25 November 2021
EMA/719541/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of marketing authorisation

COMIRNATY

International non-proprietary name: tozinameran

Procedure No. EMEA/H/C/005735/X/0077

Note

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

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
2019-nCoV	novel coronavirus 2019
AE	adverse event
AESI	adverse event(s) of special interest
ALT	alanine aminotransferase
ARDS	adult respiratory distress syndrome
BDR	blinded data review
BiPaP	bilevel positive airway pressure
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
CPaP	continuous positive airway pressure
CRP	C-reactive protein
CRF	Case Report Form
CRO	contract research organization
CSR	Clinical Study Report
CVA	cerebrovascular accident
DCT	data collection tool
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
ESR	erythrocyte sedimentation rate
EUA	emergency use authorization
FDA	Food and Drug Administration
FiO2	fraction of inspired oxygen
GCP	Good Clinical Practice
GI	gastrointestinal
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICD	informed consent document
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IL-6	interleukin 6
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IRW	interactive Web-based response
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified-intent-to-treat
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding

NT50	neutralizing titer 50
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO2	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PD	protocol deviation
PT	preferred term
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RDC	remote data capture
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription–polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SMQ	standardized MedDRA queries
SOC	system organ class
SpO2	oxygen saturation as measured by pulse oximetry
TME	targeted medical events
ULN	upper limit of normal
VE	vaccine efficacy
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

BioNTech Manufacturing GmbH submitted on 15 October 2021 an extension of the marketing authorisation.

The MAH applied for an addition of a new strength (0.1 mg/ml). The MAH applied for the following indication for COMIRNATY (0.1 mg/ml): Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in children aged 5 to 11 years.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0396/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0396/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP on the paediatric development of Comirnaty.

1.6. 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

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

The application was received by the EMA on	15 October 2021
The procedure started on	18 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 November 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 November 2021
The MAH submitted the responses to the draft List of Questions on	17 November 2021
The CHMP Co-Rapporteur's Critique was circulated to all CHMP members on	19 November 2021
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	22 November 2021
Upon request of the CHMP, the PDCO provided an opinion on the paediatric data with regard to significant therapeutic benefit based on data collected in accordance with the agreed paediatric investigation plan on	19 November 2021
The topic was discussed by ETF during the meeting on	23 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	23 November 2021
The CHMP Rapporteur's updated Assessment Report was circulated to all CHMP and PRAC members on	24 November 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to COMIRNATY on	25 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission. 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 (10 µg) are:

- **Proposed indication:** Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in children aged 5 to 11 years.
- **Dosing administration:** single 10 µg (i.e.0.2-mL) intramuscular (IM) dose followed by a second 10 µg (i.e. 0.2-mL) dose 3 weeks later

2.1.2. 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 adolescents, adults and elderly, but none for the use in children 5 to 11 years old. COVID-19 in children is mostly a mild disease although severe cases occur rarely, particularly in those with underlying, predisposing comorbidities.

2.1.3. 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.

2.1.4. 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 Centres 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
- Diarrhoea
- 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.

2.2. About the product

A conditional marketing authorization was granted for Comirnaty 30 µg by the European Medicines Agency (EMA) on 21 December 2020 for individuals ≥16 years of age and was later extended on 28 May 2021 to include individuals ≥12 years of age. This application concerns use of Comirnaty 10 µg in children from 5 to <12 years of age and a new age appropriate strength (0.1 mg/ml).

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 presently indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older as 30 µg per dose. In the current application, the formulation for children at ages between 5 to 11 contains 10 µg per dose.

2.3. Type of Application and aspects on development

Conditional marketing authorisation

Comirnaty is still authorised under a conditional marketing authorisation.

Orphan designation

Not Applicable.

Similarity with orphan medicinal products

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.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0396/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0396/2021 was not yet completed as some measures were deferred.

2.4. Quality aspects

2.4.1. Introduction

Pfizer and BioNTech have developed the Comirnaty vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus SARS-CoV-2. The vaccine is based on SARS CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs).

There are two approved formulations of Comirnaty vaccine:

- PBS/Sucrose finished product or Comirnaty, 30 microgram/dose, concentrate for dispersion for injection which received a conditional approval 21 December 2020 (EMEA/H/C/005735)
- Tris/Sucrose finished product or Comirnaty, 30 microgram/dose, dispersion for injection, approved 3 November 2021 (EMEA/H/C/005735/X/0044)

The primarily difference is the buffer used for finished product formulation and requirement for dilution prior to administration. The Tris/Sucrose finished product (Comirnaty dispersion for injection) is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4 and is filled into vials at 2.25 mL fill volume, providing 6 doses of 30 µg RNA in 0.3 mL injection volume.

This line extension supports a 10 µg dosage presentation of Tris/Sucrose finished product for immunization of children 5-11 years of age. The 10 µg dosage presentation differs from the already authorised 30 µg presentation only in the fill volume and requirement for dilution prior to administration:

- The 30 µg RNA dosage presentation is filled at 2.25 mL fill volume and is administered without dilution, providing 6 doses, each a 30 µg RNA dose in 0.3 mL injection volume.
- The 10 µg RNA dosage presentation is filled at 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 10 µg RNA dose in 0.2 mL injection volume.

This submission details the manufacture and testing of one Process Performance Qualification (PPQ) lot at Puurs, formulated at XX L batch scale and filled into vials at 1.3 mL (XX L) and 0.4 mL (XX L) fill volumes supporting 10 µg and 3 µg doses. The 3 µg dosage presentation is planned for future line extension application with clinical data supporting a paediatric presentation for younger children.

The finished product is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

2.4.2. Active Substance

The active substance used to manufacture the Tris/Sucrose finished product is identical to that used for the currently approved PBS/Sucrose finished product. Consequently, there are no changes to the active substance sections and full reference is made to the active substance data of Comirnaty, concentrate for dispersion for injection, (EMEA/H/C/005735).

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a preservative-free, sterile dispersion of RNA-containing lipid nanoparticles in an aqueous cryoprotectant buffer for intramuscular injection. There are two formulations of Comirnaty vaccine, one designated PBS/Sucrose or Comirnaty concentrate for dispersion for injection which received a conditional approval in December 2020 and one designated Tris/Sucrose or Comirnaty dispersion for injection which received an approval in November 2021 (line extension EMEA/H/C/005735/X/0044). The primary difference is the buffer used for finished product formulation and requirement for dilution prior to administration. The Tris/Sucrose finished product (Comirnaty dispersion for injection) is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4 and is filled into vials at 2.25 mL fill volume, providing 6 doses of 30 µg RNA in 0.3 mL injection volume.

This line extension (EMEA/H/C/005735/X/0077) supports a 10 µg dosage presentation of Tris/Sucrose finished product for immunisation of children 5-11 years of age.

There are two dosages of the Tris/Sucrose finished product – 30 and 10 µg RNA per dose. The two doses differ only in the fill volume and requirement for dilution prior to administration for the 10 µg RNA per dose:

- The 30 µg RNA dose is filled at 2.25 mL fill volume and is administered without dilution, providing 6 doses, each a 30 µg RNA dose in 0.3 mL injection volume.
- The 10 µg RNA dose is filled at 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 10 µg RNA dose in 0.2 mL injection volume.

The composition of the finished product, including quality standard, function, concentration and amount per dose for the 30 and 10 µg doses are provided in Table 1 and Table 2, respectively.

Table 1. Composition of BNT162b2 Tris/Sucrose Finished Product, 30 µg RNA dose in 0.3 mL Injection Volume, 6 Dose Multi-dose Vial

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per 2.25 mL vial[a]	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.1	225 µg	30 µg
ALC-0315	In-house specification	Functional lipid	1.43	[redacted]	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.18	[redacted]	0.05 mg
DSPC	In-house specification	Structural lipid	0.31	[redacted]	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	[redacted]	0.19 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	[redacted]	31 mg
Tromethamine (Tris base)[b]	USP-NF, Ph. Eur.	Buffer component	0.20	[redacted]	0.06 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[c]	In-house specification	Buffer component	1.32	[redacted]	0.4 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[d]					
[redacted]	Ph. Eur.	Processing aid	N/A		
	Ph. Eur.	Processing aid			
	Ph. Eur.	Processing aid			
	Ph. Eur.	Processing aid			
	In-house specification	Drug substance buffer component			
	Ph. Eur., USP-NF	Drug substance buffer component			

a. Values are rounded to maintain the same level of precision as the label claim, with trailing decimals not shown, where applicable.
b. Also known as Trometamol
c. Also known as Tromethamine HCl and Trometamol HCl
d. The processing aids and drug substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered ingredients (excipients).
Abbreviations:
ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)
[redacted]

Table 2. Composition of BNT162b2 Tris/Sucrose Finished Product, 10 µg RNA dose in 0.2 mL Injection Volume, 10 Dose Multi-dose Vials

Name of Ingredients	Reference to Standard	Function	Concentration Prior to Dilution (mg/mL)	Amount per vial after dilution[a,b]	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.1	130 µg	10 µg
ALC-0315	In-house specification	Functional lipid	1.43	[redacted]	0.14 mg
ALC-0159	In-house specification	Functional lipid	0.18	[redacted]	0.02 mg
DSPC	In-house specification	Structural lipid	0.31	[redacted]	0.03 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	[redacted]	0.06 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	[redacted]	10.3 mg
Tromethamine (Tris base)[c]	USP-NF, Ph. Eur.	Buffer component	0.20	[redacted]	0.02 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[d]	In-house specification	Buffer component	1.32	[redacted]	0.13 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[e]					
[redacted]	Ph. Eur.	Processing aid	N/A		
	Ph. Eur.	Processing aid			
	Ph. Eur.	Processing aid			
	Ph. Eur.	Processing aid			
	In-house specification	Drug substance buffer component			
	Ph. Eur., USP-NF	Drug substance buffer component			

a. Vials filled at 1.3 mL drug product and diluted to 2.6 mL with 0.9% sodium chloride (NaCl) prior to administration. NaCl at 11.7 mg/vial and 0.9 mg/dose after dilution.
b. Values are rounded to maintain the same level of precision as the label claim, with trailing decimals not shown, where applicable.
c. Also known as Trometamol
d. Also known as Tromethamine HCl and Trometamol HCl
e. The processing aids and drug substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered ingredients (excipients).
Abbreviations:
ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)

All excipients except the functional lipids ALC-0315 and ALC-0159, the structural lipid DSPC and the buffer component TRIS HCl comply to Ph. Eur. grade. The functional lipids ALC-0315 and ALC-0159 and the structural lipids DSPC and cholesterol are all used in both the PBS/Sucrose finished product as

well as in the Tris/Sucrose finished product. The buffer components Tris base (Trometamol) and Tris HCl (Trometamol hydrochloride) are commonly used excipients in several already approved parenteral finished products in the EU, including vaccines and products for paediatric use.

At the time of initial authorisation, ALC-0315 and ALC-0159 were novel excipients. In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, additional information have been provided as requested in specific obligations (SO) for the PBS/Sucrose finished product. The data to fulfil SO4 and SO5 were submitted by end of July 2021 and in November 2021 and are currently under assessment via variation procedure EMEA/H/C/005735/II/0054/G.

The container closure system for the commercial BNT162b2 Tris/Sucrose finished product is a 2 mL Type I borosilicate or aluminosilicate glass vial and a 13 mm bromobutyl stopper.

The processing aids used in the manufacture have been specified in the composition together with a foot note that they are essentially removed through the manufacturing process and are not considered as ingredients (excipients).

This is found acceptable.

Pharmaceutical Development

The major part of the content in section P.2 for the Tris/Sucrose finished product is contained in the dossier for the already approved Line extension EMEA/H/C/005735/X/0044. However, the section P.2 has been updated in various parts in this specific Line extension EMEA/H/C/005735/X/0077.

QTPP

The QTPP that was developed for the Tris/Sucrose finished product and provided in the already approved Line extension EMEA/H/C/005735/X/0044, has been updated to include finished product filled at 1.3 mL fill volume.

Finished product

The approved Tris/Sucrose finished product is formulated at 0.1 mg/mL RNA in Tris buffer and sucrose and is filled into vials at 2.25 mL fill volume, providing 6 doses of 30 µg RNA in 0.3 mL injection volume (EMEA/H/C/005735/X/0044).

This specific line extension (EMEA/H/C/005735/X/0077) supports a presentation of Tris/Sucrose finished product filled into vials at 1.3 mL fill volume, providing (after dilution) 10 doses of 10 µg RNA in 0.2 mL injection volume, for immunization of children 5-11 years of age. The 10 µg presentation differs from the already authorised 30 µg presentation only in the fill volume and requirement for dilution prior to administration for the 10 µg RNA per dose.

Acceptable results have been provided demonstrating that the target fill volume for the 10 µg finished product when diluted at the point of use with 0.9% sodium chloride is suitable for delivering 10 doses at 0.2 mL per multi-dose vial. This study includes assessment of hold-up volume and delivered dose volume for 10 µg dose vials after dilution with 0.9% sodium chloride. The provided results also show that the 2 mL vial can contain the total volume of 2.6 mL corresponding to 1.3 mL of finished product and 1.3 mL 0.9% sodium chloride.

There are no formula overages in the finished product, only an overfill which has been acceptably justified.

In summary, the section on finished product development has been acceptably updated to include finished product filled at 1.3 mL fill volume for 10 µg doses.

Formulation development

The formulation development of the Tris/Sucrose formulation was described in the already approved Line extension EMEA/H/C/005735/X/0044. The development of the Tris/Sucrose finished product showed quality attributes highly comparable and also within the clinical ranges of the current approved PBS/Sucrose finished product but with an improved stability profile in support of increased storage times at -20 °C and 2-8 °C that would simplify transport and administration.

Lot genealogy

Lot Genealogy for the Tris/Sucrose finished product has been provided for primary stability lots and for process performance qualification lots including both the 30 µg and 10 µg dose finished product (PPQ5). Batch Analyses data are provided.

Manufacturing process development and characterization

The section on manufacturing process development and characterisation has been updated with shear stress calculations as well as with thawing time data for vials filled at 1.3 mL fill volume. This section has also been updated with PPQ 5 that has been manufactured for filling of 1.3 mL and 0.4 mL fill volume, corresponding to 10 µg and 3 µg dose finished product. The 3 µg dose presentation is planned for a future registration with clinical trial data supporting a new paediatric indication but is not assessed in this report. The information provided is found sufficient.

Container closure system

The container closure system for the commercial Tris/Sucrose finished product is a 2 mL Type I borosilicate or aluminosilicate glass vial and 13 mm bromobutyl rubber stopper and these are compliant with the compendial requirements of the Ph. Eur. and are further addressed in section 3.2.P.7.

The dossier has been updated with satisfactory data from a study on penetrability, fragmentation and self-sealing capacity to support 11 punctures of the 10 µg dose vial. This section has also been updated for container closure integrity verification in support of freezing and shipping of finished product filled at the filling volume of 2.25 mL, considered as worst case condition of maximum filling volume. The development of container closure system is sufficiently presented and this is found acceptable.

Microbiological attributes

The dossier has been updated to add container closure integrity studies for vials filled at the filling line WSL10 at Pfizer, Puurs utilized for filling at 1.3 mL filling volume for 10 µg doses.

The BNT162b2 Tris/Sucrose finished product container closure system has been evaluated by dye ingress, vacuum decay and headspace analysis testing methods. These studies have provided acceptable data and verified that the stopper/vial/cap combinations maintain integrity when capped with low and high spring force settings. Results shown provide evidence of container closure integrity for the BNT162b2 Tris/Sucrose finished product container closure system.

Compatibility

The administration simulation and compatibility studies performed for the Tris/Sucrose finished product for the 1.3 mL fill volume demonstrate physical and chemical stability of undiluted and diluted finished product (diluted with 0.9% sodium chloride) for up to 24 hours at ambient temperature in vials. These studies also demonstrate stability of both undiluted and diluted finished product in syringes for 12 hours at ambient temperature or 24 hours at refrigerated temperature (2-8 °C).

Microbial studies have been performed for Tris/Sucrose finished product and based on physicochemical stability and microbial in-use growth results, the Tris/Sucrose finished product vials (both 2.25 mL and 1.3 mL fill volume) may be held at ambient temperatures for up to 24 hours, but once punctured, either for dilution or first use, may be held at 2°C to 25°C and should be used or discarded within 12 hours.

In summary, compatibility of the 1.3 mL fill volume Tris/sucrose finished product is acceptably demonstrated by compatibility studies provided on physicochemical stability and microbial in-use hold time.

2.4.3.2. Manufacture of the product and process controls

The manufacturing sites and the manufacturing process are the same as for the Tris/Sucrose finished product Comirnaty dispersion for injection 30 microgram/dose (EMEA/H/C/005735/X/0044) except for a different fill volume.

The manufacturing process consists of four major manufacturing steps – LNP fabrication, bulk finished product formation, sterile filtration and aseptic filling.

The commercial batch size is XX L of finished product solution corresponding to approximately XX vials at 1.3 mL fill volume. The manufacturing process is sufficiently described, and suitable in-process controls (IPCs) are applied.

Process validation has been performed on one Process Performance Qualification batch at XX L manufactured at Pfizer Puurs. The batch is split into XX L at 1.3 mL fill volume (PPQ 5a) and XX L at 0.4 mL fill volume (PPQ 5b). All data complies with the pre-specified criteria and sufficiently demonstrate that the manufacturing process is robust and provides a finished product with adequate quality. Since only the fill volume differs from the approved Tris/Sucrose finished product, the process validation for that product (2.25 ml fill volume) is considered as supportive, and a single PPQ batch (1.3 ml and 0.4 ml fill volume) is considered sufficient for process validation. In addition, Official EU batch release (for blood products and vaccines) will be performed by the OMCL.

2.4.3.3. Product specification

The finished product specifications at release and shelf life include tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD), ALC-0159 content (HPLC-CAD), DSPC content (HPLC-CAD), Cholesterol content (HPLC-CAD), vial content (volume) (USP), Lipid identities (HPLC-CAD), Identity of encoded RNA sequence (RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion). For all quality attributes tested on stability except for RNA integrity and LNP size, the acceptance criteria for release and stability testing throughout shelf life are the same.

The specifications and justifications of specifications for the Tris/Sucrose finished product are based on the specifications as contained in the dossier for the already approved Line extension EMEA/H/C/005735/X/0044. The acceptance criteria that differ between the specifications included in the approved Line extension EMEA/H/C/005735/X/0044 and this specific applied Line extension EMEA/H/C/005735/X/0077 is only the vial content (volume), not less than 1.222 mL (for 1.3 mL fill volume).

The vial content (volume) for the Tris/Sucrose finished product was determined to ensure that each 1.3 mL filled vial can deliver ten 10 µg doses of 0.2 mL each, following the addition of 1.3 mL 0.9% sodium chloride. The provided justification for vial content (volume) of 1.3 mL fill volume is found acceptable.

Validation of analytical procedure

This section has been updated to add qualification data for the container content test. A bracketing approach was used to validate the method for all Tris/Sucrose finished product presentations, with the highest and lowest fill volumes selected, 2.25 mL and 0.4 mL, respectively. This approach is found acceptable.

Batch analysis

The section on batch analysis data have been updated with release data for PPQ5, filled at 1.3 and 0.4 mL fill volume. This PPQ5 lot met all the release specifications of the Tris/Sucrose finished product specifications document.

The manufacture of PPQ5 has been detailed and the lot genealogy is provided in the dossier. In addition, PPQ5 is included in the stability program and initial testing results have been provided in dossier section P.8.

The specification, analytical procedures, and batch analysis are found acceptable, and no issues are raised.

Reference standard

Reference standards or material are identical to the approved Tris/Sucrose finished product Comirnaty dispersion for injection 30 microgram/dose (EMEA/H/C/005735/X/0044).

Container closure system

The container closure system is identical to the approved Tris/Sucrose finished product Comirnaty dispersion for injection 30 microgram/dose (EMEA/H/C/005735/X/0044).

Tris/Sucrose finished product is filled in a Type I borosilicate glass vial or an aluminosilicate glass vial. The same stoppers and seals/caps are used as for the PBS/Sucrose finished product.

2.4.3.4. Stability of the product

The proposed shelf-life for the 10 µg dosage presentation is 6 months at the long-term storage condition of -90 to -60 °C with an additional 10 weeks storage at 2-8 °C at the point of use.

The major part of the content of stability section P.8 for the Tris/Sucrose finished product is contained in the dossier for already approved Line extension EMEA/H/C/005735/X/0044. However, the section P.8 has been updated in various parts in this Line extension EMEA/H/C/005735/X/0077.

