19 October 2022
EMA/890761/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of marketing authorisation

Invented name: COMIRNATY

International non-proprietary name: tozinameran

Procedure No. EMEA/H/C/005735/X/0138

Marketing Authorisation Holder: BioNTech Manufacturing GmbH

Note

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

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List of abbreviations

Abbreviation	Definition
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ARDS	acute respiratory distress syndrome
BiPaP	bilevel positive airway pressure
BLA	(US FDA) Biologics License Application
BMI	body mass index
BNP	B-type natriuretic peptide
CBER	(US FDA) Center for Biologics Evaluation and Research
CDC	(US) Centers for Disease Control and Prevention
CFR	case fatality rate
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CPaP	continuous positive airway pressure
CRP	C-reactive protein
CSR	Clinical Study Report
CVA	cerebrovascular accident
DART	developmental and reproductive toxicity
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Application
FDA	(US) Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean-fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
IgG	immunoglobulin G
IL-6	Interleukin 6
IM	intramuscular(ly)
IND	Investigational New Drug application
iPSP	initial Pediatric Study Plan
IRC	(US Study) Internal Review Committee

Abbreviation	Definition
LDH	lactate dehydrogenase
LLN	lower limit of normal
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent-to-treat
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification testing
NHP	non-human primate
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein
PaO_2	partial pressure of oxygen
PASC	post-acute sequelae of COVID-19
PDCO	Paediatric Committee
PCR	polymerase chain reaction
PIP	Paediatric Investigational Plan
PSP	Pediatric Study Plan
PT	Preferred Term
RBD	receptor binding domain
RNA-LNP	RNA lipid nanoparticle
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
SBP	systolic blood pressure
S glycoprotein, S	spike glycoprotein
SMQ	Standard MedDRA query
SOC	System Organ Class
SpO_2	peripheral oxygen saturation
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAE(R)D	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
VE	vaccine efficacy
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

BioNTech Manufacturing GmbH submitted on 08 July 2022 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 3 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

1.2. Legal basis

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/0547/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0547/2021 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	08 July 2022
The procedure started on	18 July 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 September 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on:	29 September 2022
The CHMP Co-Rapporteur's Critique was circulated to all CHMP members on	30 September 2022
BWP discussions took place on:	04 October 2022
ETF discussions took place on:	04 October 2022
The CHMP Rapporteur's updated Assessment Report was circulated to all CHMP and PRAC members on	10 October 2022
The CHMP adopted a list of issues on:	13 October 2022
The CHMP Rapporteur's Assessment Report was circulated to all CHMP and PRAC members on	17 October 2022
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	19 October 2022

2. Scientific discussion

2.1. Problem statement

The MAH applies for an extension of the indication to children 6 months to <5 years of age to receive three doses of BNT162b2 3-µg (initial two doses 3 weeks apart followed by third dose at least 8 weeks after the second dose), based on Study C4591007 Phase 1 dose level-finding and Phase 2/3 selected-dose data on safety, tolerability, immune response, and supportive efficacy data from a population of approximately 4500 children, among whom those who received a third dose of BNT162b2 had a median of at least 2 months of follow-up post-Dose 3. The clinical data are supplemented by a Chemistry, Manufacturing and Controls (CMC) package supporting a line extension for the BNT162b2 3-µg Tris/Sucrose presentation to enable paediatric dosing.

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. At the time of this submission, the ongoing pandemic remains a significant challenge to public health, for which a licensed prophylactic vaccine is a necessary and critical mitigation across all age groups. The new strength formulation for BNT162b2 (3 µg), Comirnaty 3 micrograms/dose concentrate for dispersion for injection, includes a proposed extension of indication and dosing administration as follows:

- **Proposed indication:** Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 virus, in children aged 6 months to 4 years.
- **Dosing administration:** single 0.2-mL intramuscular (IM) dose followed by a second 0.2-mL dose 3 weeks later and a third 0.2-mL dose at least 8 weeks after the second dose.

2.1.2. Epidemiology and risk factors

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, elderly and 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

COVID-19 presentation 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 patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death.

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

2.1.5. Management

While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus during the ongoing pandemic. Currently, there is no approved vaccine against COVID-19 in EU for children below 5 years of age.

2.2. About the product

Conditional marketing authorization was granted for Comirnaty 30 µg by the European Commission (EC) on 21 December 2020 for individuals ≥16 years of age and was later expanded on 28 May 2021 to include individuals ≥12 years of age. Comirnaty 10 µg for children 5-<12 years of age was approved in EU on 26 November 2021. The conditional marketing authorisation was converted into a standard marketing authorisation, granted on the 10 October 2022.

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 as 2 dose primary series 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 and for individuals 5-11 years of age as 10 µg per dose. In current application, the formulation for children at ages between 6 months to 4 years contains 3 µg per dose and primary series contain 3 doses.

2.3. Quality aspects

2.3.1. 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). The COMIRNATY vaccine is also referred to as COVID-19 Vaccine (BioNTech code number BNT162b2, Pfizer code number PF 07302048).

Two formulations of the BNT162b2 vaccine, designated PBS/Sucrose and Tris/Sucrose, have been developed which primarily differ in the buffer used for finished product formulation and the requirement for dilution prior to administration. This application is related to the Tris/Sucrose finished product only, which is formulated as 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4. The Tris/Sucrose formulation is currently authorized for the 30 and 10 µg RNA dosages, where the strengths differ from each other and from the proposed 3 µg RNA dose exclusively due to the filling volume and requirement for dilution prior to administration as described below:

- The 30 µg RNA dosage presentation is filled at 2.25 mL per vial and is administered without dilution, providing 6 doses, each containing a 30 µg RNA dose in 0.3 mL injection volume for individuals 12+ years of age.

- The 10 µg RNA dosage is filled at 1.3 mL per vial and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each containing a 10 µg RNA dose in 0.2 mL injection volume for individuals 5 to <12 years of age.

The primary purpose of this submission is to provide details supporting the Tris/Sucrose finished product line extension to include the 3 µg RNA dose presentation, which is filled at 0.4 mL per vial. The 3 µg RNA presentation requires dilution with 2.2 mL 0.9% sodium chloride prior to administration and once diluted provides 10 doses, each containing a 3 µg RNA dose in 0.2 mL injection volume. Supporting details for the 3 µg RNA dose are provided in this application, with Process Performance Qualification (PPQ) lots FT9142 and FW9711 manufactured at commercial scale at the Pfizer Puurs site and filled into vials at 0.4 mL fill volume.

Reference is made to Procedure EMEA/H/C/005735/X/0077, which includes details for Tris/Sucrose PPQ5b lot FK5128 filled at 0.4 mL fill volume. Lot FK5128 was successfully validated and complied with the predefined protocol acceptance criteria for Tris/Sucrose finished product.

2.3.2. Active Substance

The active substance used to manufacture the Tris/Sucrose finished products (30 micrograms/dose, 10 micrograms/dose and 3 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).

2.3.3. Finished Medicinal Product

2.3.3.1. 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.

A recently approved line extension (EMEA/H/C/005735/X/0077) provided data in support of a 10 µg dosage presentation of Tris/Sucrose finished product for immunization of children 5-11 years of age.

There are two approved 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 purpose of this submission is to provide details supporting the Tris/Sucrose finished product line extension to include the 3 µg RNA dose presentation, which is filled at 0.4 mL per vial. The 3 µg RNA presentation requires dilution with 2.2 mL 0.9% sodium chloride prior to administration and once diluted provides 10 doses, each containing a 3 µg RNA dose in 0.2 mL injection volume.

The formulation is identical for the 30, 10 and 3 µg RNA/dose-presentations and differ only in fill volume. The formulation includes four lipids as well as some other excipients that are identical with the composition of the currently approved 30 and 10 µg RNA/dose-presentations.

The composition of the finished product, including quality standard, function, concentration and amount per dose for the 30, 10, and 3 µg doses are provided in Table P.1-1, Table P.1-2 and Table P.1-3, respectively.

Table P.1-1. 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	3.22 mg	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.41 mg	0.05 mg
DSPC	In-house specification	Structural lipid	0.31	0.70 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	1.40 mg	0.19 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	231.8 mg	31 mg
Tromethamine (Tris base)[b]	USP-NF, Ph. Eur.	Buffer component	0.20	0.45 mg	0.06 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[c]	In-house specification	Buffer component	1.32	2.97 mg	0.4 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[d]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	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)
HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
EDTA = edetate disodium dihydrate

Table P.1-2. 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	1.86 mg	0.14 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.23 mg	0.02 mg
DSPC	In-house specification	Structural lipid	0.31	0.40 mg	0.03 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	0.81 mg	0.06 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	133.9 mg	10.3 mg
Tromethamine (Tris base)[c]	USP-NF, Ph. Eur.	Buffer component	0.20	0.26 mg	0.02 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[d]	In-house specification	Buffer component	1.32	1.71 mg	0.13 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[e]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	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)

Table P.1-3. Composition of BNT162b2 Tris/Sucrose Finished Product, 3 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 [a,b]	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.1	40 µg	3 µg
ALC-0315	In-house specification	Functional lipid	1.43	0.57 mg	0.04 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.07 mg	0.005 mg
DSPC	In-house specification	Structural lipid	0.31	0.12 mg	0.01 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	0.25 mg	0.02 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	41.2 mg	3.2 mg
Tromethamine (Tris base) [c]	USP-NF, Ph. Eur.	Buffer component	0.20	0.08 mg	0.006 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[d]	In-house specification	Buffer component	1.32	0.53 mg	0.04 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[e]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	Ph. Eur., USP-NF	Drug substance buffer component			

a. Vials filled at 0.4 mL drug product and diluted to 2.6 mL with of 0.9% NaCl prior to administration.
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 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)

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. For further information and assessor´s comments regarding the vial, stopper and seal components, see section 3.2.P.7.

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 already approved Line extensions EMEA/H/C/005735/X/0044 and in EMEA/H/C/005735/X/0077. However, the section P.2 has been updated in various parts in this Line extension EMEA/H/C/005735/X/0138.

QTPP

The QTPP that was developed for the Tris/sucrose finished product has been updated to include the finished product 3 µg dosage presentation, filled at 0.4 mL fill volume. No changes were made to the currently approved 30 and 10 µg dosage presentations.

