment.

The 1 participant in the BNT162b2 group who reported a tic had an exacerbation of their known tic disorder (diagnosed since 2019) and was considered to be due to life stressors (as determined by the principal investigator). This event was previously reported in the adolescent interim CSR dated 14 April 2021.

Table 13. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])	n[c] (%)	IR[d]	(95% CI[e])
Any event	95 (8.4)	20.8	(16.8, 25.4)	113 (10.0)	25.1	(20.7, 30.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	9 (0.8)	2.0	(0.9, 3.7)	2 (0.2)	0.4	(0.1, 1.6)
Lymphadenopathy	9 (0.8)	2.0	(0.9, 3.7)	2 (0.2)	0.4	(0.1, 1.6)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Spine malformation	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0.2	(0.0, 1.2)	3 (0.3)	0.7	(0.1, 1.9)
Cerumen impaction	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Conductive deafness	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Ear pain	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
EYE DISORDERS	2 (0.2)	0.4	(0.1, 1.6)	1 (0.1)	0.2	(0.0, 1.2)
Eye pain	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Eyelid rash	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Retinal haemorrhage	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
GASTROINTESTINAL DISORDERS	14 (1.2)	3.1	(1.7, 5.1)	8 (0.7)	1.8	(0.8, 3.5)
Abdominal pain	2 (0.2)	0.4	(0.1, 1.6)	1 (0.1)	0.2	(0.0, 1.2)
Aphthous ulcer	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Constipation	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Diarrhoea	3 (0.3)	0.7	(0.1, 1.9)	1 (0.1)	0.2	(0.0, 1.2)
Gastritis	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Lip swelling	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Mouth swelling	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Mouth ulceration	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Nausea	5 (0.4)	1.1	(0.4, 2.6)	3 (0.3)	0.7	(0.1, 1.9)
Oral mucosal blistering	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Rectal prolapse	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Tooth impacted	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Toothache	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Vomiting	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	17 (1.5)	3.7	(2.2, 6.0)	12 (1.1)	2.7	(1.4, 4.6)
Chills	2 (0.2)	0.4	(0.1, 1.6)	1 (0.1)	0.2	(0.0, 1.2)
Fatigue	8 (0.7)	1.7	(0.8, 3.4)	4 (0.4)	0.9	(0.2, 2.3)
Injection site pain	8 (0.7)	1.7	(0.8, 3.4)	8 (0.7)	1.8	(0.8, 3.5)
Injection site swelling	2 (0.2)	0.4	(0.1, 1.6)	0	0.0	(0.0, 0.8)
Nodule	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Oedema peripheral	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)

Table 13. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])	n[c] (%)	IR[d]	(95% CI[e])
Peripheral swelling	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Pyrexia	6 (0.5)	1.3	(0.5, 2.9)	0	0.0	(0.0, 0.8)
Vessel puncture site pain	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
IMMUNE SYSTEM DISORDERS	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Food allergy	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Seasonal allergy	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
INFECTIONS AND INFESTATIONS	10 (0.9)	2.2	(1.0, 4.0)	9 (0.8)	2.0	(0.9, 3.8)
Anal abscess	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Appendicitis	0	0.0	(0.0, 0.8)	2 (0.2)	0.4	(0.1, 1.6)
Body tinea	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Candida infection	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Cellulitis	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Conjunctivitis	0	0.0	(0.0, 0.8)	2 (0.2)	0.4	(0.1, 1.6)
Ear infection	3 (0.3)	0.7	(0.1, 1.9)	0	0.0	(0.0, 0.8)
Focal peritonitis	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Infectious mononucleosis	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Otitis externa	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Otitis media	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Paronychia	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Pilonidal cyst	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Subcutaneous abscess	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Tinea capitis	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Vulval abscess	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Vulvovaginal mycotic infection	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	15 (1.3)	3.3	(1.8, 5.4)	25 (2.2)	5.5	(3.6, 8.2)
Accident	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Ankle fracture	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Bone contusion	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Clavicle fracture	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Concussion	3 (0.3)	0.7	(0.1, 1.9)	4 (0.4)	0.9	(0.2, 2.3)
Contusion	2 (0.2)	0.4	(0.1, 1.6)	2 (0.2)	0.4	(0.1, 1.6)
Fall	2 (0.2)	0.4	(0.1, 1.6)	5 (0.4)	1.1	(0.4, 2.6)
Femur fracture	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Foot fracture	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Hand fracture	1 (0.1)	0.2	(0.0, 1.2)	4 (0.4)	0.9	(0.2, 2.3)
Humerus fracture	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)

Table 13. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])	n[c] (%)	IR[d]	(95% CI[e])
Ligament sprain	1 (0.1)	0.2	(0.0, 1.2)	4 (0.4)	0.9	(0.2, 2.3)
Lip injury	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Meniscus injury	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Muscle strain	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Patella fracture	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Procedural pain	2 (0.2)	0.4	(0.1, 1.6)	3 (0.3)	0.7	(0.1, 1.9)
Radius fracture	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Skin laceration	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Tibia fracture	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Tooth fracture	0	0.0	(0.0, 0.8)	2 (0.2)	0.4	(0.1, 1.6)
Upper limb fracture	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
INVESTIGATIONS	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
SARS-CoV-2 antibody test positive	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (0.7)	1.7	(0.8, 3.4)	14 (1.2)	3.1	(1.7, 5.2)
Arthralgia	2 (0.2)	0.4	(0.1, 1.6)	4 (0.4)	0.9	(0.2, 2.3)
Back pain	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Joint swelling	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Musculoskeletal chest pain	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Myalgia	3 (0.3)	0.7	(0.1, 1.9)	2 (0.2)	0.4	(0.1, 1.6)
Neck pain	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Osteochondrosis	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Pain in extremity	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Tendonitis	0	0.0	(0.0, 0.8)	4 (0.4)	0.9	(0.2, 2.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1)	0.2	(0.0, 1.2)	3 (0.3)	0.7	(0.1, 1.9)
Fibroadenoma of breast	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Hair follicle tumour benign	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Melanocytic naevus	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Skin papilloma	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
NERVOUS SYSTEM DISORDERS	13 (1.1)	2.8	(1.5, 4.9)	13 (1.2)	2.9	(1.5, 4.9)
Dizziness	2 (0.2)	0.4	(0.1, 1.6)	1 (0.1)	0.2	(0.0, 1.2)
Headache	5 (0.4)	1.1	(0.4, 2.6)	7 (0.6)	1.6	(0.6, 3.2)
Migraine	3 (0.3)	0.7	(0.1, 1.9)	0	0.0	(0.0, 0.8)
Paraesthesia	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Presyncope	1 (0.1)	0.2	(0.0, 1.2)	4 (0.4)	0.9	(0.2, 2.3)
Syncope	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)

Table 13. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])	n[c] (%)	IR[d]	(95% CI[e])
PSYCHIATRIC DISORDERS	17 (1.5)	3.7	(2.2, 6.0)	13 (1.2)	2.9	(1.5, 4.9)
Anxiety	4 (0.4)	0.9	(0.2, 2.2)	6 (0.5)	1.3	(0.5, 2.9)
Attention deficit hyperactivity disorder	2 (0.2)	0.4	(0.1, 1.6)	4 (0.4)	0.9	(0.2, 2.3)
Conversion disorder	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Depression	6 (0.5)	1.3	(0.5, 2.9)	3 (0.3)	0.7	(0.1, 1.9)
Disorientation	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Generalised anxiety disorder	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Obsessive-compulsive disorder	0	0.0	(0.0, 0.8)	2 (0.2)	0.4	(0.1, 1.6)
Panic attack	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Sleep terror	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Suicidal ideation	4 (0.4)	0.9	(0.2, 2.2)	0	0.0	(0.0, 0.8)
Tic	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
RENAL AND URINARY DISORDERS	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Dysuria	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Amenorrhoea	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.3)	0.7	(0.1, 1.9)	8 (0.7)	1.8	(0.8, 3.5)
Epistaxis	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Nasal congestion	2 (0.2)	0.4	(0.1, 1.6)	3 (0.3)	0.7	(0.1, 1.9)
Rhinorrhoea	2 (0.2)	0.4	(0.1, 1.6)	4 (0.4)	0.9	(0.2, 2.3)
Sneezing	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	9 (0.8)	2.0	(0.9, 3.7)	16 (1.4)	3.5	(2.0, 5.8)
Acne	2 (0.2)	0.4	(0.1, 1.6)	3 (0.3)	0.7	(0.1, 1.9)
Dermatitis contact	2 (0.2)	0.4	(0.1, 1.6)	1 (0.1)	0.2	(0.0, 1.2)
Eczema	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Pityriasis rosea	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Rash	3 (0.3)	0.7	(0.1, 1.9)	5 (0.4)	1.1	(0.4, 2.6)
Rash maculo-papular	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Seborrhoeic dermatitis	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
Urticaria	2 (0.2)	0.4	(0.1, 1.6)	5 (0.4)	1.1	(0.4, 2.6)
SURGICAL AND MEDICAL PROCEDURES	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)
Wisdom teeth removal	1 (0.1)	0.2	(0.0, 1.2)	1 (0.1)	0.2	(0.0, 1.2)

Table 13. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N^a=1131, TE^b=4.6)			Placebo (N^a=1129, TE^b=4.5)		
System Organ Class Preferred Term	n^c (%)	IR^d	(95% CI^e)	n^c (%)	IR^d	(95% CI^e)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of the blinded follow-up period. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:21)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s131_all_unb1_ped6

Subgroup Analyses (Adverse Events by System Organ Class and Preferred Term [Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date])

For the baseline SARS-CoV-2 positive and negative subgroups, AEs by SOC and PT were similar to those in the overall safety population. Considering that the positive subgroup (N=46) had fewer participants than the negative subgroup (N=1083) in the BNT162b2 group, differences in SOCs were considered not clinically meaningful, and there is no evidence that individuals who are positive at baseline report AEs at a higher frequency than those who are negative at baseline.

For the ethnicity subgroups, AEs by SOC and PT were similar to those in the overall safety population for Hispanic/Latino and non-Hispanic/non-Latino participants. Considering that the Hispanic/Latino subgroup (N=132) had fewer participants than non-Hispanic/non-Latino subgroup (N=997) in the BNT162b2 group, differences in AEs by SOC and PT in these subgroups were not clinically meaningful.

For race subgroups, AEs by SOC and PT were similar to those in the overall safety population. Considering that some race subgroups had fewer participants than others (within the BNT162b2 groups: White N=970, Black or African American N=52, and 'All Others' N=109), differences in AEs by SOC and PT in these subgroups were not clinically meaningful.

For sex subgroups, AEs by SOC and PT were similar to those in the overall safety population. There was a slightly higher frequency of any event reported in the BNT162b2 group in female participants compared to males (53 [9.4%], 42 [7.4%] respectively), and of any SAEs 7 (1.2%) females, 3 (0.5%) males. Within the placebo group there were 2 (0.3%) SAEs reported in male participants and none in the females. In the BNT162b2 group, lymphadenopathy was reported in 8 (1.4%) male participants and in 1 (0.2%) female participant. AEs in the psychiatric disorders SOC were reported in 12 (2.1%) female participants compared to 5 (0.9%) male participants. Depression was the most frequently reported event in both sexes (4 [0.7%] females and 2 [0.4%] males). Anxiety was reported in 4 (0.7%) females and no males. Suicidal ideation was the next most frequently reported event: in females, 3 [0.5%], 1 (0.2%) in males.

Related Adverse Events – Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date

From Dose 1 to the unblinding date, adolescent participants with AEs assessed as related by the investigator were similar in the BNT162b2 and placebo groups (36 [3.2%] and 24 [2.1%], respectively). Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 16 (1.4%) and 10 (0.9%) participants in the BNT162b2 and placebo groups, respectively.

Related events of lymphadenopathy were reported in 7 (0.6%) adolescents in the BNT162b2 group and 1 (0.1%) adolescent in the placebo group (refer to other significant AEs in Section 2.5.5.2.7).

Immediate Adverse Events – Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date

Adolescents with immediate AEs were low in frequency (≤0.4%) after either dose of study intervention. All immediate AEs after Dose 1 were in the SOCs of general disorders and administration site conditions (injection site pain, injection site erythema, and vessel puncture site pain) and nervous system disorders (dizziness and headache).

After Dose 2, most immediate AEs were in the SOC of general disorders and administration site conditions (injection site pain, injection site bruising, injection site hyperesthesia, fatigue, chills; 1-2 participants reporting each). Other immediate AEs after Dose 2 were reported in the SOC of nervous system disorders (dizziness; 1 participant in the BNT162b2 adolescent group) or skin and subcutaneous tissue disorders (rash maculo-papular; 1 participant in the placebo adolescent group).

No allergic AEs were reported after either dose of BNT162b2 within 30 minutes after vaccination.

Severe or Life-Threatening Adverse Events – Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date

From Dose 1 to the unblinding date, severe AEs were reported in 13 (1.1%) adolescent participants in the BNT162b2 group and 5 (0.4%) participants in the placebo group.

The following severe events in the psychiatric orders SOC were previously reported in the adolescent interim CSR, dated 14 April 2021:

- One participant in the BNT162b2 group reported an SAE each of anxiety and depression (discussed in Section 2.5.5.2.5.1)
- One participant in the BNT162b2 group reported 2 SAEs of depression (first SAE discussed in Section 2.5.5.2.5.1). The second SAE was a new case not previously reported and occurred after the EUA snapshot (discussed in Section 2.5.5.2.5.1.1).
- One participant in the BNT162b2 group reported an SAE of suicidal ideation (discussed in Section 2.5.5.2.5.1).

Certain severe events discussed below are new cases which have not been previously reported:

- One participant in the placebo group reported a severe AE of urticaria (discussed in Section 2.5.5.2.3.1.3)
- One participant in the BNT162b2 group reported a severe SAE of anal abscess (discussed in Section 2.5.5.2.5.1.1).
- One participant in the BNT162b2 group reported an SAE of suicidal ideation (discussed in Section 2.5.5.2.5.1.1).

There were 3 participants (2 in the BNT162b2 and 1 in the placebo group) who reported at least 1 life-threatening (or Grade 4) AE from Dose 1 to the unblinding date.