The approved initial shelf-life for the Tris/Sucrose 30 µg finished product is 6 months when stored at the recommended long-term storage condition of -90 to -60 °C. Additionally, 10 weeks storage at 2-8 °C is approved at the point of use within the 6 months shelf-life. This 6 months shelf-life is based on the results provided in the recently approved line extension EMEA/H/C/005735/0044.

In this specific applied line extension EMEA/H/C/005735/0077, sections P.5.4 and P.8 have been updated to include the initial release testing results for the PPQ5 lot filled at 1.3 mL and 0.4 mL fill volume. The results met all acceptance criteria in the finished product specifications document.

Based on the totality of stability data available for the Tris/Sucrose finished product (both 10 µg and 30 µg dosage presentation) as well as the fact that the only difference between the PPQ5 lot of the 10 µg dosage presentation and the other 30 µg dosage batches included in the stability program is the fill volume, 2.25 mL versus 1.3 mL, the proposed shelf-life of 6 months at the recommended long-term storage condition of -90 to -60 °C and the additional 10 weeks storage at 2-8 °C at the point of use, is agreed to for the 10 µg dosage presentation.

This is found acceptable. However, it is expected that all the ongoing stability studies at long-term conditions will be continued until completion and that any results of out-of-trend or out-of-specifications will be reported to the competent authorities. A clarification should be included in stability section P.8 in the closing sequence to confirm this.

2.4.3.5. Post approval change management protocol(s)

Not applicable.

2.4.3.6. Adventitious agents

The active substance used to manufacture the Tris/Sucrose finished products (30 micrograms/dose and 10 micrograms/dose) is identical to that used for the currently approved PBS/Sucrose finished product. Consequently, there are no changes to the active substance sections and full reference is made to the active substance data of Comirnaty, concentrate for dispersion for injection (EMEA/H/C/005735). Adequate testing for bioburden, endotoxins and sterility are also included at appropriate stages of the manufacturing process of the finished product.

2.4.3.7. GMO

Not applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The Tris/Sucrose finished product is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4. There are two dosages of the Tris/Sucrose finished product – 30 and 10 µg RNA per dose. The two doses differ only in the fill volume and requirement for dilution prior to administration:

- The 30 µg RNA dose is filled at 2.25 mL fill volume and is administered without dilution, providing 6 doses, each a 30 µg RNA dose in 0.3 mL injection volume.
- The 10 µg RNA dose is filled at 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 10 µg RNA dose in 0.2 mL injection volume.

The section on pharmaceutical development is found sufficiently comprehensive and acceptable.

The manufacturing sites and the manufacturing process are the same as for the already approved Tris/Sucrose finished product, 30 µg/dose (EMEA/H/C/005735/X/0044) except for a different fill volume. The manufacturing process is sufficiently described, and suitable in-process controls (IPCs) are applied.

Process validation has been satisfactorily performed on one Process Performance Qualification batch at XX L manufactured at Pfizer Puurs and this is found sufficient.

The specifications document for the Tris/Sucrose finished product includes a comprehensive set of relevant tests and the proposed acceptance criteria are found acceptable and adequately justified for all quality attributes included and no issues are raised.

The proposed 6 months shelf-life at -90 to -60 °C and 10 weeks storage at 2-8 °C at the point of use within the 6 months shelf-life is agreed to.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that this line extension application to register Comirnaty (10 micrograms/dose) concentrate for dispersion for injection is approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

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

2.6. Clinical aspects

2.6.1. Introduction

- **Tabular overview of clinical studies**

Protocol No. Phase (Country) Start	Study Design and Objective(s)[a]	Treatment Groups	No. of Subjects
C4591007 Phase 1 (United States) **Start Date:** March 2021 (ongoing)	**Phase 1[b]** **Primary Objectives:** • Safety To describe the safety and tolerability profiles of prophylactic BNT162b2 at each dose level in each age group[c] **Secondary Objectives:** • Immunogenicity To describe the immune responses elicited by prophylactic BNT162b2 at each dose level in each age group[c]	**Phase 1[c]:** **BNT162b2** (10 µg, 20 µg, 30 µg)	**Phase 1: BNT162b2[c]** **10 µg** (5 to <12 years of age) 16 BNT162b2 **BNT162b2** **20 µg** (5 to <12 years of age) 16 BNT162b2 **BNT162b2** **30/30 µg[d]** (5 to <12 years of age) 4 BNT162b2 **BNT162b2** **30/10 µg[d]** (5 to <12 years of age) 12 BNT162b2
C4591007 Phase 2/3 (United States, Finland, Poland, Spain) **Start Date:** March 2021 (ongoing)	**Phase 2/3[e]** **Primary Objectives:** • **Safety** To define the safety profile of prophylactic BNT162b2 at the *selected dose* level in all participants randomized in Phase 2/3 in each age group[f]	**Phase 2/3[f]:** **BNT162b2** (10 µg) **Placebo**	**Phase 2/3[g]: BNT162b2** 1518 BNT162b2 750 Placebo (5 to <12 years of age)

	• **Immunogenicity** To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants atthe dose selected in each age group[f] and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection **Secondary Objectives:** • **Immunogenicity** To describe the immuneresponses elicited by prophylactic BNT162b2at the dose level selected in each age group[f] and persistence of immune response in Phase 2/3 participants without serological or virological evidence of past SARS-CoV-2 infection		
C4591001[h] Phase 2/3 (United States, Brazil, Argentina, Turkey, SouthAfrica, and Germany)		**Phase 2/3[h]: Immunobridging Subset** **16 to 25 years of age: 253 BNT162b2 30 µg**	

2.6.2. Clinical efficacy

2.6.2.1. Dose response study

Phase 1 part of paediatric Study C4591007

Children from 5 to <12 years of age received escalating dose levels of BNT162b2 (10 µg, 20 µg, or 30 µg) administered as a 2-dose series 21 days apart, with progression to higher dose levels based on recommendations from an IRC. Each dose level was planned to be administered to 16 participants, for a total of 48 vaccinated children 5 to <12 years of age. Due to reactogenicity, the 30 µg dose was only given as a first dose to 4 subjects, and the remainder of the subjects in this group received 10 µg instead. At Day 7 post-Dose 2, the GMTs were similar across the tested dose levels.

The MAH concluded that BNT162b2 elicited robust SARS-CoV-2 50% neutralizing titers by 7 days after Dose 2 at both tested dose levels when administered to healthy children 5 to <12 years of age. The 10 µg dose was selected for use in phase 2/3 of the study.

2.6.2.2. Main study

Phase 2/3 of Paediatric Study C4591007

Methods

Study Participants

Participants enrolled in Phase 2/3 of Study C4591007 were at ages 5 to less than12.

Treatments

Participants were randomized in a 2:1 ratio to receive either BNT162b2 (10 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.

Recruitment

The study started to recruit 24.03.2021 and is still ongoing.

Conduct of the study

The Phase 1/2/3 Study C4591007 was undertaken by Pfizer and BioNTech and conducted at a total of 84 sites as of the data cut-off date (06 September 2021): 11 in Finland, 8 in Poland, 10 in Spain, and 55 in the US. There were an additional 2 study centres in the US that received study drug but did not enter any participants. For Phase 1, participants were entered at US sites only.

The study was conducted by investigators contracted by and under the direction of Pfizer. The investigators were responsible for adhering to the study procedures described in the protocol, for keeping records of the study intervention, and for ensuring accurate completion of the CRFs and DCTs supplied by the sponsor.

No sites were terminated from the study as of the Phase 2/3 data cut-off date (06 September 2021).

The paediatric investigational Plan has label EMEA-002861-PIP02. The original protocol from 5.02.2021 has been amended 3 times: 5.03, 6.08 and 10.09. The last amendment did not affect the results included in current application.

Objectives

Only objectives included in the provided interim report related to phase 2/3 are shown below.

Primary safety:
To define the safety profile of prophylactic BNT162b2 at the *selected dose* level in all participants randomized in Phase 2/3 in each age group.

Primary immunogenicity:
To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the dose selected in participants 5 to <12 years of age and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection.

Secondary immunogenicity:
To describe the immune responses elicited by prophylactic BNT162b2 at the dose level selected in each age group and persistence of immune response in Phase 2/3 participants without serological or virological evidence of past SARS-CoV-2 infection.

Exploratory:
To describe COVID-19 and severe COVID-19 cases in participants in the selected-dose portion of the study with and without serological or virological evidence of past SARS-CoV-2 infection.

To describe MIS-C cases with and without evidence of past SARS-CoV-2 infection in participants in the selected-dose portion of the study.

Vaccine efficacy

If success criteria for immunobridging were successful, the secondary endpoints for estimation of vaccine efficacy (VE) against confirmed COVID-19 in Phase 2/3 participants were evaluated.

Confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up in evaluable participants without and with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection.

Sample size

A detailed sample size calculation was provided in the protocol for the Phase 2/3 selected-dose portion of the study, including power for immunobridging, VE and probabilities to observe AEs.

The Phase 2/3 selected-dose portion of the study was planned to randomize approximately 4500 participants (randomization ratio of 2:1 so that 3000 receive active vaccine and 1500 receive placebo) for the ≥5 to <12 years age group. For the lower-dose evaluation portion of the study, Phase 2/3 will include approximately 300 participants for each age group that will receive active vaccine at the selected dose level, with a total of approximately 900 participants.

In Phase 2/3, primary immunobridging assessments had an immunobridging subset sample size of 225 evaluable participants in Study C4591007 (5 to <12 years of age) and corresponding randomly selected comparator group in Study C4591001 (16 to 25 years of age), providing 90.4% and 92.6% power to declare immunobridging success based on GMR and seroresponse difference, respectively.

The initial enrolment into the 5 to <12 years of age group included N~2250 (1500 active and 750 placebo).

An additional N~2250 participants 5 to <12 years of age were enrolled and also randomized 2:1 (1500 active and 750 placebo) as a safety expansion group in the Phase 2/3 part of Study C4591007, to obtain a larger safety database to support a future application for licensure for this age group, and an additional 750 participants 5 to <12 years of age are being enrolled and randomized 2:1 (500 active and 250 placebo) to obtain serum samples for potential troponin I testing which may help characterize subclinical myocarditis.

Randomisation and blinding (masking)

Participants were randomized 2:1 active: placebo. Allocation (randomization) of participants to vaccine groups proceeded through the use of an IRT system (IWR).

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 to be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety were to be blinded. Because BNT162b2 and placebo are different in physical appearance, the study intervention syringes was to be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

Statistical methods

Immunogenicity Endpoint, Phase 2/3 Selected-Dose (primary endpint): SARS-CoV-2 Neutralizing Titers in Participants ≥5 to <12 Years (ages ≥2 to <5 Years, or ≥6 Months to <2 Years of Age in later submission) to Those 16 to 25 Years of Age in Study C4591001.

Estimand 1:

GMR (geometric mean ratio) of the SARS-CoV-2 neutralizing titers in participants ≥5 to <12 years of age to those in the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection.

Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable).

Analysis time point: 1 Month after Dose 2.

Analysis methodology: The GMRs and associated 2-sided 95% CIs will be 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 will be the younger age group minus the group 16 to 25 years of age. Immunobridging success will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.

Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence of past SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.

•• Reporting results: The GMRs and associated 2-sided 95% CIs will be provided.

Estimand 2:

The difference in percentages of participants with seroresponse in participants ≥5 to <12 years of age and the 16- to 25-year age group in Study C4591001 for participants without evidence of past SARS-CoV-2 infection

Analysis set: Evaluable immunogenicity population, all-available immunogenicity population (as applicable).

Analysis time point: 1 Month after Dose 2.

Analysis methodology: The differences in percentages of participants with seroresponse will be provided along with associated 2-sided 95% CIs calculated using the Miettinen and Nurminen2 method. Immunobridging success based on the seroresponse difference will be declared for an age group if the lower bound of the 2-sided 95% CIs for the seroresponse difference is greater than -10%.

Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed. Only participants with no serological or virological evidence of past SARS-CoV-2 infection will be included. Participants' data will be excluded from the time point that the participant has a positive NAAT or positive N-binding result.

Reporting results: Counts, percentages of participants with seroresponse, the difference in percentages, and the associated 2-sided 95% CIs will be provided.

Secondary immunogenicity endpoints were also defined in the SAP.

Vaccine Efficacy Endpoints, Phase 2/3 Selected-Dose (secondary endpoint, supporting analysis): COVID-19 Incidence per 1000 Person-Years of Blinded Follow-up

Estimands:

1) 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants without evidence of past SARS-CoV-2 infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group for the ≥5 to <12-year age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined, or across all age groups (if the required number of cases is not accrued in either of 2 individual age groups).

2) 100 × (1 - IRR) [ratio of confirmed COVID-19 illness from 7 days after Dose 2 per 1000 person-years of blinded follow-up in participants with or without evidence of past SARS-CoV-2 infection (prior to 7 days after receipt of Dose 2) for the active vaccine group to the placebo group for the ≥5 to <12-year age group and for the ≥6-month to <2-year and ≥2- to <5-year age groups combined, or across all age groups (if the required number of cases is not accrued in either of 2 individual age groups)].

Analysis set: Evaluable efficacy and all-available efficacy populations.

Analysis time point: End of the surveillance period (blinded follow-up).

Analysis methodology: Assessment of VE will be performed for confirmed COVID-19 illness from 7 days after Dose 2, and will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group. The hypothesis test for the VE objective will be performed if at least 22 cases are accrued at the time of analyses.

The assessment of VE was to be based on testing the following hypothesis: H0: VE ≤ 30% vs H1: VE >30% for VE1 and VE2, respectively.

Intercurrent events and missing data: Missing data will not be imputed.

Reporting results: VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time will be provided for the corresponding age groups.

Supplemental Analyses: The same assessment of VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time for the corresponding age groups will be performed for confirmed COVID-19 illness based on CDC-defined symptoms.

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 valid and determinate immunogenicity result after Dose 2 from the blood sample collected within an appropriate window after Dose 2 (within 6-8 days after Dose 2 for Phase 1 and within 28-42 days after Dose 2 for Phase 2/3), and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
Evaluable efficacy (seroconversion)	All eligible randomized participants who receive all vaccination(s) as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), have at least 1 N-binding antibody test result available at a post–Dose 2 visit, and have no other important protocol deviations as determined by the clinician prior to the first post–Dose 2 N-binding antibody test.
All-available efficacy (mITT)	Dose 1 all-available efficacy: All randomized participants who receive at least 1 vaccination. Dose 2 all-available efficacy: All randomized participants who complete 2 vaccination doses.
Safety	All participants who receive at least 1 dose of the study intervention.

Analysis sets

Efficacy analyses were conducted on the evaluable efficacy population (participants who received both doses within the protocol defined window and had no important protocol deviations prior to 7 days post-Dose 2), and the all-available efficacy (modified intent-to-treat [mITT] populations (all participants who received vaccination).

The VE analyses were conducted among those without evidence of past SARS-CoV-2 infection and among those with or without evidence of past SARS-CoV-2 infection.

VE estimation for confirmed COVID-19 uses the first definition (per protocol criteria). A supplemental analysis using the same assessment of VE and associated Clopper-Pearson 95% CI was performed for confirmed COVID-19 illness using the second definition (CDC criteria).

The comparator group of participants 16-25 years, used for immunobridging analysis, consisted of a random set of participants from the study C4591001.

Subgroup analyses

Subgroup analyses of efficacy endpoints were planned to be conducted based on demographics (sex, race, and ethnicity), country, SARS-CoV-2 status (positive or negative), and risk status (comorbidities that increase the risk for severe COVID-19 illness, categorized based on medical history terms previously reported with safety analyses).

Multiplicity

For the immunogenicity objectives of immunobridging of BNT162b2 in each of the 5 age groups (16 to <30 years, 12 to <16 years, ≥5 to <12 years [selected-dose and lower-dose evaluation participants], ≥2 to <5 years, and ≥6 months to <2 years of age) to the comparator group from Phase 2/3 of the C4591001 study, the hypothesis testing for each age group will be carried out separately. Each immunobridging analysis corresponds to a separate analysis of the respective age group, with a separate objective. The age groups are included in the same study to improve operational efficiency. Therefore, no type I error adjustments were applied in the immunogenicity assessments for the 5 age groups.

Within each age group, except for the ≥5 to <12-year age group, immunobridging based on GMR and seroresponse difference will be assessed sequentially in the order as specified. Within the ≥5 to <12-year age group, immunobridging based on GMR and seroresponse difference will be first assessed sequentially in participants from the selected-dose portion of the study, and then assessed sequentially in participants from the lower-dose evaluation portion of the study.

In each of the 2 age groups (≥5 to <12 years, ≥6 months to <2 years and ≥2 to <5 years combined) in the selected-dose portion of the study, where immunobridging success is declared, if the required number (21) of confirmed COVID-19 cases is accrued, then the secondary VE objectives, VE1 and VE2, will be tested sequentially in the order as stated for each age group.

Thus, this sequential testing strategy controls type I error at the desired level of 2.5% within each age group. Efficacy objectives for each of the 2 age groups will be assessed separately. No type I error adjustments will be applied in the efficacy assessments for the 2 age groups for the same reason described above for immunogenicity assessments. However, if the required number (21) of confirmed COVID-19 cases is not accrued in either of the 2 age groups where immunobridging success is declared, but 21 cases are accrued across all the age groups where immunobridging success is declared, then hypothesis testing will be conducted across the age groups with immunobridging success.

The submitted analysis was performed after 19 cases were accrued.

Immunogenicity Results

Participant flow

Immunogenicity Populations

The Phase 2/3 evaluable immunogenicity population for participants 5 to <12 years of age included 294 participants in the BNT162b2 group and 147 participants in the placebo group, and for Study C4591001 participants 16 to 25 years of age included 273 participants in the BNT162b2 group and 47 participants in the placebo group. Exclusions from the evaluable immunogenicity population were generally balanced across vaccine groups, and the most common reason for exclusion was participants not having at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2.

Disposition

The disposition of Phase 2/3 pediatric participants 5 to <12 years of age in the immunobridging subset through 1 month after Dose 2 was similar to that of all randomized participants for the BNT162b2 and placebo groups. Most participants across both groups completed the visit at 1 month after Dose 2 (≥97.7%). There were no meaningful differences in the discontinuation or withdrawal categories in this subset.

Within the immunobridging subset, most participants randomized in both age groups (≥99.1%) received Dose 1 and Dose 2. Most participants across age groups completed the visit at 1 month after Dose 2 (≥97.7%).

Baseline data

Demographic Characteristics

The demographic characteristics of the evaluable immunogenicity population, immunobridging subset, are summarised in Table 3.

Table 3. Demographic Characteristics – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) (N[a]=264) n[b] (%)	30 µg 16-25 Years (C4591001) (N[a]=253) n[b] (%)	5 to <12 Years (C4591007) (N[a]=130) n[b] (%)	16-25 Years (C4591001) (N[a]=45) n[b] (%)
Sex				
Male	140 (53.0)	126 (49.8)	72 (55.4)	16 (35.6)
Female	124 (47.0)	127 (50.2)	58 (44.6)	29 (64.4)
Race				
White	206 (78.0)	194 (76.7)	103 (79.2)	29 (64.4)
Black or African American	17 (6.4)	27 (10.7)	5 (3.8)	11 (24.4)
American Indian or Alaska Native	0	3 (1.2)	0	1 (2.2)
Asian	21 (8.0)	16 (6.3)	14 (10.8)	2 (4.4)
Native Hawaiian or other Pacific Islander	BLD			
Multiracial	16 (6.1)	11 (4.3)	6 (4.6)	1 (2.2)
Not reported	BLD			
Ethnicity				
Hispanic/Latino	BLD			
Non-Hispanic/non-Latino	223 (84.5)	158 (62.5)	110 (84.6)	32 (71.1)
Not reported	BLD			
Age at vaccination (years)				
Mean (SD)	8.3 (1.85)	20.9 (3.02)	8.3 (2.04)	20.8 (3.10)
Median	8.0	21.0	9.0	22.0
Min, max	(5, 11)	(16, 25)	(5, 11)	(16, 25)
Obese[c]				
Yes	21 (8.0)	40 (15.8)	15 (11.5)	14 (31.1)
No	243 (92.0)	213 (84.2)	115 (88.5)	31 (68.9)

Abbreviations: COVID-19 = coronavirus disease 2019; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding;
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart for 5 to <12 years of age or BMI ≥30 kg/m² for 16 to 25 years of age.