Finished product

The 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), filled into vials at 1.3 mL fill volume, providing 10 doses of 10 µg RNA in 0.2 mL injection volume after dilution with 0.9% sodium chloride (EMEA/H/C/005735/X/0077) and this specific line extension (EMEA/H/C/005735/X/0138) supports a 3 µg dosage presentation of Tris/Sucrose finished product for immunization of infants and children from 6 months to 4 years of age. The three doses 30 µg, 10 µg and 3 µg differ only in the fill volume and requirement for dilution prior to administration for the 10 µg and 3 µg RNA per dose.

Acceptable results have been provided demonstrating that the target fill volume for the 3 µg finished product when diluted at the point of use with 0.9% sodium chloride is suitable for delivering 10 doses of 3 µg at 0.2 mL per multi-dose vial. This study includes assessment of hold-up volume and delivered dose volume for 3 µg dose vials after dilution with 0.9% sodium chloride. The provided results also show that the 2 mL vial can comprise a total volume of 2.6 mL, corresponding to 0.4 mL of finished product and 2.2 mL 0.9% sodium chloride, as well as give an acceptable indication of appropriate mixing of the solution. These results also show that 10 doses can be delivered for the 3 µg dose-presentation with the use of low dead-space syringes and needles.

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

In summary, the section on finished product has been acceptably updated to include finished product filled at 0.4 mL fill volume for 3 µg doses.

Process development and characterization

The section on process development and characterization has been updated with results and details from a thawing study to determine the time required for complete thawing of the 3 µg dosage presentation and 0.4 mL fill volume. The provided results show that the thawing time required is 15 minutes at room temperature and 30 minutes at 2-8 °C for single vials filled at 0.4 mL and 30 minutes at room temperature and 90 minutes at 2-8 °C for the 10-count pack. 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 is compliant with the compendial requirements of the Ph. Eur. and is further addressed in section 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 3 µg dose/0.4 mL vial.

The development of the container closure system is found sufficiently presented and this is found acceptable.

Compatibility

The administration simulation and compatibility studies performed for the Tris/Sucrose finished product for the 3 µg presentation including 0.4 mL fill volume demonstrate physical and chemical stability of undiluted and diluted finished product 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).

In addition, the microbial studies performed for the Tris/Sucrose finished products with samples containing 0.9% sodium chloride to challenge the highest salt concentration and lowest pH, supports a hold time of up to 12 hours at up to 25 °C following first puncture of the stopper for the 3 µg presentation. Based on physicochemical stability and microbial in-use growth results, Tris/Sucrose finished product vials (for all three

fill volumes, 2.25 mL, 1.3 mL and 0.4 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 Tris/sucrose finished product with 0.4 mL fill volume is acceptably demonstrated by compatibility studies provided on physicochemical stability and microbial in-use hold time.

2.3.3.2. 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 micrograms/dose (EMEA/H/C/005735/X/0044) and 10 micrograms/dose (EMEA/H/C/005735/X/0077) except for a different fill volume. The GMP compliance of these sites has been previously confirmed.

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 0.4 mL fill volume. The batch size range is similar to the approved original Tris/Sucrose vaccine. The manufacturing process is sufficiently described, and suitable in-process controls (IPCs) are applied.

Process validation has been performed on two Process Performance Qualification (PPQ) batches at XX L bulk finished product manufactured at Pfizer Puurs. The batches are split into 1.3 mL and 0.4 mL fill volume sub-batches. All data complies with the pre-specified criteria and sufficiently demonstrate that the manufacturing process is robust and provide a finished product with adequate quality. Since only the fill volume differs from the approved Tris/Sucrose vaccines 30 micrograms/dose and 10 micrograms/dose, the process validation for these products is considered as supportive, and the provided data is sufficient for process validation.

2.3.3.3. Product specification, analytical procedures, batch analysis

The finished product specifications at release and shelf life provided in Table P.5-1 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 extensions EMEA/H/C/005735/X/0044 and EMEA/H/C/005735/X/0077. The acceptance criteria that differ between the specifications included in the approved Line extensions EMEA/H/C/005735/X/0044 and EMEA/H/C/005735/X/0077 and this specific applied Line extension EMEA/H/C/005735/X/0138 is only the vial content (volume), not less than 0.376 mL (for 0.4 mL fill volume).

The vial content (volume) for the Tris/Sucrose finished product was determined to ensure that each 0.4 mL filled vial can deliver ten 10 µg doses of 0.2 mL each, following the addition of 2.2 mL 0.9% sodium chloride. The provided justification for vial content (volume) of 0.4 fill volume is found acceptable.

Batch analysis

The section on batch analysis data have been updated with release data for the 3 µg presentation/0.4 mL fill volume for two PPQ lots FT9142 and FW9711. In addition, release data from PPQ lot FK5128 filled at 0.4 mL was supplied in the previous line extension EMEA/H/C/005735/X/0077 and is resubmitted in this application. All these three PPQ lots met all the release specifications of the specifications document in P.5.1.

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

Reference standard

Reference standards or material are identical to the already approved Tris/sucrose finished products of the 30 µg-presentation (EMEA/H/C/005735/X/0044) and the 10 µg-presentation (EMEA/H/C/005735/X/0077).

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, are compliant with the compendial requirements of the Ph. Eur. and is identical to the already approved Tris/sucrose finished products of the 30 µg-presentation (EMEA/H/C/005735/X/0044) and the 10 µg-presentation (EMEA/H/C/005735/X/0077).

2.3.3.4. Stability of the product

The proposed shelf life for this presentation is the same as the approved shelf-life for the existing Tris/Sucrose finished products; 12 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 12 months shelf-life is based on the results provided in the recently approved line extensions EMEA/H/C/005735/0044 (30 µg/dose/2.25 mL fill volume) and EMEA/H/C/005735/0077 (10 µg/dose/1.3 mL fill volume) as well as from stability results for the 3 µg/dose/0.4 mL fill volume in this specific line extension EMEA/H/C/005735/0138.

Stability for the 0.4 mL presentation is based on the 0.1 mg/mL Tris/Sucrose finished product which covers all three dosage presentations, 30, 10 and 3 µg. Stability results are provided for three commercial scale PPQ batches for the 3 µg presentation at 0.4 mL fill volume (PPQ batches FK5128, FT9142 and FW9711). Stability data are available from on-going studies at long term storage conditions of -90 to -60°C (up to 6 months data) and additional storage conditions at -20±5°C and 5±3°C (up to 3 months data). 6 months long-term stability data are provided for batches FK5128 and FT9142 and 3 months data for batch FW9711. The stability data from PPQ lot FK5128 supporting the 3 µg dose (0.4 mL fill volume) was submitted with a previous application and is referenced in this application for completeness.

The stability samples are packaged in the currently registered glass vials used for commercial packaging.

The stability 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 as well as the fact that the only difference between the 30 µg, 10 µg and 3 µg dosage presentations is the fill volume, 2.25 mL and 1.3 mL versus 0.4 mL, the proposed shelf-life of 12 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 3 µg dosage presentation.

Post-approval stability protocol and stability commitment

No information is provided in section 3.2.P.8.2. However, the applicant has confirmed that the identical Post-approval stability protocol and stability commitment in section 3.2.P.8.2 is valid for the 3 µg dosage presentation as for the 30 µg- and 10 µg-presentations of the Tris/Sucrose finished product.

2.3.3.5. Post approval change management protocol(s)

Not applicable.

2.3.3.6. Adventitious agents

The active substance used to manufacture the Tris/Sucrose finished products (30 micrograms/dose, 10 micrograms/dose and 3 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.

2.3.3.7. GMO

Not applicable.

2.3.4. Discussion and conclusions 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 three dosages of the Tris/Sucrose finished product – 30, 10 and 3 µg RNA per dose. The three 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 3 µg RNA dose is filled at 0.4 mL fill volume and requires dilution with 2.2 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 3 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) and 10 µg/dose

(EMEA/H/C/005735/X/0077) 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 two Process Performance Qualification (PPQ) batches at XX L bulk finished product 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 12 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.

2.3.5. Conclusions on chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, this line extension application to register Comirnaty (3 micrograms/dose) concentrate for dispersion for injection is approvable from the quality point of view.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

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

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Protocol No. **Phase (Country)**	**Sponsor (Agent)**	**Treatment Groups**	**No. of Subjects**	**Study Start/ Status**
C4591007 Phase 1 (United States)	BioNTech (Pfizer)	Phase 1: 2 to <5 years of age BNT162b2	Phase 1: 2 to <5 years of age BNT162b2	Start Date: March 2021 (ongoing)

Protocol No. **Phase (Country)**	**Sponsor (Agent)**	**Treatment Groups**	**No. of Subjects**	**Study Start/ Status**
		(10-µg, 3-µg) 6 months to <2 years of age BNT162b2 (3-µg)	*10-µg group* 32 BNT162b2 *3-µg group* 16 BNT162b2 6 months to <2 years of age BNT162b2 *3 µg group* 16 BNT162b2	
C4591007 Phase 2/3 (United States, Finland, Spain, Poland, Brazil)	BioNTech (Pfizer)	Phase 2/3: BNT162b2 (3-µg) Placebo	Phase 2/3: 2 to <5 years of age 1835 BNT162b2 915 Placebo 6 months to <2 years of age 1178 BNT162b2 598 Placebo	Start Date: July 2021 (ongoing)

2.5.2. Clinical efficacy

2.5.2.1. Dose response study(ies)

Phase 1 was the open- label dose level-finding part of the study, conducted in the US. Dose levels were tested in sentinel cohorts of children by age de-escalation, starting with the lowest dose level in the oldest age group. All participants were eligible to receive 2 doses of vaccine 21 days apart.

For each age group, the dose level identified as safe and tolerable and immunogenic in C4591007 Phase 1 was advanced for further evaluation in Phase 2/3.

Phase 1 was planned to enrol 16 participants per dose level tested in each age group. The doses tested and selected in each age group in current application during Phase 1 were:

- 2 to <5 years of age: dose levels 3, 10-µg – selected dose level 3-µg
- 6 months to <2 years of age: dose level 3-µg – selected dose level 3-µg

Inclusion criteria to be enrolled into Phase 1 of this study were healthy participants 6 months to <5 years of age who were determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

The primary objective was to describe the safety and tolerability profiles and immune responses of prophylactic BNT162b2 at each dose level in each age group.

