EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 May 2021
EMA/343389/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

COMIRNATY

International non-proprietary name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/II/0030

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

In addition, in order to protect the blinding of the ongoing clinical trial certain pieces of information are redacted. These redactions are shaded in black with overlay text that reads "BLD". BLD stays for "Interim results of an ongoing clinical trial impacting study blinding". These redactions are temporary and will be lifted once the study will be fully unblinded.

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List of abbreviations

Abbreviation	Definition
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CDC	(US) Centers for Disease Control and Prevention
CFR	case fatality rate
CI	confidence interval
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Application
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GMFR	geometric mean-fold rise
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
IRC	Internal Review Committee
IRR	illness rate ratio
LLN	lower limit of normal
LNP	lipid nanoparticle
MAA	Marketing Authorization 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
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein
PDCO	Paediatric Committee
PCR	polymerase chain reaction
PIP	Paediatric Investigational Plan
PSP	Pediatric Study Plan
PT	Preferred Term
RBD	receptor binding domain
RNA-LNP	RNA lipid nanoparticle
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
S glycoprotein, S	spike glycoprotein
SOC	System Organ Class
UK	United Kingdom
US	United States
USP	United States Pharmacopeia

Abbreviation	Definition
VE	vaccine efficacy
VAE(R)D	vaccine-associated enhanced (respiratory) disease
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 30 April 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the existing indication from "individuals 16 years of age and older" to "individuals 12 years of age and older" for Comirnaty; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0179/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0179/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

Timetable	Dates
Submission date	30 April 2021
Start of procedure:	03 May 2021
CHMP Rapporteur Assessment Report	20 May 2021
PRAC Rapporteur Assessment Report	17 May 2021
PRAC members comments	18 May 2021
Updated PRAC Rapporteur Assessment Report	19 May 2021
CHMP members comments	26 May 2021
PRAC Outcome	20 May 2021
ETF meeting	27 May 2021 AM
Updated CHMP Rapporteur Assessment Report	27 May 2021
Opinion/RSI	28 May 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

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. In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public, and the virus was categorized in the Betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 infections and the resulting disease COVID-19 have since then spread globally. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic.

State the claimed the therapeutic indication

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 (extension including 12-15 year olds)
- **Dosing administration:** single 0.3-mL intramuscular (IM) dose followed by a second 0.3-mL dose 3 weeks later

Epidemiology and risk factors, screening tools/prevention

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

There are currently several vaccines approved for prevention of Covid-19 in adults and elderly, but none for the use in adolescents 12-15 years old. Covid-19 in adolescents is mostly a mild disease although severe cases also occur rarely.

Aetiology and pathogenesis

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development. It has been shown that antibodies against the Spike protein neutralise the virus and prevent infection.

Clinical presentation, diagnosis

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

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

The US Centers for Disease Control and Prevention (CDC) defined COVID 19 symptoms as including 1 or more 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
- Fatigue
- Headache

- Nasal congestion or runny nose
- Nausea

In most situations, a molecular test is used to detect SARS-CoV-2 and confirm infection. The reverse transcription polymerase chain reaction (RT-PCR) test methods targeting SARS-CoV-2 viral RNA are the gold standard in vitro methods for diagnosing suspected cases of COVID-19. Samples to be tested are collected from the nose and/or throat with a swab. Molecular methods used to confirm an active infection are usually performed within a few days of exposure and around the time that symptoms may begin.

2.1.2. About the product

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.

The vaccine is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH has not applied for CHMP scientific advice on the paediatric development of Comirnaty. A PIP has been agreed (PIP P/0179/2021) and the current study is part of the PIP.

2.1.4. General comments on compliance with GCP

The MAH states that all clinical studies were performed in accordance with GCP. The current application is based on study C4591001, which was also the pivotal phase 3 study included in the application for initial approval. The study was extended to include subjects 12-15 years of age.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group)	Phase 1: Adults (18-55 years of age, 65-85 years of age)
			Phase 2: BNT162b2 (30 µg) Placebo	Phase 2: 360 randomized 1:1	Phase 2: Adults (18-55 years of age, 65-85 years of age)
			Phase 3: BNT162b2 (30 µg) Placebo	Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

Note: study information relevant to the scope of data presented in this application are summarized in this table.

2.3.2. Pharmacodynamics

Immunogenicity results are presented together with the efficacy analysis.

2.4. Clinical efficacy

2.4.1. Main study

Phase 2/3 of Study C4591001

Methods

Study participants

Initially, participants enrolled in Phase 2/3 of Study C4591001 were to be 18 to 85 years of age, in 2 age strata: 18 to 55 years ("younger participants") and 56 to 85 years ("older participants"). It was intended that a minimum of 40% of participants would be in the >55-years stratum. The protocol was later amended to lower the minimum age of participants to 16 years and to remove the upper age limit (Protocol Amendment 6, 08 September 2020).

Protocol Amendment 7 (06 October 2020) allowed for enrollment of adolescents 12 to 15 years of age as an additional age stratum. The 12- to 15-year stratum was expected to comprise up to approximately 2000 participants enrolled at selected investigational sites.

Treatments

Participants were randomized in a 1:1 ratio to receive either BNT162b2 (30 µg) or placebo (normal saline). Participants received a 2-dose regimen, administered approximately 21 days apart, at Visit 1 and at Visit 2, with Visit 2 intended to take place 19 to 23 days after Visit 1.

Objectives

Only objectives relevant to the current application are listed below:

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed Covid-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination (subgroup 12-15 years)
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination (Subgroup 12-15 years)
- To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3
- To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age (Secondary immunogenicity objective)

Outcomes/endpoints

Immunogenicity Endpoints

Due to a testing laboratory supply limitation of the qualified viral lot used during the validation of the assay and clinical testing of samples, immunogenicity analyses were performed only on samples from participants who had the required tests completed using the same available viral reagent lot. A blinded review of the samples tested at that time suggested a sufficient sample size properly balanced across age groups to perform the planned NI analysis. It was estimated that if the true geometric mean ratio (GMR) is ≥0.88, there is approximately 90% power to demonstrate NI using the number of samples currently tested, and >99% power if the true GMR is 1. This approach was mutually agreed with the US FDA.

Immunogenicity endpoints analysed for SARS-CoV-2 serum neutralizing titres included:

- geometric mean titers (GMTs) at 1 month after Dose 2
- geometric mean-fold rise (GMFR) from before vaccination to 1 month after Dose 2
- percentage of participants with a ≥4-fold rise in neutralizing titers from before vaccination to 1 month after Dose 2 (seroresponse rate)

Immunogenicity Analysis Methods

NI was assessed in participants who had no serological or virological evidence of SARS-CoV-2 infection up to 1 month after Dose 2; assessment was based on the geometric mean ratio of SARS-CoV-2

neutralizing titers (GMT in adolescents/GMT in young adults) 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.

A supportive analysis was conducted to assess the seroresponse rate, based on the proportions of participants in each age group with a ≥4-fold rise in neutralizing titers from before vaccination to 1 month after Dose 2. The difference in percentages (% adolescents minus % young adults) and the associated 2-sided 95% CI calculated using the Miettinen and Nurminen method were provided. GMTs and GMFRs of the neutralizing titers were provided with the associated 2-sided 95% CIs calculated with reference to Student's t-distribution.

Immunogenicity results were summarized for all participants with or without serological or virological evidence of SARS-CoV-2 infection before vaccination, and results were also summarized by baseline SARS-CoV-2 status. Positive baseline SARS-CoV-2 status was defined as positive N-binding antibody or positive NAAT at Visit 1, or a medical history of COVID-19; negative baseline SARS-CoV-2 status was defined as negative N-binding antibody and negative NAAT at Visit 1 and no medical history of COVID-19.

Efficacy Endpoints

The efficacy endpoints analysed and reported for adolescents 12 to 15 years of age in this Type II variation include the following endpoints:

- COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during the vaccination regimen – cases confirmed ≥7 days after Dose 2
- Severe COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during the vaccination regimen – cases confirmed ≥7 days after Dose 2.

Surveillance/Definitions /Case Determination for Confirmed COVID-19

Participants who developed any of the 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.

Confirmation of Infection with SARS-CoV-2: Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription– polymerase chain reaction 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.

Confirmed COVID-19 was defined (per FDA guidance)[1] as having a positive SARS-CoV-2 test result per central laboratory or local testing facility (using an acceptable test per protocol only if no central laboratory result was available) and the 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.

Confirmed severe COVID-19 was defined (per FDA guidance)[1] as confirmed COVID-19 and the 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, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation);
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure
- <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an intensive care unit;
- Death

In addition to the above protocol-specified definition of severe COVID-19, an efficacy analysis was conducted for ***confirmed severe COVID-19 according to the CDC-defined severe symptoms***, ie, COVID-19 illness events that resulted in hospitalization, admission to an intensive care unit, intubation or mechanical ventilation, or death.

Sample size

Approximately 2000 participants were anticipated to be 12 to 15 years of age. A random sample of 280 participants was planned to be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment using a 1.5-fold margin. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 225 evaluable participants (or 280 vaccine recipients) per age group was chosen to provide a power of 90.4% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose.

Table Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value)[a]	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power[b]
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.65	-0.2	225	90.4%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer.

a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 2).

b. At 0.05 alpha level (2-sided).

Randomisation

Allocation (randomization) of participants to vaccine groups proceeded through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) was required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel was then be provided with a vaccine assignment and randomization number. The IRT system provided a confirmation report containing the participant number, randomization number, and study intervention allocationas signed. The confirmation report was to be stored in the site's files. The study-specific IRT reference manual and IP manual provided the contact information and further details on the use of the IRT system.

Blinding (masking)

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments.

When a participant who originally received placebo received BNT162b2 per Appendix 16.1.1 of the study protocol the study team was unblinded to the participant's original study intervention allocation.

The study was unblinded in stages once all ongoing participants either had been individually unblinded or had concluded their 6-month post–Dose 2 study visit, as follows:

- Phase 1 (after Visit 8).
- Phase 2/3, ≥16 years (after Visit 4).
- Phase 3, 12 through 15 years (after Visit 4).

Participants ≥16 years of age who originally received placebo and became eligible for receipt of BNT162b2 according to recommendations detailed separately, and available in the electronic study reference portal, had the opportunity to receive BNT162b2 in a phased manner as part of the study. The investigator ensured the participant met at least 1 of the recommendation criteria.

Adolescents 12 through 15 years of age remain blinded in this study, as BNT162b2 vaccination eligibility in all markets/regions is currently for 16 years of age and older. Note that a few participants in the 12 through 15 years of age group turned 16 years of age after study enrollment and thus became eligible for unblinding to treatment assignment and vaccination under the emergency use or conditional authorization in their country/region.

Timing of the analysis

The updated efficacy analyses in the MAA Type II Variation for individuals 12-15 years of age were not event driven. The cut-off date of 13 March 2021 was used for immunogenicity, safety, and efficacy data for this age group in the pivotal study (C4591001) based on:

• timing of available immunobridging data (noninferiority analysis of SARS-CoV-2 50% neutralizing antibody titers as compared between 12-15 and 16-25 years of age groups)

• timing of safety follow-up for median of at least 2 months after Dose 2 in the 12-15 years of age group, which meets requirements for emergency use authorization and aligns to the duration of safety follow-up for individuals age 16 and older filed in the initial MAA (07 December 2020).

• timing of safety follow-up to 6 months after Dose 2 for individuals age 16 and older as required for US licensure and as planned to be submitted as an additional MAA Type II Variation in the near future.

In this regard, the number of cases of COVID-19 included in the updated efficacy analysis was not prespecified and included all confirmed cases as of the selected cut-off date. The particular cut-off date (13 March 2021) was used for multiple analyses pragmatically.

Statistical methods

Analysis methods

Updated efficacy analyses during blinded placebo-controlled follow-up were conducted for participants 12 through 15 years of age based on the data cut-off date of 13 March 2021. The point estimate of VE in the blinded follow-up period and associated 2-sided 95% CI was derived using the Clopper Pearson method adjusted for surveillance time. In addition to the protocol definition of severe COVID-19, supportive analyses using the CDC definition of severe COVID-19 was also performed. VE was estimated by 100% × (1 – IRR), where IRR was the ratio of COVID-19 illness rate in the BNT162b2 group to the corresponding illness rate in the placebo group.

Hypothesis for Immunogenicity Bridging of 12 to 15 Years to 16 to 25 Years

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:H0: $\ln(\mu 2) - \ln(\mu 1) \leq \ln(0.67)$where ln (0.67) corresponds to a 1.5-fold margin for noninferiority, $\ln(\mu 2)$ and $\ln(\mu 1)$ are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2. If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is >0.67, the noninferiority objective is met.

For participants randomized to the BNT162b2 groups with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 50% neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and 2-sided 95% CIs were provided at 1 month after Dose 2 for noninferiority assessment. The GMR and its 2-sided 95% CI were derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale were 12 to 15 years minus 16 to 25 years. Noninferiority was declared if the lower bound of the 2-sided 95% CI for the GMR was greater than 0.67, using 1.5-fold noninferiority margin. In addition, the difference in percentages of participants (12 to 15 years - 16 to 25 years) achieving a ≥4-fold rise in SARS-CoV-2 neutralizing titers from before vaccination to 1 month after Dose 2 were provided. The associated 2-sided 95% CI for the difference in percentage was calculated using the Miettinen and Nurminen method.

For immunogenicity results of SARS-CoV-2 neutralizing titers concentrations, the GMT was computed along with associated 95% CIs. The GMT was calculated as the means of assay results after making the logarithm transformation and then exponentiating the means to express results on the original scale. Two-sided 95% CIs were obtained by taking log transforms of assay results, calculating the 95% CIs with reference to Student's t-distribution, and then exponentiating the confidence limits.

The GMFR was calculated by exponentiating the mean of the difference of logarithmically transformed assay results (later time point – earlier time point). Two-sided CIs were obtained by calculating CIs

using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. The exact 95% CIs for binary endpoints were computed using the F distribution (Clopper-Pearson method). Titers below the LLOQ or denoted as BLQ were set to 0.5 × LLOQ for analysis.

Analysis sets

Population	Description
Enrolled	All participants who had a signed ICD.
Randomized	All participants who were assigned a randomization number in the IWR system.
Dose 2 evaluable immunogenicity	All eligible randomized participants who received 2 doses of the vaccine to which they were randomly assigned, with Dose 2 received within the predefined window (19-42 days after Dose 1), had at least 1 valid and determinate immunogenicity result from the blood collection within an appropriate window after Dose 2 (28-42 days after Dose 2 for Phase 2/3), and had no other important protocol deviations as determined by the clinician.
Dose 2 all-available immunogenicity	All randomized participants who received at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy (7 days)	All eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (19-42 days after Dose 1) and had no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
Dose 1 all-available efficacy	All randomized participants who received at least 1 vaccination.
Dose 2 all-available efficacy	All randomized participants who completed 2 vaccination doses.
Safety	All randomized participants who received at least 1 dose of the study intervention.

Missing data

All analyses were based on observed data.

Subgroup analyses

The adolecent population 12-15 years was defined as a subgroup in original protocol, but few subjects were enrolled. In the part of the study performed for the current application only subjects 12-15 years were enrolled. Additionally, analyses were presented for different efficacy endpoint subgroups: First COVID-19 occurrence after Dose 1, After Dose 1 to before Dose 2, ≥11 Days after Dose 1 to before Dose 2 , Dose 2 to 7 days after Dose 2, ≥7 Days after Dose 2, ≥7 days after Dose 2 to <2 Months after Dose 2 and ≥2 Months after Dose 2 to <4 Months after Dose 2.

The statistical methods are considered acceptable to the CHMP in the context of demonstrating consistency with adult vaccine efficacy.

The analyses provided in this submission are based on an amended version of the SAP, dated 17 March 2021. Endpoints for the adolescent population in this SAP are consistent with the SAP used for the previous submission, where the adolescent population 12-15 years old were defined as a subgroup rather than a separate study population. As a result, the immunogenicity endpoint for adolescents was prespecified as a secondary immunogenicity endpoint, and vaccine efficacy for adolescents was not a prespecified endpoint. Hence, the VE efficacy results should be interpreted as descriptive and estimations rather than hypothesis testing.

Results

Disposition of Participants

Participants 12 Through 15 Years of Age

Immunogenicity population

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. Reasons for participant exclusion from the evaluable immunogenicity populations are shown in Table 1. The majority of exclusions 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.

Table 1 Immunogenicity Populations – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset)

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years n[a] (%)	16-25 Years n[a] (%)	12-15 Years n[a] (%)	16-25 Years n[a] (%)
Randomized[b]	280 (100.0)	280 (100.0)	50 (100.0)	50 (100.0)
Dose 2 all-available immunogenicity population	210 (75.0)	191 (68.2)	36 (72.0)	34 (68.0)
Subjects excluded from Dose 2 all-available immunogenicity population	70 (25.0)	89 (31.8)	14 (28.0)	16 (32.0)
Reason for exclusion	BLD			
Did not receive Dose 2				
Did not have at least 1 valid and determinate immunogenicity result after Dose 2				
Dose 2 evaluable immunogenicity population	209 (74.6)	186 (66.4)	36 (72.0)	32 (64.0)
Subjects excluded from Dose 2 evaluable immunogenicity population	71 (25.4)	94 (33.6)	14 (28.0)	18 (36.0)
Reason for exclusion[c]	BLD			
Did not receive 2 doses of the vaccine to which they were randomly assigned				
Did not receive Dose 2 within 19-42 days after Dose 1				
Did not have at least 1 valid and determinate immunogenicity result after Dose 2				
Did not have blood collection within 28-42 days after Dose 2				
Had important protocol deviation(s) as determined by the clinician				

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.