Numbers analysed

	Active arm (5 to <12 years old)	Control arm (16-25 years old)
Randomized	311	286
Immunobridging Pop	264	253

Outcomes and estimation

Geometric Mean Ratio (GMR) of Neutralizing Titers

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 50% neutralizing GMT in children 5 to <12 years of age (who received the 10-µg dose level) to that of young adults 16 to 25 years of age (who received the 30-µg dose level) was 1.04 (2-sided 95% CI: 0.93, 1.18) (Table 4).

The lower bound of the 2 sided 95% CI for GMR was >0.67 and the GMR point estimate was ≥0.8, which meets the prespecified 1.5-fold margin and success criteria. Therefore, immunobridging based on GMR was achieved. Note that the observed GMR point estimate meets the requested criterion from the FDA of ≥1.

Table 4. Summary of Geometric Mean Ratios – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)								
		BNT162b2								
		10 µg 5 to <12 Years (C4591007)			30 µg 16-25 Years (C4591001)			5 to <12 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 Immunobridging Objective[e] (Yes/No)
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	264	**1197.6**	(1106.1, 1296.6)	253	**1146.5**	(1045.5, 1257.2)	**1.04**	(0.93, 1.18)	Yes

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers ([5 to <12 years] - [16-25 years]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.8.

Difference in Seroresponse Rate

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, high and equal proportions (99.2% each of children 5 to <12 years of age and young adults 16 to 25 years of age) achieved a seroresponse from before vaccination to 1 month after Dose 2. The difference in the proportions of participants who had seroresponse between the 2 age groups (children – young adults) was 0.0% (2-sided 95% CI: -2.0%, 2.2%) (Table 5).

Since immunobridging based on GMR was achieved, hypothesis of immunobridging based on seroresponse rate was tested subsequently. The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved.

Table 5. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 to <12 Years of Age to Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		BNT162b2							
		10 µg 5 to <12 Years (C4591007)			30 µg 16-25 Years (C4591001)			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	264	262 (99.2)	(97.3, 99.9)	253	251 (99.2)	(97.2, 99.9)	0.0	(-2.0, 2.2)

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (5 to <12 years – 16-25 years).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Subgroup Analysis

SARS-CoV-2 50% neutralizing titers (GMTs) were evaluated by demographic and baseline SARS-CoV-2 status subgroups. Subgroups of paediatric participants 5 to <12 years of age and young adults 16 to 25 years of age (with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2) had similar patterns of GMTs at before vaccination and 1 month after Dose 2 across the BNT162b2 and placebo groups when evaluated by sex, race, and ethnicity.

Several subgroups included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the neutralizing titers on the basis of demographic subgroups within each age group, or between the age groups. Participants who were SARS-CoV-2 baseline status positive had higher GMTs at both before vaccination and 1 month after Dose 2 compared to those negative at baseline, in both age groups.

Ancillary analyses

The MAH submitted later on also a separate report (dated 15.10.2021) which provides supportive immunogenicity data to 1 month after Dose 2 from a random subset of N~40 Study C4591007 Phase 2/3 participants 5 to <12 years of age (35 active and 5 placebo) who were included in the successful immunobridging analyses. These supportive immunogenicity data are SARS-CoV-2 serum neutralizing titers against USA-WA1/2020 (reference) and B.1.617.2 (Delta) variant strains.

Endpoints

A 50% plaque-reduction neutralization test (PRNT) was used to determine SARS-CoV-2 serum neutralizing titers as described previously. The PRNT is distinct from the validated SARS-CoV-2 neutralization assay used to determine titers for immunobridging analyses thatwere previously submitted.

PRNT titers were assessed in sera before vaccination and 1 month after BNT162b2 Dose 2. PRNT titers were determined against the designated wild-type reference strain, recombinant USA-WA1/2020 (clinical strain isolated in January 2020), and against B.1.617.2 (Delta), using a recombinant virus with the Delta variant full spike gene on the genetic background ofUSA-WA1/2020. Samples were tested at the same time for comparability.

Disposition and Datasets Analysed

PRNT titers were obtained from 38 children 5 to <12 years of age randomly selected fromthe evaluable immunogenicity population (N=34 BNT162b2 and N=4 placebo).

The majority of participants were White (84.2%) with 7.9% Black or African American, 5.3% Asian, with and 2.6% multiracial participants. Hispanic/Latino participants made up 15.8% of the population. The median age of participants was 8.0 years of age, and 50.0% ofparticipants were male. One participant, in the BNT162b2 group (2.9%), was obese.

SARS-CoV-2 Neutralizing Response

Geometric Mean Titers (GMTs)

SARS-CoV-2 PRNT GMTs substantially increased for both the reference and Delta strains after two doses of 10 µg BNT162b2 (Table 6).

At 1 month after Dose 2, the GMR of the PRNT titers against the Delta variant strain to PRNT titers against the reference strain was 0.81 (2-sided 95% CI: 0.65, 1.00).

Table 6. Summary of Geometric Mean Titers – Delta Neutralization Subset – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Phase 2/3 – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)			
		BNT162b2 10 µg		Placebo	
Assay	Dose/ Sampling Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])Time
SARS-CoV-2 plaque reduction neutralization assay - reference strain USA-WA1/2020 - NT50 (titer)	1/Prevaccination	34	10.0 (10.0, 10.0)	4	10.0 (10.0, 10.0)
	2/1 Month	34	365.3 (279.0, 478.4)	4	10.0 (10.0, 10.0)
SARS-CoV-2 plaque reduction neutralization assay - strain B.1.617.2 (delta) - NT50 (titer)	1/Prevaccination	34	10.0 (10.0, 10.0)	4	10.0 (10.0, 10.0)
	2/1 Month	34	294.9 (214.6, 405.3)	4	10.0 (10.0, 10.0)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratorysyndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visits 1 and 4, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to1-month post-Dose 2) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assays 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 correspondingCIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Efficacy results

Participant flow

Among randomized participants, the Phase 2/3 evaluable efficacy population for children 5 to <12 years of age included 1450 participants in the BNT162b2 group and 736 participants in the placebo group (Table 7), which reflects the 2:1 randomization. Exclusions from the evaluable efficacy population occurred for 5.1% of the BNT162b2 group and 2.8% of the placebo group, due to receipt of Dose 2 outside the protocol defined window of 19-42 days after Dose 1 (2.0%in BNT162b2 and 2.4% in placebo) or due to other important protocol deviations on or prior to7 days after Dose 2 (3.1% in BNT162b2 and 0.5% in placebo), being primarily related to vaccine thawing, dilution, and/or administration issues that are not applicable to placebo.

Table 7. Efficacy Populations – Phase 2/3 Initial Enrollment Group – 5 to <12 Years ofAge

	Vaccine Group (as Randomized)		
	BNT162b2 10 µg on[a] (%)	Placeb n[a] (%)	Total n[a] (%)
Randomized[b]	1528 (100.0)	757 (100.0)	2285 (100.0)
Dose 1 all-available efficacy population			
Participants without evidence of infection before Dose 1 Participants	1517 (99.3)	751 (99.2)	2268 (99.3)
excluded from Dose 1 all-available efficacy populationReason for	1384 (90.6)	686 (90.6)	2070 (90.6)
exclusion[c]	11 (0.7)	6 (0.8)	17 (0.7)
Did not receive at least 1 vaccination			
Dose 2 all-available efficacy population	11 (0.7)	6 (0.8)	17 (0.7)
Participants without evidence of infection prior to 7 days after Dose 2			
Participants excluded from Dose 2 all-available efficacy population	1514 (99.1)	747 (98.7)	2261 (98.9)
Reason for exclusion[c]	1362 (89.1)	671 (88.6)	2033 (89.0)
Did not receive 2 vaccinations	14 (0.9)	10 (1.3)	24 (1.1)
Evaluable efficacy population			
Participants without evidence of infection prior to 7 days after Dose 2	14 (0.9)	10 (1.3)	24 (1.1)
Participants excluded from evaluable efficacy population			
Reason for exclusion[c]	1450 (94.9)	736 (97.2)	2186 (95.7)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1305 (85.4)	663 (87.6)	1968 (86.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	78 (5.1)	21 (2.8)	99 (4.3)
	31 (2.0)	18 (2.4)	49 (2.1)
	47 (3.1)	4 (0.5)	51 (2.2)

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

Baseline data

The demographics of Phase 2/3 paediatric participants 5 to <12 years of age were similar in the evaluable efficacy population of participants without prior evidence of SARS-CoV-2 infection as in the safety population for the BNT162b2 and placebo groups (see table below).

In the evaluable efficacy population of participants with or without prior evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, baseline positive status for prior evidence of SARS-COV-2 infection was reported for 8.7% of the BNT162b2 group and 8.4% of the placebo group.

The overall demographics of Phase 2/3 paediatric participants 5 to <12 years of age were similar for the BNT162b2 and placebo groups in the evaluable efficacy population of participants with or without prior evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, and in theall-available (mITT) efficacy populations.

Table 8. Demographic Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 Initial Enrolment Group – 5 to <12Years of Age – Evauable Efficacy Population

	Vaccine Group (as Randomized)		
	BNT162b2 10 µg (N[a]=1305) n[b] (%)	Placebo (N[a]=663) n[b] (%)	Total (N[a]=1968) n[b] (%)
Sex			
Male	679 (52.0)	343 (51.7)	1022 (51.9)
Female	626 (48.0)	320 (48.3)	946 (48.1)
Race			
White	1018 (78.0)	514 (77.5)	1532 (77.8)
Black or African American	76 (5.8)	48 (7.2)	124 (6.3)
American Indian or Alaska Native	10 (0.8)	3 (0.5)	13 (0.7)
Asian	86 (6.6)	46 (6.9)	132 (6.7)
Native Hawaiian or other Pacific Islander	BLD		
Multiracial	102 (7.8)	45 (6.8)	147 (7.5)
Not reported	BLD		
Ethnicity			
Hispanic/Latino	BLD		
Non-Hispanic/non-Latino	1059 (81.1)	533 (80.4)	1592 (80.9)
Not reported	BLD		
Country			
Finland	153 (11.7)	81 (12.2)	234 (11.9)
Poland	81 (6.2)	38 (5.7)	119 (6.0)
Spain	107 (8.2)	64 (9.7)	171 (8.7)
USA	964 (73.9)	480 (72.4)	1444 (73.4)
Age at Vaccination			

Mean (SD)	8.2 (1.93)	8.1 (1.98)	8.2 (1.95)
Median	8.0	8.0	8.0
Min, max	(5, 11)	(5, 11)	(5, 11)
Obese[c]			
Yes	BLD		
No	1168 (89.5)	584 (88.1)	1752 (89.0)
Missing	BLD		
Comorbidities[d]			
Yes	262 (20.1)	133 (20.1)	395 (20.1)
No	1043 (79.9)	530 (79.9)	1573 (79.9)

N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and2, and negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 2) and had no medical history of COVID-19 were included in theanalysis.

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.

b. n = Number of participants with the specified characteristic.

c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).

Numbers analysed

	Active arm	Placebo arm
Randomized	1528	757
Evaluable Efficacy Population	1305	663

Outcomes and estimation

Confirmed COVID-19 per Protocol Criteria (First Definition)

The observed VE from at least 7 days after Dose 2 for BNT162b2 10 µg administered to children5 to <12 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, per protocol case criteria was 90.7% (2-sided 95% CI: 67.7%, 98.3%) based on 3 cases in the BNT162b2 group and 16 cases in the placebogroup after adjusted for surveillance time ((noting the 2:1 randomization of vaccine: placebo (Table 9)).

No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection. Hence, the observed VE from at least 7 days after Dose 2 in evaluable participants in this age group with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was essentially the same: 90.7% (2-sided 95% CI: 67.4%, 98.3%) based on the same number of observed cases (3 cases in the BNT162b2 group and 16 cases in the placebo group).

The earliest reported and confirmed COVID-19 case in this analysis was in July 2021, with most cases occurring in August and September 2021.

Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 –Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 Initial Enrolment Group – 5 to <12 Years of Age – Evaluable Efficacy Population

Efficacy Endpoint	Vaccine Group (as Randomized)				VE (%)	(95% CI[e])
	BNT162b2 10 µg (N[a]=1305)		Placebo (N[a]=663)			
	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])		
First COVID-19 occurrence from 7 days after Dose 2	3	0.322 (1273)	16	0.159 (637)	90.7	(67.7, 98.3)

Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 2) and had no medical history of COVID-19 were included in theanalysis.

a. N = number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Dose 1 All-Available Efficacy Population

The observed VE for BNT162b2 10 µg against any confirmed COVID-19 from Dose 1 onwards in the Dose 1 all-available (mITT) population (i.e., all randomized participants who received at least 1 dose of vaccination) of children 5 to <12 years of age was 91.4% (2-sided 95% CI: 70.4%, 98.4%) based on 3 cases inthe BNT162b2 group and 17 cases in the placebo group (noting the 2:1 randomization of vaccine: placebo), as of the data cut-off date (08 October 2021) (Table 10).

From Dose 1 to before receipt of Dose 2, the observed VE was 100%, noting that only 1 case was reported in the placebo group and none in the BNT162b2 group during this interval.

No cases were reported from Dose 2 up to <7 days post-Dose 2. Starting from ≥7 days after Dose 2, the observed VE was 90.9% (2-sided 95% CI: 68.3%, 98.3%) based on accrual of all3 cases reported in the BNT162b2 group and the remaining 16 cases in the placebo group.

The Kaplan-Meier curve in 2 shows that cases accrued steadily in the placebo group, starting at approximately 3 weeks after the first dose and continuing to increase up to the data cut-off date (which represents approximately 4 months since Dose 1). In contrast, the 3 cases reported in the BNT162b2 group occurred at disparate and later times, with 1 case each reportedat approximately 1.5 months, 3.5 months, and 4 months after Dose 1.

All 3 cases in the BNT162b2 group occurred ≥7 days after Dose 2, noting that 2/3 cases occurredat distant time points post-Dose 2, during a period in Fall 2021 when children in this age group were back in school and/or other related congregant settings (e.g., sports teams, after school activities, etc.). None of the cases reported in the BNT162b2 group occurred in children with high-risk comorbidities.

Table 10. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age – Dose 1 All-Available Efficacy Population

Efficacy Endpoint Subgroup	Vaccine Group (as Randomized)				VE (%)	(95% CI[e])
	BNT162b2 10 µg (N[a]=1517)		Placebo (N[a]=751)			
	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])		
First COVID-19 occurrence after Dose 1	3	0.483 (1463)	17	0.235 (719)	91.4	(70.4, 98.4)
Dose 1 to before Dose 2	0	0.086 (1463)	1	0.043 (719)	100.0	(-1832.5, 100.0)
Dose 2 to <7 days after Dose 2	0	0.028 (1461)	0	0.014 (714)	NE	NE
≥7 Days after Dose 2	3	0.369 (1461)	16	0.178 (714)	90.9	(68.3, 98.3)

Abbreviations: NE = not estimable; VE = vaccine efficacy.

a. N = number of participants in the specified group.

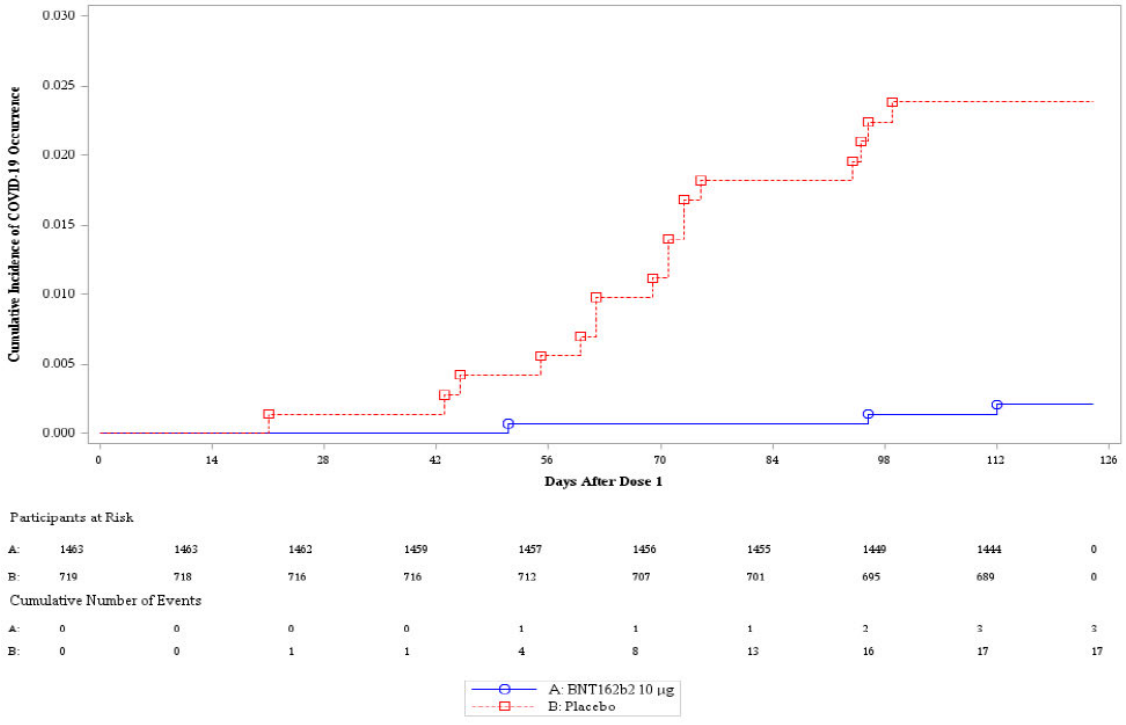
b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.

d. n2 = Number of participants at risk for the endpoint.

e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Figure 1. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Phase 2/3 Initial Enrolment Group – 5 to <12 Years of Age – Dose 1 All-Available Efficacy Population



PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (00:06) Source Data: adc19ef Table Generation: 14OCT2021 (23:16)
(Cutoff Date: 08OCT2021, Snapshot Date: 13OCT2021) Output File: /nda2_ubped/C4591007_P23_SAF_EXP_5_11/adc19ef_f001_pd1_ep3_d1aa

Vaccine Efficacy Subgroup Analyses

Vaccine efficacy was evaluated for subgroups of participants by sex, race, ethnicity, country, and at-risk status among participants without evidence of prior infection before and during the vaccination regimen. At-risk participants were those with at least one specified comorbidity or who were obese. Subgroup analyses were based on per protocol case criteria.

All subgroups had observed VE >85%, taking into account that some subgroups contain very few participants with evaluable cases and the 2-sided 95% CIs were wide, limiting the precision of these estimates, and should be interpreted with caution. These data, nevertheless, do not provide evidence to suggest that any subgroup is disadvantaged with regard to efficacy based on demographics (sex, race, ethnicity), country (noting that cases were reported only in Spain and the US), and presence of baseline comorbidities. None of the cases in the BNT162b2 group occurred in children with reported baseline comorbidities.

The observed VE results by subgroup were similar for participants with or without evidence of prior infection before and during the vaccination regimen. All participants with confirmed casesin this analysis had baseline negative status for prior SARS-CoV-2 infection.

Results for the all-available efficacy populations were similar; with no clinically meaningful differences observed in VE on the basis of subgroups of these populations.

Signs and Symptoms of COVID-19 – Phase 2/3

In the evaluable efficacy population, confirmed cases occurring at least 7 days after Dose 2 among participants in the evaluable efficacy population without evidence of SARS-CoV-2 infection before or during the vaccination regimen had signs and symptoms associated with 3 cases in the BNT162b2 group and 16 cases in the placebo group.

In the BNT162b2 group, 1 participant each (33.3%) with a confirmed COVID-19 case reported BLD signs and symptoms of COVID-19. BLD not reported in the children with confirmed COVID-19 who received BNT162b2.

In the placebo group, the majority of participants (56.2%) with a confirmed COVID-19 case reported BLD signs and symptoms of COVID-19, including 8 participants each (50.0%) with BLD symptoms.

Efficacy Against Severe COVID-19 and MIS-C – Phase 2/3

No severe COVID-19 cases (per protocol definition or per CDC definition) were reported in children 5 to <12 years of age as of the data cut-off date (08 October 2021). No cases of MIS-C (per CDC definition) were reported as of the data cut-off date.

2.6.2.3. Summary of main efficacy results

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).