Baseline characteristics. In the evaluable immunogenicity population, most Phase 1 participants 6 months to <2 years of age were White (92.3%), with 7.7% Asian participants. There were 7.7% Hispanic/Latino participants. The median age was 16.0 months and 69.2% of participants were male. The Phase 1 participants 2 to <5 years of age were White (80.4%), with 4.3% Black or African American participants and 6.5% Asian participants, and other race groups were <10%. There were 2.2% Hispanic/Latino participants. The median age was 3.0 years and 56.5% of participants were male.

Immunogenicity results 7 days after dose 2. For children 2 to <5 years of age, BNT162b2 elicited robust and comparable SARS-CoV-2 50% neutralizing titers at 7 days after Dose 2 at both tested dose levels (3-µg and 10-µg) in a population who was without evidence of SARS-CoV-2 infection in the Phase 1 study.

For children 6 months to <2 years of age, BNT162b2 elicited robust SARS-CoV-2 50% neutralizing titers at 7 days after Dose 2 at the 3-µg dose level tested in a population who was without evidence of SARS-CoV-2 infection.

Overall, two doses of BNT162b2 3-µg elicited robust immune responses in children <5 years of age (see Tables below).

Table 1. Summary of Geometric Mean Titers- participants without evidence of infections- Phase 1-2 to <5yo-Evaluable Immunogenicity population

		Vaccine Group (as Assigned)					
		3 µg			10 µg		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/Day 7	13	1350.4	(973.1, 1873.9)	29	2059.5	(1679.1, 2526.0)

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 respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the Visit 3 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visits 1, 2, and 3, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result
at any unscheduled visit prior to the Visit 3 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. 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.

Table 2. Summary of Geometric Mean Titers- participants without evidence of infections- Phase 1- 6m to <5yo-Evaluable Immunogenicity population

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Assigned) 3 µg n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/Day 7	13	1643.8	(1151.3, 2347.1)

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 respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the Visit 3 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visits 1, 2, and 3, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result
at any unscheduled visit prior to the Visit 3 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. 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.

Safety. For children 2 to <5 years of age, higher frequencies and greater severity of reactogenicity to the 10-µg dose level in comparison to the 3-µg dose level contributed to the decision to select a lower dose of 3 µg of BNT162b2 to proceed to Phase 2/3 for this age group.

For children 6 months to <2 years of age, the single dose level of 3-µg dose level tested in Phase 1 was informed by observed safety results from Phase 1 participants in the 2 to <5 years of age group. The 3-µg dose level was well tolerated in children 6 months to <2 years of age, and the observed satisfactory safety profile of 3-µg given supported its selection as the final dose level of BNT162b2 to proceed to Phase 2/3 for this age group.

Overall, two doses of BNT162b2 3-µg were well-tolerated in participants <5 years of age in Phase 1.

Dose Selection Based on Phase 1 Data

For participants 2 to <5 years of age, final dose selection of BNT162b2 was based on the similarity in post-vaccination immunogenicity reflected in Day 7 post-Dose 2 GMTs across 3-µg and 10-µg dose levels, along with the more favourable reactogenicity profile observed at the 3-µg dose level compared to the 10-µg dose level. The totality of these results led to the selection of BNT162b2 at the 3-µg dose level to proceed to Phase 2/3 evaluation for this age group.

For participants 6 months to <2 years of age, based on the age de-escalation design of the Phase 1 study, the 3-µg dose level of BNT162b2 was the only dose level tested, and Phase 1 data showed a robust immune response and favourable reactogenicity profile for this dose level in this age group.

2.5.2.2. Main studies

Title of study: Phase 2/3 Study C4591007

Methods

Children 6 Months to <5 Years of Age: A 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

Two schemes were used (2-dose and 3-dose), but the company is only seeking approval for the 3-dose scheme so this assessment will solely focus on that subset of the study.

Study Participants

Inclusion criteria

Enrolled into Phase 2/3 of this study were healthy participants 6 months to <5 years of age who were determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study. Eligibility permitted enrolment of participants with medical conditions such as stable Type 1 diabetes or hypothyroidism; stable and controlled HIV, HCV, or HBV infection; and past serological or microbiological evidence of prior (not active) SARS-CoV-2 infection. Participants were randomized 2:1 to receive vaccine or placebo at sites in the US, Finland, Poland, Spain, and Brazil.

Participants' parent(s)/legal guardian(s) had to provide signed inform consent (and verbal or written assent from the participant if appropriate); they also had to be willing and able to comply with all scheduled visits, treatment plans, laboratory tests, lifestyle considerations, and other study procedures.

Exclusion criteria

Exclusions from Phase 2/3 study participation included prior receipt of a COVID-19 vaccine or medication intended to prevent COVID-19, prior or current diagnosis of MIS-C, history of severe (ie, anaphylactic) reaction associated with any vaccine or allergy to any component of the study intervention (ie, BNT162b2), immunodeficiency or autoimmune disease requiring therapeutic intervention (other than diabetes) and other medical conditions and/or therapeutic interventions deemed incompatible with study participation.

Treatments

Participants were randomized in a 2:1 ratio to receive either BNT162b2 (3 µg) or placebo (normal saline). Participants were eligible to receive a 3-dose regimen. Doses were administered IM into the deltoid muscle for children ≥2 years of age and into the anterior thigh muscle for children <2 years of age. There was approximately 21-day interval between dose 1 and dose 2, and at least 8 weeks between dose 2 and dose 3.

The comparator group for immunobridging exercise consisted of participants 16 to 25 years of age from Phase 2/3 of the C4591001 study, receiving 2 doses of BNT162b2 (30 µg) with 21-day interval.

Objectives

Primary immunogenicity

- To immunobridge the immune response elicited by prophylactic BNT162b2 between Phase 2/3 participants at the dose selected in each age group and participants 16 to 25 years of age from the C4591001 study without serological or virological evidence of past SARS-CoV-2 infection:
    - In participants ≥2 to <5 years of age receiving 3 doses of 3 µg Comirnaty compared to participants 16 to 25 years of age receiving 2 doses of 30 µg Comirnaty
    - In participants ≥6 months to <2 years of age receiving 3 doses 3 µg Comirnaty compared to participants 16 to 25 years of age receiving 2 doses of 30 µg Comirnaty.

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.

Secondary efficacy

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 3 during the blinded follow-up period in participants ≥6 months to <5 years of age in the selected-dose portion of the study without and with or without evidence of past SARS-CoV-2 infection.

Exploratory

- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19:

– occurring from 7 days after Dose 2 to prior to Dose 3

– occurring from 7 days after Dose 3

through the blinded follow-up period in participants in the selected-dose portion of the study without, and with and without, evidence of past SARS-CoV-2 infection in each age group and in ≥6 months to <2 years and ≥2 to <5 years age groups combined.

- To describe the relative VE of prophylactic BNT162b2 against confirmed COVID-19 illness from 7 days after Dose 3 of BNT162b2 to COVID-19 illness from 7 days after Dose 2 to prior to Dose 3 of BNT162b2 during the same calendar time interval of interest. Participants from the original active vaccine group receiving 3 doses of BNT162b2 will be compared to participants from the original placebo group receiving 2 doses of BNT162b2 after unblinding in each age group and the ≥6-month to <2-year and ≥2- to <5-year age groups combined.
- To evaluate the immune response over time to prophylactic BNT162b2 at the dose level selected in each age group and persistence of immune response in Phase 2/3 participants with and without serological or virological evidence of past SARS-CoV-2 infection.
- To describe 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.

- To describe the immune response to emerging VOCs.

Outcomes/endpoints

Phase 2/3, primary and secondary immunogenicity:

- SARS-CoV-2 neutralizing titers (GMT)

Phase 2/3, secondary efficacy:

- Confirmed COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up

Sample size

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

Sample size for immunobridging Evaluation of 3-Dose Series

For evaluation of the 3-dose series immunobridging objectives in the Phase 2/3 selected-dose evaluation portion of the study, approximately 200 participants in each of the younger age groups (≥6 months to <2 years, ≥2 years to <5 years) who were enrolled prior to protocol amendment 6 and received 3 doses of BNT162b2 was to be selected and the same number of participants 16 to 25 years of age who received 2 doses of BNT162b2 from Phase 2/3 of the C4591001 study were to be randomly selected as the immunobridging subset. To maintain blinding, approximately 100 participants in each age group from the C4591007 study and 50 participants 16 to 25 years of age from the C4591001 study who received placebo were also to be selected for serology testing.

Assuming a non-evaluable rate of 35%, approximately 130 evaluable participants in each age group were approximated to contribute to the immunobridging evaluation.

Assuming that the assay standard deviation at 1 month after Dose 3 and 1 month after Dose 2 in log scale is 0.93 based on data observed in the Phase 3 third-dose portion of the C4591001 study and the GMR of the younger age group to the 16- to 25-year age group is 1, 130 evaluable participants in each age group were to provide 93.3% power to demonstrate immunobridging success of each younger age group to the 16- to 25-year age group based on GMR using a 1.5-fold margin. For comparisons based on seroresponse, a 95% response rate is assumed for each comparative group at the comparative time point. With 130 evaluable participants, the study had 90.4% power to show the immunobridging based on seroresponse rate using a 10% margin.

Randomisation and blinding (masking)

Participants was to be randomized in a 2:1 ratio to receive active vaccine or placebo.

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel were then provided with a vaccine assignment and randomization number from the IRT system, which provided a confirmation report containing the participant number, randomization number, and study intervention allocation assigned.

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were to be 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 blinded. Because BNT162b2 and placebo are different in physical appearance, the study intervention syringes were be administered in a manner that prevented the study participants from identifying the study intervention type based on its appearance. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants was to be kept to a minimum. The remaining site personnel were not to know study intervention assignments.

At the 6-month follow-up visit, all participants were to be unblinded. Participants who originally received placebo were offered the opportunity to receive BNT162b2 as part of the study.

Statistical methods

Analysis methods

Analyses for Binary Data The exact 95% CI for binary endpoints for each group were computed using the F distribution (Clopper-Pearson). The 95% CI for the between-group difference for binary endpoints were calculated using the Miettinen and Nurminen method.

Analyses for Continuous Data A validated SARS-CoV-2 neutralization assay was used to obtain titers (GMT) against the wild-type strain, with young adult group samples tested contemporaneously with pediatric group samples for comparability. Immunobridging success criteria were based on both the geometric mean ratio (GMR) of 50% neutralizing geometric mean titers (GMTs) and difference in seroresponse rates.

The geometric means were calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% Cis were obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t distribution, and then exponentiating the confidence limits.