The disposition of adolescents (12-15 years of age) and young adults (16-25 years of age) was similar in BNT162b2 and placebo groups through 1 month after Dose 2 (Table 4). Most participants randomized in both age groups (≥97.4%) received Dose 1 and Dose 2. Among adolescents, 7 participants (0.6%) in the BNT162b2 group and 17 participants (1.5%) in the placebo group

discontinued from the vaccination period and are continuing in the study for safety follow-up. Most participants across age groups completed the visit at 1 month after Dose 2 (≥94.5%).

Among adolescents who discontinued from vaccination period but continued in the study up to the 1 month post Dose 2 visit, 2 participants discontinued due to AEs, BLD (pyrexia considered by the investigator as related to study intervention, and unrelated anxiety/depression) BLD

BLD 2 participants BLD withdrew from the study before the 1 month post Dose 2 visit.

A total of 49 adolescent participants withdrew from the vaccination period when they turned 16 years of age after entering the study and became eligible to be unblinded to receive BNT162b2 vaccination; of these, 19/49 received Dose 3 and Dose 4 (BNT162b2). Participants originally randomized to placebo who received Dose 3 of BNT162b2 (per protocol;) continued in open-label follow-up in the study, but their data were censored at the time of unblinding with regard to analyses in this report.

Information for these participants are provided for SAEs or other significant AEs.

Table 2. Disposition of All Randomized Subjects Through 1 Month After Dose 2 – Subjects 12 Through 15 and 16 Through 25 Years of Age

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N^a=1134) n^b (%)	16-25 Years (N^a=1875) n^b (%)	12-15 Years (N^a=1130) n^b (%)	16-25 Years (N^a=1913) n^b (%)
Randomized	1134 (100.0)	1875 (100.0)	1130 (100.0)	1913 (100.0)
Not vaccinated	3 (0.3)	6 (0.3)	1 (0.1)	7 (0.4)
Vaccinated				
Dose 1	1131 (99.7)	1869 (99.7)	1129 (99.9)	1906 (99.6)
Dose 2	1124 (99.1)	1826 (97.4)	1117 (98.8)	1836 (96.0)
Completed 1-month post–Dose 2 visit (vaccination period)	1118 (98.6)	1803 (96.2)	1102 (97.5)	1807 (94.5)
Discontinued from vaccination period but continue in the study up to 1-month post–Dose 2 visit	7 (0.6)	13 (0.7)	17 (1.5)	42 (2.2)
Discontinued after Dose 1 and before Dose 2	BLD			
Discontinued after Dose 2 and before 1-month post–Dose 2 visit				
Reason for discontinuation from vaccination period				
No longer meets eligibility criteria	3 (0.3)	4 (0.2)	10 (0.9)	26 (1.4)
Withdrawal by subject	BLD			
Pregnancy				
Adverse event				
Physician decision				
Protocol deviation				
Lost to follow-up				
Other	1 (0.1)	1 (0.1)	5 (0.4)	7 (0.4)

Withdrawn from the study before 1-month post–Dose 2 visit	BLD
Withdrawn after Dose 1 and before Dose 2	
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	
Reason for withdrawal from the study	
Lost to follow-up	
Withdrawal by subject	
Protocol deviation	
Withdrawal by parent/guardian	
Adverse event	
Physician decision	
Other	

Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: Subjects randomized but did not sign informed consent or had a significant quality event due to lack of PI oversight are not included in any analysis population.
a. N = number of randomized subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.

Recruitment

Participants 12-15 years of age were enrolled at 28 sites in the USA. The randomization dates for this age group were between 15OCT2020 and 12JAN2021. The sites are described in Table X.

Study Site Nr.	PI Organization Name	PI Address City/Town/Village	PI Address State/Province/ County	PI Address Postal Code
1005	Rochester Clinical Research	Rochester	NEW YORK	14609
1006	J. Lewis Research, Inc. / Foothill Family Clinic	Salt Lake City	UT	84109
1007	Cincinnati Children's Hospital Medical Center	Cincinnati	OH	45229-3039
1008	Clinical Research Professionals	Chesterfield	MO	63005
1009	J. Lewis Research, Inc. / Foothill Family Clinic South	Salt Lake CIty	UT	84121
1013	Clinical Neuroscience Solutions, Inc. dba CNS Healthcare	Orlando	FLORIDA	32801
1016	Kentucky Pediatric/ Adult Research	Bardstown	KENTUCKY	40004
1039	ARC Clinical Research at Wilson Parke	Austin	TX	78726
1044	Virginia Research Center LLC	Midlothian	VIRGINIA	23114
1057	Clinical Neuroscience Solutions, Inc.	Jacksonville	FL	32256
1066	Solaris Clinical Research	Meridian	ID	83646
1077	Meridian Clinical Research LLC	Endwell	NEW YORK	13760
1084	Clinical Trials of Texas, Inc.	San Antonio	TEXAS	78229
1091	Aventiv Research Inc	Columbus	OHIO	43213
1123	Meridian Clinical Research, LLC	Omaha	NEBRASKA	68134
1124	Omega Medical Research	Warwick	RI	02886
1125	Meridian Clinical Research LLC	Norfolk	NEBRASKA	68701
1126	Kaiser Permanente Sacramento	Oakland	CALIFORNIA	94612

1131	PriMED Clinical Research	Dayton	OHIO	45419
1139	Duke Vaccine and Trials Unit	Durham	NC	27705
1140	SUNY Upstate Medical University	Syracuse	NY	13215
1142	University of Texas Medical Branch	Galveston	TEXAS	77555-1115
1147	Ochsner Clinic Foundation	New Orleans	LA	70121
1150	Senders Pediatrics	South Euclid	OH	44121
1152	California Research Foundation	San Diego	CALIFORNIA	92123-1881
1156	Acevedo Clinical Research Associates	Miami	FL	33142
1223	Yale University	New Haven	CT	06510
1235	Louisiana State University Health Sciences Center - Shreveport	Shreveport	LOUISIANA	71130

Conduct of the study

Protocol amendment nr. 7 dated 6.10.2021 reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives.

Also, statistical hypothesis and power analysis for evaluation of noninferiority of the immune response to BNT162b2 in participants 12 to 15 years of age to the response in participants 16 to 25 years of age were added.

Protocol amendment nr 10 dated 1.12.2020 states that in light of additional information to better estimate the standard deviation of SARS-CoV- 2 neutralizing titers, the sample size for the noninferiority immunogenicity analysis in adolescents 12 to 15 years of age was increased.

Baseline data

Participants 12 Through 15 Years of Age

In the Dose 2 evaluable immunogenicity population adolescent (12-15 years of age) BNT162b2 group, 50.7% of participants were male; 88.0% were White, 7.7% were Black or African American, and 2.4% were Asian; 10.5% were Hispanic/Latino; and the median age was 14 years. Baseline SARS-CoV-2 status was positive for 4.8% of adolescent participants in the BNT162b2 group. Obese adolescents (based on age- and sex-specific body mass index) made up 8.3% (placebo group) to 11.5% (BNT162b2 group) of this age group in the evaluable immunogenicity population.

Demographics were generally similar for BNT162b2 and placebo, and in 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. Likewise, the immunogenicity population demographics were generally similar to those in the safety population.

Demographic characteristics for adolescents (12-15 years of age) and young adults (16-25 years of age) were similar in the corresponding BNT162b2 and placebo groups in the safety population (Table 3).

Table 3. Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N^a=1131) n^b (%)	16-25 Years (N^a=1867) n^b (%)	12-15 Years (N^a=1129) n^b (%)	16-25 Years (N^a=1903) n^b (%)
Sex				
Male	567 (50.1)	921 (49.3)	585 (51.8)	882 (46.3)
Female	564 (49.9)	946 (50.7)	544 (48.2)	1021 (53.7)
Race				
White	971 (85.9)	1443 (77.3)	962 (85.2)	1510 (79.3)
Black or African American	52 (4.6)	189 (10.1)	57 (5.0)	179 (9.4)
American Indian or Alaska Native	4 (0.4)	32 (1.7)	3 (0.3)	18 (0.9)
Asian	72 (6.4)	108 (5.8)	71 (6.3)	108 (5.7)
Native Hawaiian or other Pacific Islander	[redacted]			
Multiracial				
Not reported	6 (0.5)	9 (0.5)	7 (0.6)	11 (0.6)
Racial designation				
Japanese	5 (0.4)	3 (0.2)	2 (0.2)	6 (0.3)
Ethnicity				
Hispanic/Latino	132 (11.7)	604 (32.4)	130 (11.5)	575 (30.2)
Non-Hispanic/non-Latino	997 (88.2)	1259 (67.4)	996 (88.2)	1322 (69.5)
Not reported	2 (0.2)	4 (0.2)	3 (0.3)	6 (0.3)
Country				
Argentina	0	282 (15.1)	0	287 (15.1)
Brazil	0	160 (8.6)	0	142 (7.5)
Germany	0	11 (0.6)	0	20 (1.1)
South Africa	0	69 (3.7)	0	75 (3.9)
Turkey	0	12 (0.6)	0	15 (0.8)
USA	1131 (100.0)	1333 (71.4)	1129 (100.0)	1364 (71.7)
Age at vaccination (years)				
Mean (SD)	13.6 (1.11)	21.0 (2.99)	13.6 (1.11)	21.0 (2.98)
Median	14.0	22.0	14.0	21.0
Min, max	(12, 15)	(16, 25)	(12, 15)	(16, 25)
Baseline SARS-CoV-2 status				
Positive[c]	46 (4.1)	100 (5.4)	47 (4.2)	104 (5.5)
Negative[d]	1028 (90.9)	1754 (93.9)	1023 (90.6)	1789 (94.0)
Missing	57 (5.0)	13 (0.7)	59 (5.2)	10 (0.5)
Body mass index (BMI) Obese[e]				
Yes	143 (12.6)	353 (18.9)	128 (11.3)	385 (20.2)
No	988 (87.4)	1514 (81.1)	1001 (88.7)	1518 (79.8)

Numbers analysed

The protocol prespecified final analysis of efficacy was completed with a data cut-off date of 14 November 2020. At that time, few adolescents (12-15 years of age) had enrolled in the study, precluding a meaningful efficacy evaluation. An analysis was performed with all accrued cases during blinded follow-up to a data cut-off date of 13 March 2021, for efficacy in adolescents.

Since the efficacy populations include nearly the same number of participants in each group as in the safety population, the demographics of the efficacy populations are essentially the same as the safety population.

Outcomes and estimation

Immunogenicity Results – Participants 12 Through 15 Years of Age

Noninferiority of Immune Response to Prophylactic BNT162b2 in Participants 12 Through 15 Years Compared with Participants 16 Through 25 Years of Age

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) (Table 20). 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.

Table 20. Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		BNT162b2 (30 µg)					
		12-15 Years		16-25 Years		12-15 Years/16-25 Years	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Noninferiority Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	190	1239.5 (1095.5, 1402.5)	170	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month 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 up to 1 month after Dose 2 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12-15 years] – Group 2 [16-25 years]) and the corresponding CI (based on the Student t distribution).
e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adva_s001_gmr_ped_ev_eval

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%) (Table 21).

Table 21. Number (%) of Subjects Achieving a ≥4-Fold Rise From Before Vaccination to Each Subsequent Time Point 1 Month After Dose 2 – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		BNT162b2 (30 µg)					
		12-15 Years		16-25 Years		Difference	
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	%[e]	(95% CI[f])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	143	140 (97.9) (94.0, 99.6)	124	124 (100.0) (97.1, 100.0)	-2.1	(-6.0, 0.9)

Abbreviations: LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month 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 up to 1 month after Dose 2 were included in the analysis.
Note: Baseline assay results below the LLOQ were set to LLOQ in the analysis.
a. Protocol-specified timing for blood sample collection.
b. N = number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of subjects with ≥4-fold rise from before vaccination for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (12-15 years – 16-25 years).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adva_s003_4fold_ped_eval

GMTs – Participants 12 Through 15 Years of Age

At 1 month after Dose 2 (Day 52) of BNT162b2, substantial increases above baseline in SARS-CoV-2 50% neutralizing GMTs were observed in both age groups, with a greater magnitude of increase in the adolescent group compared with the young adult group

(Figure 2, Figure 3). The neutralizing GMT in adolescents at 1 month after Dose 2 was approximately 1.76-fold that of the young adult group. As expected, the neutralizing GMTs were low in both placebo groups.

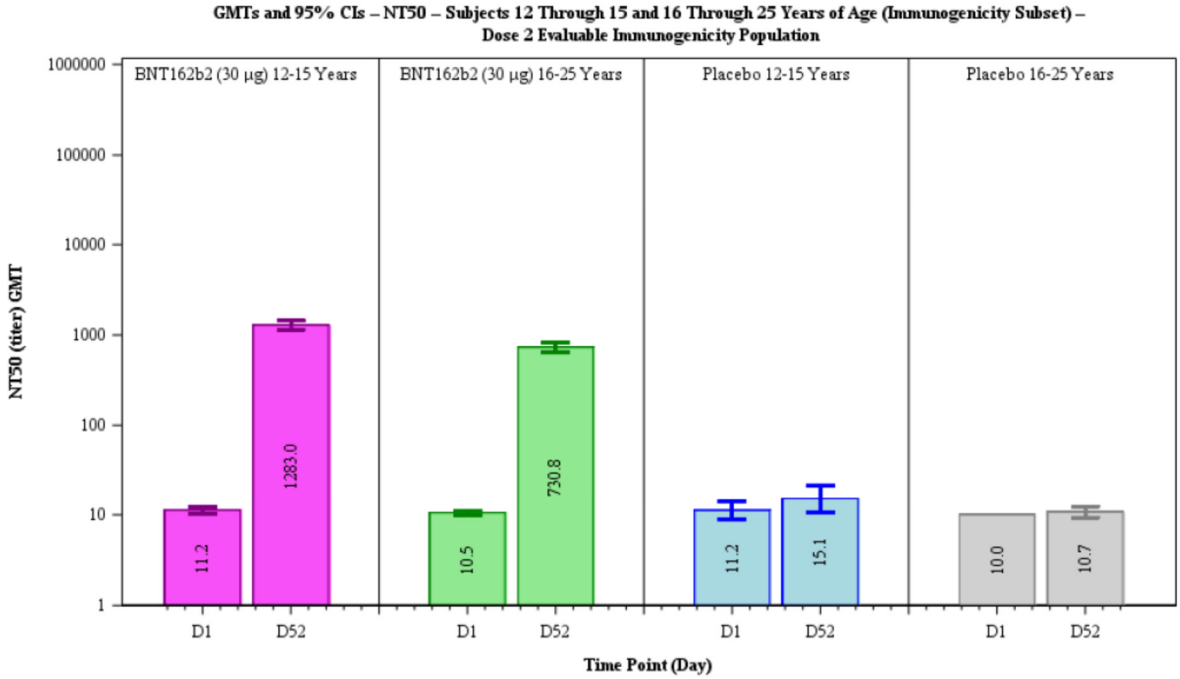
Geometric Mean Titers (GMTs) by Baseline SARS-CoV-2 Status

Vaccination with BNT162b2 induced an increased immune response (GMTs) at 1 month after Dose 2 for all participants, regardless of baseline SARS-CoV-2 positive or negative status.

Adolescents who were baseline SARS-CoV-2 positive had SARS-CoV-2 50% neutralizing GMTs approximately 1.89-fold that of adolescents who were baseline negative (Supplemental Table 14.10). A similar pattern was observed for baseline SARS-CoV-2 positive versus negative young adults.

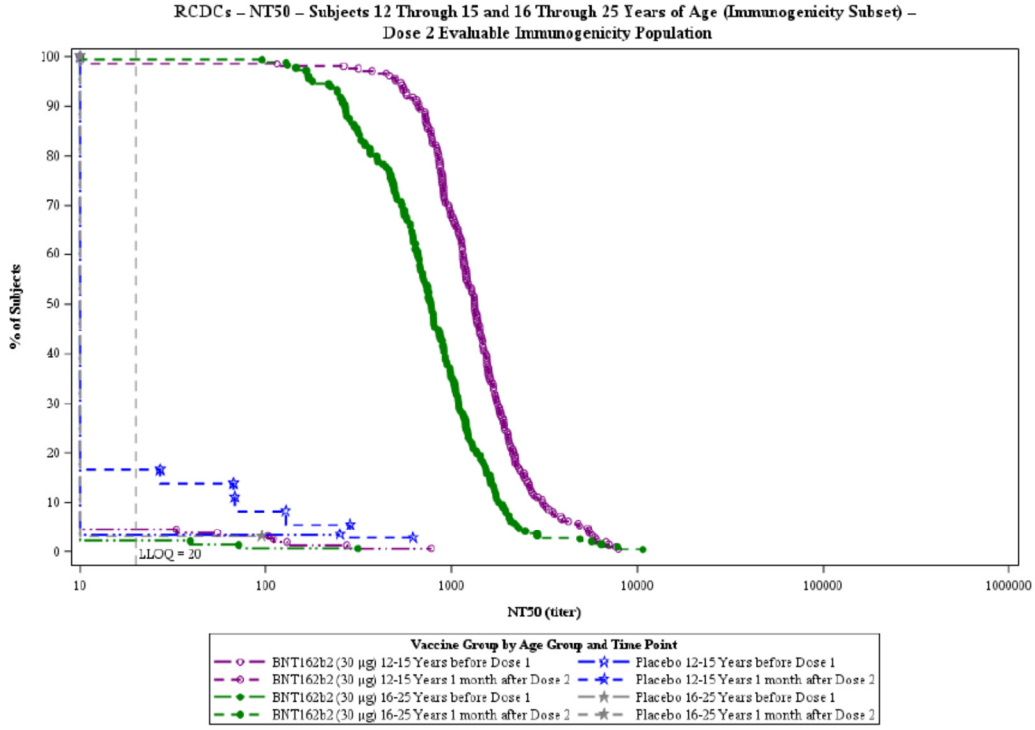
SARS-CoV-2 50% neutralizing titers for the Dose 2 all-available immunogenicity population were similar to those observed for the evaluable immunogenicity population.