Table 11. Summary of efficacy for trial C4591007 for 5 to<12 year old children

Title: Children 5 to <12 Years of Age: Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate Against COVID-19 in Healthy Children and Young Adults				
Study identifier	C4591007			
Design	Phase 2/3 randomized, observer-blind, placebo-controlled			
	Follow-up for efficacy		24.03. 2020- 06.09.2021 (immunogenicity) and 08.10.2021 (efficacy)	
Hypothesis	Superiority of vaccine vs placebo for vaccine efficacy and non-inferiority of antibody response younger vs. older age group			
Treatments groups	Active arm		BNT162b2 (10 µg), 2 doses, 21 days apart, Randomized, age group 5 to <12	
	Control arm		Saline placebo, 2 doses, 21 days apart, randomized, age group 5 to <12	
	Control arm C4591001		BNT162b2 (30 µg), 2 doses, 21 days apart, Randomized, age group 16-25	
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	
	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	06. 09.2021 for immunogenicity, 08.10.2021 for vaccine efficacy			
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	5 to <12 years old 10 µg	16-25 years old 30 µg	
	Number of subjects	264	253	Ratio, non-inferiority (Y/N)
	GMT (95% CI)	1197.6 (1106.1, 1296.6	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18) Y

Title: Children 5 to <12 Years of Age: Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate Against COVID-19 in Healthy Children and Young Adults				
	GMFR (95% CI)	118.2 (109.2, 127.9)	111.4 (101.2, 122.7)	
	Seroresponse rate % (95% CI)	262 (99.2 %) (97.3, 99.9%)	251 (99.2%) (97.2; 99.9%)	0% (-2.0, 2.2)
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=3/1305 Cases in Placebo arm N= 16/663	
		Vaccine Efficacy VE %	90.7 %	
		95% CI	(67.7, 98.3)	
	Not pre-specified endpoint	VE dose 1 modified intend to treat population	Cases in Active arm N=3/1517 Cases in Placebo arm N= 17/751	
		Vaccine Efficacy VE %	91.4 %	
		95% CI	(70.4;98.4)	
Notes	No severe COVID-19 cases were reported in individuals in the 12-15 years of age group			

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on part of the ongoing paediatric phase 1/2/3 study C4591007 including children aged 5 to <12years. Overall, the study is in agreement with the approved PIP.

Based upon review of safety and immunogenicity results from the Phase 1 portion of the study, the BNT162b2 dose level selected for further evaluation in Phase 2/3 was 10 µg for the 5 to <12 years age group. The selected dose is agreed based on the antibody response and safety results.

In Phase 2/3, the efficacy of BNT162b2 was established by immunobridging of the SARS-CoV-2 neutralizing antibody response in paediatric participants aged 5 to <12 years of age group in Study C4591007 to the response in young adult participants 16 to 25 years of age in Phase 2/3 efficacy study C4591001. This is the same approach which was used for the extension of the indication to for 12-15 year olds (type II variation II30).

A difference in this procedure, is a larger sample size and that the younger age group (5 to<12 years old) received a lower dose of vaccine. The design of the immunobridging exercise is endorsed and the use of the historical controls (16-25 years old) from study C4591001 are acceptable as these serology samples were analysed side by side with samples from 5 to<12 years old. The time shift between receipt of vaccine for study arms is expected to have no impact for immunogenicity.

The Phase 2/3 evaluable immunogenicity population for participants 5 to <12 years of age included 294 participants in the BNT162b2 group and 147 participants in the placebo group, and for Study C4591001 participants 16 to 25 years of age included 273 participants in the BNT162b2 group and 47 participants in the placebo group. This part of the study was designed and powered for immunogenicity comparison between children 5 to 12 year and young adults (16-25 years). Children

with comorbidities, with a history of prior SARS-COV2-infection or with HIV were not excluded. A supplemental descriptive analysis of vaccine efficacy among cohort 1 of study C4591007 was also provided.

The MAH also submitted supportive immunogenicity data for SARS-CoV-2 serum neutralizing titers against USA-WA1/2020 (reference) and B.1.617.2 (Delta) variant strains for 40 participants (35 in active and 5 in placebo arm). The sample size in this supportive analysis was small and the Delta neutralization assay not yet validated, therefore these data are considered supportive, but important in light of the Delta variant epidemiology.

Assessment of VE was to be performed for confirmed COVID-19 illness from 7 days after Dose 2. A supportive vaccine efficacy analysis was planned to be conducted when at least 22 confirmed cases of COVID-19 had accrued in the 5 to <12 years of age group and if success criteria for immunobridging in this age group had first been met. The statistical methods for calculating Vaccine Efficacy are considered appropriate. An efficacy analysis was submitted during the assessment (dated 18.10.2021). The efficacy analysis was based on confirmed cases among the initially enrolled N~2250 participants in the 5 to <12 years of age group of Study C4591007.

Among randomized participants, 1450 participants were included in the BNT162b2 group and 736 participants in the placebo group. This part of the study was designed and powered for vaccine efficacy evaluation between active and placebo arm. The design and study protocol for the vaccine efficacy part is endorsed. The analysis was performed before the pre-defined number of cases had been accrued, at 19 cases instead of 21. The MAH was asked to clarify this and has answered that the earlier than planned VE analysis was done due to a FDA request. Amended study protocols, and an amended analysis plan, have also been submitted. Analyses for the different age groups are performed and submitted when available. Also, updated efficacy analyses will be performed at end of the blinded follow-up period. As the presented data are preliminary, the final report with final analysis was requested when available and the MAH provided the requested timeline for the study report, as a SOB due July 2024.

The blinding procedure appears appropriate. However, due to reactogenicity it seems likely that some of the study subjects and/or their guardians, may have guessed their treatment allocation. This is unlikely to impact immunogenicity or efficacy conclusions.

No type I error control is applied between age groups. This is accepted since the age groups were included in the same study to improve operational efficiency. However, it should be noted that the hypotheses are not independent, and inconsistent results may affect the interpretation of the efficacy in other age groups. Within age groups immunobridging analyses are performed sequentially. If these were successful, secondary endpoints of vaccine efficacy were to be tested sequentially. The sequential multiple testing procedure is appropriate. In summary the statistical methods used are considered appropriate.

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, children and adolescents have higher immune responses to vaccination compared to adults, which was shown to be the case also for this Covid-19 vaccine in the previous evaluation between 12-15- and 16–26-year-olds. In the current application, where children between ages 5 to 12 received a lower dose of Comirnaty (10 µg), the neutralizing antibody titer was

non-inferior to the antibody titers among young adults 16-25 years old, who received standard 30 µg dose.

Immunobridging

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 50% neutralizing GMT in children 5 to <12 years of age (who received the 10-µg dose level) to that of young adults 16 to 25 years of age (who received the 30-µg dose level) was 1.04 (2-sided 95% CI: 0.93, 1.18). The lower bound of the 2 sided 95% CI for GMR was >0.67 and the GMR point estimate was ≥0.8, which meets the prespecified 1.5-fold margin and success criteria. Therefore, immunobridging based on GMR was achieved.

Interestingly, the GMTs from age group 16-25 years were reported as lower in the immunobridging exercise with 12-15 year-olds compared to what is now reported for the same procedure with 5-11 year-olds. As the baseline characteristics and assay should be identical for this age group, the clarification for this discrepancy was requested. The MAH responded that the randomly selected individuals in control group were not the same in 6-12 and 5-11 years old applications and also the different batches of assay reagent virus were used.

There was a similar magnitude of rise in the paediatric 5 to <12 years of age group (118.2) compared to the young adult 16 to 25 years of age group (111.4) for BNT162b2 group. High neutralizing titers were elicited to both the USA-WA1/2020 (reference) and B.1.617.2 (Delta) recombinant SARS-CoV-2 strains at 1 month after Dose 2.

High and equal proportions (99.2% each of children 5 to <12 years of age and young adults 16 to 25 years of age) of participants achieved a seroresponse. The difference in the proportions of participants who had seroresponse between the two age groups (children – young adults) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved. Subgroup analyses by demographic, baseline SARS-CoV-2 and obesity status did not show any meaningful differences in neutralizing immune response and seroresponse rate in the 5 to < 12 years group and 16-25 years group.

In the light of the above, it can be concluded that neutralizing antibody responses in children 5-11 years and in young adults are comparable.

Efficacy

Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for BNT162b2 10 µg against any confirmed COVID-19 from at least 7 days after Dose 2 was 90.7% (2-sided 95% CI: 67.7%, 98.3%) which included 3 cases in the BNT162b2 group and 16 cases in the placebo group. There were no cases among baseline SARS-CoV-2 positives. All cases occurred in children without prior history of infection. No virus sequence analyses to determine whether these cases were due to Delta variant was available at the time of submission. However, based on supportive analysis of Delta neutralizing immune responses from a subset of vaccinated/placebo sera from children 5-11 years, which showed significant neutralizing titers against the Delta variant, it can be inferred that vaccination with BNT162b2 10 µg in children 5-11 years is effective against Delta variant. Confirmatory case sequencing data for COVID-19 cases will be reported at a later time, when the sequencing analysis is completed.

The same vaccine efficacy (90.7% (CI95% 67.4, 98.3) was observed in children 5-11 years with or without evidence of infection prior to 7 days post-dose 2. Comorbidities present at baseline that increase the risk of severe COVID-19 disease (including obesity, asthma, diabetes mellitus) were present in 20.6% of participants. However, some subgroups contain very few participants.

The VE analyses were to be performed when at least 22 cases were accrued. It was however not clear from the interim report what the number of cases were at the cut-off date. In the efficacy analyses 19 cases are included, and 21 cases were included in the analyses using CDC defined symptoms. The MAH was asked to clarify. The MAH has responded that the earlier analysis was done due to the request from FDA.

For COVID-19 cases confirmed from Dose 1 onwards in the Dose 1 all-available (mITT) population, the observed VE for BNT162b2 10 µg was 91.4% (2-sided 95% CI: 70.4, 98.4%) based on 3 cases in the BNT162b2 group and 17 cases in the placebo group. However, the observed VE in the relevant interval starting from 11 days post-dose 1 to before dose 2 was not provided, whereas it was available for adolescents 12-15 years.

All subgroups had observed VE >85%, though these results should be interpreted with caution as some subgroups contain very few participants.

No severe COVID-19 cases or MIS-C were reported in the 5 to <12 years of age group, per protocol definition or per CDC definition.

Overall, BNT162b2 administered as a primary series of two doses of 10 µg given 3 weeks apart to children 5 to <12 years of age is protective against symptomatic COVID-19. The efficacy against symptomatic COVID-19 was demonstrated in the age group 5 to 12 years. The effect size was similar to that seen in adults overall. As it might be anticipated, no severe cases occurred in the study. As the study is still ongoing, the MAH is requested to submit the final results of the study when available.

Specific risk groups among children, including those immunosuppressed, or otherwise with risk of more severe disease, were not specifically studied. A study in immunocompromised children (IC) is included in the PIP. The MAH was asked to consider whether a third dose in the primary series is relevant for children with substantial immunosuppression, as has been agreed previously for adolescents and adults. The MAH responded that so far there is no information about the relevance of the third dose among IC children, but the study is ongoing with expected report timeline for end of 2022. The CHMP understands the MAH position, but as extrapolated data from adults was used also in age group 12-18, the SmPC should follow the same orientation as for adolescents.

It is currently unknown if vaccination provides protection against asymptomatic infection, and to what extent vaccination prevents further transmission. The efficacy against transmission would be of great interest to predict the impact of the vaccine against SARS-CoV-2 circulation, particularly among the paediatric population.

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

Conclusions on clinical efficacy

The immunobridging results clearly demonstrate that 10 µg BNT162b2 given to children 5-11 years of age resulted in very similar neutralising antibody responses (GMTs, GMFR and seroresponses) compared to the efficacy population; that is, 16-25 year old subjects receiving 30 µg BNT162b2. Thus, efficacy may be inferred based on immunobridging.

This is supported by clinical efficacy data. The efficacy of the BNT162b2 (2 doses 10 µg, separated by 21 days) to prevent COVID-19 in children aged 5-11 years either with and without evidence of prior SARS-CoV-2 infection, occurring at least 7 days after the second dose was considered well-established.

No severe cases were reported in children aged 5-11 years.

Taken together, efficacy and immunogenicity data support the use in children aged 5-11 years.

Efficacy on asymptomatic infection was however not assessed. These data would be of great interest to understand the indirect impact of children vaccination to prevent SARS-CoV-2 transmission.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

Description	Due Date
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591007.	July 2024

2.6.4. Clinical safety

Study C4591007 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 paediatric study in healthy children from 6 months to <12 years of age. Phase 1 was conducted in the US and the Phase 2/3 is being conducted at sites in the US, Finland, Poland, and Spain (still ongoing).

Local and systemic reactions were registered up to 7 days after each dose by using an E-diary. Adverse events (AEs) are collected from Dose 1 to 1 month after Dose 2 and serious AEs (SAEs)are collected from Dose 1 to 6 months after Dose 2. Deaths are recorded to the end of study.

This interim report includes only study objectives, analyses, and data for children 5 to <12 years of age, as follows:

- C4591007 Phase 1 dose-finding among BNT162b2 dose levels of 10, 20, and 30 µg (N=16 per group), including data for safety and tolerability up to 1 month after Dose 2 and immunogenicity at 7 days after Dose 2.
- C4591007 Phase 2/3 at the selected dose of BNT162b2 10 µg (N ~2250, randomized 2:1 BNT162b2 10 µg: placebo), including data for safety and tolerability up to 2 months after Dose 2, immunobridging analyses at 1 month after Dose 2. The initial cut-off date was 6 September 2021, however, additional data allowing for longer follow-up time of AEs, SAEs and death has been provided with the cut-off date of 08 October 2021. The participants are referred to "initial group".
- Additional supportive safety data for newly recruited N~2250 Phase 2/3 C4591007 paediatric participants 5 to <12 years who began enrolment in August 2021 in US only. The subjects were randomized 2:1 (BNT162b2 10 µg: placebo). Data cut-off is 08 October 2021, which represents at least 1 week of follow-up after Dose 2 for 98.5% of the participants and at least 2 weeks of follow-up after Dose 2 for most (>70%) participant. No reactogenicity data is available from these subjects. The participants are referred to "expansion group".

Sponsor and site personnel responsible for the ongoing conduct of Study C4591007 remain blinded to individual participants' randomization. A participant in the 5 to <12 years of age group of C4591007 could be unblinded to treatment assignment per protocol, if he or she turned 12 years of age and became eligible to receive a COVID-19 vaccine available under CMA in their country/region. Unblinded recipients originally randomized to placebo will be offered BNT162b2 vaccination and thereafter followed in an open-label manner.

2.6.4.1. Patient exposure

2.6.4.1.1. Phase 1 (data cut-off date: 16 July 2021)

In the Phase 1 study the protocol-defined age groups were studied separately, this application describes data concerning 5 to <12 years of age only. The study population includes male and female participants deemed healthy as determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with clinically important prior medical or psychiatric illness or laboratory abnormalities, past diagnosis of MIS-C, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by PCR. Local reactions, systemic events, and antipyretic medication use was registered by participants/guardians in an e-diary for the 7 following days after each dose administration. Safety assessments in Phase 1 were to support dose level selection to proceed to Phase 2/3 evaluation.

A total of 48 participants were included in the 10-µg, 20-µg, and 30 µg dose level groups (N=16 each) and received 2 doses of BNT162b2 and completed the 1-month post-Dose 2 visit. No participants were withdrawn from the study. Due to observed reactogenicity after dose 2 in the initial 4/16 participants of the 30-µg group the remaining 12 participants instead received 10 µg at Dose 2, and the 30-µg dose level was discontinued in the study.

2.6.4.1.2. Phase 2/3 Initial Group

In total, 2,285 subjects were randomized 2:1 (n=1,528 BNT162b 10 µg; n=757 placebo). Most participants in either group (≥98.7%) received Dose 1 and Dose 2.

Two participants (0.1%) in the BNT162b2 group and 2 participants (0.3%) in the placebo group discontinued from the vaccination period and were continuing in the study for safety follow-up. None of the discontinuations were reported as due to an AE. The safety population reflected the 2:1 randomization in the BNT162b2 (N=1,518) and placebo (N=750) groups. Exclusions from the safety population were due to 17 participants (0.7%) not receiving study vaccine.

Table 12. Disposition of ALL Randomized Participants – Phase 2/3 – 5 to <12 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 10 µg (N[a]=1528) n[b] (%)	Placebo (N[a]=757) n[b] (%)	Total (N[a]=2285) n[b] (%)
Randomized	1528 (100.0)	757 (100.0)	2285 (100.0)
Not vaccinated	11 (0.7)	6 (0.8)	17 (0.7)
Vaccinated	1517 (99.3)	751 (99.2)	2268 (99.3)
Dose 1	1517 (99.3)	751 (99.2)	2268 (99.3)
Dose 2	1514 (99.1)	747 (98.7)	2261 (98.9)
Completed 1-month post–Dose 2 visit (vaccination period)	1510 (98.8)	746 (98.5)	2256 (98.7)
Discontinued from vaccination period but continued in the study	2 (0.1)	2 (0.3)	4 (0.2)
Discontinued after Dose 1 and before Dose 2	2 (0.1)	2 (0.3)	4 (0.2)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	0	0
Reason for discontinuation from vaccination period			
Withdrawal by participant	BLD		
Withdrawal by parent/guardian			
Withdrawn from the study	5 (0.3)	6 (0.8)	11 (0.5)
Withdrawn after Dose 1 and before Dose 2	1 (0.1)	2 (0.3)	3 (0.1)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	2 (0.1)	2 (0.3)	4 (0.2)
Withdrawn after 1-month post–Dose 2 visit	2 (0.1)	2 (0.3)	4 (0.2)
Reason for withdrawal from the study			
Other	BLD		

Withdrawal by participant	BLD
Withdrawal by parent/guardian	

a. N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:17) Source Data: adds Table Generation: 15SEP2021 (11:59) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: ./nda2_ubped/C4591007_P23_EUA/adds_s002_disp_p2_12

Vaccine Administration and Timing

The majority (94.4% BNT162b2; 94.5% placebo) received Dose 2 in the protocol-defined window of 19 to 23 days after Dose 1 (Table 13 below).

Table 13. Vaccine Administration Timing – Phase 2/3 -5 <12 Years of Age – All Randomized Participants

	Vaccine Group (as Randomized)	
	BNT162b2 10 µg (N[a]=1528) n[b] (%)	Placebo (N[a]=757) n[b] (%)
Randomized	1528 (100.0)	757 (100.0)
Not vaccinated	11 (0.7)	6 (0.8)
Dose 1	1517 (99.3)	751 (99.2)
Dose 2[c]	1514 (99.1)	747 (98.7)
Protocol defined window		
<19 Days	10 (0.7)	3 (0.4)
19-23 Days[d]	1443 (94.4)	715 (94.5)
>23 Days	61 (4.0)	29 (3.8)
Weekly intervals		
<14 Days	0	0
14-20 Days	349 (22.8)	186 (24.6)
21-27 Days	1124 (73.6)	540 (71.3)
28-34 Days	26 (1.7)	12 (1.6)
35-41 Days	8 (0.5)	5 (0.7)
42-48 Days	2 (0.1)	1 (0.1)
49-55 Days	BLD	
>55 Days		

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Days calculated since Dose 1.
d. Protocol-specified time frame.

Demographics

Demographic characteristics (cut-off date 06 September 2021) is described in table 14 below.

Table 14. Demographic Characteristics – Phase 2/3-5 <12 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)	Total (N[a]=2268) n[b] (%)
Sex			
Male	799 (52.6)	383 (51.1)	1182 (52.1)
Female	719 (47.4)	367 (48.9)	1086 (47.9)
Race			
White	1204 (79.3)	586 (78.1)	1790 (78.9)
Black or African American	89 (5.9)	58 (7.7)	147 (6.5)
American Indian or Alaska Native	12 (0.8)	3 (0.4)	15 (0.7)
Asian	BLD		
Native Hawaiian or other Pacific Islander			

Multiracial	109 (7.2)	49 (6.5)	158 (7.0)
Not reported	9 (0.6)	7 (0.9)	16 (0.7)
Ethnicity			
Hispanic/Latino	319 (21.0)	159 (21.2)	478 (21.1)
Non-Hispanic/Non-Latino	1196 (78.8)	591 (78.8)	1787 (78.8)
Not reported	3 (0.2)	0	3 (0.1)
Age at vaccination (years)			
Mean (SD)	8.2 (1.93)	8.1 (1.97)	8.2 (1.94)
Median	8.0	8.0	8.0
Min, max	(5, 11)	(5, 11)	(5, 11)
Obese[c]			
Yes	174 (11.5)	92 (12.3)	266 (11.7)
No	1343 (88.5)	658 (87.7)	2001 (88.2)
Missing	1 (0.1)	0	1 (0.0)
Baseline SARS-CoV-2 status			
Positive[d]	133 (8.8)	65 (8.7)	198 (8.7)
Negative[e]	1385 (91.2)	685 (91.3)	2070 (91.3)
Comorbidities[f]			
Yes	312 (20.6)	152 (20.3)	464 (20.5)
No	1206 (79.4)	598 (79.7)	1804 (79.5)

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
e. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
f. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).