The following life-threatening events were previously reported in the adolescent interim CSR, dated 14 April 2021:

- One participant in the placebo group reported an SAE each of focal peritonitis and appendicitis (discussed in Section 2.5.5.2.5.1).
- One participant in the BNT162b2 group reported a Grade 4 AE of pyrexia (40.4°C) on Day 2 after Dose 1, with temperature returning to normal on Day 4. The AE was assessed by the investigator as related to study intervention, resolved, and the participant withdrew from the study.

The life-threatening event below is a new case and has not been previously reported:

- One participant in the BNT162b2 group reported a life-threatening (Grade 4) SAE of suicidal ideation, which was a new event after the EUA snapshot (discussed in discussed in Section 2.5.5.2.5.1.1)

2.5.5.2.3.1.3. New Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

Summary of New Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

The frequency of adolescent participants in the BNT162b2 group with any new AE after the EUA snapshot from Dose 1 to the unblinding date was 2.6%, which was less than the frequency in the placebo group (4.2%) (Table 14). There were 6 (0.5%) participants in the BNT162b2 group with SAEs, and all events were assessed by the investigator as not related to study intervention. No SAEs were reported in the placebo group. There were no withdrawals because of any AEs or deaths.

Table 14. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1130)		Placebo (N[a]=1126)	
Adverse Event	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	29 (2.6)	(1.7, 3.7)	47 (4.2)	(3.1, 5.5)
Related[d]	3 (0.3)	(0.1, 0.8)	3 (0.3)	(0.1, 0.8)
Severe	5 (0.4)	(0.1, 1.0)	2 (0.2)	(0.0, 0.6)
Life-threatening	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Any serious adverse event	6 (0.5)	(0.2, 1.2)	0	(0.0, 0.3)
Related[d]	0	(0.0, 0.3)	0	(0.0, 0.3)
Severe	4 (0.4)	(0.1, 0.9)	0	(0.0, 0.3)
Life-threatening	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Any nonserious adverse event	24 (2.1)	(1.4, 3.1)	47 (4.2)	(3.1, 5.5)
Related[d]	3 (0.3)	(0.1, 0.8)	3 (0.3)	(0.1, 0.8)
Severe	1 (0.1)	(0.0, 0.5)	2 (0.2)	(0.0, 0.6)
Life-threatening	0	(0.0, 0.3)	0	(0.0, 0.3)
Any adverse event leading to withdrawal	0	(0.0, 0.3)	0	(0.0, 0.3)
Related[d]	0	(0.0, 0.3)	0	(0.0, 0.3)
Severe	0	(0.0, 0.3)	0	(0.0, 0.3)
Life-threatening	0	(0.0, 0.3)	0	(0.0, 0.3)
Death	0	(0.0, 0.3)	0	(0.0, 0.3)

Abbreviation: EUA = emergency use authorization.
a. N = number of subjects in the specified group, subjects who withdrew from the study before EUA snapshot 25Mar2021 with the cutoff date 13Mar2021 are not included. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:44)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s091_all_unb2_ped6

New Adverse Events Since EUA Snapshot by System Organ Class and Preferred Term (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

New AEs after the EUA snapshot from Dose 1 to the unblinding date during the blinded placebo-controlled follow-up period are presented in Table 15.

The most frequently reported AEs in adolescents were in the psychiatric disorders SOC (11 [1.0%] and 9 [0.8%] adolescent participants in the BNT162b2 and placebo groups, respectively). These cases are discussed alongside cumulative cases during this period in Section 2.5.5.2.3.1.2 (Adverse Events by System Organ Class).

One participant in the BNT162b2 group reported a panic attack. This participant had a past medical history of attention deficit hyperactivity disorder since 2016. They had ongoing panic attacks starting 60 days post Dose 2 which was considered not related and attributed to social/environmental events. The event was nonserious, and the participant has continued in the study.

Table 15. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1130)		Placebo (N[a]=1126)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	29 (2.6)	(1.7, 3.7)	47 (4.2)	(3.1, 5.5)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Spine malformation	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
EAR AND LABYRINTH DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Conductive deafness	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
EYE DISORDERS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Eye pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
GASTROINTESTINAL DISORDERS	1 (0.1)	(0.0, 0.5)	5 (0.4)	(0.1, 1.0)
Nausea	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Abdominal pain	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Constipation	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Mouth ulceration	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Tooth impacted	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Vomiting	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Injection site pain	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Chills	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Fatigue	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Injection site swelling	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Pyrexia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
IMMUNE SYSTEM DISORDERS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Seasonal allergy	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)

Table 15. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1130)		Placebo (N[a]=1126)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
INFECTIONS AND INFESTATIONS	3 (0.3)	(0.1, 0.8)	1 (0.1)	(0.0, 0.5)
Anal abscess	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Cellulitis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Paronychia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Pilonidal cyst	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (0.5)	(0.2, 1.2)	13 (1.2)	(0.6, 2.0)
Fall	1 (0.1)	(0.0, 0.5)	4 (0.4)	(0.1, 0.9)
Hand fracture	0	(0.0, 0.3)	4 (0.4)	(0.1, 0.9)
Procedural pain	2 (0.2)	(0.0, 0.6)	1 (0.1)	(0.0, 0.5)
Concussion	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Ligament sprain	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Upper limb fracture	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Ankle fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Bone contusion	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Contusion	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Femur fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Meniscus injury	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Skin laceration	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Tibia fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INVESTIGATIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
SARS-CoV-2 antibody test positive	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	(0.0, 0.5)	6 (0.5)	(0.2, 1.2)
Tendonitis	0	(0.0, 0.3)	4 (0.4)	(0.1, 0.9)
Arthralgia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Back pain	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Musculoskeletal chest pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Melanocytic naevus	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
NERVOUS SYSTEM DISORDERS	1 (0.1)	(0.0, 0.5)	6 (0.5)	(0.2, 1.2)
Headache	0	(0.0, 0.3)	3 (0.3)	(0.1, 0.8)
Presyncope	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Migraine	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Syncope	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	11 (1.0)	(0.5, 1.7)	9 (0.8)	(0.4, 1.5)
Anxiety	3 (0.3)	(0.1, 0.8)	4 (0.4)	(0.1, 0.9)

Table 15. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1130)		Placebo (N[a]=1126)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Depression	4 (0.4)	(0.1, 0.9)	2 (0.2)	(0.0, 0.6)
Attention deficit hyperactivity disorder	2 (0.2)	(0.0, 0.6)	3 (0.3)	(0.1, 0.8)
Suicidal ideation	3 (0.3)	(0.1, 0.8)	0	(0.0, 0.3)
Obsessive-compulsive disorder	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Panic attack	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
RENAL AND URINARY DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Dysuria	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Amenorrhoea	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	(0.0, 0.5)	4 (0.4)	(0.1, 0.9)
Nasal congestion	1 (0.1)	(0.0, 0.5)	3 (0.3)	(0.1, 0.8)
Epistaxis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Rhinorrhoea	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Sneezing	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.2)	(0.0, 0.6)	3 (0.3)	(0.1, 0.8)
Acne	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Dermatitis contact	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Eczema	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Rash	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Seborrhoeic dermatitis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Urticaria	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
SURGICAL AND MEDICAL PROCEDURES	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Wisdom teeth removal	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)

Abbreviation: EUA = emergency use authorization.
Note: MedDRA (v24.0) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
a. N = number of subjects in the specified group, subjects who withdrew from the study before EUA snapshot 25Mar2021 with the cutoff date 13Mar2021 are not included. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:47)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2 unblinded/C4591001 S Peds/adae s130 all unb2 ped6

New Related Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

There were few adolescent participants with new related AEs that occurred after the EUA snapshot in both the BNT162b2 and placebo groups (3 [0.3%] participants each), and each PT was reported by 1 participant each in either group.

One participant in the BNT162b2 group reported an AE of musculoskeletal chest pain (verbatim term reported was bilateral rib pain), on Day 3 after Dose 2. The AE was moderate in severity and resolved the same day. There is no evidence that the investigator had evaluated the participant for cardiac disease.

New Severe or Life-Threatening Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

New severe AEs after the EUA snapshot were reported in 5 (0.4%) adolescent participants in the BNT162b2 group and 2 (0.2%) participants in the placebo group (Table 16).

Certain severe events are discussed below:

- One participant in the placebo group reported a severe AE of urticaria on Day 55 after Dose 2 with a duration of 8 days, and the AE was assessed by the investigator as not related to study intervention. The participant had a past medical history of penicillin allergy since 2008. The event was nonserious, resolved, and the participant continued in the study, receiving a first dose of BNT162b2 with no further urticaria reported.

- One participant in the BNT162b2 group reported a second severe SAE of depression (previously had a severe SAE and reported in the adolesecent interim CSR, dated 14 April 2021 and discussed in Section 2.5.5.2.5.1; second SAE discussed in Section 2.5.5.2.5.1.1).

- One participant in the BNT162b2 group reported a severe SAE of suicidal ideation (discussed in Section 2.5.5.2.5.1.1).

- One participant in the BNT162b2 group reported a severe SAE of anal abscess (discussed in Section 2.5.5.2.5.1.1).

From Dose 1 to the unblinding date, there was 1 participant in the BNT162b2 group who reported a life-threatening (or Grade 4) SAE of suicidal ideation (discussed in Section 2.5.5.2.5.1.1).

All new severe and life-threatening events reported after the EUA snapshot from Dose 1 to the unblinding date were assessed by the investigator as not related to study intervention. Most were resolved as of the data cutoff date (02 September 2021). For additional safety data after the EUA snapshot during blinded placebo-controlled and open-label follow-up periods for original BNT162b2 recipients 12 through 15 years of age, refer to Section 2.5.5.2.3.3.3.

Table 16. Number (%) of Subjects Reporting at Least 1 New Severe Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1130)		Placebo (N[a]=1126)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	5 (0.4)	(0.1, 1.0)	2 (0.2)	(0.0, 0.6)
INFECTIONS AND INFESTATIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Anal abscess	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.2)	(0.0, 0.6)	1 (0.1)	(0.0, 0.5)
Femur fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Procedural pain	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Upper limb fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
PSYCHIATRIC DISORDERS	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
Depression	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Suicidal ideation	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Urticaria	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)

Abbreviation: EUA = emergency use authorization.
Note: MedDRA (v24.0) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
a. N = number of subjects in the specified group, subjects who withdrew from the study before EUA snapshot 25Mar2021 with the cutoff date 13Mar2021 are not included. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:48)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s130 sev unb2 ped6

2.5.5.2.3.2. Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Recipients (Adverse Events)

2.5.5.2.3.2.1. Summary of Adverse Events (Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Recipients)

An overview of AEs from the unblinding date to the data cutoff date for adolescent participants who originally received BNT162b2 during the open-label follow-up period is

presented in Table 17 (Note: Per protocol, AEs are reported through approximately 1 month after Dose 2 and within 48 hours after a blood draw. SAEs are reported to approximately 6 months after the last dose of study intervention.)

There were 18 (1.6%) participants who experienced any AE, including 0.4%, 0.3%, and 0% who experienced related, severe, and life-threatening events, respectively (Table 17). This is markedly reduced relative to AEs from Dose 1 to the unblinding date (8.4% of BNT162b2 participants experienced any AE, including 3.2%, 1.1%, and 0.2% who experienced related, severe, and life-threatening events, respectively [Table 12]. The frequencies of SAEs and AEs leading to withdrawal during the open-label follow-up period (0.4% and 0%, respectively [Table 17]) were similar to those from Dose 1 to the unblinding date (0.9% and 0.1%, respectively [Table 12]). There were no adolescent deaths in the study.

Table 17. Incidence Rates of at Least 1 Adverse Event From Unblinding Date to Data Cutoff Date (02SEP2021) – Open-Label Follow-up Period – Subjects Who Originally Received BNT162b2 – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1107, TE[b]=3.3)		
Adverse Event	n[c] (%)	IR[d]	(95% CI[e])
Any event	18 (1.6)	5.4	(3.2, 8.5)
Related[f]	4 (0.4)	1.2	(0.3, 3.1)
Severe	3 (0.3)	0.9	(0.2, 2.6)
Life-threatening	0	0.0	(0.0, 1.1)
Any serious adverse event	4 (0.4)	1.2	(0.3, 3.1)
Related[f]	0	0.0	(0.0, 1.1)
Severe	1 (0.1)	0.3	(0.0, 1.7)
Life-threatening	0	0.0	(0.0, 1.1)
Any nonserious adverse event	14 (1.3)	4.2	(2.3, 7.0)
Related[f]	4 (0.4)	1.2	(0.3, 3.1)
Severe	2 (0.2)	0.6	(0.1, 2.2)
Life-threatening	0	0.0	(0.0, 1.1)
Any adverse event leading to withdrawal	0	0.0	(0.0, 1.1)
Related[f]	0	0.0	(0.0, 1.1)
Severe	0	0.0	(0.0, 1.1)
Life-threatening	0	0.0	(0.0, 1.1)
Death	0	0.0	(0.0, 1.1)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from the unblinding date to data cutoff date. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
f. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:31)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2 unblinded/C4591001 S Peds/adae s092 ubct1 ped6

2.5.5.2.3.2.2. Analysis of Adverse Events (Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Recipients)

Adverse Events by System Organ Class and Preferred Term (Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Recipients)

From the unblinding date to the data cutoff date (open-label follow-up period), for adolescent participants who originally received BNT162b2, the number of participants who reported at least 1 AE was 18 (1.6%) (Table 17) compared to 95 (8.4%) from Dose 1 to the unblinding date (Table 12).

Overall, the rates in all SOCs after the unblinding date were lower or remained similar to those in the blinded placebo-controlled period.

The frequency for the SOC of nervous system disorders was 6 (0.5%), including the PTs dizziness (2), headache (2), presyncope (2), and syncope (1). The frequency for the SOC of general disorders and administration site conditions was 4 (0.4%), with injection site pain (3) as the most frequently reported PT.