Figure 2. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Subjects 12-15 and 16-25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population



Abbreviations: D = day; GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:25) Source Data: adva Table Generation: 27MAR2021 (04:54)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: /nda2_unblinded/C4591001_BLA/adva_f002_sars_50_ped

Figure 3. Reverse Cumulative Distribution Curves, SARS-CoV-2 Neutralization Assay – NT50 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population



Abbreviations: LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; RCDC = reverse cumulative distribution curve; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: LLOQ value is represented using a vertical line. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: /nda2_unblinded/C4591001_BLA/adva_f003_sars_50_ped

GMFRs – Participants 12 Through 15 Years of Age

The GMFRs of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1 month after Dose 2 of BNT162b2 were robust, with a greater magnitude of rise in the adolescent group (118.3) compared with the young adult group (71.2) (Table 22).

GMFR in Titers by Baseline SARS-CoV-2 Status

The GMFRs were higher in the adolescent compared to young adult group 1 month after the second dose. Given the limited sample size for those positive at baseline, the GMFRs were numerically higher in those who were negative at baseline (Table 22).

GMFRs of SARS-CoV-2 50% neutralizing titers for the Dose 2 all-available immunogenicity population were similar to those observed for the evaluable immunogenicity population.

Table 22. Summary of Geometric Mean Fold Rise From Before Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – NT50 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	ALL	154	118.3 (101.4, 137.9)	135	71.2 (61.3, 82.7)	29	1.4 (1.0, 1.9)	24	1.1 (0.9, 1.3)
		POS	8	47.6 (26.4, 86.0)	5	47.1 (3.1, 721.4)	1	1.1 (NE, NE)	0	NE (NE, NE)
		NEG	145	125.0 (106.9, 146.2)	130	72.3 (62.9, 83.2)	27	1.4 (1.0, 2.0)	24	1.1 (0.9, 1.3)

Abbreviations: COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NE = not estimable; NEG = negative; NT50 = 50% neutralizing titer; POS = positive; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. Protocol-specified timing for blood sample collection.
b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status.
c. n = Number of subjects with valid and determinate assay results for the specified assay both prevaccination time points and at the given dose/sampling time point.
d. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adva_s002_gmfr_ped_eval

Seroresponse Rate – Participants 12 Through 15 Years of Age

Proportions of participants with a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2 of BNT162b2 (seroresponse rate) were 98.1% in adolescents and 99.3% in young adults (Table 23). As expected, very few placebo participants reached a ≥4-fold rise in SARS-CoV-2 neutralizing titers from before to 1 month after Dose 2.

Adolescents who were baseline SARS-CoV-2 positive or negative had similar seroresponse rates (100.0% vs 97.9%) (Table 23).

Table 23. Number (%) of Subjects Achieving a ≥4-Fold Rise From Before Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – NT50 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Immunogenicity Subset) – Dose 2 Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	ALL	154	151 (98.1) (94.4, 99.6)	135	134 (99.3) (95.9, 100.0)	29	1 (3.4) (0.1, 17.8)	24	1 (4.2) (0.1, 21.1)
		POS	8	8 (100.0) (63.1, 100.0)	5	4 (80.0) (28.4, 99.5)	1	0 (0.0) (0.0, 97.5)	0	0 (NE) (NE, NE)
		NEG	145	142 (97.9) (94.1, 99.6)	130	130 (100.0) (97.2, 100.0)	27	1 (3.7) (0.1, 19.0)	24	1 (4.2) (0.1, 21.1)

Abbreviations: LLOQ = lower limit of quantitation; NE = not estimable; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Baseline assay results below the LLOQ were set to LLOQ in the analysis.
a. Protocol-specified timing for blood sample collection.
b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status
c. N = number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
d. n = Number of subjects with ≥4-fold rise from before vaccination for the given assay at the given dose/sampling time point.
e. Exact 2-sided CI based on the Clopper and Pearson method.
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(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adva_s001_4fold_ped_eval

Phase 3 Immunogenicity Conclusions – Participants 12 Through 15 Years of Age

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.

Vaccine Efficacy Against COVID-19 – Participants 12 Through 15 Years of Age

Participants Without Evidence of Infection Before and During Vaccination Regimen – Participants 12 Through 15 Years of Age

As of the data cut-off date (13 March 2021), confirmed COVID-19 cases in the evaluable efficacy population adolescent group (12-15 years of age) without evidence of prior SARS-CoV-2 infection at least 7 days after Dose 2 included 0 cases in the BNT162b2 group and 16 cases in the placebo group. The observed VE was 100% (2-sided 95% CI: 75.3%, 100.0%) (Table 17).

Table 17. 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]=1005)		Placebo (N[a]=978)			
Efficacy Endpoint	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	0.154 (1001)	16	0.147 (972)	100.0	(75.3, 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.
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.

Participants With or Without Evidence of Infection Before and During Vaccination Regimen – Participants 12 Through 15 Years of Age

Confirmed COVID-19 cases in the evaluable efficacy population adolescent group (12-15 years of age) with or without evidence of prior SARS-CoV-2 infection at least 7 days after Dose 2 included 0 cases in the BNT162b2 group and 18 cases in the placebo group. The observed VE was 100.0% (2-sided 95% CI: 78.1%, 100.0%) (Table 18).

Relative to the analysis of cases in participants without prior evidence of SARS-CoV-2 infection (Table 17), 2 additional cases reported in the placebo group of the evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection before and during vaccine regimen occurred in participants who were baseline negative serostatus for SARS-CoV-2, and had a negative NAAT at Visit 1 followed by a positive NAAT (confirmed by the central laboratory) at Visit 2.

Table 18. 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]=1110)			
Efficacy Endpoint	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	0.170 (1109)	18	0.163 (1094)	100.0	(78.1, 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.
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.

All Confirmed Cases of COVID-19 After Dose 1 – All-Available Efficacy Population – Participants 12 Through 15 Years of Age

As of the data cut-off date (13 March 2021), confirmed COVID-19 cases in the Dose 1 all- available efficacy (modified intention-to-treat) population adolescent group (12-15 years of age) included 3 cases in the BNT162b2 group and 35 cases in the placebo group, with an observed VE of 91.6% (2-sided 95% CI: 73.5%, 98.4%) (Table 19).

The time interval from after Dose 1 to prior to receiving Dose 2 included 3 cases in the BNT162b2 group and 12 cases in the placebo group; these 3 cases in the BNT162 group, which comprised all COVID-19 cases reported in the BNT162b2 group in this population at any time, all occurred within the period from after Dose 1 to <11 days after Dose 1. All 3 of these cases in the BNT162b2 group occurred in participants who had baseline SARS-CoV-2 negative status.

The observed VE for BNT162b2 in adolescents in the Dose 1 all-available 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 ≥2 months after Dose 2 and <4 months after Dose 2.

Table 19. 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	0.257 (1120)	35	0.250 (1119)	91.6	(73.5, 98.4)
After Dose 1 to before Dose 2	3		12		75.0	(7.4, 95.5)
After Dose 1 to <11 days after Dose 1	3		4		25.0	(-343.3, 89.0)
≥11 Days after Dose 1 to before Dose 2	0		8		100.0	(41.4, 100.0)
Dose 2 to 7 days after Dose 2	0		5		100.0	(-9.1, 100.0)
≥7 Days after Dose 2	0		18		100.0	(77.3, 100.0)
≥7 days after Dose 2 to <2 Months after Dose 2	0		16		100.0	(74.1, 100.0)
≥2 Months after Dose 2 to <4 Months after Dose 2	0		2		100.0	(-432.5, 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.
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 for overall row).

Vaccine Efficacy Against Severe COVID-19 – Participants 12 Through 15 Years of Age

No severe COVID-19 cases (per protocol definition or CDC criteria) were reported in adolescents (12-15 years of age) as of the data cut-off date (13 March 2021)

Summary of main study

Descriptive efficacy analyses were conducted for the adolescent group on cases accrued during blinded follow-up period through the data cut-off date of 13 March 2021.

In the adolescent group, in the efficacy analyses in the evaluable efficacy population based on cases reported from at least 7 days after Dose 2 through the data cut-off date, the observed VE was 100% (0 and 16 cases in the BNT162b2 and placebo group, respectively, with 2-sided 95% CI: 75.3%, 100%) for individuals without evidence of prior SARS-CoV-2 infection before and during vaccination regimen, and 100% (0 and 18 cases in the BNT162b2 and placebo group, respectively, with 2-sided 95% CI: 78.1%, 100%) for those with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen.

The efficacy analysis for the Dose 1 all-available (modified intention-to-treat) population included 3 cases in the BNT162b2 group and 35 cases in the placebo group, with an observed VE of 91.6% (2-sided 95% CI: 73.5%, 98.4%), with no cases reported in the BNT162b2 group starting from ≥11 days after Dose 1.

No severe cases were reported in the 12-15 years of age group as of the date cut-off date. Overall, these efficacy data strongly support BNT162b2 use in adolescents 12-15 years of age.

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial C4591001

Title: A Phase 2/3, Placebo-Controlled, Randomized, Observer- Blind Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals 12-15 yo.		
Study identifier	C4591001	
Design	Phase 2/3 randomized, observer-blind, placebo-controlled	
	Follow-up for efficacy	6.10. 2020 (protocol amendment)-13.03.2021 (data base lock for interim analysis)
Hypothesis	Non-inferiority of antibody response younger vs. older age group Efficacy was also measured and presented with 95% CI	

Treatments groups	Active arm		BNT162b2 (30 µg), 2 doses, 21 days apart, randomized	
	Control arm		Saline placebo, 2 doses, 21 days apart, randomized	
Endpoints and definitions	First Primary endpoint	VE-7d-no-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow- up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2	
	Co-Primary endpoint	VE-7d-no/yes-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow- up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.	
	Not pre described endpoint	VE dose 1 intend to treat	COVID-19 incidence per 1000 person-years of follow- up in participants receiving at least 1 dose	
	Immunogenicity endpoint	GMT	geometric mean titers (GMTs) at 1 month after Dose 2	
	Immunogenicity endpoint	GMFR	geometric mean-fold rise (GMFR) from before vaccination to 1 month after Dose 2	
	Immunogenicity endpoint	seroresponse rate	percentage of participants with a ≥4-fold rise in neutralizing titers from before vaccination to 1 month after Dose 2 (seroresponse rate)	
Database lock	13.03.2021			
Results and Analysis				
Analysis description	**Immunogenicity Analysis**			
Analysis population and time point description	1 month after dose 2 Evaluable Immunogenicity population			
Descriptive statistics and estimate variability	**Treatment group**	**12-15 yo**	**16-25 yo**	
	Number of subject	190	170	Ratio, non-inferiority (Y/N)
	GMT (95% CI)	**1239.5** (1095.5; 1402.5)	**705.1** (621.4; 800.2)	1.76 (1.47-2.10) Y
	Number of subject	154	135	
	GMFR (95% CI)	**118.3** (101.4; 137.9	**71.2** (61.3; 82.7)	
	Number of subject (%)	143	124	Difference % (95% CI)
	Seroresponse rate % (95% CI)	**140 (97.9 %)** (94.0;99.6%)	**124 (100%)** (97.1;100)	-2.1% (-6.0;0.9)
Analysis description	**Primary Efficacy Analysis**			

Effect estimate per comparison	Primary endpoint	VE-7d-no-SARS- CoV-2 Evaluable Efficacy population	Cases in Active arm N=**0/1005** Cases in Placebo arm N= **16/978**
		Vaccine Efficacy VE %	**100 %**
		95% CI	(75.3;100.0)
	Co-Primary	VE-7d-no/yes- SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=**0/1109** Cases in Placebo arm N= **18/1110**
		Vaccine Efficacy VE %	**100 %**
		95% CI	(78.1; 100.)
	Not pre-specified endpoint	VE dose 1 modified intend to treat population	Cases in Active arm N=**3/1120** Cases in Placebo arm N= **35/1129**
		Vaccine Efficacy VE %	**91.6 %**
		95% CI	(73.5;98.4)
Notes	No severe COVID-19 cases were reported in individuals in the 12-15 years of age group,		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on part of the ongoing phase 3 study C4591001. The initial approval of Comirnaty was based on the phase 3 part of this study in subjects 16 years and older. The current variation is based on the part of the same study including 12-15 year old adolescents. The study was amended in October 2020 to include participants 12 to 15 years of age.

A total of 2,260 adolescents were randomised equally to receive 2-dose of BNT162b2 vaccine (n=1131) and placebo (n=1129).The study was designed and powered for immunogenicity comparison (immunobridging) between adolescents and young adults (16-25 years) but an efficacy assessment was also included in the study; however this was not type 1 error controlled. Participants of the 2 age groups 12-15 years and 16-25 years were selected as test and reference for the non-inferiority assessment of immunogenicity.

The Dose 2 evaluable immunogenicity population in the vaccine group included 209 participants 12-15 years of age and 186 participants 16-25 years of age. The study is unblinded for older subjects, according to a protocol amendment and placebo recipients are offered vaccination. The study remains blinded for the 12-15 year olds, with the exception that when a subject turns 16, he or she becomes eligible for receipt of vaccination, and study blinding is therefore interrupted.

Efficacy data and additional analyses

There is currently no serological correlate of protection for Covid-19. However, the proposed mechanism of action for this vaccine, i.e. that neutralising antibodies are crucial for protection makes immunobridging to a population where efficacy has been demonstrated a reasonable strategy for ensuring efficacy in adolescents. Generally, adolescents have higher immune responses to vaccination compared to adults, which has been shown for e.g. HPV vaccines. This was shown to be the case also

for this Covid-19 vaccine. The seroresponse rate was non-inferior (97% vs 100%) and the GMTs were in fact superior, which was not unexpected.

Specifically, at 1 month after Dose 2 of BNT162b2 (cut-off date 13-Mar-2021), substantial increase in SARS-CoV-2 50% neutralizing GMT was observed in 12-15 years and 16-25 years age groups (regardless of baseline SARS-CoV-2 status), with a greater magnitude of increase (1.76-fold) in the adolescent group compared to the young adult group. This is to be expected as a better immune response has already been observed in adolescents with other vaccines. These results show that the immune response in SARS-CoV-2 50% neutralising titers in adolescents was non-inferior to the immune response in 16-25 years participants and is even greater (lower bound CI95% for GMR at 1.47 meeting the 1.5-fold NI criterion and >0.67), which provides the immunobridging between adolescents and young adults.

Also, GMFRs of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1 month post-dose 2 were greater in the adolescent group (GMFR 118.3 (CI95% 101.4, 137.9)) than in 16-25 age group (GMFR 71.2 (CI95% 61.3, 82.7)) and were higher in participants who were negative at baseline compared to those positive at baseline (regardless of group age).

A high proportion of participants (97.9% of adolescents and 100.0% of young adults) had a $\geqslant$4-fold rise in SARS-CoV-2 50% neutralizing titers (seroresponse) in both age groups from before vaccination to 1 month after Dose 2.

Efficacy data from 1,983 participants aged 12-15 years without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 showed an observed BNT162b2 efficacy of 100% (CI95% 75.3, 100%) in preventing COVID-19 occurring at least 7 days post-dose 2 (0 COVID-19 cases in the BNT0162b2 group versus 16 COVID-19 cases in the placebo group). The same VE (100% (CI95% 78.1, 100) was observed in adolescents with or without evidence of infection prior to 7 days post-dose 2.

Moreover, the observed VE in the Dose 1 all-available population was 100% (41.4, 100) in the interval starting from 11 days post-dose 1 to before dose 2 (0 cases in the BNT0162b2 group versus 8 COVID-19 cases in the placebo group).

Efficacy against symptomatic Covid-19 was convincingly demonstrated in the age group 12-15 years). The effect size was in agreement with that seen in adults overall, which was also anticipated based on immunogenicity data (described in the pharmacology section of this report). Although there were few cases in the study (16 in the primary analysis) all occurred in the placebo group. As can be expected, no severe cases occurred in the study. The risk of severe disease increases with increasing age.

The duration of protection is unknown in adolescents, as well as among adults. The efficacy for prevention of asymptomatic infection was not assessed. The efficacy against transmission would be of great interest to predict the impact of the vaccine against SARS-CoV-2 circulation, particularly among adolescents.

The CHMP noted that the available efficacy data are insufficient to make definite conclusion about the long-term efficacy/duration of protection conveyed by the vaccine and the efficacy against asymptomatic infection; these uncertainties are raised and are therefore recommended by the CHMP to be adequately addressed post-authorisation. (Interim) results should be submitted as soon as available (**REC**).