Duration of follow-up

At the time of the current data cut-off date (08 October 2021), the median duration of follow-up for the initially enrolled Phase 2/3 participants 5 to <12 years of age was 3.3 months after Dose 2 (Table 15 below).

Table 15. Follow-up Time After Dose 2 – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)	Total (N[a]=2268) n[b] (%)
Time from Dose 2 to cutoff date			
<1 Month	7 (0.5)	4 (0.5)	11 (0.5)
≥1 to <2 Months	2 (0.1)	3 (0.4)	5 (0.2)
≥2 to <3 Months	53 (3.5)	28 (3.7)	81 (3.6)
≥3 Months	1456 (95.9)	715 (95.3)	2171 (95.7)
Mean (SD)	3.3 (0.25)	3.2 (0.31)	3.3 (0.27)
Median	3.3	3.3	3.3
Min, max	(0.0, 3.5)	(0.0, 3.5)	(0.0, 3.5)

Note: Follow-up time (months) was calculated from Dose 2 to the cutoff date or withdrawal date or the date of unblinding (per protocol), whichever date was earlier. Follow-up time after Dose 2 for participants who did not receive Dose 2 was counted as 0.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (00:06) Source Data: adsl Table Generation: 14OCT2021 (13:27) (Cutoff Date: 08OCT2021, Snapshot Date: 13OCT2021) Output File: ./nda2 ubped/C4591007 P23 SAF EXP 5 11/adsl s005 fup time eua 12

2.6.4.1.3. Phase 2/3 Expansion Group

Disposition

The additional safety expansion group safety population for Phase 2/3 paediatric participants 5 to <12 years of age (cut-off 8 October 2021) were randomized 2:1 (BNT162b2 N=1591; placebo N=788). Exclusions from the safety population were due to 15 participants (0.6%) not receiving study vaccine.

Table 16. Disposition of All Randomized Participants – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 10 µg (N[a]=1598) n[b] (%)	Placebo (N[a]=796) n[b] (%)	Total (N[a]=2394) n[b] (%)
Randomized	1598 (100.0)	796 (100.0)	2394 (100.0)
Not vaccinated	7 (0.4)	8 (1.0)	15 (0.6)
Vaccinated	1591 (99.6)	788 (99.0)	2379 (99.4)
Dose 1	1591 (99.6)	788 (99.0)	2379 (99.4)
Dose 2	1580 (98.9)	782 (98.2)	2362 (98.7)
Completed 1-month post–Dose 2 visit (vaccination period)	[redacted]		
Discontinued from vaccination period but continued in the study			
Discontinued after Dose 1 and before Dose 2			
Discontinued after Dose 2 and before 1-month post–Dose 2 visit			
Reason for discontinuation from vaccination period			
Adverse event			
Withdrawn from the study			
Withdrawn after Dose 1 and before Dose 2			
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit			
Withdrawn after 1-month post–Dose 2 visit			
Reason for withdrawal from the study			
Withdrawal by parent/guardian			

a. N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

Vaccine Administration and Timing

The majority of participants received Dose 2 in the protocol defined window of 19 to 23 days after Dose 1 in the BNT162b2 (95.6%) and placebo (94.5%) groups, as illustrated in the table below.

Vaccine Administration Timing – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age – All Randomized Participants

	Vaccine Group (as Randomized)	
	BNT162b2 10 µg (N[a]=1598) n[b] (%)	Placebo (N[a]=796) n[b] (%)
Randomized	1598 (100.0)	796 (100.0)
Not vaccinated	7 (0.4)	8 (1.0)
Dose 1	1591 (99.6)	788 (99.0)
Dose 2[c]	1580 (98.9)	782 (98.2)
Protocol defined window		
<19 Days	3 (0.2)	1 (0.1)
19-23 Days[d]	1527 (95.6)	752 (94.5)
>23 Days	50 (3.1)	29 (3.6)
Weekly intervals		
14-20 Days	447 (28.0)	229 (28.8)
21-27 Days	1110 (69.5)	543 (68.2)
28-34 Days	19 (1.2)	9 (1.1)
35-41 Days	[redacted]	
42-48 Days		

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Days calculated since Dose 1.
d. Protocol-specified time frame.

Demographics

Demographic characteristics for the Phase 2/3 safety expansion group of children 5 to <12 years of age were similar in BNT162b2 and placebo groups (Table 17 below). The demographics for the safety expansion group are similar to the demographics for the initial safety group.

Table 17. Demographic Characteristics – Safety Expansion Group – Phase 2/3-5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N*=1591) n[b] (%)	Placebo (N*=788) n[b] (%)	Total (N*=2379) n[b] (%)
Sex			
Male	810 (50.9)	396 (50.3)	1206 (50.7)
Female	781 (49.1)	392 (49.7)	1173 (49.3)
Race			
White	1198 (75.3)	613 (77.8)	1811 (76.1)
Black or African American	90 (5.7)	43 (5.5)	133 (5.6)
American Indian or Alaska Native	1 (0.1)	1 (0.1)	2 (0.1)
Asian	168 (10.6)	73 (9.3)	241 (10.1)
Native Hawaiian or other Pacific Islander	BLD		
Multiracial	126 (7.9)	54 (6.9)	180 (7.6)
Not reported	BLD		
Ethnicity			
Hispanic/Latino	207 (13.0)	106 (13.5)	313 (13.2)
Non-Hispanic/non-Latino	1383 (86.9)	682 (86.5)	2065 (86.8)
Not reported	1 (0.1)	0	1 (0.0)
Age at vaccination (years)			
Mean (SD)	7.9 (1.97)	7.8 (1.96)	7.9 (1.97)
Median	8.0	8.0	8.0
Min, max	(5, 11)	(5, 11)	(5, 11)
Obese[c]			
Yes	178 (11.2)	87 (11.0)	265 (11.1)
No	1411 (88.7)	701 (89.0)	2112 (88.8)
Missing	2 (0.1)	0	2 (0.1)
Baseline SARS-CoV-2 status			
Positive[d]	163 (10.2)	82 (10.4)	245 (10.3)
Negative[e]	1421 (89.3)	702 (89.1)	2123 (89.2)
Missing	7 (0.4)	4 (0.5)	11 (0.5)
Comorbidities[f]			
Yes	314 (19.7)	159 (20.2)	473 (19.9)
No	1277 (80.3)	629 (79.8)	1906 (80.1)

Abbreviations: BMI = body mass index; MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test;
N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
e. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
f. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).

Duration of follow-up

The duration of follow-up for the safety expansion group at the cut-off 8 October 2021 is illustrated in Table 18 below.

Table 18. Follow-up Time After Dose 2 – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1591) n[b] (%)	Placebo (N[a]=788) n[b] (%)	Total (N[a]=2379) n[b] (%)
Time from Dose 2 to cutoff date			
<1 Week	21 (1.3)	15 (1.9)	36 (1.5)
≥1 to <2 Weeks	448 (28.2)	200 (25.4)	648 (27.2)
≥2 to <3 Weeks	779 (49.0)	397 (50.4)	1176 (49.4)
≥3 to <4 Weeks	343 (21.6)	176 (22.3)	519 (21.8)
Mean (SD)	2.3 (0.74)	2.3 (0.75)	2.3 (0.74)
Median	2.4	2.4	2.4
Min, max	(0.0, 3.7)	(0.0, 3.7)	(0.0, 3.7)

Note: Follow-up time (weeks) was calculated from Dose 2 to the cutoff date or withdrawal date or the date of unblinding (per protocol), whichever date was earlier. Follow-up time after Dose 2 for participants who did not receive Dose 2 was counted as 0.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

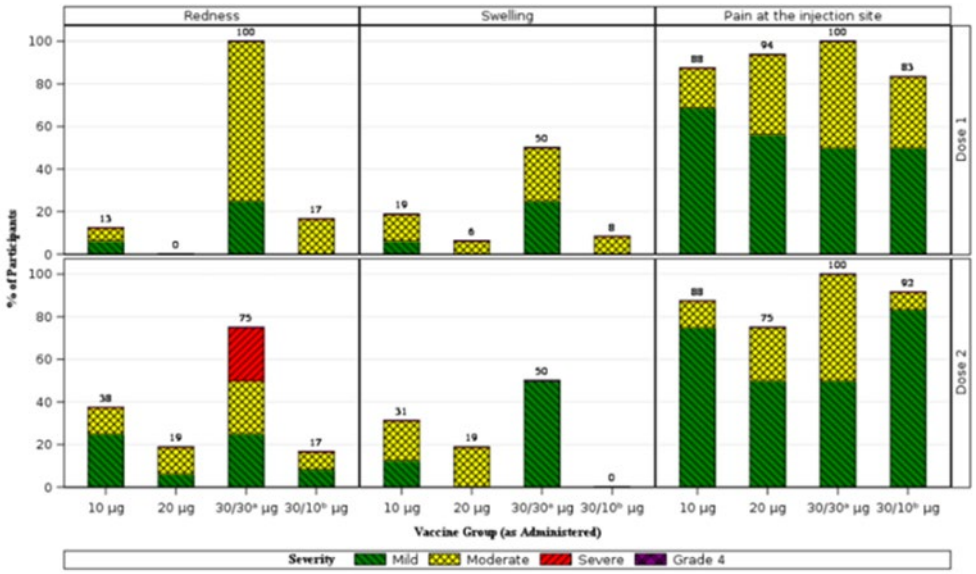
2.6.4.2. Adverse events

2.6.4.2.1. Phase 1

All local reactions were mild or moderate in severity and short-lived, except for 1 severe event of redness after Dose 2 in the 30/30-µg dose regimen (Figure 2). Systemic events were mostly mild to moderate and short-lived. Overall, reactogenicity tended to increase in a dose level- and dose number-dependent manner regarding incidence and/or severity of local reactions. Four participants received both 30 µg doses, they developed fever up to 38.9 °C and fatigue after Dose 2. Headache was mild to moderate in 3/4 participants after Dose 1 and Dose 2. This systemic event profile in these first 4 participants contributed to the IRC decision to discontinue the 30-µg dose level.

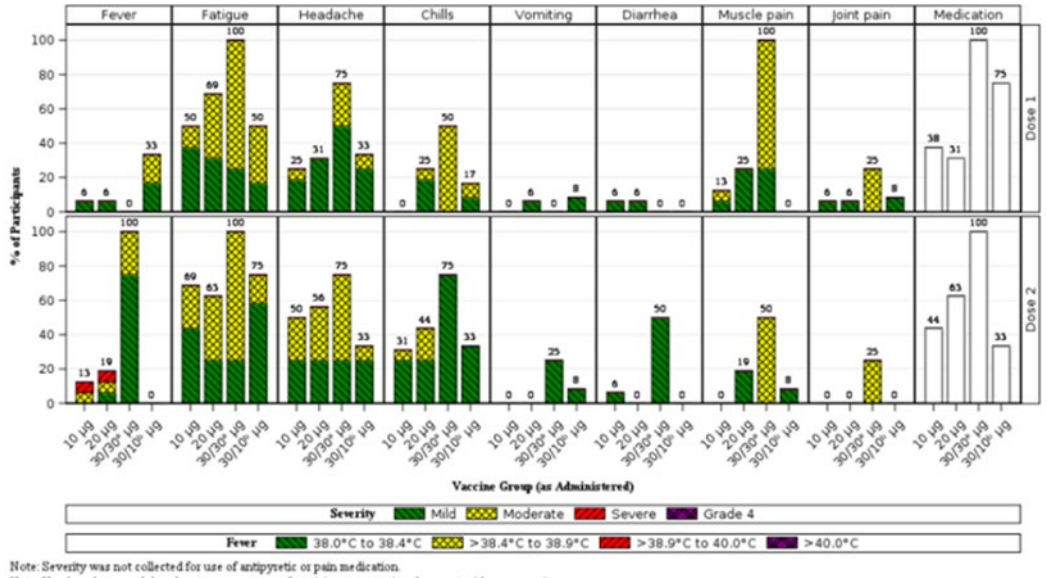
As illustrated in figure 2 and 3 below a dose dependent increase of local and systemic reactions was noted in the Phase 1 study, where 10 ug appears to be less reactogenic. It was therefore decided to continue with a dose of 10 µg for the Phase 2/3 study.

Figure 2. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 – 5 to<12 Years of Age – Safety Population



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.

Figure 3. Participants Reporting Systematic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 – 5 to<12 Years of Age – Safety Population



Note: Severity was not collected for use of antipyretic or pain medication.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.

Adverse Events

From Dose 1 to 1 month after Dose 2, AEs were reported by 7 participants (43.8%) who received BNT162b2 at 10 µg and 5 participants (31.3%) who received 20 µg. Of these, the AEs were considered related to study intervention for 4 (25.0%) and 2 (12.5%) participants in the 10 µg and 20 µg dose groups, respectively. In 4/16 participants who received both doses in the 30 µg group as assigned, AEs were reported by 2 participants with both considered by the investigator as related to study intervention BLD [redacted]. No SAEs, deaths, or AEs leading to withdrawal were reported.

2.6.4.2.2. Phase 2/3 Initial Group

Reactogenicity

Reactogenicity which includes local as well as systemic reactions was registered for 7 days following each dose by using an E-diary. The reactogenicity was evaluated in 2268 paediatric subjects (n=1518 BNT162b; n=750 placebo) included in the initial safety population of the Phase 2/3 study.

Local Reactions

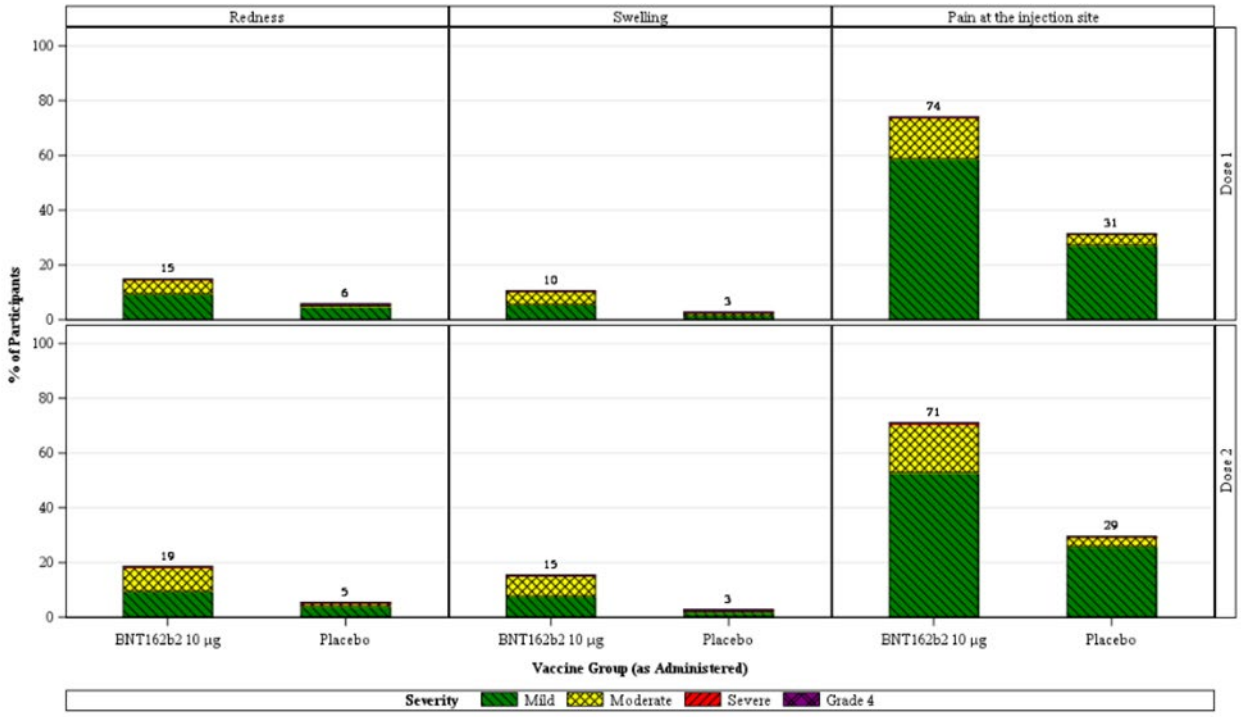
After the first and second dose, most local reactions were mild or moderate in severity. No Grade 4 local reactions were reported in either group. Across groups, median onset for all local reactions after receiving BNT162b2 was 1 to 2 days after Dose 1 or Dose 2, and all events resolved with a median duration of 1 to 2 days.

Overall, the pattern of local reactions reported in children 5 to <12 years of age after each dose was generally in line to that observed in prior analyses of adolescents and adults with regard to pain at the injection site, but children had slightly higher frequencies of swelling and redness at the injection site.

The frequencies between the SARS-CoV-2 positive or negative subjects at baseline were similar although numerically lower in those positive at baseline. Note that the baseline positive subgroup included far fewer participants the negative subgroup, so their results should be interpreted with caution.

The Phase 2/3 reported local reactions are illustrated in figure 4 below:

Figure 4. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to<12 Years of Age – Safety Population



Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.

Systemic Reactions

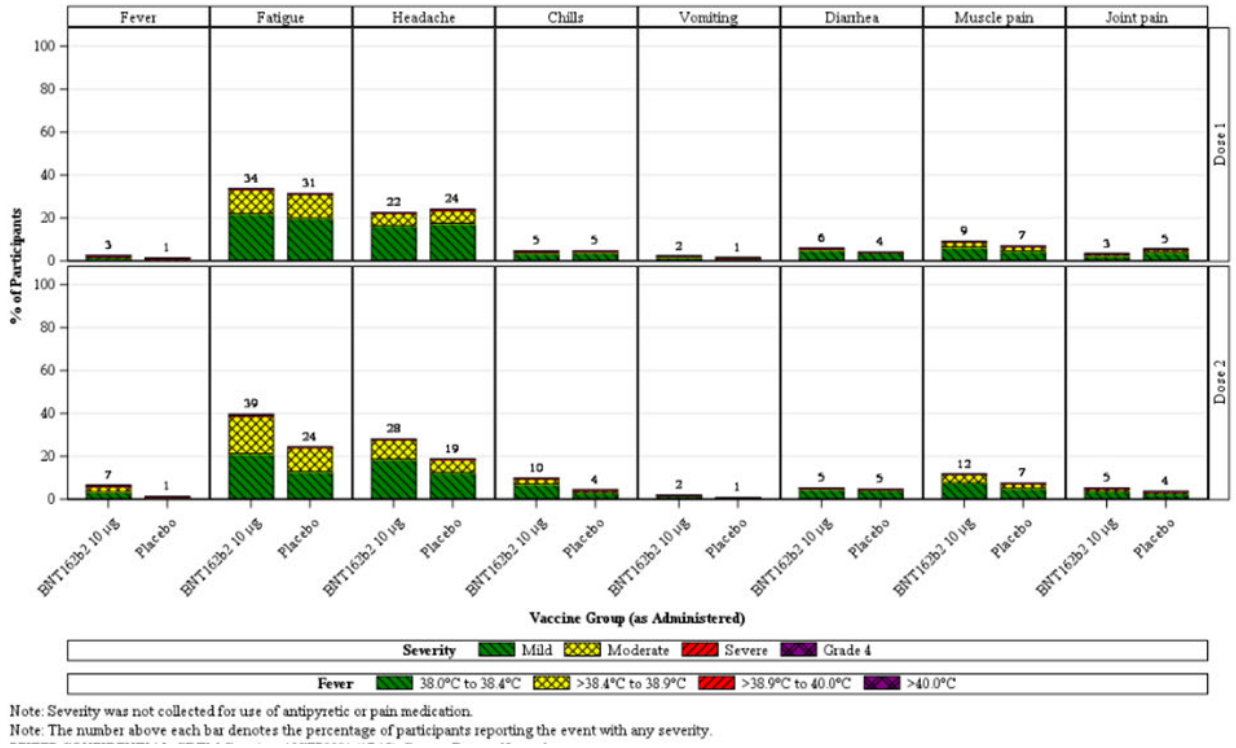
Most systemic events were mild or moderate in severity. Across groups, median onset after receiving BNT162b2 was 1 to 4 days after Dose 1 or Dose 2 (most had a median of 2 days post-dose) and all events resolved with a median duration of 1 day. None of the participants reported systemic events Grade 4.

One participant, BLD [redacted], reported fever of 40.0°C 2 days after Dose 2 which returned to normal (36.7°C) the next day, no concurrent AEs reported at this time or during the study.