Related Adverse Events – Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Participants

From the unblinding date to the data cutoff date (open-label follow-up period), for adolescent participants who originally received BNT162b2, the number of participants with AEs assessed as related by the investigator was 4 (0.4%). The frequencies of related AEs were highest for reactogenicity events and in the SOCs of general disorders and administration site conditions (injection site pain, fatigue, pyrexia, and pain) and nervous system disorders (headache and dizziness).

Severe or Life-Threatening Adverse Events – Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Participants

From the unblinding date to the data cutoff date (open-label follow-up period), 3 (0.3%) BNT162b2 participants experienced severe AEs. Two (2) participants experienced pyrexia (general disorders and administration site conditions), a term consistent with reactogenicity.

There were no life-threatening AEs reported from the unblinding date to the data cutoff date of 02 September 2021 (Table 17).

2.5.5.2.3.3. Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients (Adverse Events)

2.5.5.2.3.3.1. Summary of Adverse Events (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

There were 1113 adolescent participants who originally received BNT162b2 and had at least 6 months of follow-up time after Dose 2 including the blinded placebo-controlled and open-label follow-up periods (Table 18). There were 98 (8.8%) participants who reported at least 1 AE, and 34 (3.1%) participants reported at least 1 related AE. Severe AEs and SAEs were reported by 13 (1.2%) and 10 (0.9%) participants, respectively. There were no AEs leading to withdrawal, and there were no deaths.

The frequencies of any AEs and related AEs are 70 (6.3%) and 34 (3.1%) through 1 month after Dose 2 compared with 35 (3.1%) and no related AEs from 1 month after Dose 2 to

6 months after Dose 2, respectively (Table 19). From Dose 1 to 1 month after Dose 2, 3 (0.3%) adolescent participants reported SAEs. From 1 month to 6 months after Dose 2, 9 (0.8%) participants reported SAEs. All of the SAEs were assessed by the investigator as not related to study intervention. There were no AEs leading to withdrawal, and there were no deaths.

Table 18. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2 – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
Adverse Event	**n[b] (%)**	**(95% CI[c])**
Any event	98 (8.8)	(7.2, 10.6)
Related[d]	34 (3.1)	(2.1, 4.2)
Severe	13 (1.2)	(0.6, 2.0)
Life-threatening	0	(0.0, 0.3)
Any serious adverse event	10 (0.9)	(0.4, 1.6)
Related[d]	0	(0.0, 0.3)
Severe	7 (0.6)	(0.3, 1.3)
Life-threatening	0	(0.0, 0.3)
Any nonserious adverse event	91 (8.2)	(6.6, 9.9)
Related[d]	34 (3.1)	(2.1, 4.2)
Severe	6 (0.5)	(0.2, 1.2)
Life-threatening	0	(0.0, 0.3)
Any adverse event leading to withdrawal	0	(0.0, 0.3)
Related[d]	0	(0.0, 0.3)
Severe	0	(0.0, 0.3)
Life-threatening	0	(0.0, 0.3)
Death	0	(0.0, 0.3)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:31)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s091_6m1_ped6

Table 19. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
Adverse Event	Dose 1 to 1 Month After Dose 2 n[b] (%)	1 Month After Dose 2 to 6 Months After Dose 2 n[b] (%)
Any event	70 (6.3)	35 (3.1)
Related[c]	34 (3.1)	0
Severe	6 (0.5)	8 (0.7)
Life-threatening	0	0
Any serious adverse event	3 (0.3)	9 (0.8)
Related[c]	0	0
Severe	1 (0.1)	7 (0.6)
Life-threatening	0	0
Any nonserious adverse event	68 (6.1)	28 (2.5)
Related[c]	34 (3.1)	0
Severe	5 (0.4)	1 (0.1)
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:21)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s093_6m1_ped6

2.5.5.2.3.3.2. Analysis of Adverse Events (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

Adverse Events by System Organ Class and Preferred Term (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

There were 98 (8.8%) adolescent participants who originally received BNT162b2, had at least 6 months of follow-up time after Dose 2, and reported AEs from Dose 1 to 6 months after Dose 2 (Table 20). Frequently reported AEs included reactogenicity events in the following SOCs:

- general disorders and administration site conditions (16 [1.4%])
- musculoskeletal and connective tissue disorders (8 [0.7%])
- nervous system disorders (16 [1.4%])
- gastrointestinal disorders (16 [1.4%])

AEs were reported by 15 (1.3%) participants in the injury, poisoning, and procedural complications SOC; 10 (0.9%) participants in the infections and infestations SOC, and 16 (1.4%) participants in the psychiatric disorders SOC.

When AEs are compared from Dose 1 to 1 month after Dose 2 and from 1 month after Dose 2 to 6 months after Dose 2, the frequencies of AEs by most SOCs were lower or were similar with the additional follow-up time. The overall frequency of any AE for participants from 1 month after Dose 2 to 6 months after Dose 2 (35 [3.1%]) was less compared with the frequency during 1 month follow up time after Dose 2 (70 [6.3%]) (Table 21). Overall, AEs reported after 1 month post Dose-2 reflect age-appropriate events consistent with the general population.

All lymphadenopathy events were reported from Dose 1 to 1 month after Dose 2, and none were reported from 1 month to 6 months after Dose 2 (Table 21).

AEs in the pyschiatric disorders SOC were reported in 7 (0.6%) participants from Dose 1 to 1 month after Dose 2 and in 11 (1.0%) participants from 1 month to 6 months after Dose 2.

Table 20. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any event	98 (8.8)	(7.2, 10.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	9 (0.8)	(0.4, 1.5)
Lymphadenopathy	9 (0.8)	(0.4, 1.5)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.1)	(0.0, 0.5)
Syringomyelia	1 (0.1)	(0.0, 0.5)
EAR AND LABYRINTH DISORDERS	1 (0.1)	(0.0, 0.5)
Ear pain	1 (0.1)	(0.0, 0.5)
EYE DISORDERS	1 (0.1)	(0.0, 0.5)
Eye pain	1 (0.1)	(0.0, 0.5)
GASTROINTESTINAL DISORDERS	16 (1.4)	(0.8, 2.3)
Nausea	6 (0.5)	(0.2, 1.2)
Diarrhoea	3 (0.3)	(0.1, 0.8)
Abdominal pain	2 (0.2)	(0.0, 0.6)
Aphthous ulcer	2 (0.2)	(0.0, 0.6)
Abdominal pain upper	1 (0.1)	(0.0, 0.5)
Constipation	1 (0.1)	(0.0, 0.5)
Gastritis	1 (0.1)	(0.0, 0.5)
Lip swelling	1 (0.1)	(0.0, 0.5)
Mouth swelling	1 (0.1)	(0.0, 0.5)
Oral mucosal blistering	1 (0.1)	(0.0, 0.5)
Rectal prolapse	1 (0.1)	(0.0, 0.5)
Vomiting	1 (0.1)	(0.0, 0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (1.4)	(0.8, 2.3)
Fatigue	8 (0.7)	(0.3, 1.4)
Injection site pain	8 (0.7)	(0.3, 1.4)
Pyrexia	5 (0.4)	(0.1, 1.0)
Chills	2 (0.2)	(0.0, 0.6)
Injection site swelling	2 (0.2)	(0.0, 0.6)
Nodule	1 (0.1)	(0.0, 0.5)
Peripheral swelling	1 (0.1)	(0.0, 0.5)
IMMUNE SYSTEM DISORDERS	1 (0.1)	(0.0, 0.5)
Seasonal allergy	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	10 (0.9)	(0.4, 1.6)
Ear infection	2 (0.2)	(0.0, 0.6)

Table 20. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Anal abscess	1 (0.1)	(0.0, 0.5)
Appendicitis	1 (0.1)	(0.0, 0.5)
Body tinea	1 (0.1)	(0.0, 0.5)
Otitis externa	1 (0.1)	(0.0, 0.5)
Otitis media	1 (0.1)	(0.0, 0.5)
Paronychia	1 (0.1)	(0.0, 0.5)
Pilonidal cyst	1 (0.1)	(0.0, 0.5)
Tinea capitis	1 (0.1)	(0.0, 0.5)
Vulval abscess	1 (0.1)	(0.0, 0.5)
Vulvovaginal mycotic infection	1 (0.1)	(0.0, 0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	15 (1.3)	(0.8, 2.2)
Concussion	3 (0.3)	(0.1, 0.8)
Hand fracture	2 (0.2)	(0.0, 0.6)
Procedural pain	2 (0.2)	(0.0, 0.6)
Accident	1 (0.1)	(0.0, 0.5)
Bone contusion	1 (0.1)	(0.0, 0.5)
Clavicle fracture	1 (0.1)	(0.0, 0.5)
Contusion	1 (0.1)	(0.0, 0.5)
Fall	1 (0.1)	(0.0, 0.5)
Femur fracture	1 (0.1)	(0.0, 0.5)
Ligament sprain	1 (0.1)	(0.0, 0.5)
Meniscus injury	1 (0.1)	(0.0, 0.5)
Muscle strain	1 (0.1)	(0.0, 0.5)
Radius fracture	1 (0.1)	(0.0, 0.5)
Upper limb fracture	1 (0.1)	(0.0, 0.5)
INVESTIGATIONS	1 (0.1)	(0.0, 0.5)
SARS-CoV-2 antibody test positive	1 (0.1)	(0.0, 0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (0.7)	(0.3, 1.4)
Myalgia	3 (0.3)	(0.1, 0.8)
Arthralgia	2 (0.2)	(0.0, 0.6)
Musculoskeletal chest pain	1 (0.1)	(0.0, 0.5)
Osteochondrosis	1 (0.1)	(0.0, 0.5)
Pain in extremity	1 (0.1)	(0.0, 0.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1)	(0.0, 0.5)

Table 20. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Hair follicle tumour benign	1 (0.1)	(0.0, 0.5)
NERVOUS SYSTEM DISORDERS	16 (1.4)	(0.8, 2.3)
Headache	5 (0.4)	(0.1, 1.0)
Migraine	3 (0.3)	(0.1, 0.8)
Presyncope	3 (0.3)	(0.1, 0.8)
Dizziness	2 (0.2)	(0.0, 0.6)
Syncope	2 (0.2)	(0.0, 0.6)
Paraesthesia	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	16 (1.4)	(0.8, 2.3)
Depression	5 (0.4)	(0.1, 1.0)
Anxiety	4 (0.4)	(0.1, 0.9)
Suicidal ideation	3 (0.3)	(0.1, 0.8)
Attention deficit hyperactivity disorder	2 (0.2)	(0.0, 0.6)
Conversion disorder	1 (0.1)	(0.0, 0.5)
Disorientation	1 (0.1)	(0.0, 0.5)
Generalised anxiety disorder	1 (0.1)	(0.0, 0.5)
Panic attack	1 (0.1)	(0.0, 0.5)
Sleep terror	1 (0.1)	(0.0, 0.5)
Tic	1 (0.1)	(0.0, 0.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	(0.0, 0.5)
Amenorrhoea	1 (0.1)	(0.0, 0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.3)	(0.1, 0.8)
Nasal congestion	2 (0.2)	(0.0, 0.6)
Rhinorrhoea	2 (0.2)	(0.0, 0.6)
Sneezing	1 (0.1)	(0.0, 0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (0.7)	(0.3, 1.4)
Acne	2 (0.2)	(0.0, 0.6)
Dermatitis contact	2 (0.2)	(0.0, 0.6)
Rash	2 (0.2)	(0.0, 0.6)
Urticaria	2 (0.2)	(0.0, 0.6)
SURGICAL AND MEDICAL PROCEDURES	1 (0.1)	(0.0, 0.5)
Wisdom teeth removal	1 (0.1)	(0.0, 0.5)

Table 20. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:31)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s130 all 6m1 ped6

Table 21. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	70 (6.3)	(4.9, 7.9)	35 (3.1)	(2.2, 4.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	9 (0.8)	(0.4, 1.5)	0	(0.0, 0.3)
Lymphadenopathy	9 (0.8)	(0.4, 1.5)	0	(0.0, 0.3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Syringomyelia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
EAR AND LABYRINTH DISORDERS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Ear pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
EYE DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Eye pain	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
GASTROINTESTINAL DISORDERS	14 (1.3)	(0.7, 2.1)	3 (0.3)	(0.1, 0.8)
Nausea	5 (0.4)	(0.1, 1.0)	1 (0.1)	(0.0, 0.5)
Diarrhoea	3 (0.3)	(0.1, 0.8)	0	(0.0, 0.3)
Abdominal pain	2 (0.2)	(0.0, 0.6)	1 (0.1)	(0.0, 0.5)
Aphthous ulcer	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Abdominal pain upper	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Constipation	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Gastritis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Lip swelling	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Mouth swelling	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Oral mucosal blistering	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Rectal prolapse	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Vomiting	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (1.4)	(0.8, 2.3)	0	(0.0, 0.3)
Fatigue	8 (0.7)	(0.3, 1.4)	0	(0.0, 0.3)
Injection site pain	8 (0.7)	(0.3, 1.4)	0	(0.0, 0.3)
Pyrexia	5 (0.4)	(0.1, 1.0)	0	(0.0, 0.3)
Chills	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
Injection site swelling	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
Nodule	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Peripheral swelling	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)

Table 21. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
IMMUNE SYSTEM DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Seasonal allergy	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	6 (0.5)	(0.2, 1.2)	4 (0.4)	(0.1, 0.9)
Ear infection	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
Anal abscess	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Appendicitis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Body tinea	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Otitis externa	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Otitis media	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Paronychia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Pilonidal cyst	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Tinea capitis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Vulval abscess	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Vulvovaginal mycotic infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	9 (0.8)	(0.4, 1.5)	6 (0.5)	(0.2, 1.2)
Concussion	3 (0.3)	(0.1, 0.8)	0	(0.0, 0.3)
Hand fracture	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Procedural pain	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Accident	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Bone contusion	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Clavicle fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Contusion	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Fall	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Femur fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Ligament sprain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Meniscus injury	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Muscle strain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Radius fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Upper limb fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INVESTIGATIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
SARS-CoV-2 antibody test positive	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (0.7)	(0.3, 1.4)	0	(0.0, 0.3)
Myalgia	3 (0.3)	(0.1, 0.8)	0	(0.0, 0.3)

Table 21. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Arthralgia	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
Musculoskeletal chest pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Osteochondrosis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Pain in extremity	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Hair follicle tumour benign	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
NERVOUS SYSTEM DISORDERS	11 (1.0)	(0.5, 1.8)	5 (0.4)	(0.1, 1.0)
Headache	5 (0.4)	(0.1, 1.0)	0	(0.0, 0.3)
Migraine	2 (0.2)	(0.0, 0.6)	1 (0.1)	(0.0, 0.5)
Presyncope	1 (0.1)	(0.0, 0.5)	2 (0.2)	(0.0, 0.6)
Dizziness	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
Syncope	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Paraesthesia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
PSYCHIATRIC DISORDERS	7 (0.6)	(0.3, 1.3)	11 (1.0)	(0.5, 1.8)
Depression	2 (0.2)	(0.0, 0.6)	4 (0.4)	(0.1, 0.9)
Anxiety	1 (0.1)	(0.0, 0.5)	3 (0.3)	(0.1, 0.8)
Suicidal ideation	0	(0.0, 0.3)	3 (0.3)	(0.1, 0.8)
Attention deficit hyperactivity disorder	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Conversion disorder	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Disorientation	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Generalised anxiety disorder	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Panic attack	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Sleep terror	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Tic	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Amenorrhoea	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.2)	(0.0, 0.6)	1 (0.1)	(0.0, 0.5)
Nasal congestion	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Rhinorrhoea	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Sneezing	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6 (0.5)	(0.2, 1.2)	2 (0.2)	(0.0, 0.6)

Table 21. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Acne	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
Dermatitis contact	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Rash	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Urticaria	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.3)
SURGICAL AND MEDICAL PROCEDURES	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Wisdom teeth removal	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:21)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s132 6m1 ped6

Related Adverse Events – Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients

From Dose 1 to 6 months after Dose 2, 34 (3.1%) original BNT162b2 adolescent recipients reported AEs assessed by the investigator as related to study intervention. Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 15 (1.3%) participants. Related events of lymphadenopathy were reported by 7 (0.6%) adolescents in the BNT162b2 group (refer to other significant AEs in Section 2.5.5.2.7.1).