2.4.3. Conclusions on the clinical efficacy

It can be concluded that Comirnaty protects individuals 12-15 years of age against symptomatic covid-19 based on non-inferior immune responses, as well as a convincing exploratory analysis of efficacy.

2.5. Clinical safety

Introduction

On the 21st of December 2020, BNT162b was granted a conditional marketing authorization (CMA) for preventing covid-19 in people from 16 years of age and older. This AR presents a part of the ongoing phase 2/3 study C4591001, that includes adolescents aged 12-15 years. According to amendment 7 (6th of Oct 2021), adolescents from 12 years of age was allowed to be recruited. The cut-off date for blinded follow-up for the interim analysis that this AR was 13th of March 2021. Similar dose of BNT162b2 (30µg) as in adult subjects has been administered to the adolescent subjects, by using a 2-dose regimen administered about 3 weeks a part.

Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included. This allowed enrolment of a proportion of participants with common comorbidities such as cardiovascular diseases including hypertension, chronic pulmonary diseases, asthma, chronic liver disease, BMI > 30 kg/m2, participants with stage 3 or worse chronic kidney disease, and participants with varying disease severity. Among participants 12 to 15 years of age, 248 (21.9% ; 248/1131) of them with any baseline comorbidity were exposed to BNT162b2 (30µg): 118 subjects with chronic pulmonary disease, two with liver disease, two with diabetes with or without chronic complication and 143 obese.

The Applicant has provided data from young adults (aged 16-25 years) from study C4591001, this data is the same that was already included in the application for the CMA that was granted in December 2020. It shall be noted that this application concerns adolescents 12-15 years of age which have subsequently been recruited to the ongoing phase 3 study (C4591001) on which the initial CMA was based on (amendment in the study protocol in October 2020). The similar dose and dose regimen have been proposed as for adult subjects. As for comparison, the Applicant has provided data from young adult subjects, this population was already included in the data package that constituted the base for the granted CMA (December 2020). Since this data has already been assessed within the previous application, the focus in this report is on the new adolescent data.

Patient exposure

Demographics Demographic Characteristics –Subjects 12 through 15 and 16 Through 25 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	971 (85.9)	962 (85.2)	1933 (85.5)
Black or African American	52 (4.6)	57 (5.0)	109 (4.8)
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	BLD		
Multiracial			
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)
Age in years (at vaccination)			
12	251 (22.2)	234 (20.7)	485 (21.5)
13	288 (25.5)	288 (25.5)	576 (25.5)
14	289 (25.6)	282 (25.0)	571 (25.3)
15	303 (26.8)	325 (28.8)	628 (27.8)
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
Min, max	(12, 15)	(12, 15)	(12, 15)
Baseline SARS-CoV-2 status			
Positive[c]	46 (4.1)	47 (4.2)	93 (4.1)
Negative[d]	1028 (90.9)	1023 (90.6)	2051 (90.8)
Missing	57 (5.0)	59 (5.2)	116 (5.1)

Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but analyzed and reported separately.
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.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 10MAY2021 (09:24)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adsl_s005_demo_1215_saf_ema

Up to the cut-off date 13th of March 2021, a total of 2260 adolescents (BNT162b n=1131; placebo n=1129) aged 12-15 years have been recruited to the safety population. Within this age range the number of adolescents was similar for each age group. Gender was equally distributed. The adolescent subjects were recruited from the USA only. A majority was SARS-CoV-2 negative at baseline (>90%). Slightly more than 10% of the adolescent subjects had a BMI that suggested obesity. The safety data base for adolescent 12-15 years of age is considered acceptable.

Demographic information for the young adult population has also been provided.

The included numbers of subjects are considered sufficient to evaluate the reactogenicity profile in adolescents who received two doses of BNT162b (30µg). It will however not be possible within this study to detect rare adverse reactions if such would occur specifically in adolescents.

Exposure, disposition, and timing of administration

The table below illustrates the number of subjects that has been exposed to one and two doses of BNT162b.

Disposition of All Randomized Subjects Through 1 Month After Dose 2 –Subjects 12 through 15 and 16 Through 25 Years of Age

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N[a]=1134) n[b] (%)	16-25 Years (N[a]=1875) n[b] (%)	12-15 Years (N[a]=1130) n[b] (%)	16-25 Years (N[a]=1913) n[b] (%)
Randomized	1134 (100.0)	1875 (100.0)	1130 (100.0)	1913 (100.0)
Not vaccinated	3 (0.3)	6 (0.3)	1 (0.1)	7 (0.4)
Vaccinated				
Dose 1	1131 (99.7)	1869 (99.7)	1129 (99.9)	1906 (99.6)
Dose 2	1124 (99.1)	1826 (97.4)	1117 (98.8)	1836 (96.0)
Completed 1-month post–Dose 2 visit (vaccination period)	1118 (98.6)	1803 (96.2)	1102 (97.5)	1807 (94.5)
Discontinued from vaccination period but continue in the study up to 1-month post–Dose 2 visit	7 (0.6)	13 (0.7)	17 (1.5)	42 (2.2)
Discontinued after Dose 1 and before Dose 2	BLD			
Discontinued after Dose 2 and before 1-month post–Dose 2 visit				
Reason for discontinuation from vaccination period				
No longer meets eligibility criteria				
Withdrawal by subject				
Pregnancy				
Adverse event				
Physician decision				
Protocol deviation				
Lost to follow-up				
Other	1 (0.1)	1 (0.1)	5 (0.4)	7 (0.4)
Withdrawn from the study before 1-month post–Dose 2 visit	BLD			
Withdrawn after Dose 1 and before Dose 2				
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit				
Reason for withdrawal from the study				
Lost to follow-up				
Withdrawal by subject				
Protocol deviation				
Withdrawal by parent/guardian				
Adverse event				
Physician decision				
Other				

Timing of the administered 2nd dose is illustrated in the table below.

Vaccine Administration Timing – Subjects 12 through 15 and 16 Through 25 Years of Age (Reactogenicity Subset)

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N[a]=1131) n[b] (%)	16-25 Years (N[a]=539) n[b] (%)	12-15 Years (N[a]=1129) n[b] (%)	16-25 Years (N[a]=564) n[b] (%)
Randomized	1131 (100.0)	539 (100.0)	1129 (100.0)	564 (100.0)
Not vaccinated	0	0	0	0
Dose 1	1131 (100.0)	539 (100.0)	1129 (100.0)	564 (100.0)
Dose 2[c]	1124 (99.4)	526 (97.6)	1117 (98.9)	537 (95.2)
<14 Days	0	0	0	0
14 to 20 Days	358 (31.7)	184 (34.1)	364 (32.2)	192 (34.0)
21 to 27 Days	737 (65.2)	325 (60.3)	729 (64.6)	328 (58.2)
28 to 34 Days	23 (2.0)	7 (1.3)	15 (1.3)	6 (1.1)
35 to 41 Days	4 (0.4)	5 (0.9)	4 (0.4)	4 (0.7)
42 to 48 Days	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.2)
49 to 55 Days	[redacted]			
>55 Days				

Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
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.
c. Days calculated since Dose 1.

Follow-up Time After Dose 2 – 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] (%)
Subjects (%) with length of follow-up of:			
Total exposure from Dose 2 to cutoff date			
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Note: Follow-up time was calculated to the cutoff date or the date of unblinding, whichever date was earlier.
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.

Unblinding and vaccination of the placebo group

Subjects included in the young adult group that received placebo, has susequently after the unblinding 14th of December been been offered vaccination with BNT162b. Adolescents 12-15 years of age remain blinded in this study, as BNT162b2 vaccination eligibility in all markets/regions is currently for 16 years of age and older (note that a few participants in the 12-15 years of age group turned 16 years of age after study enrollment and thus became eligible for unblinding to treatment assignment and vaccination under emergency use or conditional marketing authorization). A total of 49 adolescent participants withdrew from the vaccination period when they turned 16 years of age after entering the study and became eligible to be unblinded to receive BNT162b2 vaccination; of these, 19/49 received Dose 3 and Dose 4 (BNT162b2). Participants originally randomized to placebo who received Dose 3 of

BNT162b2 continued in open-label follow-up in the study, but their data were censored at the time of unblinding with regard to analyses in this submission.

Sponsor and site personnel responsible for the ongoing conduct of the study remain blinded to individual adolescent (12-15 years of age) participants' randomization for any who have not been unblinded. Safety evaluation for such 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 including this submission.

Almost all adolescent subjects (99%) aged 12-15 years as well as the subjects in the young adolescent group received two doses of BNT162b2.

More than half of the adolescent safety population (BNT162b 58%; placebo 57%) had ≥2 months of follow-up after Dose 2. The median duration of follow-up was >2 months after Dose 2. Almost all (98.3%) adolescent participants had at least 1 month of follow-up after Dose 2.

The majority received their 2nd dose 14-27 days after Dose 1 (97%).

Seven adolescent subjects left the study; two subjects who received BNT162b2 discontinued due to adverse events, three did no longer meet the eligibility criteria, one discontinued due to physician decision and one subject discontinued due to other reason.

Subjects that turned 16 years of age after study enrolment became eligible for unblinding to treatment assignment and vaccination under emergency use or conditional marketing authorization.

Adverse events

Reactogenicity

Reactogenicity (local reactions and systemic events) was assessed via e-diary in all adolescents 12-15 years of age up to 7 days after each dose. The number of adolescent participants (12-15 years of age) with e-diary data were N=1131 in the BNT162b2 group and N=1129 in the placebo group post Dose 1, and N=1124 in the BNT162b2 group and N=1117 in the placebo group post Dose 2.

Young adult participants (16-25 years of age) in the reactogenicity subset with e-diary data included N=539 in the BNT162b2 group and N=564 in the placebo group post Dose 1, and N=526 in the BNT162b2 group and N=537 in the placebo group post Dose 2.

For local reactogenicity, during the reactogenicity e-diary reporting period, participants were asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persisted beyond the end of the reactogenicity e-diary period following vaccination, the participant was requested to report that information. Redness and swelling were measured and recorded in measuring device units (range:1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale. Pain at the injection site was assessed by the participant as absent, mild, moderate, or severe according the grading scale

For systemic reactogenicity, during the reactogenicity e-diary reporting period, participants were asked to assess vomiting, diarrhoea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms were assessed by the participant as absent, mild, moderate, or severe according to the grading scale. Temperature was collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period and at any time during the reactogenicity e-diary data collection periods when

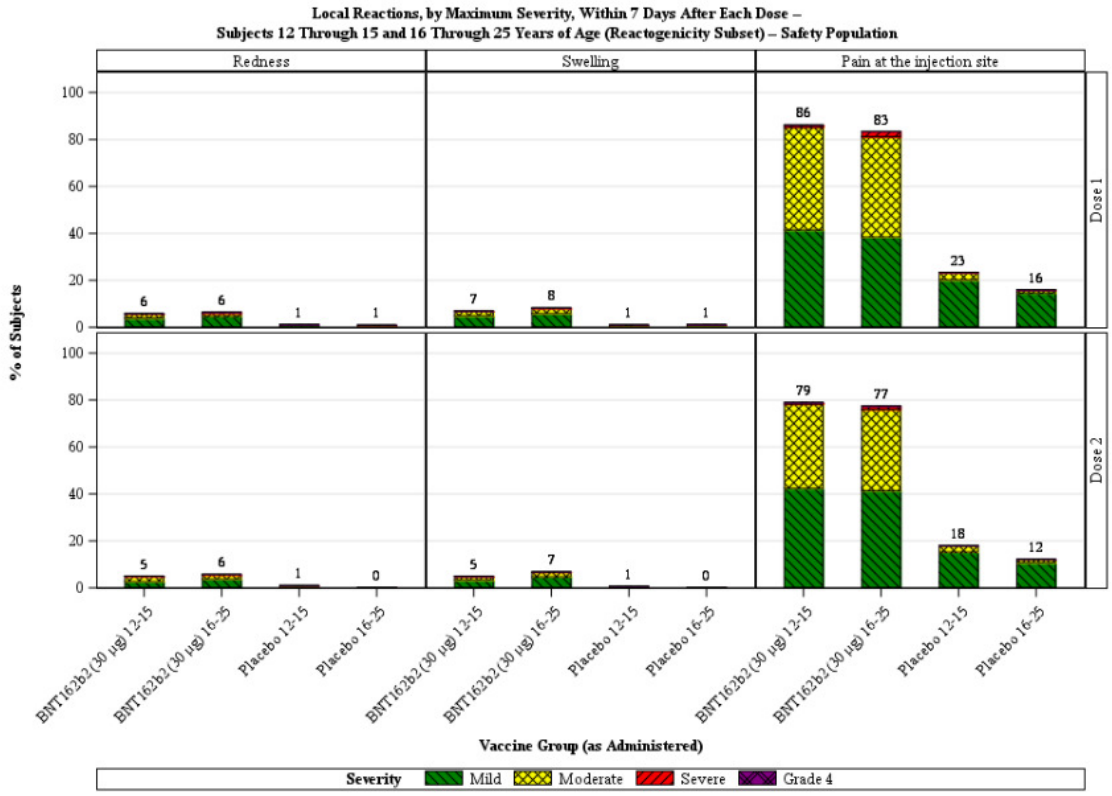
fever was suspected. Fever was defined as an oral temperature of ≥38.0°C. The highest temperature for each day was recorded in the reactogenicity e-diary.

Local reactions

In the BNT162b2 group, pain at the injection site was most frequently reported in adolescents and young adults, and frequency was similar after Dose1 and after Dose2 of BNT162b2 in adolescents (86% vs 79%).

After the first and second dose, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently (≤1.5%) across the BNT162b2 and placebo groups after any dose. No Grade 4 local reactions were reported. Median onset for all local reactions was Day 1 to Day 3 (Day 1 was the day of vaccination) and resolved with a median duration of 1-3 day.

Table 1. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Reactogenicity Subset for Phase 2/3 Analysis – Safety Population by Age Group: 12-15 Years and 16-25 Years



The most common local reaction was pain at injection site, which was reported in >85% of the adolescent subjects after the first dose. The majority of the local reactions were transient and mild to moderate at intensity. The CHMP noted that the frequency of subjects that experienced pain at injection site was slightly higher than what has been described for the adult population in the SmPC. The SmPC has been updated to separately reflect the frequency of the most commonly reported reactogenicty events in adolescents, which is endorsed by the CHMP. The Package Leaflet has been updated accordingly.

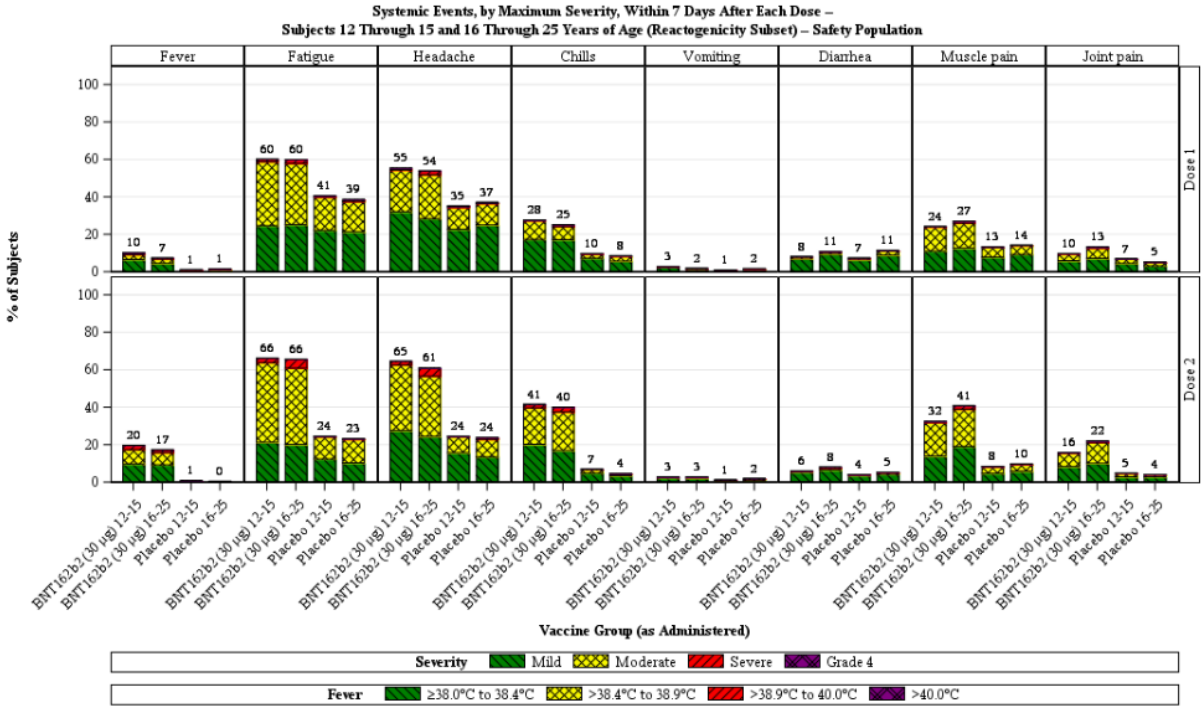
Systemic events

The frequency of the reported systemic events is described in the table below. As illustrated in the table, the rate of fever was somewhat higher in the adolescent group compared to the young adult group (10.1% vs 7.3% after Dose1, respectively), especially after the second dose (19.6% vs 17.2%, respectively)

Following both Dose 1 and Dose 2, use of antipyretic/pain medication in adolescents was 36.6% and 50.8%, which were in line with the reports from young adults (31.5% and 45.7%). Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose1 and Dose2 (ranging from 8.8% to 11.9% in both adolescents and young adults).