The GMR were calculated as the mean of the difference of logarithmically transformed assay results (e.g., SARS-CoV-2 neutralizing titers in the younger age group minus that in 16- to 25-year age group) and exponentiating the mean. Two-sided CIs were obtained by calculating CIs using Student's t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

GMFRs are defined as ratios of the results after vaccination to the results before vaccination. GMFRs are limited to participants with non-missing values at both time points. GMFRs were calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 95% CIs were obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence

Seroresponse: defined as achieving a ≥4-fold rise in SARS-CoV-2 neutralizing titers from before Dose 1. If the baseline measurement was below LLOQ, post-vaccination measure of ≥4 × LLOQ was considered to be seroresponse. Data were summarized as the difference in percentages of participants achieving seroresponse and associated 2-sided 95% CI calculated using the Miettinen and Nurminen method. Immunobridging success was declared if the lower limit of the CI for difference in seroresponse rate was greater than -10% and provided that the GMR success criteria had been met.

GMTs and geometric fold-rises (GMFRs) were summarized with 2-sided 95% CIs obtained by taking log transforms of results, calculating CIs with reference to Student's t-distribution, then exponentiating confidence limits. Titers below LLOQ were set to 0.5 × LLOQ.

Variant Neutralization assay

Descriptive analyses of SARS-CoV-2 variant neutralization were conducted on the Omicron neutralization subset. For each of the pediatric groups in Phase 2/3 Study C4591007, this included approximately 40 BNT162b2 3-µg recipients and 5 placebo recipients randomly selected from the immunobridging subset who had received three doses of study intervention, were without evidence of prior SARS-CoV-2 infection up to 1-month post-Dose 3 and had sufficient blood volume for testing at Dose 3 and 1-month post-Dose 3. The adult reference group from Phase 3 Study C4591001 included 40 participants 18 to 55 years of age randomly selected from the C4591001 evaluable immunogenicity population who had received a booster (third) dose of BNT162b2 30-µg at least 6 months after the second dose and were without evidence of prior SARS-CoV-2 infection up to 1-month post-Dose 3. Samples from the C4591007 pediatric groups and C4591001 adult group were tested contemporaneously for comparability.

A non-validated fluorescent focus reduction neutralization test (FFRNT) was used to determine SARS-CoV-2 serum neutralizing titers before Dose 3 and 1-month post-Dose 3. The FFRNT is a non-validated assay similar to the 50% plaque-reduction neutralization test (PRNT) assay which has been used to generate supportive data against the reference strain and other variants. The FFRNT assay has higher throughput and correlates well with the PRNT assay. All samples were tested at the same time to ensure comparability of results.

The 50% FFRNT titers were determined against the designated wild-type reference strain, which is a recombinant USA-WA1/2020 (clinical strain isolated in January 2020), and against recombinant Delta and Omicron (BA.1) variants, which are recombinant viruses with the Delta or Omicron variant full spike gene on the genetic background of USA-WA1/2020. Titers obtained from the FFRNT assay were reported as GMTs and GMFRs as described above.

Analysis sets

Enrolled: All participants who have a signed ICD.

Randomized: All participants who are assigned a randomization number in the IWR system.

Evaluable immunogenicity (2-dose): All eligible randomized participants who receive 2 doses of the vaccine with the same dose level to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1 for 21-day interval, within 51-61 days after Dose 1 for 8-week interval in the lower-dose evaluation portion), 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.

Evaluable immunogenicity (3-dose) All eligible randomized participants who receive 3 doses of the vaccine with the same dose level to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1 for 21-day interval, within 51-61 days after Dose 1 for 8-week interval in the lower-dose evaluation portion), with Dose 3 received within the predefined window (at least 175 days after Dose 2 for ≥5- to <12-year age group and the participants in the ≥2- to <5-year age group turning 5 years of age prior to crossing over, at least 60 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled before Protocol Amendment 6, within 54-70 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled after Protocol Amendment 6), have at least 1 valid and

determinate immunogenicity result after Dose 3 from the blood sample collected within an appropriate window after Dose 3 (within 28-42 days after Dose 3), and have no other important protocol deviations as determined by the clinician.

All-available immunogenicity *Dose 2 all-available immunogenicity:* All randomized participants who receive 2 doses of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2 from the blood sample collected at 1 month after Dose 2 visit regardless of visit window.

Dose 3 all-available immunogenicity: All randomized participants who receive 3 doses of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 3.

Evaluable efficacy (2-dose) All eligible randomized participants who receive 2 doses of the vaccine with the same dose level to which they are 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 before 7 days after Dose 2.

Evaluable efficacy (3-dose) All eligible randomized participants who receive 3 doses of the vaccine with the same dose level to which they are randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), with Dose 3 received within the predefined window (at least 175 days after Dose 2 for ≥5- to <12-year age group and the participants in the ≥2- to <5-year age group turning 5 years of age prior to crossing over, at least 60 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled before Protocol Amendment 6, within 54-70 days after Dose 2 for ≥6-month to <2-year and ≥2- to <5-year age groups enrolled after Protocol Amendment 6), and have no other important protocol deviations as determined by the clinician before 7 days after Dose 3.

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.

Dose 3 all-available efficacy: All randomized participants who complete 3 vaccination doses.

Safety All participants who receive at least 1 dose of the study intervention.

Missing data

A partial AE start date (missing day or missing both month and day) was to be imputed by assigning the earliest possible start date using all available information. A complete missing start date for an AE was not allowed in the data collection.

Values below the LLOQ for each assay, denoted as BLQ, were be set to 0.5 × LLOQ for analysis. However, this calculation could be adjusted based upon additional data from the assay.

No additional imputation were applied to other missing data.

Subgroup analyses

For Phase 2/3, subgroup analyses based on sex, race, ethnicity, and baseline SARS-CoV-2 status were to be performed on all primary safety and immunogenicity endpoints (as supplemental analyses).

Multiplicity

For the immunogenicity objectives of immunobridging of BNT162b2 after the 2-dose series in each of the 5 age groups (≥16 to <18 years, ≥12 to <16 years, ≥5 to <12 years, ≥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 was to 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 was to be applied in the immunogenicity assessments for the 5 age groups.

Within each age group, immunobridging based on GMR and seroresponse difference was to be assessed sequentially.

The primary immunogenicity and secondary efficacy objectives after the 3-dose series for the ≥6-month to <2-year and ≥2- to <5-year age groups were to be evaluated separately from the objectives after 2-dose series. The hypothesis testing for immunobridging of the ≥6-month to <2-year and ≥2- to <5-year age groups was to be carried out separately in the same way as for the 2-dose series; no type I error adjustments were to be applied for the assessments of the 2 age groups for the same reason described above. If immunobridging success was declared for both age groups, the secondary efficacy objectives was to be tested sequentially in the order as stated for the 2 age groups combined.

Interim analyses

No formal interim analysis was to be conducted for this study, but statistical analyses were to be carried out when the final data for specified objectives are available while the study is ongoing.

Results

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 cutoff date (29 April 2022): 11 in Finland, 8 in Poland, 10 in Spain, and 55 in the US. There were an additional 2 study centers 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 cutoff date (29 April 2022).

The paediatric investigational Plan has label EMEA-002861-PIP02. The original protocol from 5.02.2021 has been amended 7 times: 5.03.2021, 6.08.2021, 10.09.2021, 29.09.2021, 15.11.2021, 4.01.2022 and 10.03.2022. The 2 last amendments affected the results included in current application.

The Study Protocol Amendment 6 dated on 04.01.2022 focussed on age group below 5 years. The primary immunogenicity analysis demonstrated that the immune response elicited by BNT162b2 in participants ≥2 to <5 years of age (2 doses at 3 µg) did not meet immunobridging criteria when compared to participants 16 to 25 years of age from the C4591001 study. As a result, and given the emerging data in individuals 16 years of age and older, an additional (third) dose of BNT162b2 was to be administered to all Phase 1 dose-finding and Phase 2/3 selected-dose participants and the protocol amended accordingly. Also, an additional 4500 Phase 2/3 selected-dose participants ≥6 months to <2 years and ≥2 to <5 years of age are permitted to enrol to enlarge the size of the pediatric safety database. For participants <5 years of age, all positive RT-PCR cases confirmed by the central laboratory would undergo BioFire testing to detect coinfections.

The Study Protocol Amendment 7 dated on 10.03.2022 added a relative VE objective for 3-dose BNT162b2 from original active vaccine group vs 2-dose BNT162b2 from placebo crossover. The relative VE calculation for those receiving 3 doses of BNT162b2 is being compared to those who received 2 doses of BNT162b2 after originally receiving placebo (as opposed to comparing to those who received 2 doses of BNT162b2, as originally randomized) due to the emergence of different variants over time; the timing of cases for these 2 groups are similar, therefore making it more likely to compare cases of the same variant.

Immunogenicity Results post-dose 3 – Study C4591007, Phase 2/3

Children 2 to <5 years of age:

Disposition and Data Sets Analysed

The Dose 3 evaluable immunogenicity population included 204 children 2 to <5 years of age who received three doses of BNT162b2 3-µg and 92 who received placebo, of whom 143 and 59 participants, respectively, were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3. The comparator group of young adults 16 to 25 years of age included 183 participants in the BNT162b2 30-µg group and 45 participants in the placebo group of Study C4591001, of whom 170 and 38 participants, respectively, were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2.

Exclusions from the Dose 3 evaluable population were reported in similar proportions of the BNT162b2 groups of the pediatric (6.4%) and adult (8.5%) populations, most due to lack of a valid and determinate assay immunogenicity result after Dose 3 or Dose 2, respectively.

Among children 2 to <5 years of age in the immunobridging subset who received three doses of BNT162b2 3-µg or placebo, 100% completed the 1-month post-Dose 3 visit. In the comparator adult group who received two doses of BNT162b2 30-µg or placebo, most (≥99.5%) completed the 1-month post-Dose 2 visit.

All children 2 to <5 years of age in the immunobridging subset received all three doses of BNT162b2 3-µg, and all comparator adults 16 to 25 years of age received two doses of BNT162b2 30-µg. Most pediatric and adult participants (>85%) received Dose 2 within the protocol defined window of 19 to 23 days after Dose 1.