2.5.5.2.3.3.3. New Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

Summary of New Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

From the time after the EUA snapshot for adolescent BNT162b2 recipients who had at least 6 months of follow-up time after Dose 2 during the blinded placebo-controlled and open-label follow-up periods, there were 36 (3.2%) participants who reported at least 1 AE, and 3 (0.3%) participants reported at least 1 related AE (Table 22). Severe AEs and SAEs were reported by 6 (0.5%) and 7 (0.6%) participants, respectively. There were no AEs leading to withdrawal, and there were no deaths.

When frequencies of new AEs for participants with at least 6 months of follow-up time are examined by time since the second dose, the frequency of any AEs and related AEs is 6 (0.5%) and 3 (0.3%) through 1 month after Dose 2 compared with 32 (2.9%) and no related AEs from 1 month after Dose 2 to 6 months after Dose 2 (Table 23). At 1 month after Dose 2, no adolescent participants reported severe AEs or SAEs. From 1 month to 6 months after Dose 2, the number of participants with severe AEs and total SAEs was 6 (0.5%) and 7 (0.6%), respectively. All of the new SAEs and all of the AEs reported from 1 month after Dose 2 to 6 months after Dose 2 were assessed by the investigator as not related to study intervention.

Table 22. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2 – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
Adverse Event	n[b] (%)	(95% CI[c])
Any event	36 (3.2)	(2.3, 4.4)
Related[d]	3 (0.3)	(0.1, 0.8)
Severe	6 (0.5)	(0.2, 1.2)
Life-threatening	0	(0.0, 0.3)
Any serious adverse event	7 (0.6)	(0.3, 1.3)
Related[d]	0	(0.0, 0.3)
Severe	5 (0.4)	(0.1, 1.0)
Life-threatening	0	(0.0, 0.3)
Any nonserious adverse event	30 (2.7)	(1.8, 3.8)
Related[d]	3 (0.3)	(0.1, 0.8)
Severe	1 (0.1)	(0.0, 0.5)
Life-threatening	0	(0.0, 0.3)
Any adverse event leading to withdrawal	0	(0.0, 0.3)
Related[d]	0	(0.0, 0.3)
Severe	0	(0.0, 0.3)
Life-threatening	0	(0.0, 0.3)
Death	0	(0.0, 0.3)

Table 22. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2 – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
Adverse Event	**n[b] (%)**	**(95% CI[c])**

Abbreviation: EUA = emergency use authorization.
Note: EUA snapshot 25Mar2021 with the cutoff date 13Mar2021.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:49)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2 unblinded/C4591001 S Peds/adae s091 6m2 ped6

Table 23. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
Adverse Event	Dose 1 to 1 Month After Dose 2 n[b] (%)	1 Month After Dose 2 to 6 Months After Dose 2 n[b] (%)
Any event	6 (0.5)	32 (2.9)
Related[c]	3 (0.3)	0
Severe	0	6 (0.5)
Life-threatening	0	0
Any serious adverse event	0	7 (0.6)
Related[c]	0	0
Severe	0	5 (0.4)
Life-threatening	0	0
Any nonserious adverse event	6 (0.5)	26 (2.3)
Related[c]	3 (0.3)	0
Severe	0	1 (0.1)
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

Abbreviation: EUA = emergency use authorization.
Note: EUA snapshot 25Mar2021 with the cutoff date 13Mar2021.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:45)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s093_6m2_ped6

New Adverse Events Since EUA Snapshot by System Organ Class and Preferred Term (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

Most of the new AEs reported after the EUA snapshot in adolescent participants with at least 6 months of follow-up time after Dose 2 were in the psychiatric disorders SOC (11 [1.0%]) (Table 24).

When AEs are compared from Dose 1 to 1 month after Dose 2 and from 1 month after Dose 2 to 6 months after Dose 2, AEs reported in the psychiatric disorders SOC were 1 (0.1%) and 10 (0.9%) participants, respectively (Table 25). All of the AEs in this SOC were assessed by the investigator as not related to study intervention.

Table 24. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any event	36 (3.2)	(2.3, 4.4)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.1)	(0.0, 0.5)
Syringomyelia	1 (0.1)	(0.0, 0.5)
EYE DISORDERS	1 (0.1)	(0.0, 0.5)
Eye pain	1 (0.1)	(0.0, 0.5)
GASTROINTESTINAL DISORDERS	3 (0.3)	(0.1, 0.8)
Abdominal pain upper	1 (0.1)	(0.0, 0.5)
Aphthous ulcer	1 (0.1)	(0.0, 0.5)
Constipation	1 (0.1)	(0.0, 0.5)
Nausea	1 (0.1)	(0.0, 0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	(0.0, 0.5)
Chills	1 (0.1)	(0.0, 0.5)
Fatigue	1 (0.1)	(0.0, 0.5)
Injection site pain	1 (0.1)	(0.0, 0.5)
Injection site swelling	1 (0.1)	(0.0, 0.5)
Pyrexia	1 (0.1)	(0.0, 0.5)
IMMUNE SYSTEM DISORDERS	1 (0.1)	(0.0, 0.5)
Seasonal allergy	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	4 (0.4)	(0.1, 0.9)

Table 24. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Anal abscess	1 (0.1)	(0.0, 0.5)
Appendicitis	1 (0.1)	(0.0, 0.5)
Paronychia	1 (0.1)	(0.0, 0.5)
Pilonidal cyst	1 (0.1)	(0.0, 0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (0.5)	(0.2, 1.2)
Procedural pain	2 (0.2)	(0.0, 0.6)
Bone contusion	1 (0.1)	(0.0, 0.5)
Femur fracture	1 (0.1)	(0.0, 0.5)
Hand fracture	1 (0.1)	(0.0, 0.5)
Meniscus injury	1 (0.1)	(0.0, 0.5)
Upper limb fracture	1 (0.1)	(0.0, 0.5)
INVESTIGATIONS	1 (0.1)	(0.0, 0.5)
SARS-CoV-2 antibody test positive	1 (0.1)	(0.0, 0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	(0.0, 0.5)
Musculoskeletal chest pain	1 (0.1)	(0.0, 0.5)
NERVOUS SYSTEM DISORDERS	4 (0.4)	(0.1, 0.9)
Presyncope	2 (0.2)	(0.0, 0.6)
Migraine	1 (0.1)	(0.0, 0.5)
Syncope	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	11 (1.0)	(0.5, 1.8)
Anxiety	4 (0.4)	(0.1, 0.9)
Depression	4 (0.4)	(0.1, 0.9)
Attention deficit hyperactivity disorder	2 (0.2)	(0.0, 0.6)
Suicidal ideation	2 (0.2)	(0.0, 0.6)
Panic attack	1 (0.1)	(0.0, 0.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	(0.0, 0.5)
Amenorrhoea	1 (0.1)	(0.0, 0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	(0.0, 0.5)
Nasal congestion	1 (0.1)	(0.0, 0.5)
Rhinorrhoea	1 (0.1)	(0.0, 0.5)
Sneezing	1 (0.1)	(0.0, 0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.2)	(0.0, 0.6)
Acne	1 (0.1)	(0.0, 0.5)
Dermatitis contact	1 (0.1)	(0.0, 0.5)

Table 24. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
SURGICAL AND MEDICAL PROCEDURES	1 (0.1)	(0.0, 0.5)
Wisdom teeth removal	1 (0.1)	(0.0, 0.5)

Abbreviation: EUA = emergency use authorization.
Note: EUA snapshot 25Mar2021 with the cutoff date 13Mar2021.
Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:50)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s130 all 6m2 ped6

Table 25. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	6 (0.5)	(0.2, 1.2)	32 (2.9)	(2.0, 4.0)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Syringomyelia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
EYE DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Eye pain	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
GASTROINTESTINAL DISORDERS	0	(0.0, 0.3)	3 (0.3)	(0.1, 0.8)
Abdominal pain upper	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Aphthous ulcer	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Constipation	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Nausea	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Chills	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Fatigue	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Injection site pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Injection site swelling	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Pyrexia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
IMMUNE SYSTEM DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Seasonal allergy	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	0	(0.0, 0.3)	4 (0.4)	(0.1, 0.9)
Anal abscess	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Appendicitis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Paronychia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Pilonidal cyst	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	(0.0, 0.3)	6 (0.5)	(0.2, 1.2)
Procedural pain	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Bone contusion	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Femur fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Hand fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)

Table 25. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Meniscus injury	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Upper limb fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INVESTIGATIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
SARS-CoV-2 antibody test positive	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Musculoskeletal chest pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
NERVOUS SYSTEM DISORDERS	0	(0.0, 0.3)	4 (0.4)	(0.1, 0.9)
Presyncope	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Migraine	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Syncope	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	1 (0.1)	(0.0, 0.5)	10 (0.9)	(0.4, 1.6)
Anxiety	1 (0.1)	(0.0, 0.5)	3 (0.3)	(0.1, 0.8)
Depression	0	(0.0, 0.3)	4 (0.4)	(0.1, 0.9)
Attention deficit hyperactivity disorder	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Suicidal ideation	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Panic attack	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Amenorrhoea	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Nasal congestion	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Rhinorrhoea	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Sneezing	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Acne	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Dermatitis contact	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
SURGICAL AND MEDICAL PROCEDURES	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Wisdom teeth removal	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)

Table 25. Number (%) of Subjects Reporting at Least 1 New Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])

Abbreviation: EUA = emergency use authorization.
Note: EUA snapshot 25Mar2021 with the cutoff date 13Mar2021.
Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:45)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2 unblinded/C4591001 S Peds/adae s132 6m2 ped6

New Related Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

There were few new related AEs reported (3 [0.3%]), and most of these events reflected reactogenicity events (including chills, fatigue, injection site pain and swelling, and pyrexia). One (1) participant in the BNT162b2 group experienced musculoskeletal chest pain, which is discussed in Section 2.5.5.2.3.1.3 [New Related Adverse Events Since EUA Snapshot (Blinded Follow-Up Period from Dose 1 to the Unblinding Date)].

2.5.5.2.3.4. Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding (Adverse Events)

2.5.5.2.3.4.1. Summary of Adverse Events (Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding)

An overview of AEs for 1,010 original placebo recipients who then were unblinded and received BNT162b2 (Dose 3 of the study vaccine, but 1st dose of BNT162b2) to the data cutoff date during the open-label follow-up period is presented in Table 26.

The exposure time is shorter among the original placebo recipients who received BNT162b2 after unblinding than those who originally received BNT162b2 (2.9 per 100 PY vs 4.6 per 100 PY, respectively [Table 26 and Table 12]).

After participants who originally received placebo were unblinded and then received BNT162b2 after unblinding, events related to reactogenicity were not reported using an e-diary but were instead reported as AEs. Because an e-diary was not used after original placebo recipients received open-label BNT162b2, in comparison to participants randomized to BNT162b2 from Dose 1 to the unblinding date, the frequencies for any AE and at least 1 related AE for participants who originally received placebo and then received BNT162b2 are greater (26.2% and 24.0%) than the frequencies (8.4% and 3.2%) for participants who originally received BNT162b2, respectively (Table 26 and Table 12). However, the frequencies for severe, life-threatening AE, SAE, AEs leading to withdrawal and deaths were similar (1.2%, 0%, 0.6%, 0%, 0% [Table 26] versus 1.1%, 0.2%, 0.9%, 0.1%, 0% [Table 12], respectively). There was 1 related SAE of appendicitis for a placebo recipient who was vaccinated with BNT162b2 (see Section 2.5.5.2.5.4).