After the first and second dose, most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently in adolescents (≤3.5%) and young adults (≤6.0%) across BNT162b2 and placebo groups after any dose. One adolescent [redacted] had Grade 4 pyrexia (40.4°C) on Day 2 after Dose 1, with temperature returning to normal on Day 4 (reported as an AE leading to withdrawal). Median onset for all systemic events after either dose of BNT162b2 was Day 1 to Day 4 (Day1 was the day of vaccination). Systemic events resolved post each dose with a median duration of 1 day, except fatigue and chills which resolved within a median of 1-2 days.

Table 2. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population by Age Group: 12-15 Years and 16-25 Years



The most common systemic events were fatigue, headache, chills and muscle pain. It is noted that fever was reported in 10% of the adolescent subjects after the first dose and in 20% after the second dose, which is higher than reported for both young adults (as included in this report) and adults (as

described in the SmPC). Most of the systemic events resolved within 3 days and were mild to moderate at intensity. The frequency of subjects that experienced systemic events such as fatigue, headache, chills and fever were in general slightly higher than what is described for the adult population in the SmPC. The SmPC has been updated to describe the frequency of the most commonly reported reactogenicty events in adolescents, which is endorsed by the CHMP. The Package Leaflet has been updated accordingly.

AEs reported by the participants

Principal AE recording

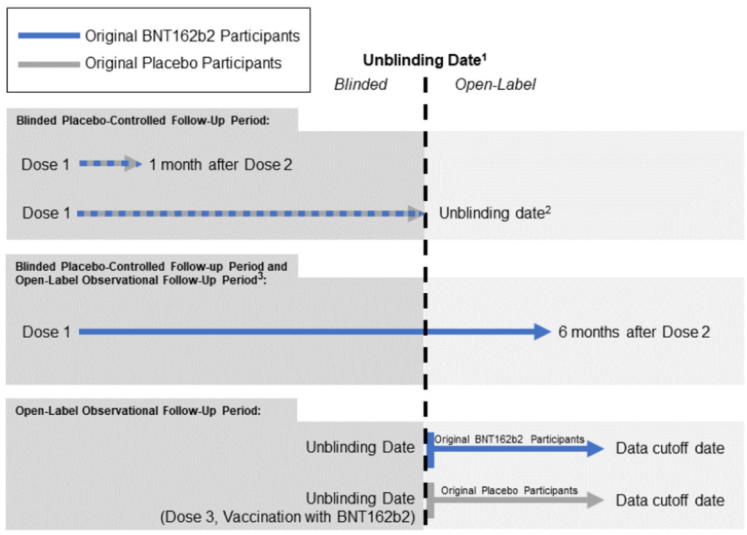
The time periods and safety analysis groups for the study are presented in Figure 8 below. In this clinical study report, AE results are from the blinded placebo-controlled follow-up period:

- Blinded placebo-controlled follow-up period from Dose 1 to 1 month after Dose 2 (frequencies): adolescents (12-15 years of age), young adults (16-25 years of age), and adults (16-55 years of age))
- Blinded placebo-controlled follow-up period from Dose 1 to the data cut-off date (13 March 2021): adolescents (12-15 years of age)
- Blinded placebo-controlled follow-up period from Dose 1 to the unblinding date (IRs): adults (16-55 years of age)

For AE analyses beyond 1 month after Dose 2 in adult participants, IRs are reported (as opposed to frequencies) to account for the variable exposure since unblinding began for individual participants.

Safety data from participants 16 through 55 years of age are included for comparative purposes, and a full independent safety evaluation of this age group along with participants >55 years of age will be reported separately at a later time.

Figure 8. Phase 2/3 Safety Analyses: Time Periods and Analysis Groups



[1] Will vary by participant. Adverse event data analyzed from Dose 1 to unblinding date (on or after 14 December 2020), or from unblinding date to data cutoff date, are reported as incidence rates adjusted for exposure time.
[2] Up to ~6 months after Dose 2.
[3] Cumulative BNT162b2 follow-up to at least 6 months after Dose 2.

In adolescents (age 12-15 years) AEs were analysed in two time frames, ie from dose 1 to 1 month after dose 2 and until the cut-off (13 march 2021), respectively. Young adults were analyzed from dose 1 to one month after dose 2 for comparative reasons. Data for young adults has been evaluated in a previous application and is therefore not analysed in depth within this AR.

Likewise, safety data from participants 16 through 55 years of age (older adults) are included for comparative purposes. In the age group 16-55 years AEs were analysed in from dose 1 to 1 month after dose 2 (given as frequencies) or up to the unblinding date reporting IRS (not frequencies), to account for the variable exposure since unblinding began for individual participants.

Dose 1 to 1 Month After Dose 2– Participants 12 Through 15 Years of Age

An overview of AEs from Dose 1 to one month after Dose 2 for adolescents (12-15 years of age) and young adults (16-25 years of age; utilizing the reactogenicity subset) is shown below. The number of participants with any AE were similar in the BNT162b2 and placebo groups for both age groups.

Table 24. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg)		Placebo	
Adverse Event	12-15 Years (N[a]=1131) n[b] (%)	16-25 Years (N[a]=536) n[b] (%)	12-15 Years (N[a]=1129) n[b] (%)	16-25 Years (N[a]=561) n[b] (%)
Any event	68 (6.0)	58 (10.8)	67 (5.9)	45 (8.0)
Related[c]	33 (2.9)	33 (6.2)	21 (1.9)	12 (2.1)
Severe	7 (0.6)	9 (1.7)	2 (0.2)	3 (0.5)
Life-threatening	1 (0.1)	0	1 (0.1)	0
Any serious adverse event	4 (0.4)	2 (0.4)	1 (0.1)	2 (0.4)
Related[c]	0	0	0	0
Severe	BLD			
Life-threatening				
Any adverse event leading to withdrawal				
Related[c]				
Severe				
Life-threatening				
Death	0	0	0	0

Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
Note: This table includes all subjects 12 through 15 years of age (all of whom are in the reactogenicity subset) and the subset of subjects 16 through 25 years of age who received an electronic diary (e-diary).
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: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (01:37)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s091_pd2_ped_saf

For all following AE and SAE analyses the MAH compared the adolescent subset (12-15 year old children) with the reactogenicity subset of young adults (16-25 years of age; 537 and 561 individuals) for the time frame first dose to one month after the second dose.

AEs were lower in the adolescent group compared to young adults (6.0% versus 10.8 %) and comparable to placebo. SAE rates were low in both age groups (≤0.4%). No adolescent died.

AE frequencies from dose 1 to one month after dose 2 in adults 16-55 years were clearly higher (32.6% versus 14.4%) in the vaccine arm compared to placebo and also higher when comparing with

children and young adults. Rates of SAEs and AEs leading to withdrawal were low in adults (0.4%, and 0.2%, respectively).

Dose 1 to Data Cut-off Date – Participants 12 Through 15 Years of Age

An overview of AEs from Dose 1 to the cut-off date for 2260 adolescents (12-15 years of age) during the blinded safety follow-up is presented in table below. Data for young adults are not included since they had different follow-up time up to the data cut-off date due to enrollment starting time for the age groups into the study and due to unblinding of individuals ≥16 years of age per protocol for vaccination under EUA (unlike the adolescents who remain blinded to treatment assignment).

Table 25. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (13MAR2021), Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)
Any event	72 (6.4)	71 (6.3)
Related[c]	33 (2.9)	21 (1.9)
Severe	9 (0.8)	3 (0.3)
Life-threatening	1 (0.1)	1 (0.1)
Any serious adverse event	5 (0.4)	2 (0.2)
Related[c]	0	0
Severe	BLD	
Life-threatening		
Any adverse event leading to withdrawal		
Related[c]		
Severe		
Life-threatening		
Death	0	0

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. 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: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (01:37)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s091_d1_cut_ped_saf

AEs from dose 1 to the cut-off date were analysed and presented for all 2260 adolescents (12-15 years of age) during the blinded safety follow-up. Data for young adults are not included since they had different follow-up time up to the data cut-off date.

AEs, SAEs and withdrawel rates due to AEs were overall comparable between verum and placebo arm in adolescents.

In older adults, AEs from dose 1 to participants' unblinding date IR of at least 1 AE reported in the vaccine group as compared with the placebo group was 88.4 versus 43.5 per 100 PYs. Severe AEs, SAEs, and AEs leading to withdrawal were reported at IRs of ≤3.9, ≤2.4, and ≤0.6 per 100 PYs, respectively, in both study arms.

Analysis of Adverse Events, SOCs and PTs

Participants 12 Through 15 Years of Age Dose 1 to 1 Month After Dose 2

AEs reported from Dose 1 to 1 month after Dose 2 for all adolescents and for young adults (in the reactogenicity subset) are presented in Table 28. AEs reported in adolescents were generally similar to

young adults within the respective BNT162b2 and placebo groups. Most of the AEs after Dose 1 up to 1 month after Dose 2 were reactogenicity events reported as AEs (ie, headache, nausea, and diarrhoea). In adolescents, AE frequencies in these reactogenicity SOCs (BNT162b2 vs placebo) were:

- general disorders and administration site conditions (16 [1.4%] vs 11 [1.0%])
- musculoskeletal and connective tissue disorders (9 [0.8%] vs 8 [0.7%])
- nervous system disorders (12 [1.1%] vs 7 [0.6%])
- gastrointestinal disorders (14 [1.2%] vs 3 [0.3%])

In young adults, AE frequencies in these reactogenicity SOCs (BNT162b2 vs placebo) were:

- general disorders and administration site conditions (21 [3.9%] vs 10 [1.8%])
- musculoskeletal and connective tissue disorders (12 [2.2%] vs 8 [1.4%])
- nervous system disorders (13 [2.4%] vs 7 [1.2%])
- gastrointestinal disorders (5 [0.9%] vs 6 [1.1%])

Overall, AEs reported in adolescents and young adults at 1 month after Dose 2 were largely attributable to reactogenicity events. This observation provides a reasonable explanation for the greater rates of AEs observed overall in the BNT162b2 group compared with the placebo group.

Table 28. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event								
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
Lymphadenopathy								
CARDIAC DISORDERS								
Tachycardia								
EAR AND LABYRINTH DISORDERS								
Ear pain								
Cerumen impaction								
EYE DISORDERS								
Eye pain								
Eyelid rash								
Ocular hyperaemia								
Retinal haemorrhage								
GASTROINTESTINAL DISORDERS								
Nausea								
Diarrhoea								
Abdominal pain								
Aphthous ulcer								
Lip swelling								

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System Organ Class Preferred Term	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Vomiting	BLD							
Gastritis								
Inguinal hernia								
Mouth swelling								
Oral mucosal blistering								
Rectal prolapse								
Toothache								
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
Injection site pain								
Fatigue								
Pyrexia								
Chills								
Injection site erythema								
Injection site swelling								
Oedema peripheral								
Pain								
Chest pain								
Injection site bruising								
Injection site discomfort								
Injection site hyperaesthesia								
Nodule								

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System Organ Class Preferred Term	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Peripheral swelling	BLD							
Vessel puncture site pain								
IMMUNE SYSTEM DISORDERS								
Food allergy								
INFECTIONS AND INFESTATIONS								
Ear infection								
Appendicitis								
Conjunctivitis								
Otitis externa								
Otitis media								
Sinusitis								
Tonsillitis								
Vulvovaginal mycotic infection								
Body tinea								
Candida infection								
Cellulitis								
Cystitis								
Focal peritonitis								
Folliculitis								
Genital herpes								
Genital herpes simplex								

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	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N^a=1131)		16-25 Years (N^a=536)		12-15 Years (N^a=1129)		16-25 Years (N^a=561)	
System Organ Class Preferred Term	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])
Impetigo	BLD							
Infectious mononucleosis								
Oral fungal infection								
Pharyngitis streptococcal								
Pilonidal cyst								
Subcutaneous abscess								
Tinea capitis								
Tinea infection								
Urinary tract infection								
Vulval abscess								
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
Ligament sprain								
Concussion								
Accident								
Clavicle fracture								
Contusion								
Exposure during pregnancy								
Fall								
Muscle strain								
Procedural pain								
Tooth fracture								

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	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N^a=1131)		16-25 Years (N^a=536)		12-15 Years (N^a=1129)		16-25 Years (N^a=561)	
System Organ Class Preferred Term	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])
Fibula fracture	BLD							
Flail chest								
Foot fracture								
Hand fracture								
Humerus fracture								
Joint dislocation								
Lip injury								
Meniscus injury								
Patella fracture								
Radius fracture								
Road traffic accident								
INVESTIGATIONS								
Electrocardiogram QT prolonged								
METABOLISM AND NUTRITION DISORDERS								
Decreased appetite								
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
Arthralgia								
Myalgia								
Back pain								
Pain in extremity								

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	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N^a=1131)		16-25 Years (N^a=536)		12-15 Years (N^a=1129)		16-25 Years (N^a=561)	
System Organ Class Preferred Term	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])
Arthropathy	BLD							
Joint swelling								
Limb mass								
Mobility decreased								
Musculoskeletal chest pain								
Musculoskeletal discomfort								
Neck pain								
Osteochondrosis								
Plantar fasciitis								
Spinal disorder								
Torticollis								
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
Fibroadenoma of breast								
Skin papilloma								
NERVOUS SYSTEM DISORDERS								
Headache								
Dizziness								
Migraine								
Presyncope								
Burning sensation								

Table 28. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N^a=1131)		16-25 Years (N^a=536)		12-15 Years (N^a=1129)		16-25 Years (N^a=561)	
System Organ Class Preferred Term	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])	n^b (%)	(95% CI[c])
Neuralgia	BLD							
Paraesthesia								
PSYCHIATRIC DISORDERS								
Depression								
Anxiety								
Attention deficit hyperactivity disorder								
Depressed mood								
Disorientation								
Generalised anxiety disorder								
Sleep terror								
Tic								
REPRODUCTIVE SYSTEM AND BREAST DISORDERS								
Cervical dysplasia								
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
Rhinorrhoea								
Oropharyngeal pain								
Asthma								
Nasal congestion								
Reflux laryngitis								
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
Rash								

Table 28. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Urticaria	BLD							
Acne								
Dermatitis contact								
Macule								
Pityriasis rosea								
Rash erythematous								
Rash maculo-papular								
Seborrhoeic dermatitis								
SURGICAL AND MEDICAL PROCEDURES								
Sclerotherapy								
Tooth extraction								
Wisdom teeth removal								

Note: MedDRA (v23.1) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
Note: This table includes all subjects 12 through 15 years of age (all of whom are in the reactogenicity subset) and the subset of subjects 16 through 25 years of age who received an electronic diary (e-diary).
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: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (01:37)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s130_1md2_soc_ped_saf

Table 28. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Urticaria	BLD							
Acne								
Dermatitis contact								
Macule								
Pityriasis rosea								
Rash erythematous								
Rash maculo-papular								
Seborrhoeic dermatitis								
SURGICAL AND MEDICAL PROCEDURES								
Sclerotherapy								
Tooth extraction								
Wisdom teeth removal								

Note: MedDRA (v23.1) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
Note: This table includes all subjects 12 through 15 years of age (all of whom are in the reactogenicity subset) and the subset of subjects 16 through 25 years of age who received an electronic diary (e-diary).
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: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (01:37)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s130_1md2_soc_ped_saf

AEs reported from dose 1 to one month after dose 2 for all adolescents and for young adults in the reactogenicity subset were generally a little bit lower in adolescents compared to young adults. AEs were similar in adolescents between vaccine and placebo arm and marginally higher in the vaccine arm compared to placebo in young adults. Most often occuring SOCs were similar in adolescents and young adults, and represented by general disorders and administration site conditions (injection site pain, fatigue, pyrexia, chills), musculoskeletal and connective tissue disorders (arthralgia, myalgia), nervous system disorders (headache, dizziness) and gastrointestinal disorders (nausea, diarrhoea). Thus, the safety profile in both age groups was comparable to that already known for adults.

To mention are 0.8% vs 0.2% (9 vs 2) cases of lympadenopathy in adolescents (vaccine/placebo) compared to 0.2% versus 0.0% cases in young adults. Pain in extremity was observed in 0.1% and 0.0% cases in adolescents (1 vs 0 cases, vaccine versus placebo; no cases in young adults). Different

forms of rash (2 vs. 5 cases) or urticaria (2 vs. 4 cases) were reported for each term in 0.2%/0.4% cases in adolescents (vaccine/placebo).

Dose 1 to Data Cut-off Date – Participants 12 Through 15 Years of Age

AEs reported from Dose 1 to the data cut-off date for adolescents (13 March 2021) are presented in the table below.

AEs reported in adolescents through the data cut-off date were similar in the BNT162b2 and placebo groups. The most frequently reported AEs in adolescents through the data cut-off date included lymphadenopathy (9 [0.8%]), injection site pain (7 [0.6%]), fatigue (7 [0.6%]), pyrexia (5 [0.4%]), nausea (5 [0.4%]), and headache (5 [0.4%]).