Most pediatric participants in the immunobridging subset received Dose 3 of BNT162b2 3-µg at least 8 weeks after Dose 2, most commonly between 8 and <13 weeks post-Dose 2 (84.4%). The median timing of Dose 3 administration after Dose 2 of BNT162b2 was 10.7 weeks (range: 8.1 to 15.6 weeks) and of placebo was 10.7 weeks (range: 8.6 to 16.0 weeks).

Baseline data

Demographic Characteristics

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

In total, most participants in this pediatric population were White (69.2%). The median age was 3.0 years and 44.1% of participants were male. There were 6.3% of participants reported as obese.

In the evaluable immunogenicity population (regardless of evidence of prior infection), 11/204 participants (5.4%) were baseline positive for prior SARS-CoV-2 infection.

Table 3. Demographic Characteristics-Immunobridging subset-participants without evidence of infection-Study C4591007 Phase 2/3 to <5 years of age and Study C4591001 Phase 2/3 16 through 25 years of age-Evaluable Immunogenicity Population.

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	3 µg 2 to <5 Years (C4591007) (N[a]=143) n[b] (%)	30 µg 16-25 Years (C4591001) (N[a]=170) n[b] (%)	2 to <5 Years (C4591007) (N[a]=59) n[b] (%)	16-25 Years (C4591001) (N[a]=38) n[b] (%)
Sex				
Male	63 (44.1)	79 (46.5)	26 (44.1)	16 (42.1)
Female	80 (55.9)	91 (53.5)	33 (55.9)	22 (57.9)
Race				
White	99 (69.2)	130 (76.5)	47 (79.7)	28 (73.7)
Black or African American	8 (5.6)	15 (8.8)	2 (3.4)	5 (13.2)
American Indian or Alaska Native	0	3 (1.8)	0	0
Asian	16 (11.2)	13 (7.6)	4 (6.8)	3 (7.9)
Native Hawaiian or other Pacific Islander	0	1 (0.6)	0	0
Multiracial	17 (11.9)	7 (4.1)	6 (10.2)	2 (5.3)
Not reported	3 (2.1)	1 (0.6)	0	0
Ethnicity				
Hispanic/Latino	16 (11.2)	51 (30.0)	5 (8.5)	7 (18.4)
Non-Hispanic/Non-Latino	126 (88.1)	119 (70.0)	54 (91.5)	31 (81.6)
Not reported	1 (0.7)	0	0	0
Country				
Argentina	0	24 (14.1)	0	4 (10.5)
Brazil	0	13 (7.6)	0	1 (2.6)
Germany	0	0	0	2 (5.3)
South Africa	0	6 (3.5)	0	5 (13.2)
Turkey	0	1 (0.6)	0	0
USA	143 (100.0)	126 (74.1)	59 (100.0)	26 (68.4)
Age at vaccination (years)				
Mean (SD)	2.7 (0.76)	21.2 (2.95)	3.1 (0.75)	21.0 (3.30)
Median	3.0	22.0	3.0	21.5
Min, max	(2, 4)	(16, 25)	(2, 4)	(16, 25)
Obese[c]				
Yes	9 (6.3)	30 (17.6)	3 (5.1)	7 (18.4)
No	134 (93.7)	140 (82.4)	56 (94.9)	31 (81.6)

Abbreviations: CDC = Centers for Disease Control and Prevention; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as
having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and at any unscheduled visit
prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart for participants 2 to <5 years of age or
BMI ≥30 kg/m^2 for participants 16 to 25 years of age. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Numbers analysed

Active arm		**Placebo**	
Children 2- <5 y	Young adults 16-25 y	Children 2- <5 y	Young adults 16-25 y
143	170	59	38

Outcomes and estimation

Immunobridging results are presented for 50% SARS-CoV-2 neutralizing antibody responses against the wild-type strain, for participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection. Immunobridging success criteria were based on the GMR and difference in seroresponse rate, comparing neutralizing titers from children 2 to <5 years of age (1-month post-Dose 3) to those from young adults (1-month post-Dose 2).

GMR of Neutralizing Titers – Children 2 to <5 Years of Age

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the GMR of SARS-CoV-2 50% neutralizing titers in children 2 to <5 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.30 (2-sided 95% CI: 1.13, 1.50) (Table below).

The lower bound of the 2-sided 95% CI for GMR was >0.67 and the GMR point estimate was >0.8 (protocol specified criterion) and >1.0 (requested by FDA), indicating the prespecified immunobridging success criterion for the GMR was met.

Table 4. Summary of Geometric Ratios NT50-Participants without evidence of Infection-Immunobridging subset- Study C4591007 Phase 2/3 to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

	Vaccine Group (as Randomized)								
	BNT162b2								
	3 µg 2 to <5 Years (C4591007) (1 Month After Dose 3)			30 µg 16-25 Years (C4591001) (1 Month After Dose 2)			2 to <5 Years/16-25 Years		
Assay	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	GMR[c]	(95% CI[c])	Met Immunobridging Objective[d] (Yes/No)
SARS-CoV-2 neutralization assay - NT50 (titer)	143	1535.2	(1388.2, 1697.8)	170	1180.0	(1066.6, 1305.4)	1.30	(1.13, 1.50)	Yes

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers ([2 years to <5 years] - [16-25 years]) and the corresponding CI (based on the Student t distribution).

Difference in Seroresponse Rates – Children 2 to <5 Years of Age

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the difference in proportions who achieved seroresponse (≥4-fold rise in SARS-CoV-2 neutralizing titers from before Dose 1) among children 2 to <5 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.2% (2-sided 95% CI: -1.5%, 4.2%) (Table below).

The lower limit of the 2-sided 95% CI for the difference in seroresponse rate was greater than -10%, and the immunobridging success criterion based on the GMR was achieved, indicating the prespecified immunobridging success criterion for difference in seroresponse was met.

Table 5. Difference in % of participants with seroresponse-Participants without evidence of infection-Immunobridging subset- Comparison of Study C4591007 Phase 2/3 to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

	Vaccine Group (as Randomized)							
	BNT162b2							
	3 µg 2 to <5 Years (C4591007) (1 Month After Dose 3)			30 µg 16-25 Years (C4591001) (1 Month After Dose 2)			Difference	
Assay	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	%[d]	(95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	141	141 (100.0)	(97.4, 100.0)	170	168 (98.8)	(95.8, 99.9)	1.2	(-1.5, 4.2)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
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 included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. N = number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (2 to <5 years – 16-25 years).
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

SARS-CoV-2 Neutralizing Titers – Phase 2/3 – Children 2 to <5 Years of Age – Wild-type Strain

Results from the evaluable immunogenicity population (regardless of evidence of prior SARS-CoV-2 infection) and the all-available immunogenicity population were generally similar, noting that inclusion of individuals with prior SARS-CoV-2 infection typically results in elevated baseline (before vaccination) and post-vaccination neutralizing titers compared with individuals without evidence of prior infection.

Subgroup analyses based on demographic characteristics at baseline generally showed no meaningful differences in the immunogenicity profile. The subgroup with evidence of prior SARS-CoV-2 infection at baseline ('baseline positive') generally had higher neutralizing titers both at baseline (pre-vaccination) and post-vaccination compared with the 'baseline negative' subgroup, which is predictable in the setting of vaccinating after prior exposure. These should be interpreted with caution as some subgroups include a limited number of participants.

Neutralizing titers are summarized below for children 2 to <5 years of age from before Dose 1 to 1-month post-Dose 3, and for young adults from before Dose 1 to 1-month post-Dose 2.

GMTs – Children 2 to <5 Years of Age

Among children 2 to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.7) was still robust at post-Dose 2 and prior to Dose 3 (401.1), and then substantially increased at 1-month post-Dose 3 (1535.2) (Table below). In the comparator group of young adults 16 to 25 years of age, the observed GMT before vaccination (21.3) was substantial increased at 1-month post-Dose 2 (1180.0).

Table 6. Summary of Geometric Mean Titers-NT50- Participants without evidence of infection-Immunobridging subset- Comparison of Study C4591007 Phase 2/3 to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)											
		BNT162b2						Placebo					
		3 µg 2 to <5 Years (C4591007)			30 µg 16-25 Years (C4591001)			2 to <5 Years (C4591007)			16-25 Years (C4591001)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	141	20.7	(20.3, 21.2)	170	21.3	(20.0, 22.8)	57	20.5	(20.5, 20.5)	38	20.5	(20.5, 20.5)
	2/1 Month				170	1180.0	(1066.6, 1305.4)				38	20.5	(20.5, 20.5)
	3/Prevax	143	401.1	(361.7, 444.7)				59	20.9	(20.1, 21.8)			
	3/1 Month	143	1535.2	(1388.2, 1697.8)				59	22.9	(19.5, 26.8)			

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 respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

GMFRs – Children 2 to <5 Years of Age

Among children 2 to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 3 was 73.3 (2-sided 95% CI: 66.3, 81.1) (Table below). The GMFR from before Dose 3 to 1-month post-Dose 3 was 3.8 (2-sided 95% CI: 3.5, 4.2). In the comparator group of young adults 16 to 25 years of age, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 2 was 55.3 (2-sided 95% CI: 49.6, 61.6).

Table 7. Summary of Geometric Mean fold rises from before vaccination to each subsequent time point- NT50- Participants without evidence of infection- Immunobridging subset- Study C4591007 Phase 2/3 to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)											
		BNT162b2						Placebo					
		3 µg 2 to <5 Years (C4591007)			30 µg 16-25 Years (C4591001)			2 to <5 Years (C4591007)			16-25 Years (C4591001)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month				170	55.3	(49.6, 61.6)				38	1.0	(1.0, 1.0)
	3/Prevax	141	19.2	(17.4, 21.3)				57	1.0	(1.0, 1.1)			
	3/1 Month	141	73.3	(66.3, 81.1)				57	1.1	(0.9, 1.3)			

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both prevaccination and the given dose/sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Seroresponse Rates – Children 2 to <5 Years of Age

Among children 2 to <5 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the seroresponse rate at 1-month post-Dose 3 was 100% (2-sided 95% CI: 97.4%, 100%) (Table below). In the comparator group of young adults 16 to 25 years of age, the seroresponse rate at 1-month post-Dose 2 was 98.8% (2-sided 95% CI: 95.8%, 99.9%).