Table 26. Incidence Rates of at Least 1 Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021) – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1010, TE[b]=2.9)		
Adverse Event	n[c] (%)	IR[d]	(95% CI[e])
Any event	265 (26.2)	90.3	(79.7, 101.8)
Related[f]	242 (24.0)	82.5	(72.4, 93.5)
Severe	12 (1.2)	4.1	(2.1, 7.1)
Life-threatening	0	0.0	(0.0, 1.3)
Any serious adverse event	6 (0.6)	2.0	(0.8, 4.4)
Related[f]	1 (0.1)	0.3	(0.0, 1.9)
Severe	3 (0.3)	1.0	(0.2, 3.0)
Life-threatening	0	0.0	(0.0, 1.3)
Any nonserious adverse event	262 (25.9)	89.3	(78.8, 100.8)
Related[f]	241 (23.9)	82.1	(72.1, 93.2)
Severe	9 (0.9)	3.1	(1.4, 5.8)
Life-threatening	0	0.0	(0.0, 1.3)
Any adverse event leading to withdrawal	0	0.0	(0.0, 1.3)
Related[f]	0	0.0	(0.0, 1.3)
Severe	0	0.0	(0.0, 1.3)
Life-threatening	0	0.0	(0.0, 1.3)
Death	0	0.0	(0.0, 1.3)

Note: Dose 3 = First dose of BNT162b2 (30 µg).
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 3 to data cutoff date. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
f. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:31)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s092 cut1 ped6

2.5.5.2.3.4.2. Analysis of Adverse Events (Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding)

Adverse Events by System Organ Class and Preferred Term (Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding)

From vaccination with Dose 3 (first dose of BNT162b2) for the original placebo recipients to the data cutoff date (open-label follow-up period), 265 (26.2%) reported at least 1 AE (Table 27).

Most AEs reported from Dose 3 (first dose of BNT162b2) to the data cutoff date were in SOCs with reactogenicity events.

- general disorders and administration site conditions (225 [22.3%])
- nervous system disorders (75 [7.4%])
- musculoskeletal and connective tissue disorders (48 [4.8%])
- gastrointestinal disorders (20 [2.0%])

As shown in Table 27, the most frequently reported AEs overall were injection site pain (15.5%), fatigue (10.3%), headache (7.0%), pyrexia (6.3%), chills (4.5%), myalgia (3.8%), pain (3.5%), nausea (1.2%), pain in extremity (0.9%), vomiting (0.7%), malaise (0.7%), and injection site erythema (0.5%).

Table 27. Incidence Rates of at Least 1 Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021), by System Organ Class and Preferred Term – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1010, TE[b]=2.9)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])
Any event	265 (26.2)	90.3	(79.7, 101.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.2)	0.7	(0.1, 2.5)
Lymphadenitis	1 (0.1)	0.3	(0.0, 1.9)
Lymphadenopathy	1 (0.1)	0.3	(0.0, 1.9)
CARDIAC DISORDERS	1 (0.1)	0.3	(0.0, 1.9)
Myocarditis	1 (0.1)	0.3	(0.0, 1.9)
EAR AND LABYRINTH DISORDERS	2 (0.2)	0.7	(0.1, 2.5)
Ear pain	1 (0.1)	0.3	(0.0, 1.9)

Table 27. Incidence Rates of at Least 1 Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021), by System Organ Class and Preferred Term – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1010, TE[b]=2.9)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])
Motion sickness	1 (0.1)	0.3	(0.0, 1.9)
ENDOCRINE DISORDERS	1 (0.1)	0.3	(0.0, 1.9)
Autoimmune thyroiditis	1 (0.1)	0.3	(0.0, 1.9)
Thyroid mass	1 (0.1)	0.3	(0.0, 1.9)
GASTROINTESTINAL DISORDERS	20 (2.0)	6.8	(4.2, 10.5)
Abdominal pain upper	2 (0.2)	0.7	(0.1, 2.5)
Diarrhoea	1 (0.1)	0.3	(0.0, 1.9)
Nausea	12 (1.2)	4.1	(2.1, 7.1)
Tooth impacted	1 (0.1)	0.3	(0.0, 1.9)
Vomiting	7 (0.7)	2.4	(1.0, 4.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	225 (22.3)	76.7	(67.0, 87.4)
Adverse drug reaction	1 (0.1)	0.3	(0.0, 1.9)
Axillary pain	1 (0.1)	0.3	(0.0, 1.9)
Chest discomfort	1 (0.1)	0.3	(0.0, 1.9)
Chest pain	1 (0.1)	0.3	(0.0, 1.9)
Chills	45 (4.5)	15.3	(11.2, 20.5)
Fatigue	104 (10.3)	35.4	(29.0, 42.9)
Injection site bruising	3 (0.3)	1.0	(0.2, 3.0)
Injection site erythema	5 (0.5)	1.7	(0.6, 4.0)
Injection site hypoaesthesia	1 (0.1)	0.3	(0.0, 1.9)
Injection site pain	157 (15.5)	53.5	(45.5, 62.5)
Injection site reaction	1 (0.1)	0.3	(0.0, 1.9)
Injection site swelling	4 (0.4)	1.4	(0.4, 3.5)
Malaise	7 (0.7)	2.4	(1.0, 4.9)
Non-cardiac chest pain	1 (0.1)	0.3	(0.0, 1.9)
Pain	35 (3.5)	11.9	(8.3, 16.6)
Pyrexia	64 (6.3)	21.8	(16.8, 27.8)
Thirst	1 (0.1)	0.3	(0.0, 1.9)
IMMUNE SYSTEM DISORDERS	1 (0.1)	0.3	(0.0, 1.9)
Food allergy	1 (0.1)	0.3	(0.0, 1.9)
INFECTIONS AND INFESTATIONS	12 (1.2)	4.1	(2.1, 7.1)
Appendicitis	1 (0.1)	0.3	(0.0, 1.9)
Cellulitis	1 (0.1)	0.3	(0.0, 1.9)
Ear infection	2 (0.2)	0.7	(0.1, 2.5)
Hand-foot-and-mouth disease	1 (0.1)	0.3	(0.0, 1.9)
Herpes zoster	1 (0.1)	0.3	(0.0, 1.9)

Table 27. Incidence Rates of at Least 1 Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021), by System Organ Class and Preferred Term – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1010, TE[b]=2.9)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])
Otitis externa	1 (0.1)	0.3	(0.0, 1.9)
Otitis media	1 (0.1)	0.3	(0.0, 1.9)
Paronychia	1 (0.1)	0.3	(0.0, 1.9)
Pharyngitis streptococcal	1 (0.1)	0.3	(0.0, 1.9)
Sinusitis	1 (0.1)	0.3	(0.0, 1.9)
Skin candida	1 (0.1)	0.3	(0.0, 1.9)
Tinea infection	1 (0.1)	0.3	(0.0, 1.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (1.1)	3.7	(1.9, 6.7)
Arthropod bite	1 (0.1)	0.3	(0.0, 1.9)
Concussion	1 (0.1)	0.3	(0.0, 1.9)
Facial bones fracture	1 (0.1)	0.3	(0.0, 1.9)
Hand fracture	1 (0.1)	0.3	(0.0, 1.9)
Hyphaema	1 (0.1)	0.3	(0.0, 1.9)
Joint injury	1 (0.1)	0.3	(0.0, 1.9)
Ligament rupture	1 (0.1)	0.3	(0.0, 1.9)
Ligament sprain	1 (0.1)	0.3	(0.0, 1.9)
Meniscus injury	1 (0.1)	0.3	(0.0, 1.9)
Muscle strain	1 (0.1)	0.3	(0.0, 1.9)
Sports injury	1 (0.1)	0.3	(0.0, 1.9)
Sunburn	1 (0.1)	0.3	(0.0, 1.9)
Traumatic renal injury	1 (0.1)	0.3	(0.0, 1.9)
Wound	1 (0.1)	0.3	(0.0, 1.9)
INVESTIGATIONS	3 (0.3)	1.0	(0.2, 3.0)
Body temperature increased	3 (0.3)	1.0	(0.2, 3.0)
METABOLISM AND NUTRITION DISORDERS	3 (0.3)	1.0	(0.2, 3.0)
Decreased appetite	1 (0.1)	0.3	(0.0, 1.9)
Glucose tolerance impaired	1 (0.1)	0.3	(0.0, 1.9)
Vitamin D deficiency	2 (0.2)	0.7	(0.1, 2.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	48 (4.8)	16.4	(12.1, 21.7)
Arthralgia	2 (0.2)	0.7	(0.1, 2.5)
Musculoskeletal chest pain	1 (0.1)	0.3	(0.0, 1.9)
Musculoskeletal stiffness	1 (0.1)	0.3	(0.0, 1.9)
Myalgia	38 (3.8)	12.9	(9.2, 17.8)
Neck pain	1 (0.1)	0.3	(0.0, 1.9)
Pain in extremity	9 (0.9)	3.1	(1.4, 5.8)

Table 27. Incidence Rates of at Least 1 Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021), by System Organ Class and Preferred Term – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1010, TE[b]=2.9)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1)	0.3	(0.0, 1.9)
Skin papilloma	1 (0.1)	0.3	(0.0, 1.9)
NERVOUS SYSTEM DISORDERS	75 (7.4)	25.6	(20.1, 32.0)
Dizziness	4 (0.4)	1.4	(0.4, 3.5)
Epilepsy	1 (0.1)	0.3	(0.0, 1.9)
Headache	71 (7.0)	24.2	(18.9, 30.5)
Somnolence	1 (0.1)	0.3	(0.0, 1.9)
Syncope	1 (0.1)	0.3	(0.0, 1.9)
PSYCHIATRIC DISORDERS	1 (0.1)	0.3	(0.0, 1.9)
Major depression	1 (0.1)	0.3	(0.0, 1.9)
RENAL AND URINARY DISORDERS	1 (0.1)	0.3	(0.0, 1.9)
Dysuria	1 (0.1)	0.3	(0.0, 1.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.3)	1.0	(0.2, 3.0)
Cough	1 (0.1)	0.3	(0.0, 1.9)
Nasal congestion	1 (0.1)	0.3	(0.0, 1.9)
Rhinorrhoea	1 (0.1)	0.3	(0.0, 1.9)
Upper-airway cough syndrome	1 (0.1)	0.3	(0.0, 1.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (0.5)	1.7	(0.6, 4.0)
Hyperhidrosis	1 (0.1)	0.3	(0.0, 1.9)
Ingrowing nail	2 (0.2)	0.7	(0.1, 2.5)
Photosensitivity reaction	1 (0.1)	0.3	(0.0, 1.9)
Urticaria	1 (0.1)	0.3	(0.0, 1.9)

Note: Dose 3 = First dose of BNT162b2 (30 µg).
Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 3 to data cutoff date. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:31)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s131_cut1_ped6

Analysis of Reactogenicity Terms Reported Within 7 Days After Each Dose (Adverse Events by System Organ Class and Preferred Term [Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding])

An analysis was conducted to evaluate if the imbalance in AEs (higher frequencies of some PTs relative to others) observed from Dose 3 to the data cutoff date was attributed to reactogenicity events. The analysis examined the AEs reported within 7 days after each dose (Dose 3 and Dose 4 [first and second dose of BNT162b2 30 µg]), which represented the reactogenicity reporting period.

PTs reported from Dose 3 to 7 days after Dose 3 and from Dose 4 to 7 days after Dose 4 in the SOCs of general disorders and administration site conditions (injection site pain, fatigue, chills, pyrexia, and pain), nervous system disorders (headache), musculoskeletal and connective tissue disorders (myalgia), and gastrointestinal disorders (nausea) represented the majority of PTs reported in those SOCs.

An SAE of myocarditis was reported in 1 participant within 7 days after Dose 4 (previously reported to CBER and discussed by the Advisory Committee on Immunization Practices [ACIP]). Full details are discussed in Section 2.5.5.2.7.1.

In addition to analysis of AEs corresponding to e-diary terms, consideration was given to additional AEs that were reported within 7 days after Dose 3 or Dose 4 such as but not limited to pain in extremity, decreased appetite, malaise, and hyperhidrosis. Similar to the analysis that examined these events 7 days within Dose 1 and Dose 2 of BNT162b2 in blinded placebo-controlled follow-up (adolescent interim CSR, dated 14 April 2021, Section 12.3.2.1.1.1), these events reported in open-label follow-up are interpreted as largely attributable to the experience of local reactions and systemic events after vaccination with Dose 3 and Dose 4 (first and second dose of BNT162b2).

Related Adverse Events – Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding

From vaccination with BNT162b2 to the data cutoff date (open-label follow-up period) for original placebo recipients who then received BNT162b2 after unblinding, 242 (24.0%) experienced AEs that were assessed as related by the investigator. Related AEs were highest for reactogenicity events and in the SOC of general disorders and administration site conditions (223 [22.1%]) for the following PTs:

- injection site pain (157 [15.5%])
- fatigue (104 [10.3%])
- pyrexia (63 [6.2%])
- chills (45 [4.5%])

Frequently reported related AEs also included PTs of headache 70 (6.9%) and myalgia 37 (3.7%).

Related events of lymphadenitis and appendicitis were reported in 1 participant each:

- One participant experienced a nonserious adverse event of lymphadenitis (right axillary adenitis) on Day 6 after Dose 3. It was moderate in severity, lasted for 24 days, and then resolved.

- See Section 2.5.5.2.5.4 for details on related SAE of appendicitis.

Immediate Adverse Events – Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding

After vaccination with BNT162b2 (Dose 3/4), 7 (0.7%) placebo adolescent participants who received BNT162b2 after unblinding reported immediate AEs. Most AEs reported were injection site pain for 6 (0.6%) participants, and 1 (0.1%) participant reported injection site erythema.

No allergic AEs were reported after either dose of BNT162b2 within 30 minutes after vaccination.

Severe or Life-Threatening Adverse Events – Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding

From vaccination with BNT162b2 to the data cutoff date (open-label follow-up period) for original placebo participants who then received BNT162b2 after unblinding, 12 (1.2%) reported severe AEs. Three (3) participants reported pyrexia, 2 reported fatigue, and 1 reported malaise (all PTs in the general disorders and administration site conditions SOC), and 1 participant reported myalgia (musculoskeletal and connective tissue disorders SOC), all of which are terms that are consistent with reactogenicity.

One participant experienced a severe SAE of myocarditis (See Section 2.5.5.2.5.4).

There were no life-threatening AEs reported from vaccination with BNT162b2 to the data cutoff date (Table 26).

2.5.5.2.4. Deaths

There were no deaths reported for adolescent participants as of the data cutoff date (02 September 2021).