Table 29. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (13MAR2021), by System Organ Class and Preferred Term – Subjects 12 Through 15 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=1131)	Placebo (N[a]=1129)
System Organ Class Preferred Term	n[b] (%)	n[b] (%)
Any event		
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Lymphadenopathy		
EAR AND LABYRINTH DISORDERS		
Ear pain		
Cerumen impaction		
EYE DISORDERS		
Eyelid rash		
Retinal haemorrhage		
GASTROINTESTINAL DISORDERS		
Nausea		
Diarrhoea		
Abdominal pain		
Aphthous ulcer		
Constipation		
Gastritis		
Lip swelling		
Mouth swelling		
Oral mucosal blistering		
Rectal prolapse		
Toothache		
Vomiting		

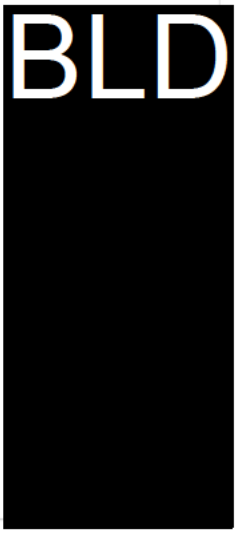

Table 29. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (13MAR2021), by System Organ Class and Preferred Term – Subjects 12 Through 15 Years of Age – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	 Placebo (N[a]=1129) n[b] (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Injection site pain		
Fatigue		
Pyrexia		
Chills		
Injection site swelling		
Nodule		
Oedema peripheral		
Peripheral swelling		
Vessel puncture site pain		
IMMUNE SYSTEM DISORDERS		
Food allergy		
INFECTIONS AND INFESTATIONS		
Ear infection		
Appendicitis		
Conjunctivitis		
Body tinea		
Candida infection		
Focal peritonitis		
Infectious mononucleosis		
Otitis externa		
Otitis media		
Pilonidal cyst		
Subcutaneous abscess		
Tinea capitis		
Vulval abscess		
Vulvovaginal mycotic infection		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Concussion		
Ligament sprain		
Accident		
Clavicle fracture		
Contusion		
Fall		
Muscle strain		
Procedural pain		
Tooth fracture		
Foot fracture		

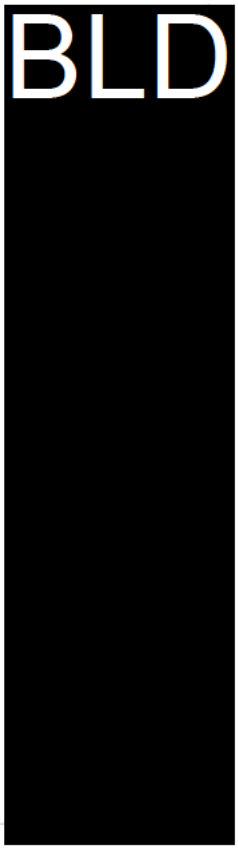

Table 29. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (13MAR2021), by System Organ Class and Preferred Term – Subjects 12 Through 15 Years of Age – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	 Placebo (N[a]=1129) n[b] (%)
Hand fracture	BLD	
Humerus fracture		
Lip injury		
Patella fracture		
Radius fracture		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia		
Myalgia		
Joint swelling		
Limb mass		
Mobility decreased		
Musculoskeletal chest pain		
Neck pain		
Osteochondrosis		
Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Fibroadenoma of breast		
Skin papilloma		
NERVOUS SYSTEM DISORDERS		
Headache		
Dizziness		
Presyncope		
Migraine		
Neuralgia		
Paraesthesia		
Syncope		
PSYCHIATRIC DISORDERS		
Depression		
Anxiety		
Attention deficit hyperactivity disorder		
Disorientation		
Generalised anxiety disorder		
Sleep terror		
Suicidal ideation		
Tic		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Rhinorrhoea		

Table 29. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (13MAR2021), by System Organ Class and Preferred Term – Subjects 12 Through 15 Years of Age – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	 Placebo (N[a]=1129) n[b] (%)
Nasal congestion	BLD	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash		
Urticaria		
Acne		
Dermatitis contact		
Pityriasis rosea		
Rash maculo-papular		

Note: MedDRA (v23.1) 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. 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.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (04:09)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s130_d1_cut_soc_ped_saf

AEs reported from dose 1 to the data cut-off date for adolescents (13 March 2021) occurred in overall low frequency (6.3%/6.4%, vaccine/placebo). Most often occuring SOCs were slightly more common in the vaccine arm compared to placebo with general disorders (1.4% / 1.0% vaccine/ placebo; most often occuring PTs injection site pain, fatigue), gastrointestinal disroders (1.2% / 0.3% vaccine / placebo; most common PTs nausea, diarrhoea) neurological disorders (1.1% / 0.6% vaccine / placebo ; most common PTs headache, dizziness), inury poisening and procedural complications (0.8% / 1.2% vaccine / placebo; most common PTs concussion, accident) and musculoskeletal disorders (0.8% / 0.7% vaccine / placebo; most common PTs arthralgia, myalgia).

PTs of interest and known to occur with the vaccine occurred in overall low frequency, i.e. lymphadenopathy (0.8% (9 cases) vs 0.2% (2 cases)), injection site pain (0.6% vs 0.6%), fatigue (0.6% vs 0.4%), pyrexia (0.4% vs 0%), nausea (0.4% vs 0.1%), headache (0.4% vs 0.4%), myalgia (0.2% vs 0.3%) and arthralgia (0.2% vs. 0.3%). To mention also are one case of neuralgia (not related, see also below) and 1 case of paraesthesia BLD

In comparison, AEs in adults 16-55 years of age belonged mostly to the SOCs general disorders and administration site conditions (3161 [24.3%] vs 681 [5.2%]), musculoskeletal and connective tissue disorders (1201 [9.2%] vs 303 [2.3%]), nervous system disorders (1067 [8.2%] vs 393 [3.0%]), and gastrointestinal disorders (440 [3.4%] vs 288 [2.2%)] one month after dose 2. A similar picture was observed for the time frame first dose up to unblinding. Thus, SOCs occurring in adolescents were comparable to those seen in adults.

Related Adverse Events by System Organ Class and Preferred Term

Dose 1 to 1 Month After Dose 2 – Participants 12 Through 15 Years of Age

From Dose 1 to 1 month after Dose 2, AEs assessed as related by the investigator in adolescents and young adults were similar in the BNT162b2 group and in the placebo group (Table 24). Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 15 adolescents (1.3%) and 19 young adults (3.5%) in the BNT162b2 group compared with 9 adolescents (0.8%) and 9 young adults (1.6%) in the placebo group. Related events of lymphadenopathy were reported in the 7 adolescents in the BNT162b2 group and 1 adolescent in the placebo group, compared with 1 young adult BLD .

14.29. Number (%) of Subjects Reporting at Least 1 Related Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N^a=1131)	16-25 Years (N^a=536)	12-15 Years (N^a=1129)	16-25 Years (N^a=561)
System Organ Class Preferred Term	n^b (%) (95% CI[c])	n^b (%) (95% CI[c])	n^b (%) (95% CI[c])	n^b (%) (95% CI[c])
Any event				
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Lymphadenopathy				
EYE DISORDERS				
Eyelid rash				
GASTROINTESTINAL DISORDERS				
Nausea				
Diarrhoea				
Abdominal pain				
Aphthous ulcer				
Lip swelling				
Mouth swelling				
Oral mucosal blistering				
Vomiting				
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Injection site pain				
Fatigue				
Pyrexia				
Chills				
Injection site erythema				
Injection site swelling				
Injection site bruising				
Injection site discomfort				
Injection site hyperaesthesia				
Pain				
Peripheral swelling				
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite				
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Myalgia				
Arthralgia				
Back pain				
Musculoskeletal discomfort				
NERVOUS SYSTEM DISORDERS				
Headache				
Dizziness				
Migraine				
Presyncope				
PSYCHIATRIC DISORDERS				
Anxiety				
Disorientation				
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Oropharyngeal pain				
Rhinorrhoea				
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Urticaria				
Rash				
Rash maculo-papular				

BLD

BLD

Note: MedDRA (v23.1) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
Note: This table includes all subjects 12 through 15 years of age (all of whom are in the reactogenicity subset) and the subset of subjects 16 through 25 years of age who received an electronic diary (e-diary).
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: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (01:37)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s130_1md2_rel_ped_saf

Related AEs up to one month after dose 2 were lower in frequency in adolescents (2.9%/1.9%; vaccine/placebo) compared to young adults (6.2%/2.1%) and occurred more often in the vaccine compared to placebo arm. Most related AEs were reactogenicity events (SOC of general disorders and administration site conditions). Lymphadenopathy was more often observed and evaluated as related in adolescents who received vaccine compared to placebo (7 vs. 1 individuals). Those events were less frequent in young adults BLD . Related AE frequencies were clearly higher in adults 16-55 years with 26.8% versus 6.8% (vaccine vs. placebo) and occurred more often with the vaccine. As for adolescents, events belonged mostly to the SOC general disorders and administration site conditions (24.0% vs. 4.7%, vaccine vs. placebo).

Immediate Adverse Events – Participants 12 Through 15 Years of Age

After Dose 1, adolescents and young adults with immediate AEs were low in frequency (≤0.4%) and were reported only in the placebo groups. 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, adolescents and young adults with immediate AEs were low in frequency (≤0.4%) in BNT162b2 and placebo groups. Most immediate AEs after Dose 2 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 BLD [redacted]) or skin and subcutaneous tissue disorders (rash maculo-papular; 1 participant BLD [redacted].

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

14.32. Number (%) of Subjects Reporting at Least 1 Immediate Adverse Event After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N[a]=1124)	16-25 Years (N[a]=523)	12-15 Years (N[a]=1117)	16-25 Years (N[a]=535)
System Organ Class Preferred Term	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])
Any event	BLD			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Injection site pain				
Fatigue				
Chills				
Injection site bruising				
Injection site hyperaesthesia				
NERVOUS SYSTEM DISORDERS				
Dizziness				
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash maculo-papular				

Note: MedDRA (v23.1) coding dictionary applied.
Note: This table includes all subjects 12 through 15 years of age (all of whom are in the reactogenicity subset) and the subset of subjects 16 through 25 years of age who received an electronic diary (e-diary).
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
Note: Subjects who did not receive Dose 2 or who received a different vaccine at each dose were excluded from this table.
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: 25MAR2021 (20:15) Source Data: adae Table Generation: 29MAR2021 (04:22)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s130_immd_vax2_ped_saf

Immediate AEs were low in frequency (≤0.4%) after dose 1 and were reported only in the placebo groups in adolsecents and young adults.

After Dose 2, adolescents and young adults with immediate AEs were low in frequency (≤0.4%) in vaccine and placebo arm. Isolated AEs such as injection site pain or dizziness were seen in the vaccine arm of adolescents. No allergic AEs were reported with the vaccine within 30 minutes after vaccination.

Severe or Life-Threatening Adverse Events

Dose 1 to 1 Month After Dose 2 – Participants 12 Through 15 Years of Age

From Dose 1 to 1 month after Dose 2, severe AEs reported in adolescents and young adults were overall low in number and frequency: 7 (0.6%) participants in the BNT162b2 group versus 2 (0.2%) participants in the placebo group among adolescents, and 9 (1.7%) participants in the BNT162b2 group versus 3 (0.5%) in the placebo group among young adults (Table 24).

Among adolescents, 2 participants (1 each in the BNT162b2 and placebo groups) had at least 1 life-threatening (or Grade 4) AE from Dose 1 to 1 month after Dose 2. These included:

- Focal peritonitis and appendicitis reported in 1 adolescent BLD occurring concurrently 19 days after Dose 2 with a duration of 2 days, and considered by the investigator as not related to study intervention; both events were reported as SAEs, resolved, and the participant continued in the study
- Pyrexia (40.4°C) reported as Grade 4 in 1 adolescent BLD, occurred on Day 2 after Dose 1, with temperature returning to normal on Day 4), and was considered by the investigator as related to study intervention; the event was reported by the investigator as non-serious, resolved, and the participant withdrew from the study (also recorded in the e-diary as reactogenicity systemic event). Additionally, 2 participants in the adolescent age group had life-threatening AEs that occurred after they turned 16 years of age during the study and were unblinded to receive BNT162b2 and were therefore not included in analyses of blinded data (per protocol).
- Anaphylactoid reaction reported in 1 participant originally randomized to the placebo group, 3 days after receiving the first dose of BNT162b2 (Dose 3) with a duration of 1 day, considered by the investigator as related to study intervention; the event was reported as an SAE, resolved, and the participant withdrew from the study. The participant has ongoing medical history of drug hypersensitivity, food allergy, and seasonal allergy.
- Depression reported in 1 participant originally randomized to the placebo group, 7 days after receiving the first dose of BNT162b2 (Dose 3) reported as ongoing at the time of the data cut-off date, considered by the investigator as not related to study intervention; the event was reported as an SAE due to hospitalization and reported as resolving, and the participant continued in the study. Among young adults, there were no life-threatening AEs reported from Dose 1 to 1 month after Dose 2 (Table 24).

Severe AEs were low in frequency in adolescents (0.6%/0.2% vaccine/placebo) and less common compared to young adults (1.7%/ 0.5%).

Two adolescents (one each in vaccine and placebo arm) showed grade 4 AEs, ie focal peritonitis and appendicitis BLD and one case of pyrexia (40.4°C) BLD (occurrence day 2 after dose 1, normalization day 4).The participant withdrew from the study. Furthermore, two adolescents reported life-threatening AEs after having turned 16 years of age after unblinding and vaccination with verum (dose 3), i.e. anaphylactoid reaction (3 days after the first dose of BNT162b2 (dose 3), considered related, see also SAE section) and depression (7 days after receiving the first dose of BNT162b2 (dose 3), not related to study intervention, reported as SAE due to hospialization). In comparison, among young adults, there were no life-threatening AEs reported from Dose 1 to one month after dose 2.

Older adults showed severe AEs in frequencies of 1.2% vs. 0.6% (vaccine/placebo), mainly due to events in the SOC general disorders and administration site conditions. As for adolescents, frequencies of life-threatening events were infrequent (0.1% in vaccine and placebo arm).

Adverse Events of Clinical Interest

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). If an AE of clinical interest was not observed in the 12-15 years of age group, narratives were not provided for individuals 16 and above. AEs of clinical interest occurring in the adolescent group were reviewed along with corresponding reference information from adults and are summarized below.

Anaphylaxis

No cases of anaphylaxis or anaphylactoid reactions were reported during blinded follow-up.

in the adolescent (12-15 years of age) or young adult (16-25 years of age) groups as of the data cut-off date (13 March 2021). One young adult participant (reported with both the 16-25 years of age and 16-55 years of age group data) who was originally randomized to the placebo group and unblinded to receive BNT162b2 had an anaphylactoid reaction (specific symptoms not specified) assessed as related, 3 days post Dose 3 (first dose of BNT162b2), with an event duration of 1 day; the event was reported as an SAE, reported as resolved, and the participant withdrew from the study (this participant has an ongoing medical history of drug hypersensitivity, food allergy, and seasonal allergy). Note that this event was not counted in the summary safety tables which only included blinded follow-up data. In adults (16-55 years of age), 1 other participant had an SAE of anaphylaxis caused by exposure to an allergen that was not considered related to study intervention.

Lymphadenopathy

Lymphadenopathy is identified as an adverse reaction for BNT162b2 vaccine. In adolescents (12-15 years of age), 7 participants (0.6%) in the BNT162b2 group and 1 participant (0.1%) in the placebo group had lymphadenopathy events assessed by the investigator as related to study intervention. The majority of these events occurred in the arm and neck region, were reported within 2-10 days after vaccination, and approximately half of events resolved within 1-10 days (others were ongoing at the time of the data cut-off date). In young adults (16-25 years of age), 1 related event of lymphadenopathy was reported up to the data cut-off date, occurring in the axilla within 1 day of Dose 2 and resolved within 5 days. In adults (16-55 years of age), 52 participants (0.4%) in the BNT162b2 group and 2 participants (0.0%) in the placebo group had lymphadenopathy events reported up to the unblinding date and assessed by the investigator as related to study intervention. The majority of these events occurred in the arm and neck region, were reported within 2-4 days after vaccination (usually after Dose 2), and typically resolved within approximately 1 week.

Appendicitis

In adolescents (12-15 years of age), 2 participants BLD had events of appendicitis reported as SAEs and considered as not related to study intervention. In young adults (16-25 years of age), 1 participant BLD had an event of appendicitis reported as an SAE and considered as not related to study intervention. In adults (16-55 years of age), 12 cases of appendicitis were reported in the BNT162b2 group and 7 cases in the placebo group during blinded follow-up through the unblinding date. All were considered as SAEs, not related to study intervention, and all participants recovered.

Bell's Palsy/Facial Paralysis/Facial Paresis

No cases of facial paralysis were reported in adolescents (12-15 years of age) as of the data cut-off date (13 March 2021).

No cases of anaphylaxis were reported in the adolescent group (12-15 years) compared to one case in the young adult group. This subject developed an anaphylactoid reaction after unblinding and receipt

of vaccine (originally randomised to the placebo arm in the adolescent group, and received vaccine after turning 16 years).