Table 8. Number (%) of participants with seroresponse, Participants without evidence of infection- Immunobridging subset- Study C4591007 Phase 2/3 to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)											
		BNT162b2						Placebo					
		3 µg 2 to <5 Years (C4591007)			30 µg 16-25 Years (C4591001)			2 to <5 Years (C4591007)			16-25 Years (C4591001)		
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month				170	168	98.8 (95.8, 99.9)				38	0	0.0 (0.0, 9.3)
	3/Prevax	141	128	90.8 (84.7, 95.0)				57	0	0.0 (0.0, 6.3)			
	3/1 Month	141	141	100.0 (97.4, 100.0)				57	1	1.8 (0.0, 9.4)			

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
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 included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both 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.

Ancillary analyses

SARS-CoV-2 Neutralizing Titers – Phase 2/3 – Children 2 to <5 Years of Age – Omicron and Delta Variants

Non validated FFRNT assay results are summarized below for the Omicron neutralization subset of the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection. Titers were obtained in the FFRNT assay against Omicron and Delta variants and a wild-type reference strain.

Results in the evaluable immunogenicity population (regardless of evidence of prior infection) and the all-available immunogenicity population were generally similar, noting that inclusion of individuals with prior SARS-CoV-2 infection typically results in elevated baseline (before vaccination) and post-vaccination neutralizing titers compared with individuals without evidence of prior infection.

GMTs – Children 2 to <5 Years of Age

Among 34 children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, neutralizing GMTs prior to vaccination with Dose 3 against Delta (68.0) and Omicron (14.0) were increased at 1-month post-Dose 3 with respect to both Delta (471.4) and Omicron (82.5) (Table below). Correspondingly, increases were also observed for the reference strain from before Dose 3 (70.1) to 1-month post-Dose 3 (471.4).

Similar patterns were observed for 40 adults 18 to 55 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 30-µg, for whom neutralizing GMTs prior to vaccination with Dose 3 against Delta (36.4) and Omicron (12.7) were increased at 1-month post-Dose 3 with respect to both Delta (1153.6) and Omicron (340.0) titers. Increases were also observed for the reference strain from before Dose 3 (33.9) to 1-month post-Dose 3 (1067.1).

Notably, the dosing interval between Dose 2 and Dose 3 in adults was approximately 6 months, as compared with the dosing interval between Dose 2 and Dose 3 in the pediatric age group of approximately 2 to 3 months. The longer interval, as well as potential differences in antibody waning over time, may contribute to the higher increase in GMTs observed in adults as compared to the pediatric population.

Noting that adults had a longer dosing interval between Dose 2 and Dose 3 (approximately 6 months) at a time when antibody levels may be waning and the effects of a booster may be more pronounced, compared with children in this age group (approximately 2 to 3 months), a higher GMFR in the adults compared to the pediatric population may be expected.

Table 9. Summary of Geometric mean Titers-Omicron neutralization subset- Participants without evidence of infection- Study C4591007 Phase 2/3 to <5 years of age and Study C4591001 Phase 3 booster 18 through 55 years of age -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)								
		BNT162b2						Placebo		
		3 µg 2 to <5 Years (C4591007)			30 µg 18-55 Years (C4591001)			2 to <5 Years (C4591007)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.1 - NT50 (titer)	3/Prevax	34	14.0	(10.6, 18.5)	40	12.7	(11.0, 14.8)	4	10.0	(10.0, 10.0)
	3/1 Month	34	82.5	(55.4, 122.9)	40	340.0	(253.8, 455.6)	4	10.0	(10.0, 10.0)
SARS-CoV-2 FFRNT - Delta - NT50 (titer)	3/Prevax	34	68.0	(49.5, 93.3)	40	36.4	(26.5, 49.9)	4	10.0	(10.0, 10.0)
	3/1 Month	34	471.4	(341.2, 651.1)	40	1153.6	(886.4, 1501.4)	4	10.0	(10.0, 10.0)
SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	3/Prevax	34	70.1	(51.1, 96.0)	40	33.9	(26.1, 44.1)	4	10.0	(10.0, 10.0)
	3/1 Month	34	471.4	(344.6, 644.8)	40	1067.1	(834.4, 1364.5)	4	10.0	(10.0, 10.0)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.

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

GMFR – Children 2 to <5 Years of Age

For children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, there was an observed 6.9-fold increase in Delta and 5.9-fold increase in Omicron neutralizing titers obtained in the FFRNT assay from before Dose 3 to 1-month post-Dose 3 (Table below). The GMFR for the reference strain from before Dose 3 to 1-month post-Dose 3 was 6.7.

For adults 18 to 55 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 30-µg, there was an observed 31.7-fold increase in Delta and 26.7-fold increase in Omicron neutralizing titers obtained in the FFRNT assay from before Dose 3 to 1-month post-Dose 3. The GMFR for the reference strain from before Dose 3 to 1-month post- Dose 3 was 31.5.

Table 10. Summary of Geometric mean fold rises from before dose 3 to 1 month after dose 3- Omicron neutralization subset- Participants without evidence of infection- Study C4591007 Phase 2/3 to <5 years of age and Study C4591001 Phase 3 booster 18 through 55 years of age -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)								
		BNT162b2						Placebo		
		3 µg 2 to <5 Years (C4591007)			30 µg 18-55 Years (C4591001)			2 to <5 Years (C4591007)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.1 - NT50 (titer)	3/1 Month	34	5.9	(3.9, 9.0)	40	26.7	(20.2, 35.2)	4	1.0	(1.0, 1.0)
SARS-CoV-2 FFRNT - Delta - NT50 (titer)	3/1 Month	34	6.9	(4.9, 9.8)	40	31.7	(23.3, 43.2)	4	1.0	(1.0, 1.0)
SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	3/1 Month	34	6.7	(5.1, 8.9)	40	31.5	(23.6, 41.9)	4	1.0	(1.0, 1.0)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both before Dose 3 and the given dose/sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Updated Supportive Analysis

An additional descriptive immunogenicity analysis of Omicron neutralizing titers was conducted using the FFRNT assay, to compare children with adults who received a third dose of BNT162b2 at a similar interval between Dose 2 and Dose 3. This analysis compared Phase 2/3 pediatric participants in Study C4591007 with a subset of adults 18 to 50 years of age in Phase 3 Study C4591017 (lot consistency study) who had received a two-dose primary series followed by a booster (third) dose of BNT162b2 30-µg. The dosing interval between Dose 2 and Dose 3 was a median of 13.0 weeks (range: 11.9 to 14.3 weeks) for adults and 10.6 weeks (range: 8.6 to 13.7 weeks) for children 2 to <5 years of age. At 1-month post-Dose 3, among 34 children 2 to <5 years of age without evidence of prior SARS-CoV-2 infection, the neutralizing GMT was 114.3; correspondingly, among 27 adults 18 to 50 years of age without evidence of prior SARS-CoV-2 infection, the neutralizing GMT at 1-month post-Dose 3 was 164.2. These data show that for populations who received three doses of BNT162b2 at the age-appropriate dose level and administered at a comparable dosing interval, the Omicron specific neutralization titers are very similar across pediatric population and an adult comparator group (18 to 50 years of age) for whom high efficacy was observed.

Children 6 months to <2 years of age:

Disposition and Data Sets Analysed

The Dose 3 evaluable immunogenicity population included 132 children 6 months to <2 years of age who received three doses of BNT162b2 3-µg and 67 who received placebo, of whom 82 and 49 participants, respectively, were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3 (Table below).

The comparator group of young adults 16 to 25 years of age included 183 participants in the BNT162b2 30-µg group and 45 participants in the placebo group of Study C4591001, of whom 170 and 38 participants,

respectively, were without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2. (Note: this is the same adult group used for immunobridging analysis for the 2 to <5 years of age group.)

Exclusions from the Dose 3 evaluable population were reported in similar proportions of the BNT162b2 groups of the pediatric (10.8%) and adult (8.5%) populations, most due to lack of a valid and determinate assay immunogenicity result after Dose 3 or Dose 2, respectively.

Among children 6 months to <2 years of age in the immunobridging subset who received three doses of BNT162b2 3-µg or placebo, 100% completed the 1-month post-Dose 3 visit. In the comparator adult group who received two doses of BNT162b2 30-µg or placebo, most (>99.5%) completed the 1-month post-Dose 2 visit.

Vaccine Administration and Timing – Children 6 Months to <2 Years of Age

All children 6 months to <2 years of age in the immunobridging subset received all three doses of BNT162b2 3-µg, and all comparator adults 16 to 25 years of age received two doses of BNT162b2 30-µg. Most pediatric and adult participants (>88.5%) received Dose 2 within the protocol defined window of 19 to 23 days after Dose 1.

Most pediatric participants in the immunobridging subset received Dose 3 of BNT162b2 3-µg at least 8 weeks after Dose 2, most commonly between 8 and <13 weeks post-Dose 2 (50.0%). The median timing of Dose 3 administration after Dose 2 of BNT162b2 was 12.9 weeks (range: 8.6 to 20.0 weeks) and of placebo was 12.2 weeks (range: 8.4 to 20.0 weeks).

Baseline data

Demographics of the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 3 of BNT162b2 3-µg, which was comprised of 82 participants 6 months to <2 years of age, are included in table below. The adult comparator population is also shown for reference.

In total, most participants in this pediatric population were White (72.0%). The median age was 16.0 months and 62.2% of participants were male. In the evaluable immunogenicity population (regardless of evidence of prior infection), 6/132 participants (4.5%) were baseline positive for prior SARS-CoV-2 infection.

Table 11. Demographic characteristics-Immunobridging subset- Participants without evidence of infection-Study C4591007 Phase 2/3 6m to <5 years of age and Study C4591001 Phase2/ 3 16 through 25 years of age -Evaluable Immunogenicity Population.