Overall, the pattern of systemic events reported in children 5 to <12 years of age after each dose was generally comparable to, or less than, that observed in prior analyses of Phase 2/3 adolescents or adult participants.

In the BNT162b2 group the use of antipyretic/pain medication was slightly higher after Dose 2 compared to after Dose 1 (Dose 1 [14.4%]; Dose 2 [19.7%]). Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and similar after both Doses (8.3% and 8.1%).

Figure 5. Participants Reporting Systematic Evets, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to<12 Years of Age – Safety Population



Note: Severity was not collected for use of antipyretic or pain medication.
Note: The number above each bar denotes the percentage of participants reporting the event with any severity.

Adverse Events Phase 2/3 (Initial Group)

From Dose 1 to the current cut-off date (08 October 2021), the proportions of participants with any AE were similar in the BNT162b2 (13.0%) and placebo (11.1%) groups.

Table 19. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (08 Oct 2021) – Phase 2/3 Initial Enrollment Group – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 10 µg (N[a]=1518)	Placebo (N[a]=750)
Adverse Event	n[b] (%)	n[b] (%)
Any adverse event	197 (13.0)	83 (11.1)
Related[c]	46 (3.0)	16 (2.1)
Severe	BLD	
Life-threatening	0	0
Any serious adverse event	1 (0.1)	1 (0.1)
Related[c]	0	0
Severe	BLD	
Life-threatening	0	0
Any nonserious adverse event	197 (13.0)	82 (10.9)
Related[c]	46 (3.0)	16 (2.1)
Severe	BLD	
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Serious	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 13OCT2021 (23:06) Source Data: adae Table Generation: 14OCT2021 (23:34) (Cutoff Date: 08OCT2021, Snapshot Date: 13OCT2021) Output File: ./nda2 ubped/C4591007 P23 SAF EXP 5 11/adae s130 1md2 p2 12 cut1

The number of subjects reporting at least one AE are described in table 20 below by SOCs. Please note that the cut-off date for this table is 6 September 2021. After the initial cut-off and up to 8 October 2021, new AEs were reported by 23 (1.5%) participants in the BNT162b2 group and 10 (1.3%) participants in the placebo group. All newly reported AEs from 2 months post-Dose 2 up to the present 3 months post-Dose 2 were non-serious, unrelated to study intervention, and mild to moderate at intensity. These newly reported AEs primarily included events consistent with mild common infections (e.g., sore throat, cough, rhinitis, enterovirus, pyrexia, fatigue) and limb fractures, which could be expected and commonly reported in the general pediatric population. No new AEs were reported that correspond to AESIs, no cases of myocarditis were reported. Overall, the additional follow-up to approximately 3 months post-Dose 2 for this initial enrolment group showed no clinically important change to the AE profile reported at the initial cut-off (6 September 2021).

Table 20. Number (%) Participants Reporting at Least 1 Adverse Event Form Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N[a]=1518)		Placebo (N[a]=750)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	166 (10.9)	(9.4, 12.6)	69 (9.2)	(7.2, 11.5)
Blood and lymphatic system disorders				
Lymphadenopathy				
Lymph node pain				
Cardiac disorders				
Angina pectoris				
Congenital, familial and genetic disorders				
Phimosis				
Ear and labyrinth disorders				
Ear pain				
Cerumen impaction				
Otorrhoea				
Eye disorders				
Conjunctivitis allergic				
Dry eye				
Hypermetropia				
Periorbital oedema				
Vision blurred				
Gastrointestinal disorders				
Nausea				
Vomiting				
Abdominal pain				
Diarrhoea				
Abdominal pain upper				
Toothache				
Aphthous ulcer				
Flatulence				
Gastrooesophageal reflux disease				
Odynophagia				
Oral pain				
Pancreatitis				
Rectal haemorrhage				
General disorders and administration site conditions				
Injection site pain				
Pyrexia				
Fatigue				
Injection site erythema				
Axillary pain				
Malaise				
Non-cardiac chest pain				
Injection site haemorrhage				
Injection site induration				
Injection site rash				

Peripheral swelling	BLD
Swelling	
Swelling face	
Thirst	
Immune system disorders	
Seasonal allergy	
Allergy to animal	
Hypersensitivity	
Mite allergy	
Infections and infestations	
Otitis externa	
Nasopharyngitis	
Hordeolum	
Cellulitis	
Impetigo	
Upper respiratory tract infection	
Conjunctivitis	
Ear infection	
External ear cellulitis	
Folliculitis	
Gastroenteritis viral	
Herpes zoster	
Molluscum contagiosum	
Onychomycosis	
Oral candidiasis	
Otitis media	
Paronychia	
Parotitis	
Pharyngitis	
Rhinitis	
Tonsillitis	
Tooth abscess	
Urinary tract infection	
Viral infection	
Vulvovaginal mycotic infection	
Injury, poisoning and procedural complications	
Fall	
Arthropod bite	
Contusion	
Skin laceration	
Sunburn	
Ligament sprain	
Upper limb fracture	
Accident	
Arthropod sting	
Back injury	
Burns first degree	
Concussion	
Foreign body	
Hand fracture	
Head injury	
Heavy exposure to ultraviolet light	
Joint dislocation	
Joint injury	
Limb fracture	
Limb injury	
Muscle strain	
Radius fracture	
Investigations	
Body temperature increased	
Serum ferritin decreased	
Metabolism and nutrition disorders	
Decreased appetite	
Musculoskeletal and connective tissue disorders	
Pain in extremity	
Musculoskeletal chest pain	
Arthralgia	
Muscle mass	
Myalgia	
Osteitis	
Synovitis	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Pyogenic granuloma	

Nervous system disorders		BLD
Headache		
Disturbance in attention		
Dizziness		
Dyslexia		
Migraine		
Paraesthesia		
Somnolence		
Psychiatric disorders		
Attention deficit hyperactivity disorder		
Irritability		
Poor quality sleep		
Tic		
Renal and urinary disorders		
Dysuria		
Reproductive system and breast disorders		
Balanoposthitis		
Respiratory, thoracic and mediastinal disorders		
Nasal congestion		
Cough		
Oropharyngeal pain		
Epistaxis		
Rhinorrhoea		
Asthma		
Sneezing		
Throat irritation		
Tonsillolith		
Skin and subcutaneous tissue disorders		
Urticaria		
Rash		
Dermatitis contact		
Erythema		
Rash papular		
Eczema		
Cold sweat		
Dermatitis		
Dermatitis allergic		
Macule		
Mechanical urticaria		
Pruritus		
Rash erythematous		
Rash macular		
Rash pruritic		
Surgical and medical procedures		
Suture insertion		
Tooth extraction		

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI based on the Clopper and Pearson method.

Many of the AEs reflected the reactogenicity events that were reported as AEs (ie, headache, vomiting, and injection site pain). Overall, several of the other commonly reported AEs are consistent with events that would be expected in a general population of healthy children in this age group and/or showed no imbalance between the vaccine and placebo groups. The most reported SOCs were:

Infections and infestations 1.9% vs 2.0%. The events reported in this SOC are common types of infections for this age group, including ear infections, conjunctivitis, and terms consistent with common colds and infections.

Gastrointestinal disorders 1.6% vs 1.7%. The events reported in this SOC are common types of disorders for this age group, including ear infections, conjunctivitis, and terms consistent with common colds and infections.

Injury, poisoning and procedural complications 1.7% vs 0.7%. The overall numerical difference between BNT162b2 and placebo groups is primarily due to unrelated events of insect bites, sunburns,

and a variety of concurrent events (i.e., fall and contusion) reported in a limited number of participants in the BNT162b2 group, which is a larger group of participants due to the 2:1 randomization.

Skin and subcutaneous disorders 1.4% vs 0.8%, the difference reflects reactogenicity evens in the vaccinated subjects.

Overall, a similar AE profiles was noted from Dose 1 up to cut-off with regard to most frequently reported events by SOC and PT across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status.

Related Adverse Events

Most of the AEs that were considered related to study drug by the investigator were reactogenicity events and in the SOC of general disorders and administration site conditions (1.1% vs 0.9%).

- From Dose 1 to 1 month after Dose 2, AEs assessed as related by the investigator were reported at a slightly higher frequency in the BNT162b2 group (3.0%) than in the placebo group (2.1%).
- Non-serious, non-severe, related events of lymphadenopathy were reported in 0.7% of participants BLD . All cases were considered mild.
- Non-serious related events of rash, urticaria, and other skin and subcutaneous tissue disorders (0.4% vs 0.5%).
- One non-serious, non-severe event of angina pectoris considered by the investigator as related to study intervention was reported by a participant BLD . This event lasted 1 minute, with an onset of 2 days after Dose 2, and resolved with no sequalae or further investigation deemed warranted by the investigator.
- One related non-serious, psychiatric disorder event of tic Grade 3 was reported in a participant BLD . The onset was 7 days after dose 2 and resolved at the time of cut-off. The AE was considered related to study intervention by the investigator, the neurologist that examined the patient later determined the event as unrelated and recommended lifestyle change.

Immediate Adverse Events

After Dose 1, immediate AEs (reported within 30 minutes of the first vaccination) were low in frequency (≤0.4%) in both groups, predominantly injection site pain (3 vs 2 subjects). No other immediate AEs post-Dose 1 were reported in the BNT162b2 group.

After Dose 2, immediate AEs (reported within 30 minutes of the second vaccination) were low in frequency (0.3%) in both groups, predominantly injection site pain, (1 vs 2 subjects). Injection site erythema, erythema and nausea were reported in 1 subject each BLD .

Severe or Life-Threatening and Serious Adverse Events

From Dose 1 to 1 month after Dose 2, severe AEs were low in frequency (0.1%) in both groups.

From Dose 1 to 1 month after Dose 2, severe AEs (i.e., Grade 3) were low in both arms BLD Three severe AEs BLD (tic, upper limb fracture fracture and rash) were reported up to the cut-off 8 October 2021. No participants reported any life-threatening (i.e., Grade 4) AEs.

Adverse Events of Clinical Interest

Adverse events of specific clinical interest, such as those in the CDC list of AESIs for COVID-19, were reviewed. Information on events of clinical interest included terms requested by the FDA: anaphylaxis, appendicitis, Bell's palsy, and lymphadenopathy. The protocol defined AESI of myocarditis/pericarditis was also considered in the safety review. Among the FDA-requested AEs of clinical interest, no cases were reported in the 5 to <12 years of age group up to the data cut-off date of anaphylaxis, myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), or appendicitis.

No cases of anaphylaxis or anaphylactic/anaphylactoid reaction were reported in the study and no cases of hypersensitivity were reported BLD .

Eighteen participants (1.2%) in the BNT162b2 group and 6 participants (0.8%) in the placebo group had events in angioedema/hypersensitivity SMQs. Events in the SMQ of angioedema reported BLD included face swelling (caused by an insect bite and considered by the investigator as not related to study intervention) (n=1) and urticaria (n=3). Urticaria was also reported BLD (n=3). Events in the SMQ of hypersensitivity more commonly reported in the BNT162b2 group than the placebo group were dermatitis (including contact and allergic dermatitis BLD) of which all cases were deemed as not related to vaccine; and rash (including pruritic, macular, injection site rash, BLD). Of the rashes BLD , 4 were considered by the investigator as related to study intervention: all Grade 1, typically with an onset of 7 days or more post-vaccination; only 1 injection site rash was reported with earlier onset at 3 days post-Dose 2. All but 1 event (rash on torso with onset at 11 days post-Dose 2) were reported as resolved. These related rashes were observed on the arm, torso, face and/or body with no clear pattern, and 2 participants had other skin reactions in the same anatomical location a short time before or after the reported SMQ event (i.e., prior erythema reaction to medical dressing patch on arm, or subsequent rash on face due to insect sting). One case in each group of allergic conjunctivitis and eczema were also reported. All angioedema/hypersensitivity SMQ events were mild or moderate, with the exception of 1 participant BLD who had a Grade 3 rash (reaction to topical cosmetic cream). Rash is considered an adverse reaction to vaccine and is noted as such in the current product labelling.

Lymphadenopathy is considered an adverse reaction to vaccine and is noted as such in the current product labelling. Lymphadenopathy was reported at a higher frequency among the vaccinated subjects (13 [0.9%] vs 1 [0.1%]). The mean time to onset after Dose 1 was 6.2 days (median 3 days), and after Dose 2 was 2.6 days (median 2 days). The mean duration of the events was 4.7 days (median 3.5 days, range 1 to 14 days). BLD had an onset at 22 days post-Dose 1 with a duration of 2 days. All reported cases of lymphadenopathy were mild.

Other Adverse Events of Clinical Interest

No cases have been reported in this population with regard to the CDC list of AESIs included (but were not limited to): thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, neuritis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome. No cases of severe COVID-19 have been reported.

One event of arthralgia grade 1 that resolved after one day was reported BLD , the AE was considered related to study intervention by the investigator.

One event of paresthesia grade 2 with onset 1 day after dose 2 and resolved 3 days after onset, was reported BLD . The AE was considered related to study intervention by the investigator.

2.6.4.2.3. Adverse Events Phase 2/3 Expansion group

From Dose 1 to the current cut-off date (08 October 2021) which represents at least 2 weeks follow-up after dose 2 for >70% of the participants but less than 4 weeks follow-up for all subjects, the proportions of participants in the safety expansion group reporting any AE were similar (BNT162b2 [7.2%] vs placebo [6.3%]).

Table 21. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (08 Oct 2021) – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 10 µg (N[a]=1591)	Placebo (N[a]=788)
Adverse Event	n[b] (%)	n[b] (%)
Any adverse event	115 (7.2)	50 (6.3)
Related[c]	55 (3.5)	14 (1.8)
Severe	BLD	
Life-threatening	0	0
Any serious adverse event	BLD	
Related[c]	0	0
Severe	BLD	
Life-threatening	0	0
Any nonserious adverse event	BLD	
Related[c]	55 (3.5)	14 (1.8)
Severe	BLD	
Life-threatening	0	0
Any adverse event leading to withdrawal	BLD	
Related[c]		
Serious	0	0
Severe	BLD	
Life-threatening	0	0
Death	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.

Many of the AEs were reflective of reactogenicity events that were reported as AEs. AE frequencies in SOCs containing the most common reactogenicity AEs (BNT162b2 vs placebo) were:

- general disorders and administration site conditions: 2.3% vs 1.8%
- gastrointestinal disorders: 0.8% vs 0.8%
- nervous system disorders: 0.6% vs 0.4%
- musculoskeletal and connective tissue disorders: 0.4% vs 0.4%

Other categories of events reported in the safety expansion group are discussed below by SOC and PT.

Infections and infestations (0.8% vs 0.4%). Most events reported in this SOC are typical for this age group, including ear infections, conjunctivitis, and terms consistent with common colds and infections. The overall numerical difference between BNT162b2 and placebo groups is due to unrelated events of unrelated skin and ear, nose, and throat infections reported in a limited number of participants in the BNT162b2 group, which is a larger group of participants due to the 2:1 randomization of BNT162b2: placebo.

Skin and subcutaneous disorders (1.0% vs 0.5%). Events reported more frequently in the BNT162b2 group included rashes, urticaria, angioedema, dermatitis, pruritis, night sweats, and Henoch-Schoenlein purpura. Events in this SOC are discussed further with AEs of clinical interest.

Immune system disorders BLD including 1 event reported as Type 4 hypersensitivity reaction and other non-drug allergies.

General disorders and administrative site conditions included reactogenicity events as well as chest discomfort or chest pain in 1 participant each (0.1%) in both groups. Events reported as non-cardiac chest pain were reported in 2 participants (0.1%) in the BNT162b2 group (both considered by the investigator as related to study intervention and 3 participants (0.4%) in the placebo group (1 considered by the investigator as related to study intervention).

Table 22. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 Through Cutoff Date (08 Oct 2021) –by System Organ Class and Preferred Term - Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 10 µg (N[a]=1591)		Placebo (N[a]=788)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	115 (7.2)	(6.0, 8.6)	50 (6.3)	(4.7, 8.3)
Blood and lymphatic system disorders	BLD			
Lymphadenopathy				
Neutropenia				
Eye disorders				
Conjunctival haemorrhage				
Conjunctivitis allergic				
Eye movement disorder				
Eye swelling				
Gastrointestinal disorders				
Vomiting				
Abdominal pain				
Diarrhoea				
Abdominal pain upper				
Dyspepsia				
Haematochezia				
Nausea				
Rectal haemorrhage				
Toothache				
General disorders and administration site conditions				
Injection site pain				
Fatigue				
Non-cardiac chest pain				
Pyrexia				
Chills				
Vaccination site pain				
Injection site bruising				
Axillary pain				

Chest discomfort	
Chest pain	
Injection site erythema	
Injection site lymphadenopathy	
Injection site rash	
Peripheral swelling	
Puncture site erythema	
Immune system disorders	
Allergy to animal	
Food allergy	
Type IV hypersensitivity reaction	
Infections and infestations	
Ear infection	
Pharyngitis streptococcal	
Arthritis infective	
Body tinea	
Cellulitis	
Conjunctivitis	
Impetigo	
Otitis externa	
Otitis media	
Perianal streptococcal infection	
Skin infection	
Tinea versicolour	
Urinary tract infection	
Injury, poisoning and procedural complications	
Arthropod bite	
Fall	
Animal scratch	
Ankle fracture	
Epiphyseal fracture	
Foot fracture	
Foreign body in ear	
Foreign body ingestion	
Hand fracture	
Limb fracture	
Muscle strain	
Skin abrasion	
Skin laceration	
Venomous sting	
Investigations	
Cardiac murmur	
Cardiac murmur functional	
Metabolism and nutrition disorders	
Decreased appetite	
Musculoskeletal and connective tissue disorders	
Arthralgia	
Myalgia	
Pain in extremity	
Costochondritis	
Joint swelling	
Neck pain	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Hair follicle tumour benign	
Nervous system disorders	
Headache	
Dizziness	
Hypogeusia	
Syncope	
Psychiatric disorders	
Irritability	
Renal and urinary disorders	

BLD

Nephrolithiasis	BLD
Respiratory, thoracic and mediastinal disorders	
Cough	
Oropharyngeal pain	
Nasal congestion	
Rhinorrhoea	
Asthma	
Epistaxis	
Sneezing	
Throat irritation	
Tonsillar inflammation	
Skin and subcutaneous tissue disorders	
Rash	
Rash papular	
Rash maculo-papular	
Urticaria	
Rash macular	
Acne	
Angioedema	
Dermatitis contact	
Henoch-Schonlein purpura	
Night sweats	
Pruritus	
Surgical and medical procedures	
Caecostomy	
Uncoded term	
SORE THROAT@@	
TYPE 1 DIABETES@@	

Note: MedDRA (v24.0) coding dictionary applied.
Note: Preferred terms with @@ denote uncoded terms.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI based on the Clopper and Pearson method.

One event of mild Henoch-Schoenlein purpura (HSP) with onset 21 days after Dose 1 was reported in a study participant with no past medical history BLD The event was considered as not related to study intervention by the investigator. On Day 16 post dose 1, ankle swelling that resolved 2 days later was noted by the parents and no medical attention was received. On Day 19, the study participant reported abdominal pain. On Day 20, the study participant bumped the knee and was evaluated by the primary care physician (PCP). The PCP diagnosed the HSP, with etiology reported as unknown. At that visit, the participant had mild abdominal pain and mild rash of palpable purpura at abdominal wall, stomach, and back. The abdominal pain resolved later that day. On Day 21, light rash on the abdomen and back was observed by the Investigator/Principal Investigator. There was no palpable purpura according to the principle investigator's assessment. Vitals reported included temperature of 98.7 °F (37°C), blood pressure of 100/69 mm HG, HR 90 bpm, and RR 21 bpm. No laboratory studies, including biopsy or urinalysis, were performed by the PCP. Treatment plan included prescription of steroids and pain medication to be used as needed. There were no other infections or non-study vaccinations reported from time of vaccination to diagnosis of HSP. Re-evaluation by PCP or referral to specialist did not occur. The HSP resolved 14 days after initial diagnosis with no treatment administered. Dose 2 was not administered.

One participant BLD had an event reported by the investigator as a mild Type IV hypersensitivity reaction considered by the investigator as related to study intervention. Following information about this case was available: this participant was enrolled BLD and reported as an AE of mild Type IV hypersensitivity reaction with rash (on head and arm) with onset of 3 days after Dose 1. The study participant was seen by a dermatologist who diagnosed as a Type IV hypersensitivity reaction and characterized the rash as `plaque, erythematous and minimal crusting,

and prescribed triamcinolone and acrivastine creams. The event reported as resolving 18 days after onset without sequelae. This participant had no other reported AEs. This participant had no reported medical history and received no prohibited concomitant treatments or non-study vaccines. This participant received Dose 2 without any additional AEs reported post-dose.