In adolescents (12-15 years of age), 7 participants (0.6%) in the vaccine arm and one participant (0.1%) in the placebo group showed lymphadenopathy assessed by the investigator as related to study intervention. The majority occurred in the arm and neck region, 2-10 days after vaccination, and about half of events resolved within 1-10 days. In young adults (16-25 years of age), one related event of lymphadenopathy was reported up to the data cut-off date, occurring in the axilla within 1 day of dose 2 and resolved within 5 days. In adults (16-55 years of age), 52 participants (0.4%) in the vaccine group and two participants (0.0%) in the placebo group had lymphadenopathy events reported up to the unblinding date and assessed by the investigator as related to study intervention. The majority of these events occurred in the arm and neck region, were reported within 2-4 days after vaccination (usually after Dose 2), and typically resolved within approximately 1 week.

No cases of facial paresis were observed in adolescents.

No cases of appendicitis occurred in adolescents with the vaccine (two cases BLD). In young adults one participant BLD developed appendicitis, considered as not related to study intervention by the study physician. In adults (16-55 years of age), 12 cases of appendicitis were reported in the vaccine group and 7 cases in the placebo group during blinded follow-up through the unblinding date. All were considered as SAEs and not related to study intervention.

Other Safety Assessments

Severe COVID-19 Illness

The protocol had prespecified stopping rules that included monitoring of severe COVID-19 cases, and these stopping criteria were not met. As of the data cut-off date (13 March 2021), no severe COVID-19 cases were reported in adolescents 12-15 years of age in Study C4591001, suggesting no evidence for vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD).

Pregnancy

As of the data cut-off date (13 March 2021), no pregnancies were reported in participants 12-15 years of age. Four pregnancies were reported in the young adults (16-25 years of age) that led to discontinuation from the vaccination period, and 1 additional participant in the young adult group withdrew from the study due to a reported AE of exposure during pregnancy; none of these participants has given birth as of the data cut-off date.

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in adolescent (12-15 years of age) or young adult (16-25 years of age) groups evaluated in safety analyses up to the data cut-off date (13 March 2021).

Participants 12 Through 15 Years of Age

Dose 1 to 1 Month After Dose 2 – Participants 12 Through 15 Years of Age from Dose 1 to 1 month after Dose 2, the proportions of adolescents and young adults (in the reactogenicity subset) who reported at least 1 SAE were similar (Table 30). Overall, ≤0.4% of participants in both age groups reported any SAE after receiving BNT162b2 or placebo.

No participants in either age group had SAEs assessed by the investigator as related to study intervention.

In the adolescent group, SAEs up to 1 month after Dose 2 were reported BLD in 2 participants with depression, 1 participant with concurrent events of anxiety and depression, and 1 participant with neuralgia and 1 participant BLD with concurrent events of appendicitis and focal peritonitis that were both Grade 4.

The SAE of neuralgia was reported in 1 study participant who had 3 emergency room visits beginning 1 day after the second dose. The study participant reported concurrent non-serious AEs of genital abscess, gastritis, and contact dermatitis. The study participant subsequently had SAEs of abdominal pain and constipation. The study participant had an extensive work-up including serial physical and laboratory examinations and was diagnosed with functional abdominal pain; the study participant was referred to psychology and physical therapy, after which symptoms were reported as gradually improving.

In the young adult age group, SAEs up to 1 month after Dose 2 were reported by 2 participants BLD (1 participant with abdominal pain and 1 participant with appendicitis) and 2 participants BLD (1 participant had inguinal hernia, and 1 participant had flail chest associated with an accident). All SAEs in the young adult group were reported as resolved.

Table 30. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	BLD							
GASTROINTESTINAL DISORDERS								
Abdominal pain								
Inguinal hernia								
INFECTIONS AND INFESTATIONS								
Appendicitis								
Focal peritonitis								
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
Flail chest								
NERVOUS SYSTEM DISORDERS								
Neuralgia								
PSYCHIATRIC DISORDERS								
Depression								
Anxiety								

Table 30. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])

Note: MedDRA (v23.1) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
Note: This table includes all subjects 12 through 15 years of age (all of whom are in the reactogenicity subset) and the subset of subjects 16 through 25 years of age who received an electronic diary (e-diary).
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: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (01:37)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s130_1md2_ser_ped_saf

The rates of SAEs were similar and very low in adolscents and young adults and similar between vaccine arm and placebo in the time frame dose 1 to one month after dose 2 (≤0.4%). None of the SAE were assessed by the investigator as related to study intervention. The two participants reporting 4 SAEs in adolescents showed anxiety/depression (3), and neuralgia (1), respectively. Neuralgia was reported in connection to genital abscess, gastritis, and contact dermatitis, abdominal pain and constipation in one participant. In the young adult age group, SAEs up to one month after dose 2 were reported by two participants BLD (one participant with abdominal pain and one participant with appendicitis).

In older adults, 0.4% in each study arm reported SAEs up to one month after vaccination.

Dose 1 to Data Cut-off Date – Participants 12 Through 15 Years of Age

From Dose 1 to the data cut-off date (13 March 2021), the proportions of adolescents who reported at least 1 SAE were similar in the BNT162b2 and placebo groups (Table 31). Data for young adults are not included since they had different follow-up time up to the data cut-off date (due to enrollment starting time into the study and due to unblinding of individuals ≥16 years of age per protocol, for vaccination under EUA; refer to Section 9.1). Up to the data cut-off date, 5 adolescents (0.4%) in the BNT162b2 group and 2 adolescents (0.02%) in the placebo group reported any SAE. None of the SAEs were assessed by the investigator as related to study intervention. In addition to the SAEs that were previously reported up to 1 month after Dose 2, SAEs reported from after 1 month post Dose 2 up to the data cut-off date included abdominal pain and constipation reported concurrently in 1 participant (who also previously reported an SAE of neuralgia) BLD This participant was ultimately diagnosed with functional abdominal pain after an extensive work-up. An SAE of suicidal ideation was reported in 1 participant BLD and an SAE of appendicitis was reported in 1 participant BLD. All SAEs were reported as resolved/resolving except for the events of abdominal pain and constipation which remained unresolved as of the data cut-off date. Additionally, 2 adolescents originally randomized to the placebo group had SAEs that occurred after they turned 16 years of age during the study and were unblinded to receive BNT162b2, therefore the data are not included in the blinded analyses. These events were also considered as life-threatening: an anaphylactoid reaction reported in 1 participant 3 days after receiving the first dose of BNT162b2 (Dose 3) with a duration of 1 day, considered by the investigator as related to study intervention and leading to study withdrawal; and depression reported in 1 participant 7 days after receiving the first dose of BNT162b2 (Dose 3) reported as ongoing/resolving at the time of the data cut-off date, considered by the investigator as not related to study intervention.

Table 31. Number (%) of Subjects Reporting at Least 1 Serious Adverse Event From Dose 1 Through Cutoff Date (13MAR2021), by System Organ Class and Preferred Term – Subjects 12 Through 15 Years of Age – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	 Placebo (N[a]=1129) n[b] (%)
Any event	BLD	
GASTROINTESTINAL DISORDERS		
Abdominal pain		
Constipation		
INFECTIONS AND INFESTATIONS		
Appendicitis		
Focal peritonitis		
NERVOUS SYSTEM DISORDERS		
Neuralgia		
PSYCHIATRIC DISORDERS		
Depression		
Anxiety		
Suicidal ideation		

Note: MedDRA (v23.1) 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. 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.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (04:09)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adae_s130_d1_cut_ser_ped_saf

The proportions of adolescents who reported at least 1 SAE were similar in the vaccine and placebo group (0.4% vs 0.2%) in the time frame dose 1 to the data cut-off date (13 March 2021). None of the SAEs were assessed by the investigator as related to study intervention. The SAEs abdominal pain and constipation were reported concurrently in one participant, who also previously reported an SAE of neuralgia BLD (not related), and who was diagnosed with functional abdominal pain after an extensive work-up. Furthermore, one SAE of suicidal ideation was reported in one participant BLD

Two adolescents originally randomized to the placebo group had SAEs that occurred after they turned 16 years of age during the study and were unblinded to receive BNT162b2: An anaphylactoid reaction reported in one participant 3 days after receiving the first dose of BNT162b2 (Dose 3) with a duration bof 1 day, considered by the investigator as related to study intervention and leading to study withdrawal; and depression reported in 1 participant 7 days after receiving the first dose of BNT162b2 (Dose 3) reported as ongoing/resolving at the time of the data cut-off date, considered by the investigator as not related to study intervention.

From Dose 1 to the unblinding date, the IRs of adult participants (16-55 years of age) with at least 1 SAE were similar in vaccine (2.1) and placebo (2.4) arm.

Laboratory findings

N/A

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Safety-Related Participant Withdrawals

Participants 12 Through 15 Years of Age

From Dose 1 to 1 month after Dose 2, few adolescents and young adults in the BNT162b2 group (≤ 0.2%) and in the placebo group (≤0.4%) were withdrawn due to AEs (Table 32) In the adolescent group, 1 participant BLD had an AE leading to withdrawal that was considered by the investigator as related to study intervention (pyrexia) BLD

In the young adult group, one participant BLD a had an AE leading to withdrawal that was considered by the investigator as related to study treatment (severe injection site pain that started 2 days after Dose 1 and resolved after 1 day BLD

Table 32. Number (%) of Subjects Withdrawn Because of Adverse Events From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg)				Placebo			
	12-15 Years (N[a]=1131)		16-25 Years (N[a]=536)		12-15 Years (N[a]=1129)		16-25 Years (N[a]=561)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	BLD							
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
Injection site pain								
Pyrexia								
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
Exposure during pregnancy								
NERVOUS SYSTEM DISORDERS								
Headache								
PSYCHIATRIC DISORDERS								
Anxiety								
Depression								

Note: MedDRA (v23.1) coding dictionary applied.
Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary.
Note: This table includes all subjects 12 through 15 years of age (all of whom are in the reactogenicity subset) and the subset of subjects 16 through 25 years of age who received an electronic diary (e-diary).
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: 25MAR2021 (20:15) Source Data: adae Table Generation: 27MAR2021 (01:37)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: /nda2_unblinded/C4591001_BLA/adae_s130_1md2_wd_ped_saf

Two adolescent subjects BLD discontinued or were withdrawn from the study. One subject experienced fever (40.5°C) which was considered related to study intervention which led to discontinuation, and one that experienced psychiatric disorders (anxiety and depression, not considered related to study intervention). No other reported AEs led to discontinuation.

Overall, seven adolescent subjects left the study; two subjects who received BNT162b2 discontinued due to adverse events, three did no longer meet the eligibility criteria, one discontinued due to physician decision and one subject discontinued due to other reason.

Post marketing experience

Comirnaty received a conditional marketing authorization (CMA) in EU 21st of December 2020 for use in subjects 16 years and older. Since then, the vaccine has been extensively used worldwide. For further safety details, please see the EMA Monthly Summary Safety Reports (MSSRs) that has been executed on monthly basis since the vaccine received its CMA.

2.5.1. Discussion on clinical safety

This application concerns adolescents 12-15 years of age which have subsequently been recruited to the ongoing phase 3 study (C4591001) on which the initial CMA was based. Similar dose of BNT162b2 (30µg) as in adult subjects has been administered to the adolescent subjects, by using 2-dose regimen three weeks a part.

Up to the cut-off date (13 Mar 2021), a total of 2260 adolescents (BNT162b n=1131; placebo n=1129) aged 12-15 years have been included in the safety population. Within this age range the number of adolescents was similar for each age group. Gender was equally distributed. The adolescent subjects were recruited from the USA only. The included numbers of subjects are considered sufficient to evaluate the reactogenicity profile in adolescent that receive two doses of BNT162b. However, if any rare adverse events were to occur specifically or more commonly in adolescent subjects, it would not be possible to detect these in this study. Notably, the safety data base for adult subjects is at this stage quite extensive given the >300 million administered doses worldwide that had occurred since December 2020.

All adolescent subjects received the first dose and >99% received the second dose. The safety data base constitutes mainly of subjects with a follow-up time after the 2nd dose of ≥1 to <2 months (41%) and those which had ≥2 to <3 months of follow-up after dose 2 (54%). The majority received their 2nd dose 14-27 days after dose 1 (97%).

Reactogenicity: Pain at the injection site was the most frequently reported local reaction in adolescents (86% dose1; 79% dose2), which was significantly higher compared to placebo (23% dose1; 18% dose2). Redness (6% dose1; 5% dose2) and swelling (7% dose1; 5% dose2) were also more frequently reported in the vaccinated group compared to placebo.

The most commonly reported systemic events among the adolescent subjects that received BNT162b2 were fatigue (60% dose1; 66% dose2), headache (55% dose1; 65% dose2), chills (28% dose1; 42% dose2), muscle pain (24% dose1; 32% dose2), joint pain (10% dose1; 16% dose2), fever (10% dose1; 20% dose2). Vomiting and diarrhoea was reported infrequently after both doses.

The use of antipyretic/pain medication among adolescents was higher after the second dose (37% dose1; 51% dose2), among the placebo treated adolescents the use of antipyretic medication was about 10%.

Most of the local and systemic events resolved within 3 days and were mild to moderate at intensity. In general, the reactogenicity appears to be higher than what has been described for the adult population. The SmPC has been updated to describe the frequency of the most reported local and systemic events in adolescents, which is endorsed by the CHMP.

In light of the above, and considering the high GMTs elicited in children 12-15 years of age, the CHMP would recommend that further dose-finding in the paediatric population be performed post-authorisation (**REC**).

In adolescents (12-15 years) AEs were analyzed in two different time intervals, i.e. from dose 1 to 1 month after dose 2 or until the cut-off date (13 Mar 2021). For comparative reasons, young adults (reactogenicity subgroup, 16-25 years) and older adults (16-55) were analyzed from dose 1 to one month after dose 2 and in case of older adults also up to cut-off reporting incidence ratios (IR) to account for the variable exposure. Data for young adults and older adults have been evaluated in a previous application and are therefore not analysed in depth within this AR.

AEs up to one month after dose 2 were lower in the adolescent group compared to young adults (6.0% versus 10.8 %). Event rates were roughly comparable to placebo in the adolescent age group. Same pattern was seen for AEs from dose 1 to the cut-off date.

Related AEs were lower in frequency in adolescents (2.9%/1.9%; vaccine/placebo) compared to young adults (6.2%/2.1%) and older adults (26.8.%/6.8%, vaccine/placebo) and occurred more often in the vaccine compared to placebo arm. Most of the related AEs were reactogenicity events (SOC of general disorders and administration site conditions). Lymphadenopathy was more often observed and evaluated as related in adolescents who received vaccine compared to placebo (all cases: 9 vs 2; related cases:7 vs. 1).

Severe AEs were low in frequency in adolescents (0.6%/0.2%, vaccine/placebo) and less common compared to young adults (1.7%/ 0.5%). One adolescent showed and grade 4 AE BLD **i.e.** pyrexia (40.4°C, start day 2 after dose 1, normalization day 4). Two adolescents reported life-threatening AEs after having turned 16 years of age after unblinding and vaccination with verum, i.e. anaphylactoid reaction (3 days after the first dose of BNT162b2), considered related.

In case of **AESIs,** no cases of anaphylaxis were reported in the adolescent group (12-15 years) compared to one case in the young adult/ adult, group who developed an anaphylactoid reaction after unblinding and receipt of vaccine (see also above). In adolescents, 7 vs 1 cases (0.6% vs 0.1%, vaccine/placebo) showed lymphadenopathy assessed by the investigator as related to study intervention; all cases in adolescents up to cut-off date: 9 (0.8%) vs 2 (0.2%)). No cases of facial paresis were observed in adolescents. No cases of appendicitis occurred in adolescents BLD BLD No severe Covid-19 cases were reported for adolescents.

The study is not large enough to determine whether there is rare adverse reaction with a higher frequency in adolescents compared to what has been seen in trials and real-life use in an older population.

Additional expert consultations

None

Assessment of paediatric data on clinical safety

The safety and efficacy of BNT162b2 in participants< 12 years of age have not been established as part of this extension of indication for the paediatric population above 12 years of age; further study of paediatric use of the vaccine and/or immunobridging study will be undertaken to characterise the vaccine response in children.

2.5.2. Conclusions on clinical safety

The safety evaluation is based on an ongoing phase 2/3 study that has included 2260 (BNT162b n=1131; placebo n=1129) adolescent subjects aged 12-15 years. The same dose and dose regimen as for the adult population has been used. Overall, the reported reactogenicity profile is in line with what was observed in the adult population, even though a slightly higher frequency was noted in adolescents which is reflected in the updated SmPC. The reactogenicity profile is considered acceptable. The frequency of reported AEs and SAEs were low. The sample size does not allow detection of rare adverse reactions.