2.5.5.2.5. Serious Adverse Events

2.5.5.2.5.1. Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date (Serious Adverse Events)

From Dose 1 to the unblinding date, there were 10 (0.9%) and 2 (0.2%) adolescent participants who reported at least 1 SAE in the BNT162b2 and placebo groups, respectively

(Table 28). All SAEs were assessed by the investigator as not related to study intervention (Table 12).

Certain SAEs discussed below were previously reported in the adolescent interim CSR, dated 14 April 2021:

- One participant in the placebo group reported a life-threatening (Grade 4) SAE each of focal peritonitis and appendicitis concurrently on Day 19 after Dose 2 with a duration of 2 days, and the event was assessed by the investigator as not related to study intervention. Both events were resolved, and the participant continued in the study.

- One participant reported an SAE each of anxiety and depression (both severe) reported concurrently on Day 8 after Dose 1 with a duration of 27 days, and both events were assessed by the investigator as not related to study intervention. This was a worsening of pre-existing anxiety and depression in a 13-year-old female. The participant had an extensive psychiatric past medical history of attention deficit hyperactivity disorder and separation anxiety disorder from 2010, disruptive mood dysregulation disorder since 2012, depression, anxiety, and recurring insomnia from 2014, post-traumatic stress disorder and recurring nightmares since 2015 and aggressive behaviors in 2017. The participant had been prescribed duloxetine hydrochloride and citalopram hydrobromide for depression since October 2019 and October 2020 respectively, however these were both stopped during this event, and the participant was prescribed aripiprazole and venlafaxine to manage this event. Both events resolved and the participant continued in the study. No further exacerbations were reported after receiving Dose 2.

- One participant reported an SAE of suicidal ideation on Day 40 after Dose 2 with a duration of 28 days, and the event was assessed by the investigator as not related to study intervention. This 14-year-old female had a past medical history of attention deficit hyperactivity disorder since 2015, and anxiety and depression since 2020. The participant had been prescribed methylphenidate hydrochloride for attention hyperactivity disorder; this was changed to dexmethylphenidate hydrochloride extended release approximately 22 days before being hospitalized for this event. After discharge the participant has continued an extensive outpatient therapy program, combined with fluoxetine. The event resolved and the participant continued in the study.

- One participant reported a severe SAE of depression on Day 16 after Dose 1 with a duration of 5 days, and the event was assessed by the investigator as not related to study intervention. This was a worsening of pre-existing depression in a 15-year-old male. The participant had a past medical history of attention deficit hyperactivity disorder, depression, and anxiety from 2018. The participant had been prescribed escitalopram oxalate for depression/anxiety from December 2020 which was stopped during this event and the participant was prescribed fluvoxamine and risperidone to manage the event. The event was reported as an SAE, resolved, and the participant continued in the study. This participant reported another severe SAE of depression,

which occurred after the EUA snapshot (second SAE discussed in Section 2.5.5.2.5.1.1).

Table 28. Incidence Rates of at Least 1 Serious Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])	n[c] (%)	IR[d]	(95% CI[e])
Any event	10 (0.9)	2.2	(1.0, 4.0)	2 (0.2)	0.4	(0.1, 1.6)
GASTROINTESTINAL DISORDERS	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Abdominal pain	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Constipation	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
INFECTIONS AND INFESTATIONS	1 (0.1)	0.2	(0.0, 1.2)	2 (0.2)	0.4	(0.1, 1.6)
Anal abscess	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Appendicitis	0	0.0	(0.0, 0.8)	2 (0.2)	0.4	(0.1, 1.6)
Focal peritonitis	0	0.0	(0.0, 0.8)	1 (0.1)	0.2	(0.0, 1.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Femur fracture	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
PSYCHIATRIC DISORDERS	8 (0.7)	1.7	(0.8, 3.4)	0	0.0	(0.0, 0.8)
Anxiety	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Conversion disorder	1 (0.1)	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)
Depression	3 (0.3)	0.7	(0.1, 1.9)	0	0.0	(0.0, 0.8)
Suicidal ideation	4 (0.4)	0.9	(0.2, 2.2)	0	0.0	(0.0, 0.8)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of the blinded follow-up period. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:21)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s131_sae_unb1_ped6

Subgroup Analyses (Serious Adverse Events [Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date])

There were 10 (0.9%) and 2 (0.2%) adolescent participants who reported at least 1 SAE in the BNT162b2 and placebo groups, respectively (Table 28). Overall, no clinically meaningful differences in frequencies of SAEs were observed by baseline SARS-CoV-2 status, ethnicity, race, or sex subgroups.

2.5.5.2.5.1.1. New Serious Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date)

There were 6 (0.5%) adolescent participants in the BNT162b2 group who reported an SAE after the EUA snapshot, and none were reported in the placebo group (Table 29).

Certain SAEs are discussed below:

- One participant reported a second severe SAE of depression on Day 57 after Dose 2 with a duration of 5 days, and the event was assessed by the investigator as not related to study intervention. The first SAE is discussed in Section 2.5.5.2.5.1, which was also previously reported in the adolescent interim CSR, dated 14 April 2021. This was a second episode of worsening of pre-existing depression in a 15-year-old male. The participant had a past medical history of attention deficit hyperactivity disorder, depression, and anxiety from 2018. They had been prescribed fluvoxamine and risperidone to manage the previously reported event (discussed in Section 2.5.5.2.5.1). The event was reported as resolved, and the participant continued in the study.

- One participant reported a severe SAE of suicidal ideation on Day 76 after Dose 2 with a duration of 2 days, and the event was assessed by the investigator as not related to study intervention. This 15-year-old male had a past medical history of anxiety and depression since March 2020, and had been prescribed fluoxetine for the depression. They were hospitalized with suicidal ideation for 2 days, after discharge they continued an intensive outpatient therapy program, combined with escitalopram oxalate and hydroxyzine. The event was resolved, and the participant continued in the study.

- One participant in the BNT162b2 group reported a life-threatening (Grade 4) SAE of suicidal ideation on Day 70 after Dose 2 with a duration of 10 days, and the event was assessed by the investigator as not related to study intervention. This 14-year-old female participant (aged 13 when initially enrolled) had a past medical history of anxiety since 2018, major depression since 2018 for which they were hospitalized in November 2020, and post-traumatic stress disorder since 2020. They had been prescribed sertraline hydrochloride for anxiety/depression from 2019. After being discharged from the hospital the participant has continued with outpatient treatment including an increase in the dose of sertraline and additional aripiprazole. The event was resolved, and the participant continued in the study.

- One participant in the BNT162b2 group reported a moderate SAE of suicidal ideation on Day 44 after Dose 2 with a duration of 5 days. The event was reported as resolved, and the participant continued in the study.

- One participant in the BNT162b2 group reported a severe SAE of anal abscess on Day 78 after Dose 2, and the event was recovering/resolving as of the data cutoff date.

Overall, all the SAEs occurred long after vaccination.

Table 29. Number (%) of Subjects Reporting at Least 1 New Serious Adverse Event After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1130)		Placebo (N[a]=1126)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	6 (0.5)	(0.2, 1.2)	0	(0.0, 0.3)
INFECTIONS AND INFESTATIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Anal abscess	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Femur fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
PSYCHIATRIC DISORDERS	4 (0.4)	(0.1, 0.9)	0	(0.0, 0.3)
Suicidal ideation	3 (0.3)	(0.1, 0.8)	0	(0.0, 0.3)
Depression	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)

Abbreviation: EUA = emergency use authorization.
Note: MedDRA (v24.0) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
a. N = number of subjects in the specified group, subjects who withdrew from the study before EUA snapshot 25Mar2021 with the cutoff date 13Mar2021 are not included. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:47)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s130_sae_unb2_ped6

2.5.5.2.5.2. Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Recipients (Serious Adverse Events)

From unblinding date to the data cutoff date, 4 (0.4%) original BNT162b2 adolescent participants experienced at least 1 SAE. Of these, 2 participants experienced appendicitis long after vaccination from Dose 2 (Day 148 and Day 177) (infections and infestations SOC); both events were assessed by the investigator as not related.

2.5.5.2.5.3. Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients (Serious Adverse Events)

From Dose 1 to 6 months after Dose 2, during the blinded placebo-controlled and open-label follow-up periods, 10 (0.9%) adolescent participants who originally received BNT162b2 reported at least 1 SAE (Table 30).

Comparison of SAEs reported from Dose 1 to 1 month after Dose 2 to SAEs reported from 1 month after Dose 2 to 6 months after Dose 2 shows that the frequency of SAEs was 0.3% and 0.8%, respectively (Table 31). The frequency of SAEs reported in the psychiatric disorders SOC was similar from Dose 1 to 1 month after Dose 2 versus 1 month after Dose 2 to 6 months after Dose 2.

Table 30. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any event	10 (0.9)	(0.4, 1.6)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.1)	(0.0, 0.5)
Syringomyelia	1 (0.1)	(0.0, 0.5)
GASTROINTESTINAL DISORDERS	1 (0.1)	(0.0, 0.5)
Abdominal pain	1 (0.1)	(0.0, 0.5)
Constipation	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	2 (0.2)	(0.0, 0.6)
Anal abscess	1 (0.1)	(0.0, 0.5)
Appendicitis	1 (0.1)	(0.0, 0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	(0.0, 0.5)
Femur fracture	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	6 (0.5)	(0.2, 1.2)
Suicidal ideation	3 (0.3)	(0.1, 0.8)
Depression	2 (0.2)	(0.0, 0.6)
Conversion disorder	1 (0.1)	(0.0, 0.5)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:31)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s130_ser_6m1_ped6

Table 31. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (Na=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	3 (0.3)	(0.1, 0.8)	9 (0.8)	(0.4, 1.5)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Syringomyelia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
GASTROINTESTINAL DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Abdominal pain	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Constipation	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Anal abscess	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Appendicitis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Femur fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	3 (0.3)	(0.1, 0.8)	4 (0.4)	(0.1, 0.9)
Suicidal ideation	0	(0.0, 0.3)	3 (0.3)	(0.1, 0.8)
Depression	2 (0.2)	(0.0, 0.6)	1 (0.1)	(0.0, 0.5)
Conversion disorder	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:22)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s132 ser 6m1 ped6

2.5.5.2.5.3.1. New Serious Adverse Events Since EUA Snapshot (Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients)

For original BNT162b2 adolescent recipients with at least 6 months of follow-up time after Dose 2, there were 7 (0.6%) new SAEs reported after the EUA snapshot (Table 32), and all

of the SAEs were reported from 1 month after Dose 2 to 6 months after Dose 2 (Table 33; also discussed in Section 2.5.5.2.3.3.3 [Summary of New Adverse Events Since EUA Snapshot]).

Table 32. Number (%) of Subjects Reporting at Least 1 New Serious Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1113)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any event	7 (0.6)	(0.3, 1.3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.1)	(0.0, 0.5)
Syringomyelia	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	2 (0.2)	(0.0, 0.6)
Anal abscess	1 (0.1)	(0.0, 0.5)
Appendicitis	1 (0.1)	(0.0, 0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	(0.0, 0.5)
Femur fracture	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	3 (0.3)	(0.1, 0.8)
Suicidal ideation	2 (0.2)	(0.0, 0.6)
Depression	1 (0.1)	(0.0, 0.5)

Abbreviation: EUA = emergency use authorization.
Note: EUA snapshot 25Mar2021 with the cutoff date 13Mar2021.
Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:50)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s130_ser_6m2_ped6

Table 33. Number (%) of Subjects Reporting at Least 1 New Serious Adverse Event After the EUA Snapshot, From Dose 1 to 6 Months After Dose 2, by System Organ Class and Preferred Term and Time Period – Subjects With at Least 6 Months of Follow-up Time After Dose 2 – Phase 2/3 Subjects 12 Through 15 Years of Age (Subjects Who Originally Received BNT162b2) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (Na=1113)			
	Dose 1 to 1 Month After Dose 2		1 Month After Dose 2 to 6 Months After Dose 2	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	0	(0.0, 0.3)	7 (0.6)	(0.3, 1.3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Syringomyelia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Anal abscess	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Appendicitis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Femur fracture	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
PSYCHIATRIC DISORDERS	0	(0.0, 0.3)	3 (0.3)	(0.1, 0.8)
Suicidal ideation	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Depression	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)

Abbreviation: EUA = emergency use authorization.
Note: EUA snapshot 25Mar2021 with the cutoff date 13Mar2021.
Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:46)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s132_ser_6m2_ped6

2.5.5.2.5.4. Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding (Serious Adverse Events)

From Dose 3 (first dose of BNT162b2) to the data cutoff date, 6 (0.6%) adolescent participants who originally received placebo then received BNT162b2 after unblinding reported at least 1 SAE (Table 34).

1 SAE, appendicitis, was assessed by the investigator as related to study intervention. The event of appendicitis occurred in a 13-year-old female (aged 12 years when initially enrolled), on Day 4 after Dose 4 (second dose of BNT162b2), an ultrasound performed in the hospital confirmed the diagnosis, as did macroscopic inspection of the appendix during surgery and the pathology report received post appendectomy. The event lasted for 1 day, as the participant underwent surgery and was considered resolved post surgery.

1 SAE, epilepsy, was assessed by the investigator as not related to study intervention. This event occurred in a 12-year-old male on Day 8 after Dose 4, there was no past medical history of febrile seizures in early childhood, however, there was a positive family history of epilepsy (maternal uncle). The diagnosis of epilepsy was confirmed by electroencephalogram, the participant was not prescribed any medication and remains on neurology follow-up. There have been no further seizures upon continued follow-up with the participant.

An SAE of myocarditis was reported in a 16-year-old male participant who experienced chest pain on Day 3 after Dose 2 of BNT162b2 (previously reported to CBER and discussed by ACIP). Full details are discussed in Section 2.5.5.2.7.1.