Related Adverse Events

From Dose 1 to the data cut-off date (08 October 2021), AEs assessed as related by the investigator were reported at a higher frequency in the BNT162b2 group (3.5%) than in the placebo group (1.8%). Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions. The most common reported event in this SOC was injection site pain (1.1% in BNT162b2 vs 0.3% in placebo).

One participant BLD had 2 AEs of pyrexia and neutropenia ('worsening from baseline') see section discontinuation due to AEs.

One participant BLD had a non-serious AE reported by the investigator as moderate haematochezia considered by the investigator as related to study intervention. The event was reported 4 days after Dose 2, the participant had hemoccult positive stool; was seen in the emergency department, and had no further tests done; and went home and the event resolved the same day without sequelae. This participant had a medical history of asthma and nondrug allergy and had no other reported AEs.

Two participants (0.1%) in the BNT162b2 group and 1 participant (0.1%) in the placebo group had events of non-cardiac chest pain considered by the investigator as related to study intervention. All events were mild and reported as resolved within 1 to 2 days of onset.

Immediate Adverse Events

After Dose 1, immediate AEs (reported within 30 minutes of the first vaccination) were low in frequency (≤0.2%) in both groups and included injection site pain reported in 1 participant (0.1%) in each group. Events reported BLD only following Dose 1 included vaccination site pain and pruritis, each event reported in 1 participant (0.1%).

After Dose 2, immediate AEs (reported within 30 minutes of the second vaccination) were low in frequency (≤0.1% vs 0) One participant (0.1%) reported each: fatigue, injection site pain, and an event reported by the investigator as tinea versicolor which was diagnosed at the time of the Dose 2 vaccination visit (i.e., reported on day of second vaccination and ongoing at the time of the data cut-off date). No allergic reactions to BNT162b2 were reported as immediate events after either dose.

Severe and Life-Threatening Adverse Events

According to table 21, the frequency of severe (i.e., Grade 3) AEs were low in both arms BLD subjects) from Dose 1 to the data cut-off date.
Severe events in the BNT162b2 group is described in table 23 below. The case that reported neutropenia and pyrexia is described in section discontinuation due to AEs.
No participants reported any life-threatening (i.e., Grade 4) AEs.

Table 23. Severe AEs form Dose 1 Through the Data Cutoff Date (08 Oct 2021) – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age – Safety

AE(s)	Other Notes	Participant Group
Neutropenia, pyrexia	AEs leading to study withdrawal, participant with medical history of transient benign neutropenia	BLD
Food allergy BLD BLD	Unrelated	
Arthritis infective BLD	SAE, unrelated	
Foreign body ingestion BLD	SAE, unrelated	
Epiphyseal fracture	SAE, unrelated	

Adverse Events of Clinical Interest

Adverse events of specific clinical interest, such as those in the CDC list of AESIs for COVID-19, were reviewed based on AEs reported up to the cut-off date. Information on events of clinical interest included terms requested by the FDA included: anaphylaxis, appendicitis, Bell's palsy, and lymphadenopathy. The protocol defined AESI of myocarditis/pericarditis was also considered in the safety review.

No cases of myocarditis/pericarditis, anaphylaxis, appendicitis, or Bell's palsy/facial paralysis/facial paresis was reported up to data cut-off date (08 October 2021).

Lymphadenopathy is considered an adverse reaction to vaccine and is noted as such in the current product labelling. Lymphadenopathy was reported at a higher frequency among the vaccinated subjects (6 [0.4%]) BNT162b2; 3 [0.4%] placebo). The mean time to onset after Dose 1 was 11 days (median 11 days), and after Dose 2 the mean time to onset was 1 day (median 1 day), the same day as vaccination. The mean duration of events was 3.0 days (median 3 days). All reported cases of lymphadenopathy were mild. Most cases were in the cervical nodes, with a few in the axilla.

Rashes is considered an adverse reaction to vaccine and is noted as such in the current product labelling. In the safety expansion group, no serious or severe, related rashes were reported after BNT162b2 vaccination.

Table 24. Selected Standard MedDRA queries From Dose 1 Through Cutoff Date (08 Oct 2021) – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age – Safety Population

SMQ	Overall SMQ System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 10 µg (N[a]=1591) n[b] (%)	 Placebo (N[a]=788) n[b] (%)
	Participants with any unsolicited adverse events within SMQ	BLD	
Angioedema (SMQ)	Any unsolicited adverse events within Angioedema (SMQ)		
	Eye disorders		
	Eye swelling		
	Skin and subcutaneous tissue disorders		
	Angioedema		
	Urticaria		
Arthritis (SMQ)	Any unsolicited adverse events within Arthritis (SMQ)		
	Infections and infestations		
	Arthritis infective		
Convulsions (SMQ)	Any unsolicited adverse events within Convulsions (SMQ)		
Demyelination (SMQ)	Any unsolicited adverse events within Demyelination (SMQ)		
Hypersensitivity (SMQ)	Any unsolicited adverse events within Hypersensitivity (SMQ)		
	Eye disorders		
	Conjunctivitis allergic		
	General disorders and administration site conditions		
	Injection site rash		
	Immune system disorders		
	Type IV hypersensitivity reaction		
	Skin and subcutaneous tissue disorders		
	Dermatitis contact		
	Rash		
	Rash macular		
	Rash maculo-papular		
Peripheral neuropathy (SMQ)	Any unsolicited adverse events within Peripheral neuropathy (SMQ)		
Vasculitis (SMQ)	Any unsolicited adverse events within Vasculitis (SMQ)		
	Skin and subcutaneous tissue disorders		
	Henoch-Schonlein purpura		

Abbreviation: SMQ = Standardized MedDRA query.
Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any unsolicited adverse events within SMQ," n = the number of participants reporting at least 1 occurrence of any unsolicited adverse events within SMQ.
PFIZER CONFIDENTIAL SDTM Creation: 13OCT2021 (23:06) Source Data: adae Table Generation: 14OCT2021 (15:34) (Cutoff Date: 08OCT2021, Snapshot Date: 13OCT2021) Output File:

Other Adverse Events of Clinical Interest

In addition to FDA-requested AEs of clinical interest, notable pertinent negatives (i.e., no cases reported in this safety expansion group as of the data cut-off for this submission) with regard to the CDC list of AESIs included (but were not limited to): thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, neuritis, convulsions, peripheral neuropathy, Kawasaki disease, MIS-C, or acute respiratory distress syndrome.

Additional AEs of clinical interest, regardless of inclusion on the CDC AESI list, were evaluated based on sponsor safety data review.

Arthralgia was reported by a total of 2 participants, 1 each in the BNT162b2 (0.1%) and placebo (0.1%) groups.

Severe infective arthritis was reported by 1 participant BLD (Table 24), considered an unrelated SAE; and earlier described.

Chest pain, non-cardiac chest pain, or chest discomfort were reported by 3 participants (0.2%) in the BNT162b2 group and 4 participants (0.5%) in the placebo group. None of these events had any reported cardiac involvement.

Syncope was reported by 1 participant BLD.

2.6.4.3. Serious adverse event/deaths/other significant events

2.6.4.3.1. Phase 2/3 Initial Group

Deaths

No deaths were reported up to 8 October 2021.

Serious Adverse Events

Up to 8 October 2021 one participant (0.1%) in each group reported a total of 3 SAEs after receiving BNT162b2 or placebo. These SAEs were all assessed by the investigator as not related to study intervention.

- The participant BLD reported a non-serious Grade 3 AE of fall 45 days after receiving Dose 2; this was concurrent with a reported Grade 3 SAE of upper limb fracture identified the same day (45 days post-Dose 2) as being due to a 'traumatic accident' (i.e., fall). The fracture was reported as recovering/resolving at the time of the data cut-off. The SAE was considered by the investigator as not related to study intervention.
- The participant BLD reported an SAE of Grade 3 pancreatitis (noted as occurring 'post-injury') with onset at 4 days post-Dose 2 and reported as resolved within 7 days of onset with concomitant drug treatment. This same participant reported a second Grade 3 SAE of abdominal pain with onset at 11 days post-Dose 2 and reported as resolved within 6 days after onset. Both SAEs were considered by the investigator as not related to study intervention. This participant had no reported medical history and received no prohibited concomitant treatments or non-study vaccines.

2.6.4.3.2. Phase 2/3 Expansion Group

Deaths

No deaths were reported up to 08 October 2021.

Serious Adverse Events

A total of 3 SAEs were reported in the Phase 2/3 paediatric safety expansion group of children 5 to <12 years of age up to the data cut-off date (08 October 2021), which represents at least 2 weeks of follow-up after Dose 2 for most (>70%) participants.

The SAEs were all assessed by the investigator as not related to study intervention. SAEs were reported by 3 participants BLD .

- One study participant BLD had an SAE of severe arthritis infective with onset of 15 days after Dose 1, considered by the investigator as not related to study intervention, and reported as resolved 21 days after onset. This participant had no other reported AEs. No further information was available at the time of this submission.
- One study participant BLD had an SAE of severe foreign body ingestion with onset of 17 days after Dose 1, considered by the investigator as not related to study intervention, and reported as resolved 2 days after onset. This participant had one other unrelated AE of streptococcal pharyngitis.
- One study participant BLD had an SAE of severe epiphyseal fracture with onset of 20 days after Dose 1, considered by the investigator as not related to study intervention, and reported as resolving at data cut-off date. This participant had no other reported AEs.

2.6.4.4. Laboratory findings

N/A

2.6.4.5. In vitro biomarker test for patient selection for safety

N/A

2.6.4.6. Safety in special populations

N/A

2.6.4.7. Immunological events

N/A

2.6.4.8. Safety related to drug-drug interactions and other interactions

N/A

2.6.4.9. Discontinuation due to adverse events

No AEs leading to discontinuation were reported in the Phase 2/3 initial study including paediatric population of children 5 to <12 years of age.

In the Phase 2/3 paediatric safety expansion group (cut-off date of 08 October 2021), one participant BLD discontinued due to AEs, the narrative is provided below:

One study participant in the BNT162b2 group had an AE of severe pyrexia (40.1 °C) with onset of 2 days after Dose 1 considered by the investigator as related to study intervention that resolved at 1 day after onset. Severe neutropenia ('worsening from baseline') with onset of 3 days after Dose 1 considered by the investigator as related to study intervention was reported as resolving at the time of the data cut-off date. Medical history included gingivitis (since 2020), otitis media (in 2021), and benign transient neutropenia of unknown ethology (since 2021).). Prior to study enrolment, a full haematology work-up (including for possible leukaemia) was performed with baseline absolute neutrophil count (ANC) of 480 cells/mm^3 (Reference value ANC 1800-8000 cells/mm^3); the haematologist indicated no concerns with study participation. After Dose 1, on the day of vaccination, the

participant reported one loose stool with a temperature of 37.8 °C and mild injection site pain; on Day 2 post-Dose 1 temperature of 40.1 °C (as noted above) with mild injection site pain and fatigue was reported; and on Day 3 post-Dose 1 the study participant was afebrile with mild injection site pain. Routine laboratory tests were performed two days post Dose 1, and the ANC was 20 cells/mm^3 and platelets were reported as normal (no platelet count value specified). No other symptoms or infections were reported at that time. Subsequently on Day 19 after Dose 1, the investigator was contacted by the participant's caregiver who reported the participant had bleeding gums for 1 week prior. On Day 23, the participant attended Visit 2 to be seen by the investigator, had a follow-up blood draw that showed the ANC had improved to 70 cells/mm^3, and was reported to be doing well. Dose 2 was not administered, and the participant was withdrawn from study intervention and remains in study follow-up. The study participant had previously received routine childhood immunizations on schedule. This participant reported no other AEs and received no prohibited concomitant medications or non-study vaccines during the study vaccination period.

2.6.4.10. Post marketing experience

N/A

2.6.5. Discussion on clinical safety

The safety database to evaluate use of BNT162b 10µg in paediatric subjects aged 5 to <12 years of age constitutes of a Phase 1/2/3 Study C4591007. In the Phase 1 study the dose levels 10, 20, and 30 µg were evaluated in 48 (n=16 each group) paediatric subjects. The Phase 2/3 study constitutes of two study groups randomized 2:1 that was initiated at two different time points.

The initial safety group included 2,285 subjects (n=1,528 BNT162; n=757 placebo) first cut-off 6 September 2021, and the safety expansion group included 2,394 subjects (n=1,598 BNT162b; n=795 placebo) cut-off 8 October 2021. When data for the expansion safety group was submitted, the MAH also provided data up to 8 October for the initial safety group. The Phase 2/3 study is still ongoing.

Disposition was similar in the two Phase 2/3 groups where very high exposure rates to both dose 1 (99.3% initial; 99.4% expansion) and dose 2 (99.3% initial; 98.7% expansion) was reached. For the initial study group an excessive number of participants completed the 1-month post dose 2 visit (98.5%), and a majority (95,9%) had a follow-up time of ≥3 months after dose 2 at the cut-off 8 October 2021.

For the expansion group >70% had a follow-up time >2 weeks but none of the subjects had a follow-up time >4 weeks after dose 2. Withdrawal rates were overall low in both study arms of the initial group (0.3% BNT162b;0.4% placebo) and the expansion group (0.1% each arm).

Most of the participants received Dose 2 within the protocol defined window of 19-23 days after Dose 1 ([initial 95.6% BNT162b; 94.5% placebo], [expansion 94.4% BNT162b; 94.5% placebo]). Demographic characteristics are considered well balanced between vaccine and placebo arm. Both study groups in the Phase 2/3 study were comparable in terms of age, gender, race, ethnicity, obesity, baseline SARS-CoV-2 and comorbidities. None of the subjects were HIV+.

A dose dependent increase of local and systemic reactions was noted in the Phase 1 study, where 10 ug appears to be less reactogenic. The MAH decided to continue with a dose of 10 µg for the Phase 2/3 study, which is endorsed from a safety perspective.

Reactogenicity was evaluated in 2,268 paediatric subjects from the initial safety group of the Phase 2/3 study. The most common local reaction was pain at injection site, which was reported in 74% of the paediatric subjects after Dose 1 and in 71% after Dose 2 of BNT162b. Most of the local reactions were transient and mild to moderate at intensity. No Grade 4 local reactions were reported in either group.

Among the reported systemic reactions, fatigue (>34%) and headache (>22%) was the most common in the subjects that received BNT162b. A tendency to a higher frequency of systemic events after dose 2 compared to dose 1 was noted. Most of the systemic events were mild or moderate in severity. Across groups, median onset after receiving BNT162b2 was 1 to 4 days after Dose 1 or Dose 2.

Antipyretic/pain medication after vaccination with BNT162b increased slightly from dose 1 (14.4%) to dose 2 (19.9%), supporting a somewhat higher frequency of the systemic reactions after dose 2.

Overall, the pattern of systemic events reported after each dose can be expected from a vaccine.

Up to the cut-off date (8 October 2021) 197 (13%) vs 83 (11.1%) subjects in the initial safety group of Phase 2/3, reported at least one AE. Most often occurring SOCs were general disorders and administration site conditions (injection site pain, fatigue), gastrointestinal disorders (vomiting, abdominal pain), nervous system disorders (headache), musculoskeletal and connective tissue disorders (myalgia, arthralgia), infections and infestations (otitis externa), injury poisoning and procedural complications (fall, arthropod bite).

Among the subjects included in the safety expansion group 115 (7.2%) vs 50 (6.3%) of subjects reported at least one AE. Most often occurring SOCs in the safety expansion group were general disorders and administration site conditions (2.3% vs 1.8%), which was mainly driven by reactogenicity events such as injection site pain and fatigue, followed by gastrointestinal disorders (vomiting, abdominal pain), nervous system disorders (headache) and musculoskeletal and connective tissue disorders (myalgia, arthralgia).

Overall, in both initial and expansion safety group, many of the reported AEs were either related to the reactogenicity of vaccination or events that would be expected in a general population of healthy children in this age group. No imbalance between the vaccine and placebo groups was noted.

From Dose 1 to 1 month after Dose 2, severe AEs (Grade 3) were low in both arms (3 vs 1) in the initial safety group. Three severe AEs BLD were reported up to the cut-off 6 September 2021 (tic, upper limb fracture and rash). In the expansion safety group, BLD subjects reported severe AEs (food allergy, arthritis infective, foreign body, pyrexia/neutropenia epiphyseal fracture). No participants reported any life-threatening (Grade 4) AEs.

Lymphadenopathy was reported in a higher frequency among the vaccinated subjects compared to placebo (initial group 13 vs 1: expansion group 6 vs 3). The item is considered an adverse reaction to vaccine and is noted as such in the SmPC.

In the initial study 18 participants (1.2% vs 0.8%) reported events in angioedema/hypersensitivity SMQs (insect bite, urticaria, dermatitis, rash). In the expansion group hypersensitivity reactions (mostly rash) was reported in 3 vs 4 subjects. Rash is included in the SmPC as an ADR.

In the safety expansion group, arthralgia was reported in one subject in each treatment arm, one event of syncope was reported BLD and chest pain was reported in 3 vs 4 subjects, none of them with cardiac involvement.

One case BLD safety expansion group was by the investigator reported to have an AE with Henoch-Schoenlein purpura, considered by the investigator as mild and not related to study intervention. If there is no other causal explanation to this AE, it cannot be excluded that this event was related to study intervention and that other AEs reported in this case could have been the first clinical signs of Henoch-Schonlein purpura. Additional information was provided by the MAH describing clinical symptoms not completely aligned with Henoch Schönlein purpura, however, urine sample is lacking and therefore evaluation of vasculitis engaging the kidneys is not possible. No events of vasculitis such as Henoch-Schönlein purpura was reported post-marketing up to 16 November 2021. This topic should be monitored, and any emerging data presented in the upcoming MSSRs.

Another participant BLD safety expansion group had an event reported by the investigator as a mild type IV hypersensitivity reaction considered by the investigator as related to study intervention. Several drugs can trigger type IV hypersensitivity reactions leading to drug hypersensitivity and other clinical syndromes and some of them can lead to more serious life-threatening type, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or acute generalized exanthematous pustulosis. Thereby, it is important to exclude that this clinical condition described in this case was not a precursor to a more severe type IV hypersensitivity reaction. Since this was confirmed to be a mild case only seen after the first dose, no further action is proposed. This topic should be monitored and any emerging data presented in the upcoming MSSRs.

SAEs occurred at a very low frequency in both placebo and vaccine arm in both study groups. In the expansion safety groups one subject BLD reported one SAE (upper limb fracture fracture). No event of death was reported.

AEs of clinical interest, such as the CDC's list of AESIs for COVID-19, which both include terms potentially indicative of severe COVID-19 or serious autoimmune and neuroinflammatory disorders, were considered in the review of reported events. Up to the cut-off 8 October 20201 no cases of myocarditis/pericarditis, anaphylaxis, appendicitis, Kawasaki disease, convulsions, peripheral neuropathy, MIS-C, severe COVID-19, autoimmune or demyelination events Bell's palsy/facial paralysis/facial paresis was reported in the two groups included in the Phase 2/3 study.

The rate of subjects discontinuing the study due to AE was low, in total one subject BLD discontinued due to AEs (fever and neutropenia).

The study size did not allow detection of rare adverse events, or to evaluate whether the characteristics of identified, but rarer risks differ compared with the adolescent and adult populations.

In response to a request from the Rapporteur, the MAH provided additional information on AEs in children from 5 to less than 12 years of age during the post-marketing phase. One case of myocarditis and one case of perimyocarditis have been reported. For the first case, no previous medical history was reported, TTO was 5 days after dose 2 and the child was hospitalized for 8 days for myocarditis. A negative COVID-19 test was reported, but no other laboratory data has been provided. In the second case, the child was admitted to hospital after dose 2 to see a cardiologist and was reported to have perimyocarditis. Besides clinical symptoms no information regarding laboratory data, medical history, TTO, concomitant medication or hospitalization has been provided. Due to assumed off-label use of 30 µg dose in the age group 5-11 years, and very limited information provided for each case, , it is not possible to draw firm conclusions regarding the relevance of this information for the applied dose of 10 microgram in the age group 5-11 years.

2.6.6. Conclusions on the clinical safety

The safety evaluation is based on one still ongoing Phase 2/3 study including 2,285 (initial group) +2,394 (expansion group) paediatric subjects randomized 2:1, who received either two doses of BNT162b 10 µg (n=1,528+1,598) or placebo (n=757+795).