The long-term safety of BNT162b2 mRNA vaccine is unknown at present, however further safety data are being collected in ongoing Study C4591001 for up to 2 years following administration of dose 2 of BNT162b2 mRNA vaccine in all age groups. Additionally, active surveillance studies are planned to follow long-term safety in vaccine recipients.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Important Identified Risks	Anaphylaxis
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Pharmacovigilance plan

On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Category 2					
C4591001 *Ongoing*	Global	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities	CSR submission upon regulatory request:	Any time
				CSR submission 6 months post Dose 2:	31-Dec-2021

On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
		COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	(C4591001 subset) Long term safety data.	Final CSR submission with supplemental follow-up:	31-Aug-2023

On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Category 3					
C4591011 *Planned*	US	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021
					31-Dec-2021
					30-Jun-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023

On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
C4591012 *Planned*	US	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021
					31-Dec-2021
					30-Jun-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023
C4591010 *Planned*	EU	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final draft protocol submission for EMA review:	31-Jan-2021
				Final CSR submission:	31-Mar-2024

On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
C4591015 *Planned*	Not available	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	Protocol draft submission:	28-Feb-2021
				Final CSR submission:	30-Apr-2023
C4591014 *Planned*	US	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Protocol draft submission:	31-Mar-2021
				Final CSR submission:	30-Jun-2023
WI235284 *Planned*	US	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Protocol draft submission:	31-Mar-2021
				Final CSR submission:	30-Jun-2023
WI255886 *Planned*	Ex-EU**Error! Reference source not found.**	To estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Protocol draft submission:	31-Mar-2021
				Final CSR submission:	30-Jun-2023

On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
BNT162-01 Cohort 13 *Ongoing*	EU	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission:	30-Sep-2021
				Final CSR submission:	31-Dec-2022
C4591018 *Planned*	US	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	Protocol submission:	28-Feb-2021
				IA submission:	31-Dec-2021
Safety and immunogenicity in high risk adults *Planned*	EU, US	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Protocol submission:	30-Jun-2021
				Final CSR submission:	31-Dec-2022

On-going and Planned Additional Pharmacovigilance Activities

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
ACCESS/VAC4EU *Planned*	EU	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long term safety data.	Protocol submission:	28-Feb-2021
				Final CSR submission:	31-Jan-2024
Co-administration study with seasonal influenza vaccine *Planned*	Not available	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
				Final CSR submission:	31-Dec-2022

The MAH was requested to confirm that adolescents of 12-15 years will be included in each of the post-authorisation studies stated in the pharmacovigilance plan and comment on the envisaged paediatric sample size for each post-authorisation study, if applicable. The MAH responded that 5 of the 13 post-authorisation studies will included participants of 12-15 years old, which was endorsed; in 7 post-authorisation studies the MAH will not include participants of 12-15 years, which is also endorsed given the studies objectives and design. One (C4591018, Phase II, US) of the 13 post-authorisation studies stated in the RMP was not presented by the MAH. However, this study will include immunocompromised adults with autoimmune disease rheumatoid arthritis, so the request was not applicable.

Risk minimisation measures

Safety Concern	Routine risk minimisation activities
Important Identified Risk	
Anaphylaxis	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk	
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Missing Information	
Use in pregnancy and while breast feeding	Routine risk communication: SmPC section 4.6 Fertility, pregnancy and lactation PL section 2. What you need to know before you receive Comirnaty Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

Use in immunocompromised patients	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic properties. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk communication: SmPC section 5.1 Pharmacodynamic properties. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in patients with autoimmune or inflammatory disorders	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Interaction with other vaccines	Routine risk communication: SmPC section 4.5 Interaction with other medicinal products and other forms of interaction Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Long term safety data	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

2.7. Update of the Product information

The CHMP adopted an extension to the existing indication (section 4.1) as follows:

> *"Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals ~~16~~ **12** years of age and older."*

As a consequence of this new indication, sections 4.2, 4.8, and 5.1 of the SmPC have also been

updated. The Package Leaflet has been updated accordingly.

Detailed recommendations for the use of this product is described in the updated summary of product characteristics (SmPC).

2.7.1. User consultation

No user consultation with additional target patient groups for the new indication applied, on the package leaflet has been performed. Since no major text changes has been added, except for change of age, this has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak.

Covid-19 in adolescents is mostly a mild disease. Severe cases occur rarely, and predominantly in subjects with underlying conditions.

The applicant is seeking an extension of the indication for Comirnaty (BNT162b2) to adolescents 12-15 years.

3.1.2. Available therapies and unmet medical need

There are currently no vaccines against Covid-19 approved for the use in adolescents 12-15 years of age.

3.1.3. Main clinical studies

The application for extension of the indication to include adolescents 12-15 years of age is based on a single pivotal phase 1/2/3 study C4591001. It is an extension of the pivotal efficacy study in adults assessed in the initial approval of Comirnaty.

The phase 3 part of the study was designed to enrol 2,260 participants aged 12-15 years in US (randomised 1:1 to BNT162b2 or placebo) to receive BNT162b2 at the dose of 30 µg, given as 2 IM injections 21 day apart (same dosing regimen than for adults). In the BNT162b2 and placebo groups, the majority of adolescents received dose 2 between 21 to 27 days after dose 1 (65.2% versus 64.6%) followed by 14 to 20 days after dose 1 (31.7% versus 32.2%).

The primary objective was the assessment of the safety profile.

Overall efficacy in those above 16 was also a primary objective in the study, while the analysis of vaccine efficacy against confirmed symptomatic cases and severe cases of COVID-19 in 12-15 years old is considered exploratory objective. The inferential analysis for the 12-15 year olds which was to demonstrate non-inferior immune responses in this age cohort, compared to subjects 16-25 years from the initial efficacy part of the same study. Almost all (98.3%) of adolescent participants had at least 1 month of follow-up after dose 2 and 57.9% had at least 2month of follow-up after dose 2.

3.2. Favourable effects

Comirnaty was shown to elicit non-inferior immune responses in subjects 12-15 years of age without previous Covid-19 compared to subjects 16-25 years in terms of geometric mean titres of neutralising antibodies one-month post dose 2.

Specifically, responses in adolescents were superior to the older age group, reflecting by greater geometric mean-fold rise (GMFR) of SARS-CoV-2 50% serum neutralizing titers in the 12-15 years group (GMFR 118.3 (CI95% 101.4, 137.9)) compared to 16-25 age group (GMFR 71.2 (CI95% 61.3, 82.7) at 1 month after dose 2). Note that GMFRs were higher in participants who were seronegative at baseline compared to those who were positive at baseline (regardless of the age group).

A high proportion of participants (97.9% of adolescents and 100.0% of young adults) had a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month post-dose 2.

Efficacy can be inferred for adolescents based on immune-bridging, as neutralising antibodies are thought to be a major mechanism of protection with Comirnaty.

In addition to immune responses, efficacy was also studied. Although a limited number of symptomatic covid-19 cases occurred in the study, they were all in the placebo group. The efficacy of the vaccine (BNT162b2, 2 doses of 30 µg, separated by 21 days) to prevent COVID-19 in the adolescents aged 12-15 years either without or with and without evidence of prior SARS-CoV-2 infection, occurring at least 7 days after the second dose, was 100.0% (CI95% 75.3, 100) vs VE was 95.0% (95% CI: 90.3%, 97.6%) respectively). No severe cases occurred in adolescents.
The vaccine efficacy after one dose was 100% (CI95% 41.4, 100) from 11 days after dose 1 to before dose 2.

3.3. Uncertainties and limitations about favourable effects

Specific risk groups among adolescents, including those immunosuppressed, or otherwise with risk of more severe disease due to underlying conditions, were not specifically studied. A study in immunocompromised children is included in the PIP.

It is currently unknown to what extent vaccination provides protection against asymptomatic infection, and whether vaccination prevents further transmission. The efficacy of the vaccine in preventing SARS-CoV-2 shedding and transmission should be evaluated post-authorisation, as was planned for adults (through seroconversion of N-binding antibody in BNT162b2 and placebo recipients who did not experience COVID-19).

The duration of protection is unknown in adolescents, as well as among adults.

The long-term efficacy in adolescents aged 12-15 years is unknown. Indeed, the available data on the efficacy against COVID-19 occurring 7 days after post-dose 2 are limited in term of follow-up (95.7% of adolescents were followed less than 3 months post-dose 2). As for subjects 16 years of age and older, the assessment of the VE over a period of at least 6 months is expected to determine the need and the appropriate time of a booster dose. Based on higher immune response in 12-15 years group compared to 16-25 years group, a comparable duration of protection is expected in adolescents.

3.4. Unfavourable effects

The safety of Comirnaty administered to adolescent subjects aged 12-15 years has been evaluated in a total of 2260 (BNT162b n=1131; placebo n=1129) adolescents subjects which have subsequently been recruited to the ongoing phase 3 study (C4591001). The same dose (30µg) and dose regimen as for adult subjects have been used in the study.

At the time of the analysis of the adolescent population aged 12-15 years (data up to the cut-off date of 13 March 2021), a total of 1,308 (n=660 Comirnaty; n=648 placebo) adolescent subjects were evaluated for safety for at least 2 months after the second dose of Comirnaty.

Regarding reactogenicity, the most frequent adverse reactions in adolescent participant aged 12-15 years was pain at the injection site (86% dose1; 79% dose2), fatigue (60% dose1; 66% dose2), headache (55% dose1; 65% dose2), chills (28% dose1; 42% dose2), muscle pain (24% dose1; 32% dose2), joint pain (10% dose1; 16% dose2) and fever (10% dose1; 20% dose2). Vomiting and diarrhoea was reported infrequently after both doses.

Most of the local and systemic events resolved within 3 days and were mild to moderate at intensity. The reactogenicity profile is similar to what has been reported in adult subjects, but the frequency appears in general to be slightly higher. The SmPC has been updated to describe the frequency of the most reported local and systemic events in adolescents, which is endorsed.

The frequency of AEs and SAEs was in general low and no new safety concerns have been detected compared to what was reported for the adult population. A few vaccine related events of lymphadenopathy (BNT162b2 0.8% (9 cases); placebo 0.2% (2 cases)) have been reported.

3.5. Uncertainties and limitations about unfavourable effects

There is a limited number of adolescent subjects aged 12-15 years included in the study, which does not allow detection of rare adverse events. A reassuring number of adult subjects has been exposed to the vaccine (>300 million) without any serious, emerging safety issues. However, if any rare adverse events were to occur specifically or more commonly in adolescent subjects compared to adults, it would not be possible to detect these in this study.

Long term safety data for adolescent subjects are not available at this stage, however the Phase 2/3 study will follow the included subjects up to 2 years post vaccination, so these data are expected post-authorisation.

Limited information is available on use in frail adolescent subjects due to the small study size.

Limited information is available on use in seropositive adolescent subjects due to the small study size.

There is an ongoing PRAC review of cases of 'myocarditis/pericarditis', which have been observed in the post-authorization phase, mainly in adult males below the age of 30. Two such events were

reported in the clinical trials, one in a subject receiving Comirnaty (a 65+year old male) and one in a placebo recipient. Consequently, this is presumed to be a rare event. A reliable frequency estimate is not available, and the impact of age on this possible risk is not understood. Causality has presently not been established.

This safety is being assessed by PRAC, via the monthly safety summary reports (MSSRs) for Comirnaty. The outcome of the current variation to extend to 12 to 15 years old is without prejudice to the outcome of the review of this safety topic at PRAC and any conclusions from such review. The result of this, including any potential recommendations for the terms of the marketing authorisation will be appropriately implemented.

3.6. Effects Table

Table 1. Effects Table for Comirnaty. Intended for active immunisation against SARS CoV-2, thereby preventing Covid-19 in subjects aged 12-15 years (data cut-off: 13 Mar 2021).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Vaccine efficacy		**% (95% CI)**	**Cases in active arm/** Number of subjects at risk for the endpoint	**Cases in placebo arm/** Number of subjects at risk for the endpoint		
	First COVID-19 occurrence from 7days after Dose 2, **without** prior SARS-COV-2,	**100 %** (75.3;100.0)	**0/** 1005	**16/**978	Data with fewer observations, but with similar efficacy confirmed in adults	Evaluable efficacy population (7 days post dose 2) - Study C4951001
	First COVID-19 occurrence from 7days after Dose 2, **with** and **without** prior SARS-COV-2,	**100 %** (78.1;100.0)	**0**/1109	**18**/1110		
	VE after dose 1	**91.6 %** (73.5;98.4)	**3**/1120	**35**/1129	Robust data with sufficient observations. All cases in vaccine arm occurred before 11 days from dose 1	Modified intend to treat population C4951001
Immunogenicity		**Ratio**	**12-15 yo**	**16-25 yo**		1 month after dose 2 Evaluable Immunogenicity population C4951001
	GMT (95% CI)		**N=190**	**N=170**	Sufficient number of subjects to evaluate	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					immunogenicity	
	Ab titer Ratio **younger vs older** age group	**1.76** (1.47-2.10)	**1239.5** (1095.5; 1402.5)	**705.1** (621.4; 800.2)	Non-inferiority demonstrated convincingly	
	GMFR (95% CI)		**N=154**	**N=135**		
	Ab titer ratio **after vaccination vs baseline**		**118.3** (101.4; 137.9	**71.2** (61.3; 82.7)		
	Seroresponse rate % (95% CI)	Difference % 95% CI	**N=143**	**N=124**		
	% subject achieving ≥4-fold rise of Ab titer after vaccination vs baseline	**2.1%** (-6.0;0.9)	N=140 **(97.9 %)** (94.0;99.6 %)	N=124 **(100%)** (97.1;100 %)		
Unfavourable Effects						
Pain at injection site	12-15 years	%	Dose 1 86% Dose 2 79%	Dose 1 23% Dose 2 18%	Transient events, majority mild to moderate intensity	N=1903 (n=1131 BNT162b2; n=1129 placebo)
Fatigue	12-15 years	%	Dose 1 60% Dose 2 66%	Dose 1 41% Dose 2 24%	Transient events, majority mild to moderate intensity	N=1903 (n=1131 BNT162b2; n=1129 placebo)
Headache	12-15 years	%	Dose 1 55% Dose 2 65%	Dose 1 35% Dose 2 24%	Transient events, majority mild to moderate intensity	N=1903 (n=1131 BNT162b2; n=1129 placebo)
Fever	12-15 years	%	Dose 1 10% Dose 2 20%	Dose 1 1% Dose 2 1%	Transient events, majority mild to moderate intensity One event led to discontinuation.	N=1903 (n=1131 BNT162b2; n=1129 placebo)

Abbreviations:

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefit of Comirnaty in adolescents 12-15 years of age has been clearly demonstrated in terms of bridging via neutralising antibody titers, as well as protection against symptomatic disease. The known

unfavourable effects are considered acceptable in terms of reactogenicity, which occurred at a slightly higher frequency compared to the adult population that was evaluated in a previous application. No new safety concerns were observed; however, the study size did not allow detection of rare adverse events.

The CHMP noted that there is an ongoing PRAC review of cases of 'myocarditis/pericarditis', which have been observed in the post-authorization phase, mainly in adult males below the age of 30. Two such events were reported in the clinical trials, one in a subject receiving Comirnaty (a 65+year old male) and one in a placebo recipient. Consequently, this is presumed to be a rare event. A reliable frequency estimate is not available, and the impact of age on this possible risk is not understood. Causality has presently not been established.

Notwithstanding this uncertainty, the B/R balance in the sought indication is considered positive, particularly in adolescent people with comorbidities that increase the risk of severe COVID 19. No statements in the product information are warranted.

This safety is being assessed by PRAC, via the monthly safety summary reports (MSSRs) for Comirnaty. The outcome of the current variation to extend to 12 to 15 years old is without prejudice to the outcome of the review of this safety topic at PRAC and any conclusions from such review. The result of this, including any potential recommendations for the terms of the marketing authorisation will be appropriately implemented.

The following identified uncertainties should be adequately addressed post-authorisation: the long-term efficacy and the duration of protection conveyed by the vaccine, the efficacy on asymptomatic infection, the efficacy in special groups among adolescents.

3.7.2. Balance of benefits and risks

The demonstrated benefits outweigh the identified risks.

3.8. Conclusions

The overall B/R of Comirnaty is considered positive in adolescent subjects aged 12-15 years.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		Type	Annex(es) affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II	I and IIIB

Extension of the existing indication from "individuals 16 years of age and older" to "individuals 12 years of age and older" for Comirnaty; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0179/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

The application for extension of the indication to include adolescents 12-15 years of age is based on a single pivotal phase 1/2/3 study C4591001. It is an extension of the pivotal efficacy study in adults assessed in the initial approval of Comirnaty. The inferential analysis for the 12-15 year olds which was to demonstrate non-inferior immune responses in this age cohort, compared to subjects 16-25 years from the initial efficacy part of the same study.

The effects of Comirnaty in children were investigated in 2,260 children aged 12 to 15 years. The trial showed that the immune response to Comirnaty in this group was comparable to the immune response in the 16 to 25 age group. The efficacy of Comirnaty was calculated in close to 2,000 children from 12 to 15 years of age who had no sign of previous infection. These received either the vaccine or a placebo. Of the 1,005 children receiving the vaccine, none developed COVID-19 compared to 16 children out of the 978 who received the placebo. This means that, in this study, the vaccine was 100% effective at preventing COVID-19 (although the true rate could be between 75% and 100%).

The most common side effects in children aged 12 to 15 are similar to those in people aged 16 and above. They include pain at the injection site, tiredness, headache, muscle and joint pain, chills and fever. These effects are usually mild or moderate and improve within a few days from the vaccination.

The CHMP concluded that the benefits of Comirnaty in this age group outweigh the risks.

The CHMP also noted that due to the limited number of children included in the study, the trial could not have detected rare side effects. The committee also noted that EMA's safety committee PRAC is currently assessing very rare cases of myocarditis and pericarditis that occurred after vaccination with Comirnaty, mainly in people under 30 years of age. Currently there is no indication that these cases are due to the vaccine and EMA is closely monitoring this issue.

Despite this uncertainty, the CHMP considered that benefits of Comirnaty in children aged 12 to 15 outweigh the risks, in particular in children with conditions that increase the risk of severe COVID-19.