Table 34. Incidence Rates of at Least 1 Serious Adverse Event From Dose 3 to Data Cutoff Date (02SEP2021), by System Organ Class and Preferred Term – Open-Label Follow-up Period – Subjects Who Originally Received Placebo and Then Received BNT162b2 After Unblinding – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1010, TE[b]=2.9)		
System Organ Class Preferred Term	n[c] (%)	IR[d]	(95% CI[e])
Any event	6 (0.6)	2.0	(0.8, 4.4)
CARDIAC DISORDERS	1 (0.1)	0.3	(0.0, 1.9)
Myocarditis	1 (0.1)	0.3	(0.0, 1.9)
INFECTIONS AND INFESTATIONS	1 (0.1)	0.3	(0.0, 1.9)
Appendicitis	1 (0.1)	0.3	(0.0, 1.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	0.3	(0.0, 1.9)
Traumatic renal injury	1 (0.1)	0.3	(0.0, 1.9)
NERVOUS SYSTEM DISORDERS	2 (0.2)	0.7	(0.1, 2.5)
Epilepsy	1 (0.1)	0.3	(0.0, 1.9)
Somnolence	1 (0.1)	0.3	(0.0, 1.9)
PSYCHIATRIC DISORDERS	1 (0.1)	0.3	(0.0, 1.9)
Major depression	1 (0.1)	0.3	(0.0, 1.9)

Note: Dose 3 = First dose of BNT162b2 (30 µg).
Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 3 to data cutoff date. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:31)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s131 ser cut1 ped6

2.5.5.2.6. Adverse Events Leading to Withdrawal

2.5.5.2.6.1. Blinded Placebo-Controlled Follow-Up Period From Dose 1 to the Unblinding Date (Adverse Events Leading to Withdrawal)

From Dose 1 to the unblinding date, 1 (0.1%) participant in the BNT162b2 group had an AE of pyrexia leading to withdrawal that was assessed by the investigator as related to study

intervention (previously reported in Section 12.3.2.4.1 of the adolescent interim CSR dated 14 April 2021).

2.5.5.2.6.2. Open-Label Follow-Up Period From the Unblinding Date to the Data Cutoff Date – Original BNT162b2 Recipients (Adverse Events Leading to Withdrawal)

From the unblinding date to the data cutoff date, there were no original BNT162b2 adolescent participants who were withdrawn because of AEs (Table 17).

2.5.5.2.6.3. Blinded Placebo-Controlled and Open-Label Follow-Up Periods From Dose 1 to 6 Months After Dose 2 – Original BNT162b2 Recipients (Adverse Events Leading to Withdrawal)

From Dose 1 to 6 months after Dose 2 during the blinded placebo-controlled and open-label follow-up periods, there were no adolescent participants with at least 6 months of follow-up time after Dose 2 who were withdrawn because of AEs (Table 18).

2.5.5.2.6.4. Open-Label Follow-Up Period From Dose 3 to the Data Cutoff Date – Original Placebo Recipients Who Then Received BNT162b2 After Unblinding (Adverse Events Leading to Withdrawal)

From Dose 3 (first dose of BNT162b2 30 µg) administration to the data cutoff date, there were no original placebo adolescent participants who were withdrawn because of AEs (Table 26).

2.5.5.2.7. Other Significant Adverse Events – Phase 3

Adverse events of clinical interest include AESIs, such as those in the CDC list of AESIs for COVID-19 that include events potentially indicative of severe COVID-19 or autoimmune and neuroinflammatory disorders, were considered, in addition to program-defined TMEs, in the review of reported events for the adolescent group. Narratives were prepared for such events reported in adolescents (12-15 years of age). AEs of clinical interest occurring in the adolescent group were reviewed for the blinded placebo-controlled period.

2.5.5.2.7.1. FDA-Requested Adverse Events of Clinical Interest

No cases of anaphylaxis, hypersensitivity, Bell's palsy, or vaccine-related appendicitis were reported as of the data cutoff date (02 September 2021) during the blinded placebo-controlled period. Other events that were reported in the safety database are summarized below.

Lymphadenopathy

Lymphadenopathy is identified as an adverse reaction for BNT162b2 vaccine.

During the blinded placebo-controlled follow-up period, 9 and 2 participants in the BNT162b2 and placebo groups reported AEs of lymphadenopathy, respectively (Table 35). All events were mild or moderate in severity (only 1 moderate AE in the BNT162b2 group). The majority of these events occurred in the arm and neck region. Median onset was 8.0 days (after Dose 1 but before Dose 2) and 3.0 days (after Dose 2) in the BNT162b2 group and none (after Dose 1 but before Dose 2) and 12.5 days (after Dose 2) in the placebo group. The

events resolved with median duration of 6.0 days in the BNT162b2 group and 25.5 days in the placebo group.

Table 35. Subjects Reporting an Adverse Event of Lymphadenopathy – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=9) n[b] (%)	Placebo (N[a]=2) n[b] (%)
Severity		
Mild	8 (88.9)	2 (100.0)
Moderate	1 (11.1)	0
Severe	0	0
Life-threatening	0	0
Onset day after Dose 1 and before Dose 2		
n	5	0
Mean (SD)	8.2 (2.28)	NE (NE)
Median	8.0	NE
Min, max	6 - 12	NE - NE
Onset day after Dose 2		
n	4	2
Mean (SD)	9.0 (12.70)	12.5 (3.54)
Median	3.0	12.5
Min, max	2 - 28	10 - 15
Duration (days)		
n	8	2
Mean (SD)	10.8 (11.03)	25.5 (24.75)
Median	6.0	25.5
Min, max	1 - 29	8 - 43
Unknown[c]	1	0

Abbreviation: NE = not estimable.
Note: For each event, the worst severity, earliest onset, and longest duration will be counted.
a. N = number of subjects reporting lymphadenopathy. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event.
c. Includes those events where the resolution date is partial or missing.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (21:24)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2 unblinded/C4591001 S Peds/adae lym unb 1

Appendicitis

During the blinded placebo-controlled follow-up period, 2 participants in the placebo group each had an SAE of appendicitis, and both events were assessed by the investigator as not related to study intervention.

During the open-label follow-up period:

- Two original BNT162b2 recipients each had an SAE of appendicitis long after vaccination from Dose 2 (Day 148 and Day 177), and both events were assessed by the investigator as not related to study intervention (discussed in Section 2.5.5.2.5.2).

- One original placebo recipient had an SAE of appendicitis that was assessed by the investigator as related to study intervention (discussed in Section 2.5.5.2.5.4).

Myocarditis/pericarditis

One original placebo participant 16 years of age had an SAE of myocarditis on Day 3 after Dose 2 of BNT162b2 (previously reported to CBER and discussed by ACIP). The participant had been participating in a dance class prior to reporting the symptom and visited the emergency room (ER) the same evening, where he was hospitalized for further investigation and treatment. An electrocardiogram (EKG), performed and reviewed by a cardiologist, showed diffuse ST elevations, and troponin levels were elevated on serial measurements throughout the admission, (maximum measurement was 0.71 ng/mL [normal range 0 to <0.01 ng/mL]). The chest pain was considered by the investigator to be most likely due to an ongoing viral infection, which could have caused myopericarditis. This conclusion was based on the participant's recent history (one week previously) of a temperature of 100.5°F associated with cough and rhinorrhea, and clinical symptoms at the time of the event (temperature 100.1°F; rhinovirus PCR was positive on a respiratory virus panel, but negative for enterovirus and parvovirus B19, SARS-CoV-2 RNA PCR was negative). The chest pain resolved within 24 hours upon receiving ketorolac, and the participant was discharged home after 2 days hospitalization and treatment. Further continuing cardiology follow-up of this participant confirmed that the condition has resolved and the participant has resumed gym exercises. The investigator considered the event was not related to study intervention. However, Pfizer considers that there is a reasonable possibility that this event is related to the administration of BNT162b2, considering the prior reports of myocarditis/pericarditis in recipients of mRNA vaccines in younger individuals.

2.5.5.2.7.2. Other Adverse Events of Special Interest

Additional AEs of clinical interest, including those on the CDC AESI list, were evaluated based on sponsor agent safety data review. These AEs were identified from the C4591001 study database as of the data cutoff date (02 September 2021). From this analysis, notable pertinent negatives (ie, no cases reported in this population as of the data cutoff for this submission) with regard to the CDC list of AESIs included (but were not limited to): thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, optic neuritis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome.

An analysis of AEs of clinical interest for potential numerical imbalance (based on risk difference >0) between BNT162b2 and placebo SOC and PT as shown in Table 36, with most PTs showing no numerical difference between the BNT162b2 and placebo groups. SOCs which did include PTs more frequently reported after BNT162b2 compared to placebo, or otherwise considered of particular clinical interest, are summarized below.

Table 36. Incidence Rates of at Least 1 Adverse Event of Special Interest From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)			Difference	
System Organ Class Preferred Term	n[c]	IR[d]	(95% CI[e])	n[c]	IR[d]	(95% CI[e])	IRD[f]	(95% CI[g])
EYE DISORDERS								
Retinal haemorrhage	0	0.0	(0.0, 0.8)	1	0.2	(0.0, 1.2)	-0.22	(-0.66, 0.21)
GASTROINTESTINAL DISORDERS								
Lip swelling	1	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)	0.22	(-0.21, 0.65)
Mouth swelling	1	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)	0.22	(-0.21, 0.65)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
Pyrexia	6	1.3	(0.5, 2.9)	0	0.0	(0.0, 0.8)	1.31	(0.26, 2.36)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
Bone contusion	1	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)	0.22	(-0.21, 0.65)
Contusion	2	0.4	(0.1, 1.6)	2	0.4	(0.1, 1.6)	-0.01	(-0.87, 0.86)
INVESTIGATIONS								
SARS-CoV-2 antibody test positive	1	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)	0.22	(-0.21, 0.65)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
Arthralgia	2	0.4	(0.1, 1.6)	4	0.9	(0.2, 2.3)	-0.45	(-1.51, 0.61)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
Epistaxis	0	0.0	(0.0, 0.8)	1	0.2	(0.0, 1.2)	-0.22	(-0.66, 0.21)
Sneezing	1	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.8)	0.22	(-0.21, 0.65)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
Rash	3	0.7	(0.1, 1.9)	5	1.1	(0.4, 2.6)	-0.45	(-1.68, 0.77)
Urticaria	2	0.4	(0.1, 1.6)	5	1.1	(0.4, 2.6)	-0.67	(-1.82, 0.47)

Table 36. Incidence Rates of at Least 1 Adverse Event of Special Interest From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg) (N[a]=1131, TE[b]=4.6)			Placebo (N[a]=1129, TE[b]=4.5)			Difference	
System Organ Class Preferred Term	n[c]	IR[d]	(95% CI[e])	n[c]	IR[d]	(95% CI[e])	IRD[f]	(95% CI[g])

Note: MedDRA (v24.0) coding dictionary applied.
Note: The 95% confidence interval quantifies the precision of the incidence rate difference estimate. Confidence intervals are not adjusted for multiplicity. They should only be used to identify potentially important adverse events.
a. N = number of subjects in the specified group.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of the blinded follow-up period. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
f. Difference in incidence rate (BNT162b2 [30 µg] - placebo).
g. 2-sided Wald CI for the incidence rate difference.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (18:29) Source Data: adae Table Generation: 03NOV2021 (10:41)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_s131_sp_unb1_ped6

General Disorders and Administration Site Conditions

There was a numerical difference for events of pyrexia, which was reported by 6 participants in the BNT162b2 group and none in the placebo group (Table 36). These are recognized as reactogenicity events known to be associated with BNT162b2 vaccination.

Arthralgia

There was no imbalance of arthralgia being reported more frequently in the BNT162b2 group. During the blinded placebo-controlled follow-up period, 2 participants (1 moderate and 1 severe) and 4 participants (2 mild and 2 moderate) in the BNT162b2 and placebo groups reported AEs of arthralgia, respectively (Table 37).

Table 37. Subjects Reporting an Adverse Event of Arthralgia – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=2) n[b] (%)	Placebo (N[a]=4) n[b] (%)
Severity		
Mild	0	2 (50.0)
Moderate	1 (50.0)	2 (50.0)
Severe	1 (50.0)	0
Life-threatening	0	0
Onset day after Dose 1 and before Dose 2		
n	2	3
Mean (SD)	3.0 (2.83)	9.0 (6.24)
Median	3.0	7.0
Min, max	1 - 5	4 - 16
Onset day after Dose 2		
n	0	1
Mean (SD)	NE (NE)	131.0 (NE)
Median	NE	131.0
Min, max	NE - NE	131 - 131
Duration (days)		
n	2	4
Mean (SD)	13.0 (16.97)	14.5 (15.59)
Median	13.0	9.5
Min, max	1 - 25	3 - 36

Abbreviation: NE = not estimable.
Note: For each event, the worst severity, earliest onset, and longest duration will be counted.
a. N = number of subjects reporting arthralgia. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 10NOV2021 (15:42)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File: ./nda2_unblinded/C4591001_S_Peds/adae_arth_unb_1

2.5.5.2.7.2.1. New Adverse Events of Special Interest After the EUA Snapshot

New AEs of special interest after the EUA snapshot from Dose 1 to the unblinding date during the blinded placebo-controlled follow-up period are presented in Table 38. New AEs reported in adolescents were similar in the BNT162b2 and placebo groups (0.4% each), and PTs were reported in 1 participant each.

Table 38. Number (%) of Subjects Reporting at Least 1 New Adverse Event of Special Interest After the EUA Snapshot, From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=1130)		Placebo (N[a]=1126)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	4 (0.4)	(0.1, 0.9)	5 (0.4)	(0.1, 1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Pyrexia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Bone contusion	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
Contusion	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
INVESTIGATIONS	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
SARS-CoV-2 antibody test positive	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Arthralgia	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	(0.0, 0.5)	1 (0.1)	(0.0, 0.5)
Epistaxis	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Sneezing	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	(0.0, 0.3)	2 (0.2)	(0.0, 0.6)
Rash	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)
Urticaria	0	(0.0, 0.3)	1 (0.1)	(0.0, 0.5)

Abbreviation: EUA = emergency use authorization.
Note: MedDRA (v24.0) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
a. N = number of subjects in the specified group, subjects who withdrew from the study before EUA snapshot 25Mar2021 with the cutoff date 13Mar2021 are not included. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 05OCT2021 (17:29) Source Data: adae Table Generation: 11NOV2021 (09:52)
(Data Cutoff Date: 02SEP2021, Database Snapshot Date: 27SEP2021) Output File:
./nda2 unblinded/C4591001 S Peds/adae s130 sp unb2 ped6

2.5.5.3. Other Safety Assessments

2.5.5.3.1. Severe COVID-19 Illness

No AEs were reported that suggested any potential cases of severe COVID-19 among adolescent participants as of the data cutoff date (02 September 2021).