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	3 µg 6 Months to <2 Years (C4591007) (N[a]=82) n[b] (%)	30 µg 16-25 Years (C4591001) (N[a]=170) n[b] (%)	6 Months to <2 Years (C4591007) (N[a]=49) n[b] (%)	16-25 Years (C4591001) (N[a]=38) n[b] (%)
Sex				
Male	51 (62.2)	79 (46.5)	23 (46.9)	16 (42.1)
Female	31 (37.8)	91 (53.5)	26 (53.1)	22 (57.9)
Race				
White	59 (72.0)	130 (76.5)	33 (67.3)	28 (73.7)
Black or African American	1 (1.2)	15 (8.8)	3 (6.1)	5 (13.2)
American Indian or Alaska Native	1 (1.2)	3 (1.8)	0	0
Asian	11 (13.4)	13 (7.6)	7 (14.3)	3 (7.9)
Native Hawaiian or other Pacific Islander	0	1 (0.6)	0	0
Multiracial	10 (12.2)	7 (4.1)	6 (12.2)	2 (5.3)
Not reported	0	1 (0.6)	0	0
Ethnicity				
Hispanic/Latino	13 (15.9)	51 (30.0)	3 (6.1)	7 (18.4)
Non-Hispanic/Non-Latino	69 (84.1)	119 (70.0)	46 (93.9)	31 (81.6)
Country				
Argentina	0	24 (14.1)	0	4 (10.5)
Brazil	0	13 (7.6)	0	1 (2.6)
Germany	0	0	0	2 (5.3)
South Africa	0	6 (3.5)	0	5 (13.2)
Turkey	0	1 (0.6)	0	0
USA	82 (100.0)	126 (74.1)	49 (100.0)	26 (68.4)
Age at vaccination[c]				
Mean (SD)	15.7 (4.84)	21.2 (2.95)	15.8 (5.54)	21.0 (3.30)
Median	16.0	22.0	16.0	21.5
Min, max	(6, 23)	(16, 25)	(6, 23)	(16, 25)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as
having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and at any unscheduled visit
prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
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. Age at vaccination in months for C4591007 6 months to <2 years age group, age at vaccination in years for C4591001 16 through 25 years age group.

Numbers analysed

Active arm		Placebo	
Children 6m- <2 y	Young adults 16-25 y	6m- <2 y	Young adults 16-25 y
82	170	49	38

Outcomes and estimation

Immunobridging results are presented for 50% SARS-CoV-2 neutralizing antibody responses against the wild-type strain, for participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection. Immunobridging success criteria were based on the GMR and difference in seroresponse rate, comparing neutralizing titers from children 6 months to <2 years of age (1-month post-Dose 3) those from young adults (1-month post-Dose 2).

GMR of Neutralizing Titers – Children 6 Months to <2 Years of Age

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the GMR of SARS-CoV-2 50% neutralizing titers in children 6 months to <2 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.19 (2-sided 95% CI: 1.00, 1.42) (Table below).

The lower bound of the 2-sided 95% CI for GMR was >0.67 and the GMR point estimate was >0.8 (protocol specified criterion) and >1.0 (requested by FDA), indicating the prespecified immunobridging success criterion for the GMR was met.

Table 12. Summary of Geometric mean ratios-NT50- Participants without evidence of infection-Immunobridging subset- Study C4591007 Phase 2/3 6m to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

	Vaccine Group (as Randomized)								
	BNT162b2								
	3 µg 6 Months to <2 Years (C4591007) (1 Month After Dose 3)			30 µg 16-25 Years (C4591001) (1 Month After Dose 2)			6 Months to <2 Years/16-25 Years		
Assay	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	GMR[c]	(95% CI[c])	Met Immunobridging Objective[d] (Yes/No)
SARS-CoV-2 neutralization assay - NT50 (titer)	82	1406.5	(1211.3, 1633.1)	170	1180.0	(1066.6, 1305.4)	1.19	(1.00, 1.42)	Yes

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers ([6 months to <2 years] - [16-25 years]) and the corresponding CI (based on the Student t distribution).
d. 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 Rates – Children 6 Months to <2 Years of Age

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the difference in proportions who achieved seroresponse among children 6 months to <2 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.2% (2-sided 95% CI: -3.4%, 4.2%) (Table below).

The lower limit of the 2-sided 95% CI for the difference in seroresponse rate was greater than -10%, and the immunobridging success criterion based on the GMR was achieved, indicating the prespecified immunobridging success criterion for difference in seroresponse was met.

Table 13. Difference in percentages of Participants with seroresponse- Participants without evidence of infection- Immunobridging subset- Comparison of Study C4591007 Phase 2/3 6m to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) - Evaluable Immunogenicity Population.

	Vaccine Group (as Randomized)							
	BNT162b2							
	3 µg 6 Months to <2 Years (C4591007) (1 Month After Dose 3)			30 µg 16-25 Years (C4591001) (1 Month After Dose 2)			Difference	
Assay	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	%[d]	(95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	80	80 (100.0)	(95.5, 100.0)	170	168 (98.8)	(95.8, 99.9)	1.2	(-3.4, 4.2)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
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 included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. N = number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (6 months to <2 years – 16-25 years).
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

SARS-CoV-2 Neutralizing Titers – Phase 2/3 – Children 6 Months to <2 Years of Age – Wild-Type Strain

Immunogenicity results are presented for 50% SARS-CoV-2 neutralizing antibody responses against the wild-type strain, for participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection. Results from the evaluable immunogenicity population (regardless of evidence of prior SARS-CoV-2 infection) and the all-available immunogenicity population were generally similar, noting that inclusion of individuals with prior SARS-CoV-2 infection typically results in elevated baseline (before vaccination) and post-vaccination neutralizing titers compared with individuals without evidence of prior infection.

Subgroup analyses based on demographic characteristics at baseline generally showed no meaningful differences in the immunogenicity profile. The subgroup with evidence of prior SARS-CoV-2 infection at baseline ('baseline positive') generally had higher neutralizing titers both at baseline (pre-vaccination) and post-vaccination compared with the 'baseline negative' subgroup, which is predictable in the setting of vaccinating after prior exposure. These should be interpreted with caution as some subgroups include a limited number of participants.

Neutralizing titers are summarized below for children 6 months to <2 years of age from before Dose 1 to 1-month post-Dose 3, and for young adults from before Dose 1 to 1-month post- Dose 2.

GMTs – Children 6 Months to <2 Years of Age

Among children 6 months to <2 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the observed GMT before vaccination (20.8) was still robust at post-Dose 2 and prior to Dose 3 (317.0), and then substantially increased at 1-month post-Dose 3 (1406.5) (Table below). In the comparator group of young adults 16 to 25 years of age, the observed GMT before vaccination (21.3) was substantially increased at 1-month post-Dose 2 (1180.0).

Table 14. Summary of Geometric mean titers-NT50- Participants without evidence of infection-Immunobridging subset- Study C4591007 Phase 2/3 6m to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)											
		BNT162b2						Placebo					
		3 µg 6 Months to <2 Years (C4591007)			30 µg 16-25 Years (C4591001)			6 Months to <2 Years (C4591007)			16-25 Years (C4591001)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	80	20.8	(20.2, 21.5)	170	21.3	(20.0, 22.8)	48	20.5	(20.5, 20.5)	38	20.5	(20.5, 20.5)
	2/1 Month				170	1180.0	(1066.6, 1305.4)				38	20.5	(20.5, 20.5)
	3/Prevax	81	317.0	(268.8, 373.9)				49	24.2	(19.7, 29.8)			
	3/1 Month	82	1406.5	(1211.3, 1633.1)				49	22.3	(18.8, 26.4)			

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 respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

GMFRs – Children 6 Months to <2 Years of Age

Among children 6 months to <2 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 3 was 68.4 (2-sided 95% CI: 58.2, 80.4) (Table below). The GMFR from before Dose 3 to 1-month post-Dose 3 was 4.4 (2-sided 95% CI: 3.8, 5.2). In the comparator group of young adults 16 to 25 years of age, the GMFR of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 2 was 55.3 (2-sided 95% CI: 49.6, 61.6).

Table 15. Summary of Geometric mean fold rises from before vaccination to each subsequent time point – NT50-Participants without evidence of infection- Immunobridging subset- Study C4591007 Phase 2/3 6m to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)											
		BNT162b2						Placebo					
		3 µg 6 Months to <2 Years (C4591007)			30 µg 16-25 Years (C4591001)			6 Months to <2 Years (C4591007)			16-25 Years (C4591001)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month				170	55.3	(49.6, 61.6)				38	1.0	(1.0, 1.0)
	3/Prevax	79	15.4	(12.9, 18.3)				48	1.2	(1.0, 1.5)			
	3/1 Month	80	68.4	(58.2, 80.4)				48	1.1	(0.9, 1.3)			

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both prevaccination and the given dose/sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Seroresponse Rates – Children 6 Months to <2 Years of Age

Among children 6 months to <2 years of age in the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection, the seroresponse rate from before vaccination to 1-month post-Dose 3 was 100% (2-sided 95% CI: 95.5%, 100%) (Table below). In the comparator group of young adults 16 to 25 years of age, the seroresponse rate from before vaccination to 1-month post-Dose 2 was 98.8% (2-sided 95% CI: 95.8%, 99.9%).

Table 16. Number (%) of participants with seroresponse - Participants without evidence of infection-Immunobridging subset- Study C4591007 Phase 2/3 6m to <5 years of age (1 month after dose 3) and Study C4591001 Phase 2/3 16 through 25 years of age (1 month after dose 2) -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)											
		BNT162b2						Placebo					
		3 µg 6 Months to <2 Years (C4591007)			30 µg 16-25 Years (C4591001)			6 Months to <2 Years (C4591007)			16-25 Years (C4591001)		
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])	N[b]	n[c]	% (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month				170	168	98.8 (95.8, 99.9)				38	0	0.0 (0.0, 9.3)
	3/Prevax	79	65	82.3 (72.1, 90.0)				48	2	4.2 (0.5, 14.3)			
	3/1 Month	80	80	100.0 (95.5, 100.0)				48	1	2.1 (0.1, 11.1)			

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
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 included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both 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.

Ancillary analyses

SARS-CoV-2 Neutralizing Titers – Phase 2/3 – Children 6 Months to <2 Years of Age – Omicron and Delta Variants

Non validated FFRNT assay results are summarized below for the Omicron neutralization subset of the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection. Titers were obtained in the FFRNT assay against Omicron and Delta variants and a wild-type reference strain.

Results in the evaluable immunogenicity population (regardless of evidence of prior infection) and the all-available immunogenicity population were generally similar, noting that inclusion of individuals with prior SARS-CoV-2 infection typically results in elevated baseline (before vaccination) and post-vaccination neutralizing titers compared with individuals without evidence of prior infection.

Note that the adult booster population used for reference in this analysis is the same as included for the 2 to <5 years of age group.

GMTs – Children 6 Months to <2 Years of Age

Among 32 children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, neutralizing GMTs prior to vaccination with Dose 3 against Delta (94.1) and Omicron (16.3) were increased at 1-month post-Dose 3 with respect to both Delta (606.3) and Omicron

(127.5) (Table below). Correspondingly, increases were also observed for the reference strain from before Dose 3 (103.7) to 1-month post-Dose 3 (640.0).