Overall, the reported reactogenicity profile are in line with what can be anticipated from a vaccine with mostly mild to moderate reactions.

The frequency of reported AEs and SAEs were low. The observed adverse reactions have been included in the SmPC.

There are no new safety concerns based on the study conducted; however, the study size did not allow detection of rare adverse events, or to evaluate whether the characteristics of identified, but rarer risks

differ compared with the adolescent and adult populations. Post-marketing data on safety, as additionally requested from the MAH, informed about two cases of myocarditis, myopericarditis after assumed off-label use of the higher 30 microgram dose, and with very limited clinical information. No additional concern is currently raised based on this information.

The CHMP considers the following measures necessary to address the missing safety data in this age range in the context of this conditional MA:

Description	Due Date
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591007.	July 2024

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of Safety Concerns

Important Identified Risks	Anaphylaxis Myocarditis and Pericarditis
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

No changes in the list of safety concerns was introduced in the updated RMP

2.7.2. Pharmacovigilance plan

Study Status	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 imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in frail patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
				CSR submission 6 months post Dose 2:	31-May-2021
				Final CSR submission with supplemental follow-up:	31-Dec-2023
C4591007 *Ongoing*	Global	The purpose of the dose-finding/selected-dose study is to rapidly describe the safety, tolerability, immunogenicity, and efficacy of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy children	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long term safety data.	Final study report submission:	31-Jul-2024

Category 3					
C4591009 *Planned*	US	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System.	Myocarditis and pericarditis AESI-based safety events of interest Use in pregnancy Use in immunocompromised patients Use in persons with a prior history of COVID-19	Protocol submission	31 August 2021
				Monitoring report submission	31 October 2022
				Interim Analysis submission:	31 October 2023
				Final study report submission:	31 October 2025
C4591011 *Planned*	US	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.	Myocarditis and pericarditis 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:	31-Dec-2021
					30-Jun-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023
C4591012 *Ongoing*	US	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.	Myocarditis and pericarditis 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 *Ongoing*	EU	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final CSR submission:	30-Sep-2024
C4591015 *Ongoing*	Global	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.	Use in pregnancy and while breast feeding.	Final CSR submission:	30-Apr-2023
C4591014 *Planned*	US	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
WI235284 *Planned*	US[a]	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
WI255886 *Planned*	Ex-EU[a,b]	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
BNT162-01 Cohort 13 *Ongoing*	EU	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission: Final CSR submission:	30-Sep-2021 31-Dec-2022

C4591024 (former Safety and immunogenicity in high-risk adults) *Planned*	Global	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal 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.	Protocol submission: Final CSR submission:	30-Jun-2021 30-Jun-2023
C4591021 (former ACCESS/VAC4EU) *Ongoing*	EU	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	Myocarditis and Pericarditis 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.	Final CSR submission:	30-Sep-2024
C4591038 (former C4591021 substudy) *Planned*	EU	To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine	Myocarditis and Pericarditis Long term safety data	Protocol submission: Final CSR submission:	31-Jan-2022 30-Sep-2024
C4591036 (former Pediatric Heart Network Study) *Planned*	US/CA	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis	Myocarditis/pericarditis Long term safety data	Protocol submission: Final CSR submission	30-Nov-2021 31-Oct-2025

C4591030 (Co-administration study with seasonal influenza vaccine) *Planned*	Not available	Safety and immunogenicity of COVID-19 mRNA vaccine 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

a. Case-control study nested in a prospective surveillance cohort, conducted as a research collaboration.
b. United Kingdom.

Study C4591007 imposed as a specific obligation of the marketing authorisation was added in the RMP as a Category 2 study. This study will address the following safety concerns: Anaphylaxis, Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), Long term safety data. Additional AESI will be captured in this trial.

MAH will evaluate safety in the following number paediatric 5 to <12 year-old subjects in the following studies:

C4591021(EU)	source population about 2.5 million
C4591038 (former C4591021 substudy) (EU)	not known (protocol submission Jan2022)
C4591009 (US)	source population about 2 million
C4591011 (US)	source population about 750,000
C4591036 (US and Canada)	not known (protocol submission 30Nov2021)
C4591024 (global)	60
C4591007	4000

The recruitment of this population in the studies will be reported in the PSURs.

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Anaphylaxis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine. Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591001 (31-Dec-2023) • C4591007 (31-Jul-2024) • C4591009 (31-Oct-2025) • C4591010 (30-Sep-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) 30-Sep-2024).
Myocarditis and pericarditis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: DHCP letter and communication plan	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591009 (31-Oct-2025) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024). • C4591038 (former C4591021 substudy) (30-Sep-2024) • C4591036 [former Pediatric Heart Network study] (31-Oct-2025).
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED (PART **Error! Reference source not found.** and Annex 4). Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591001 (31-Dec-2023) • C4591007 (31-Jul-2024) • C4591009 (31-Oct-2025) • C4591011[b] (31-Dec-2023) • C4591012[b] (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30 Sep-2024)[b].

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591010[a](30-Sep-2024) • C4591009 (31-Oct-2025) • C4591011[a] (31-Dec-2023) • C4591015 (30-Apr-2023) • C4591021 (former ACCESS/VAC4EU)[a] (30-Sep-2024).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR or IA Due Date) • BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Dec-2022) • C4591010[c] (30-Sep-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)**Error! Bookmark not defined.**
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date submission) • C4591001 subset (31-Dec-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024) • C4591024 (former Safety and immunogenicity in high-risk adults) (30-Jun-2023)
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	No risk minimisation measures.	Additional pharmacovigilance activities: • C4591030 (Co-administration study with seasonal influenza vaccine) (31-Dec-2022).
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date or IA CSR submission) • C4591001 (31-Dec-2023) • C4591007 (31-Jul-2024) • C4591010 (30-Sep-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591021 (former ACCESS/VAC4EU) (30-Sep-2024). • C4591038 (former C4591021 substudy) (30-Sep-2024) • C4591036 (former PHN) (31-Oct-2025)

a. Please note that studies C4591009, C4591010, C4591011 and C4591021 (former ACCESS/VAC4EU) address only "Use in pregnancy".
b. Addresses AESI-based safety events of interest including vaccine associated enhanced disease
c. Addresses AESI-based safety events of interest.

No changes to the Risk minimisation measures are proposed within the updated RMP.

While medication errors are not an important risk in the context of the RMP, the MAH has implemented measures to mitigate the risk of medication errors e.g. distinctive colours of flip off caps in line with the colour used on the labelling, as well as making information available to HCPs on the proper preparation and differentiation available via the QR code/URL and provided to the Member States who require them to support the national vaccination and/or communication campaigns.

In addition, the MAH took the opportunity to merge editorially the version submitted in this procedure with the latest approved RMP version.

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 4.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Quick Response (QR) code

The following additional elements have been agreed to be provided through a QR code as part of this line extension:

- A formulation comparison table to guide Healthcare Professionals and vaccine recipients on the different formulations
- Dropdowns to get access to the SmPC, PIL and related documents for each of the presentations available.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004 (REG), Comirnaty (tozinameran) is included in the additional monitoring list for the following reasons: Conditional marketing authorisation / New active substance and new biological.

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 children is mostly a mild disease. Severe cases occur rarely, and predominantly in subjects with underlying conditions. The MAH is seeking an indication for Comirnaty (BNT162b2) 10 µg formulation to children 5 to <12 years of age.

3.1.2. Available therapies and unmet medical need

There are currently no vaccines against COVID-19 approved in the EU for the use in children below 12 years of age.

3.1.3. Main clinical studies

The application is based on the ongoing paediatric phase 1/2/3 study C4591007, which includes 5 to <12-year-old children. The study is in agreement with the approved PIP. The study population was randomized 2:1 to receive either 10 µg Comirnaty or saline placebo, given as 2 IM injections 21 day apart.

In the Phase 2/3, the efficacy of BNT162b2 was established by immunobridging of the SARS CoV-2 neutralizing antibody response in paediatric participants aged 5 to <12 years of age group in Study C4591007 to the response in participants being 16 to 25 years of age in the Phase 2/3 efficacy study C4591001. The Phase 2/3 evaluable immunogenicity population for participants 5 to <12 years of age included 294 participants in the BNT162b2 group and 147 participants in the placebo group, and for Study C4591001 participants 16 to 25 years of age included 273 participants in the BNT162b2 group and 47 participants in the placebo group. In the BNT162b2 and placebo groups, the majority of adolescents received dose 2 between 19 to 23 days after dose 1 (94.4% versus 94.5%).

A supportive vaccine efficacy analysis was planned to be conducted when at least 21 confirmed cases of COVID-19 had accrued in the 5 to <12 years of age group and if success criteria for immunobridging in this age group had first been met. The efficacy analysis is based on cases confirmed among the initially enrolled N~2250 participants in the 5 to <12 years of age group of Study C4591007. Among randomized participants, 1450 participants were included in the BNT162b2 group and 736 participants in the placebo group.

3.2. Favourable effects

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 50% neutralizing GMT in children 5 to <12 years of age (who received the 10-µg dose level) to that of young adults 16 to 25 years of age (who received the 30-µg dose level) was 1.04 (2-sided 95% CI: 0.93, 1.18). The lower bound of the 2 sided 95% CI for GMR was >0.67 and the GMR point estimate was ≥0.8, which meets the prespecified 1.5-fold margin and success criteria. Therefore, immunobridging based on GMR was achieved.

There was a similar magnitude of rise in antibody titers in the 5 to <12 years of age group (118.2) compared with the young adult 16 to 25 years of age group (111.4) for the BNT162b2 group. Neutralizing titers were elicited to both the USA-WA1/2020 (reference) and B.1.617.2 (Delta) recombinant SARS-CoV-2 strains at 1 month after Dose 2.

Equal proportions (99.2% each of children 5 to <12 years of age and young adults 16 to 25 years of age) of participants achieved a seroresponse. The difference in the proportions of participants who had seroresponse between the 2 age groups (children – young adults) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved.

Subgroup analyses by demographic, baseline SARS-CoV-2 and obesity status did not show any meaningful differences in neutralizing immune response and seroresponse rate in the 5 to < 12 years group and 16-25 years group.

In support of the immunobridging a preliminary analysis of efficacy was submitted. Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for BNT162b2 10 µg against any confirmed COVID-19 from at least 7 days after Dose 2 was 90.7% (2-sided 95% CI: 67.7%, 98.3%) which included 3 cases in the BNT162b2 group and 16 cases in the placebo group. Exploratory analysis of Delta neutralizing immune responses from a subset of

vaccinated/placebo sera from children 5-11 years, which showed significant neutralizing titers against the Delta variant, support the effectiveness of the BNT162b2 10µg against Delta variant. Confirmatory case sequencing data for COVID-19 cases will be reported at a later time, when the sequencing analysis is completed. The same vaccine efficacy (90.7% (95% CI: 67.4%, 98.3%)) was observed in children 5 to <12 years of age with or without evidence of infection prior to 7 days post-dose 2. There were no cases of COVID-19 among subjects who were SARS-CoV-2 positive at baseline. As might be anticipated, no severe cases were reported in children aged 5-11 years.

Based on these data, it can be inferred that BNT162b2 vaccine is effective to prevent symptomatic COVID-19 in adolescents 5-11 years of age.

3.3. Uncertainties and limitations about favourable effects

The efficacy analysis is considered supportive as it is based on preliminary data and a final analysis is anticipated when available.

Specific risk groups among children, including those immunosuppressed, or otherwise with risk of more severe disease, were not specifically studied. A study in immunocompromised children is included in the PIP. The MAH was asked to consider whether a third dose in the primary series is relevant for children with substantial immunosuppression, as has been agreed previously for adolescents and adults. The MAH responded that the ongoing study in IC children is planned to be finished in the end of the 2022. The CHMP understands the MAH's position, but as extrapolated data from adults was used also in age group 12-18, the SmPC should follow the same orientation as for adolescents.

It is currently unknown if vaccination provides protection against asymptomatic infection, and to what extent vaccination prevents further transmission.

The duration of protection is unknown in children, as well as among adults. The median duration of follow-up for the initially enrolled Phase 2/3 participants aged 5-11 years was 3.3 months post-dose 2. As for subjects ≥ 12 years of age, the assessment of the vaccine efficacy over a period of at least 6 months is expected to determine the need and the appropriate time of a booster dose.

3.4. Unfavourable effects

The safety of Comirnaty administered to subjects aged 5 to <12 years has been evaluated in a still ongoing Phase 2/3 study (C4591007) that includes two safety groups of subjects recruited at two different time points. The initial group included a total of 2,285 subjects (n=1,528 BNT162; n=757 placebo) and the safety expansion group included 2,394 subjects (n=1,598 BNT162b; n=795 placebo). A new dose (10µg) was used in the study, which was administered with the same dose regimen as for adolescent and adult subjects.

At the time of the analysis (8 October 2021), a total of 2,171 (n=1,456 Comirnaty; n=715 placebo) paediatric subjects in the initial groups were evaluated for safety for at least 3 months after the second dose of Comirnaty. In the expansion group 1,695 (n=1,122 Comirnaty; n=573 placebo) of the subjects were evaluated for safety for at least 2 weeks after dose 2, none of them had a follow-up time of ≥4 weeks after the second dose.

Regarding reactogenicity, the most frequent adverse reactions in participants aged 5-<12 years was pain at the injection site (74% dose1; 71% dose2), fatigue (34% dose1; 39% dose2), headache (22% dose1; 28% dose2), chills (5% dose1; 10% dose2), muscle pain (9% dose1; 12% dose2) and fever (3% dose1; 7% dose2). Vomiting and diarrhoea were reported infrequently after both doses to a similar extent in the placebo and vaccine group.

Most of the local and systemic events resolved within 3 days and were mild to moderate at intensity.

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 adolescent and adult population. No cases of myocarditis or pericarditis were observed. One event of type IV hypersensitivity reaction and one event of Henoch-Schoenlein purpura were reported among subjects who received Comirnaty 10 µg in the expansion safety group.

3.5. Uncertainties and limitations about unfavourable effects

A large number of adolescent and adult subjects has been exposed to the vaccine worldwide (>1,4 billion (1 Dec 2020-30 Sept 2021). The short to midterm safety is considered relatively well characterized in adults so far. However, the present study size does not allow for the characterisation of less common child-specific risks, or if the magnitudes of identified but rarer risks differ compared with higher age groups.

Long term safety data for paediatric subjects are also 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 as SOB.

There are no data available on interaction with other vaccines given concomitantly.

One case of Henoch-Schoenlein purpura was reported post vaccination. The causality assessment of "not related" is questioned. This entity is generally more common in children compared to adults. Additional information was provided by the MAH describing clinical symptoms not completely aligned with Henoch Schönlein purpura, however, urine sample is lacking and therefore evaluation of vasculitis engaging the kidneys is not possible. This topic will be monitored, and any emerging data presented in the upcoming MSSRs.

Furthermore, one case of mild type IV dermal hypersensitivity was reported. This topic will be monitored, and any emerging data presented in the upcoming MSSRs.

3.6. Effects Table

Table 25. Effects Table for Comirnaty. Intended for active immunisation against SARS CoV-2, thereby preventing COVID-19 in subjects aged 5 to <12 years (data cut-off: 08 October 2021)

Effect	Short Description	Unit	BNT162b2 (10 µg)	Placebo	Uncertainties / Strength of evidence	References
Vaccine efficacy	First COVID-19 occurrence from 7 days after Dose 2, **without** prior SARS-COV-2	**% (95% CI)**	**90.7 %** (67.7; 98.3)			
		Cases/ Number of subjects at risk for the endpoint	**3**/ 1517	**16**/663	Data with fewer observations, but with similar efficacy confirmed in adolescence and adults	Evaluable efficacy population (7 days post dose 2) - Study C4951007

	VE after 1 dose	**% (95% CI)**	**91.4 %** (70.4;98.4)			Modified intend to treat population C4951007
		Cases/ Number of subjects at risk for the endpoint	**3**/1517	**17**/751		
Immunogenicity	Endpoint	**Treatment group**	**5 to <12 years old**	**16-25 years old**	Sufficient number of subjects to evaluate immunogenicity	1 month after dose 2 Evaluable Immunogenicity population C4951001
		N of subjects	264	253		
	GMT (95% CI)	**Ratio** 1.04 (0.93, 1.18)	**1197.6** (1106.1, 1296.6	**1146.5** (1045.5, 1257.2)	**Noninferior**	
	GMFR (95% CI)		**118.2** (109.2, 127.9)	**111.4** (101.2, 122.7)		
	Seroresponse rate % (95% CI)	Difference% (95% CI) -**0%** (-2.0, 2.2)	**262 (99.2 %)** (97.3, 99.9%)	**251 (99.2%)** (97.2; 99.9%)		
Unfavourable Effects						
Pain at injection site	5-<12 years	%	Dose 1 74% Dose 2 71%	Dose 1 31% Dose 2 29%	Transient events, majority mild to moderate intensity	Reactogenicity subset of initial safety group Phase 2/3 N=2,268 (n=1,158 BNT162b2;n=750 placebo)
Fatigue	5-<12 years	%	Dose 1 34% Dose 2 39%	Dose 1 31% Dose 2 24%		
Headache	5-<12 years	%	Dose 1 22% Dose 2 28%	Dose 1 24% Dose 2 19%		
Fever	5-<12 years	%	Dose 1 3% Dose 2 7%	Dose 1 1% Dose 2 1%		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefit of Comirnaty 10µg, administered as a course of two doses with about 3 weeks in between, in paediatric subjects 5 to <12 years of age has been clearly demonstrated in terms of bridging via similar neutralising antibody titers as seen in young adults treated in the efficacy study that was pivotal to initial approval, as well as protection against symptomatic disease. . The efficacy of Comirnaty (2 doses of 10 µg, separated by 21 days) to prevent COVID-19 in children aged 5-11 years with and without evidence of prior SARS-CoV-2 infection, occurring at least 7 days after the second dose, was 90.7% (CI95% 67.4; 98.3) and considered well-established. However, some uncertainties,

such as long-term efficacy and safety, and possibly duration of protection, should be adequately addressed post-authorization in the context of a conditional MA.

While severe COVID-19 is rare in 5 to <12-year-old, this occasionally occurs, particularly in children with underlying risk factors. Furthermore, the inflammatory condition MIS-C has been associated with paediatric COVID-19. The importance of vaccination of children for reaching herd immunity has been suggested, but there are no data on the impact of childhood vaccination on overall community transmission of SARS-CoV-2.

The known unfavourable effects are considered acceptable in terms of reactogenicity. No cases of myocarditis were observed in the clinical trial. There are no new safety concerns based on the study conducted; however, the study size did not allow detection of rare adverse events, or to evaluate whether the characteristics of identified, but rarer risks differ compared with the adolescent and adult populations. The myocarditis/pericarditis entity will continue to be closely followed up and further characterized within the ongoing pharmacovigilance activities. Two reported post-marketing cases of myocarditis, perimyocarditis have been observed in connection to the use of a higher dose in the age group 5-11 years, also providing very limited clinical information in both cases. No additional safety concern is raised based on this data.

3.7.2. Balance of benefits and risks

The favourable effects outweigh the unfavourable effects for Comirnaty in the sought indication, particularly in children with comorbidities that increase the risk of severe COVID 19.

3.7.3. Additional considerations on the benefit-risk balance

Comirnaty is currently authorised as a conditional marketing authorisation.

The new paediatric indication aims as well at the prevention of COVID-19, which is to be used in response to a public health threat duly recognised by the World Health Organisation and EU.

The CHMP considers that this new indication also fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the MAH will be able to provide comprehensive data.
- The present application is based on part of the ongoing paediatric study C4591007. As stated above, safety data are limited with respect to the ability to detect rare side effects. Furthermore, the duration of follow-up is relatively limited. The MAH will continue the ongoing paediatric study C4591007 in order to confirm the efficacy and safety of Comirnaty in this paediatric indication. Therefore, the delivery of the final study report from the above-mentioned trial, is required to provide a comprehensive efficacy and safety dataset and therefore should be designated a specific obligation (**SOB**).
- An unmet medical need will be addressed in a situation of a global pandemic. There is an unmet medical need for the vaccination of children 5-11 years old, as there are no products approved for this use.
- Based on the presented data for this new indication, the benefits to public health of the immediate availability is considered to outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of COMIRNATY is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of COMIRNATY 0.1 mg/mL is favourable in the following indication:

Comirnaty 10 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the extension of the marketing authorisation for COMIRNATY subject to the following conditions[1]:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

[1] Of note, the variations related to the fulfilment of the quality specific obligations listed below are currently under assessment by CHMP.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591007.	July 2024