2.5.5.3.2. Pregnancies

No pregnancies were reported in the Phase 3 BNT162b2 booster group from Dose 3 to the data cutoff date (02 September 2021)

2.5.5.3.3. Adverse Drug Reactions

Adverse drug reactions (ADRs), defined as AEs for which there is reason to conclude that the vaccine caused the event, have been identified from clinical study safety data and are specified in the current product labeling. No new ADRs were identified from updated safety data as of the 02 September 2021 data cutoff date.

2.5.5.4. Safety in Special Groups and Situations

2.5.5.4.1. Geriatric Use

Clinical studies of BNT162b2 (30 µg) include participants ≥65 years of age whose data contribute to overall assessment of safety and efficacy. The clinical data have demonstrated a predominantly mild reactogenicity profile in older adults, overall and compared with younger adults. This is coupled with evidence of robust immune response following the two-dose vaccination regimen, and overwhelming efficacy comparable to younger adults (>90%).

2.5.5.4.2. Pediatric Use

Clinical pediatric study of BNT162b2 (10 µg) includes participants 5 to <12 years of age. The clinical data have demonstrated a predominantly mild reactogenicity profile in this age group, overall and compared with adults. This is coupled with evidence of robust immune response following the two-dose vaccination regimen that is comparable to adults who received the 30 µg vaccine dose level, and efficacy was comparable to adults (>90%). Further study of pediatric use of the vaccine and/or immunobridging study will be undertaken to characterize the vaccine response in children <5 years of age.

2.5.5.4.3. Use During Pregnancy and Lactation

Individuals who were pregnant or breastfeeding were not eligible to participate in Study C4591031. No pregnancies were reported in the 12-15 years of age group as of the data cutoff date (02 September 2021).

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In a DART study, no vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for vaccination with BNT162b2 and any potential adverse effects on the breastfed child from BNT162b2 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

2.5.5.4.4. Use in Immunocompromised Individuals

Individuals who are immunocompromised or taking immunosuppressive therapy at the time of vaccine administration may have diminished response to immunization. Study C4591001 and C4591031 included enrollment of individuals with medical history of immunocompromised condition or immunosuppressive therapy. There are limited data on the safety and effectiveness of the vaccine in this patient population at the time of this submission.

A third dose of BNT162b2 30 µg may be given to individuals ≥12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

2.5.5.4.5. Other Safety Considerations

Overdose

In Study C4591001, any dose of study intervention exceeding 30 µg within a 24-hour time period was considered an overdose (refer to Module 5.3.5.1 C4591001 Protocol Section 8.4). An error in dilution during the study resulted in 52 participants (≥16 years of age) receiving a higher than intended dose of BNT162b2: instead of receiving 30 µg, an actual dose of 58 µg BNT162b2 was administered. These participants did not report an increase in reactogenicity or AEs.

Drug Abuse and Withdrawal and Rebound

Not applicable for BNT162b2.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

BNT162b2 has no or negligible influence on the ability to drive and use machines.

2.5.5.5. Post-Authorization Safety Summary

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

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

Investigation (350), Infections and infestations (229), Psychiatric disorders (188) and Vascular disorders (167).

The safety profile of BNT162b2 remains aligned with the approved label. There was no new significant information emerging from the close monitoring for anaphylaxis and myocarditis/pericarditis, and the analyses of cumulative post-authorization safety data, including a review of AESIs, are consistent with the analysis of the pivotal clinical study (C4591001) and has confirmed the favorable benefit-risk profile of the vaccine.

Further details regarding the cumulative analysis of post-authorization safety data are presented in Module 5.3.6.

2.5.5.6. Safety Conclusions

Based on Phase 3 data from 2260 participants 12-15 years of age with up to at least 6 months of follow-up after Dose 2 in Study C4591001, BNT162b2 at 30 µg was safe and well-tolerated and aligned with that previously demonstrated for 16 yrs and older. The AE profile did not suggest any new safety concerns. The incidence of SAEs was low in the context of the number of participants enrolled and comparable in the BNT162b2 and placebo groups. Only 1 participant discontinued from the study due to an AE (related nonserious AE of pyrexia [previously reported]), and there were no deaths.

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

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

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

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

2.5.6. Benefits and Risks Conclusions

The updated efficacy and safety data as of the 02 September 2021 data cutoff date are consistent with the data reported in the adolescent interim CSR (dated 14 April 2021) as well as the data reported in the C4591001 6-Month update interim CSR (dated 29 April 2021).

2.5.6.1. Benefits

COVID-19 is a serious and potentially fatal or life-threatening human infection. Based on the available clinical data in adolescents, including previously submitted efficacy data and immunobridging data between adolescents and young adults, it is expected that BNT162b2 will elicit an immune response that is likely to confer protection against COVID-19 in individuals 12-15 years of age. The duration of protection is currently unknown.

Previous descriptive efficacy analyses showed observed VE for the evaluable efficacy population was 100% for adolescent participants (reported in the adolescent interim CSR, dated 14 April 2021). Updated descriptive efficacy analyses for adolescents were consistent with prior analyses. During the blinded placebo-controlled follow-up period, median follow-up time for adolescent participants was 4.4 months. Based on confirmed COVID-19 cases reported from at least 7 days after Dose 2 through the data cutoff date (02 September 2021), estimated VE was 100.0% (2-sided 95% CI: 86.8%, 100.0%) for individuals without evidence of prior SARS-CoV-2 infection before and during vaccination regimen, and 100.0% (2-sided 95% CI: 87.5%, 100.0%) for individuals with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen. Sequencing data shows that most variants were neither VOI nor VOC except for B.1.1.7 (Alpha), which was found in 23.3% of placebo participants.

In the Dose 1 all-available (modified intention-to-treat) population, 3 participants in the BNT162b2 group and 48 participants in the placebo group had COVID-19 cases occurring after Dose 1, for an estimated VE against confirmed COVID-19 occurring after Dose 1 of 94.0% (2-sided 95% CI: 81.3%, 98.8%). All 3 cases in the BNT162b2 group were SARS-CoV-2 negative at baseline, occurred within the period from after Dose 1 up to <11 days after Dose 1 (prior to Dose 2), after which time the VE was 100.0% for BNT162b2. Note that for the Dose 1 all-available population, VE remained 100% for follow-up up to ≥4 months after Dose 2 (whereas VE had decreased to 83.7% in the same population primarily consisting of participants ≥16 years of age [refer to Section 11.1.2.1.3 of 6-Month update interim CSR, dated 29 April 2021, Module 5.3.5.1 C4591001 6-Month Update Interim CSR]). Possible loss of efficacy will continue to be monitored.

No severe COVID-19 cases were reported in individuals in the 12-15 years of age group, based on either protocol definition (ie, per FDA criteria) or per CDC criteria for severity.

The updated efficacy data strongly support the positive benefit for the BNT162b2 2-dose regimen in adolescents 12-15 years of age.

2.5.6.2. Risks

The long-term AE profile among 2260 participants 12-15 years of age enrolled to date as of the most recent safety cutoff date (02 September 2021), was mostly reflective of reactogenicity events with low incidences of severe and/or related events. Lymphadenopathy has been identified as related to BNT162b2 in study participants ≥16 years of age and is also identified as related to BNT162b2 in adolescents. The incidence of SAEs was low and similar in the vaccine and placebo groups.

All SAEs in the blinded placebo-controlled follow-up period, including SAEs in the psychiatric disorders SOCs, were assessed by the investigator as not related to study intervention. During this period, the number of participants with psychiatric disorder AEs were comparable in the BNT162b2 and placebo groups. In the BNT162b2 group, the 4 participants who reported suicidal ideation had an ongoing past medical history of depression and/or anxiety and all were taking concomitant medications for psychiatric disorders. Half of the 6 BNT162b2 participants who reported depression had a known past medical history of ongoing depression.

One (1) participant reported an SAE of myocarditis (previously reported to CBER and discussed with the ACIP), which was assessed by the investigator as not related to study intervention. However, Pfizer considers that there is a reasonable possibility that this event is related to the administration of BNT162b2, considering the prior reports of myocarditis/pericarditis in recipients of mRNA vaccines in younger individuals. In the post-authorization setting, myocarditis was reported predominantly in adolescents and young adult male vaccine recipients and typically within the 14 days following vaccination. These were typically mild cases, and individuals tended to recover within a short time following standard treatment and rest. In addition, data reported by the United States (US) Centers for Disease Control and Prevention (CDC) were considered.[16] CDC review of stratified data in Vaccine Adverse Event Reporting System (VAERS) showed that reporting rates of myocarditis are higher following second dose of vaccine in males 12 to 29 years of age. VSD data showed increased rates of myocarditis in the 7 days after receipt of Dose 1 or Dose 2 of an mRNA COVID-19 vaccine compared with the risk 22 to 42 days after the second dose, particularly among younger males after Dose 2.

Only 1 participant was withdrawn from the study because of an AE. No deaths occurred in the adolescent group. Review of AEs, SAEs, and events of clinical interest suggested no clear patterns or additional safety concerns among adolescents.

Safety analyses from Dose 1 to 6 months after Dose 2 for participants who were randomized to BNT162b2, inclusive of cumulative blinded and open-label data, showed no new safety findings or signals over a longer duration of follow-up.

For participants randomized to placebo and then unblinded to receive BNT162b2 vaccination, open-label data from the time of unblinding to the data cutoff date (02 September 2021) showed no new safety findings or signals. Open-label safety data for participants originally randomized to placebo who were unblinded to receive BNT162b2 followed generally similar patterns relative to those who were originally randomized to BNT162b2 during blinded follow-up. This supports the overall consistency of the safety profile of the BNT162b2 30 µg two-dose vaccination regimen across study phases and follow-up periods.

The AE profile of new events after the EUA snapshot were consistent with those observed cumulatively and did not reveal additional safety concerns among adolescents.

Safety analyses of study participants across various demographic subgroups and by baseline SARS-CoV-2 prior infection status have not shown any clinically important differences in the BNT162b2 safety profile for the duration of blinded follow-up.

As of the 02 September 2021 data cutoff date, no AEs were reported that suggested any potential cases of severe COVID-19 among adolescent participants.

Study participants will continue to be followed for 2 years or end of study.

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

The Phase 3 Study C4591001 updated efficacy results are supported by contemporaneous real-world data from Israel and the United States demonstrating high vaccine effectiveness (90%) of two doses of BNT162b2 against symptomatic COVID-19 in the adolescent population.[17,18,19,20,21,22]

Two studies from Israel examined short-term VE against infection up to 3-4 weeks after the second dose among adolescents without prior SARS-CoV-2 infection.[17,18] Among individuals aged 12-15 years who received their second dose between July 1, 2021 and July 24, 2021 (i.e., during the early stages of the delta variant outbreak in Israel), adjusted VE against infection in the 8-28 days after the second dose was 92% (95% CI: 88-94).[17] Similarly, in another study of adolescents aged 12-18 years vaccinated between June 8-September 14, 2021, a time period when the delta variant accounted for over 95% of all new cases in Israel, VE in the 7-21 days after the second dose was 90% (95% CI: 88-92) against infection and 93% (95% CI: 88-97) against symptomatic COVID-19.[18]

Results from two studies reporting VE against infection among US adolescents are remarkably consistent with the results observed in Israel.[19,20] Among Kaiser Permanente Southern California (KPSC) members aged 12-15 years, the adjusted VE against infection through August 8, 2021 was 91% (95% CI: 88-93). Further, protection against infection remained high through 3 months following the second dose (the latest follow-up available with sufficient sample size for evaluation); adjusted VE at <1 month, 1 to <2 months, and 2 to <3 months was 91% (95%: 86-94), 92% (95% CI: 88-94), and 88% (95% CI: 68-96), respectively.[19] In another US study examining Kaiser Permanente Northwest enrollees during July 4-September 11, 2021, a period of delta predominance, the incidence rate ratio for infection comparing vaccinated (≥2 doses) versus unvaccinated adolescents aged 12-17 years was 8.9 (95% CI: 6.6-11.9), which can be calculated as a VE against infection of approximately 91%.[20]

Two CDC studies that assessed protection against hospitalization among the adolescent population reported VE estimates of approximately 90%.[21,22] Among US patients aged 12-18 years hospitalized at 19 pediatric hospitals across 16 states, adjusted VE against hospitalization during June 1-September 30, 2021 was 93% (95% CI: 83-97). Results were similar when stratified by age group; VE was 91% (95% CI: 74-97) among patients aged 12-15 years and 94% (95% CI: 78-99) among patients aged 16-18 years. The median (interquartile range [IQR]) duration between the second dose and illness onset was 72 (45-97) days.[21] The second study estimated the risk of hospitalization by vaccination status among adolescents aged 12-17 years from June 20-July 31, 2021. This study reported an incidence rate ratio of 10.1 (95% CI: 3.7-27.9), which can be calculated as a VE of approximately 90%. It should be noted, however, that the sample size of this analysis was small (n=68).[22]

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

Real-world safety surveillance data has shown that rare cases of post-vaccination myocarditis may occur in individuals 12−15 years of age (21.5 per million second doses administered based on VAERS).[23] These events tend to occur more frequently after the second dose and among males (39.9 *vs* 3.9 per million second doses administered in males versus females, respectively).[23]

2.5.6.4. Benefit-Risk Conclusions

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

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

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

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

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

Overall, the potential risks and benefits in adolescents, as assessed by the updated safety and efficacy profiles of BNT162b2, are balanced in favor of the potential benefits to prevent COVID-19 in immunized individuals 12-15 years of age. Important risks of BNT162b2 are described in the Pharmacovigilance Plan and will continue to be assessed and minimized as described in the updated Pharmacovigilance Plan. The public health impacts that include individual and community health, education, and socio-economic outcomes also weigh in favor of full licensure of BNT162b2 for immunization of individuals 12-15 years of age.

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