Similar patterns were observed for 40 adults 18 to 55 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 30-µg, for whom neutralizing GMTs prior to vaccination with Dose 3 against Delta (36.4) and Omicron (12.7) were increased at 1-month post-Dose 3 with respect to both Delta (1153.6) and Omicron (340.0) titers. Increases were also observed for the reference strain from before Dose 3 (33.9) to 1-month post-Dose 3 (1067.1).

Notably, the dosing interval between Dose 2 and Dose 3 in adults was approximately 6 months, as compared with the dosing interval between Dose 2 and Dose 3 in the pediatric age group of approximately 2 to 3 months. The longer interval, as well as potential differences in antibody waning over time, may contribute to the higher increase in GMTs observed in adults as compared to the pediatric population.

Table 17. Summary of Geometric mean titers-Omicron neutralization subset-Participants without evidence of infection- Study C4591007 Phase 2/3 6m to <5 years of age and Study C4591001 Phase 3 booster 18 through 55 years of age -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)								
		BNT162b2						Placebo		
		3 µg 6 Months to <2 Years (C4591007)			30 µg 18-55 Years (C4591001)			6 Months to <2 Years (C4591007)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.1 - NT50 (titer)	3/Prevax	32	16.3	(12.8, 20.8)	40	12.7	(11.0, 14.8)	5	10.0	(10.0, 10.0)
	3/1 Month	32	127.5	(90.2, 180.1)	40	340.0	(253.8, 455.6)	5	10.0	(10.0, 10.0)
SARS-CoV-2 FFRNT - Delta - NT50 (titer)	3/Prevax	32	94.1	(67.9, 130.5)	40	36.4	(26.5, 49.9)	5	10.0	(10.0, 10.0)
	3/1 Month	32	606.3	(455.5, 806.9)	40	1153.6	(886.4, 1501.4)	5	10.0	(10.0, 10.0)
SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	3/Prevax	32	103.7	(78.4, 137.3)	40	33.9	(26.1, 44.1)	5	10.0	(10.0, 10.0)
	3/1 Month	32	640.0	(502.6, 815.0)	40	1067.1	(834.4, 1364.5)	5	10.0	(10.0, 10.0)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.

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

GMFR – Children 6 Months to <2 Years of Age

For children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 3-µg, there was an observed 6.4-fold increase in Delta and 7.8-fold increase in Omicron neutralizing titers obtained in the FFRNT assay from before Dose 3 to 1-month post-Dose 3 (Table below). The GMFR for the reference strain from before Dose 3 to 1-month post-Dose 3 was 6.2.

For adults 18 to 55 years of age without evidence of prior SARS-CoV-2 infection who received three doses of BNT162b2 30-µg, there was on observed 31.7-fold increase in Delta and 26.7-fold increase in Omicron neutralizing titers obtained in the FFRNT assay from before Dose 3 to1-month post-Dose 3. The GMFR for the reference strain from before Dose 3 to 1-month post- Dose 3 was 31.5.

Noting that adults had a longer dosing interval between Dose 2 and Dose 3 (approximately 6 months) at a time when antibody levels may be waning and the effects of a booster may be more pronounced, compared with children in this age group (approximately 2 to 3 months), a higher GMFR in the adults compared to the pediatric population may be expected.

Table 18. Summary of Geometric mean fold rises from before dose 3 to 1 month after dose 3-Omicron neutralization subset-Participants without evidence of infection- Study C4591007 Phase 2/3 6m to <5 years of age and Study C4591001 Phase 3 booster 18 through 55 years of age -Evaluable Immunogenicity Population.

		Vaccine Group (as Randomized)								
		BNT162b2						Placebo		
		3 µg 6 Months to <2 Years (C4591007)			30 µg 18-55 Years (C4591001)			6 Months to <2 Years (C4591007)		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])	n[b]	GMFR[c]	(95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.1 - NT50 (titer)	3/1 Month	32	7.8	(6.0, 10.2)	40	26.7	(20.2, 35.2)	5	1.0	(1.0, 1.0)
SARS-CoV-2 FFRNT - Delta - NT50 (titer)	3/1 Month	32	6.4	(4.6, 9.1)	40	31.7	(23.3, 43.2)	5	1.0	(1.0, 1.0)
SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	3/1 Month	32	6.2	(4.7, 8.2)	40	31.5	(23.6, 41.9)	5	1.0	(1.0, 1.0)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 3 study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both before Dose 3 and the given dose/sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Updated Supportive Analysis

An additional descriptive immunogenicity analysis was conducted using the FFRNT assay, to compare children with adults who received a third dose of BNT162b2 at a similar interval between Dose 2 and Dose 3. This analysis compared Phase 2/3 pediatric participants in Study C4591007 with a subset of adults 18 to 50 years of age in Phase 3 Study C4591017 (lot consistency study) who had received a two-dose primary series followed by a booster (third) dose of BNT162b2 30-µg. The dosing interval between Dose 2 and Dose 3 was a median 13.0 weeks (range: 11.9 to 14.3 weeks) for adults and 12.9 weeks (range: 8.6 to 20.0 weeks) for children 6 months to <2 years of age). At 1-month post-Dose 3, among 32 children 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection, the neutralizing GMT was 128.8; correspondingly, among 27 adults 18 to 50 years of age without evidence of priorSARS-CoV-2 infection, the neutralizing GMT at 1-month post-Dose 3 was 164.2. These data show that for populations who received three doses of BNT162b2 at the age-appropriate dose level and administered at a comparable dosing interval, the Omicron specific neutralization titers are very similar in the pediatric population and an adult comparator group for whom high efficacy was observed.

Immunogenicity results for entire immunogenicity study population Children 6 months to <5 Years of Age

GMR of Neutralizing Titers – Children 6 months to <5 Years of Age

As a response to the list of questions at the primary round, the MAH submitted immunogenicity analyses for entire study population. The result is very similar to the one demonstrated for two separate young cohorts as expected.

Table 19. Summary of Geometric Mean Ratios – NT50 – Participants Without Evidence of Infection – Immunobridging Subset – Study C4591007 Phase 2/3 6 Months to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Trough 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	BNT162b2							
	3 µg 6 Months to <5 Years (C4591007) (1 Month After Dose 3)			30 µg 16-25 Years (C4591001) (1 Month After Dose 2)			6 Months to <5 Years/16-25 Years	
Assay	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	GMR[c]	(95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	225	1487.0	(1367.9, 1616.5)	170	1180.0	(1066.6, 1305.4)	1.26	(1.11, 1.43)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers ([6 months to <5 years] - [16-25 years]) and the corresponding CI (based on the Student t distribution).

Seroresponse Rates – Children 6 months to <5 Years of Age

Table 20. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection – Immunobridging Subset – Comparison of Study C4591007 Phase 2/3 6 Months to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	BNT162b2							
	3 µg 6 Months to <5 Years (C4591007) (1 Month After Dose 3)			30 µg 16-25 Years (C4591001) (1 Month After Dose 2)			Difference	
Assay	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	%[d]	(95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	221	221 (100.0)	(98.3, 100.0)	170	168 (98.8)	(95.8, 99.9)	1.2	(-0.5, 4.2)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Evaluable population refers to Dose 3 evaluable immunogenicity population for C4591007 and Dose 2 evaluable immunogenicity population for C4591001.
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 included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection. Having no evidence of past SARS-CoV-2 infection was defined as having a negative N-binding antibody (serum) result at the Dose 1, Dose 3 (C4591007), and 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 (C4591007) study visits and any unscheduled visit prior to the 1-month post–Dose 2 (C4591001) or 1-month post–Dose 3 (C4591007) study blood sample collection; and no medical history of COVID-19.
a. N = number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (6 months to <5 years – 16-25 years).
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Efficacy Results – Study C4591007

Combined analysis across age groups from 6 months to <5 years of age:

- VE from at least 7 days after Dose 3 in blinded placebo-controlled follow-up in the total population of participants 6 months to <5 years of age randomized 2:1 to BNT162b2 3-µg vs placebo, including 992 BNT162b2 recipients and 464 placebo recipients who received three doses of study intervention; RVE comparing three vs two doses of BNT162b2 during the same calendar interval of 07 February 2022 to 29 April 2022.

Vaccine Efficacy from at Least 7 Days After Dose 3 to Cutoff Date

The observed VE from at least 7 days after Dose 3 to the cutoff date (29 April 2022) across the total population of children 6 months to <5 years of age was 80.3% (2-sided 95% CI: 13.9%, 96.7%) based on 3 cases in the BNT162b2 group and 7 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine: placebo) (Table below). Note the post-Dose 3 cases were all reported in February through April 2022. None of these participants had reported evidence of prior SARS-CoV-2 infection at baseline.

Table 21. Vaccine efficacy-first COVID-19 Occurrence from 7 Days after dose 3-blinded follow up period-phase 2/3- 6m to <5yo-Dose 3-All available efficacy population

	Vaccine Group (as Randomized)					
	BNT162b2 (3 µg) (N[a]=992)		Placebo (N[a]=464)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3	3	0.086 (758)	7	0.039 (348)	80.3	(13.9, 96.7)

Abbreviations: 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 7 days after Dose 3 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.

Relative Vaccine Efficacy of Three vs Two Doses

The RVE of BNT162b2 3-µg against symptomatic COVID-19 based on 4 cases reported at least 7 days after Dose 3 (original BNT162b2 group who received three doses) compared with 6 cases reported at least 7 days after Dose 2 (original placebo group who were unblinded and received two doses of BNT162b2) during the period of 07 February 2022 to 29 April 2022 was 76.2% (2-sided 95% CI: -0.5%, 95.1%) (Table below).

Table 22. Relative Vaccine Efficacy -1st COVID-19 occurrence from 7FEB2022 TO 29APR 2022-Participatns who received 3 doses of vaccine or placebo crossover participants who received 2 doses of vaccine -6m to <5yo- Dose 1-All available efficacy population.

	Vaccine Group					
	Original BNT162b2 (3 µg)		Placebo Crossover to BNT162b2 (3 µg)			
Efficacy Endpoint	n1[a]	Surveillance Time[b] (n2[c])	n1[a]	Surveillance Time[b] (n2[c])	RVE (%)	(95% CI[d])
First COVID-19 occurrence from 7 days after the third dose of BNT162b2 (original BNT162b2) or second dose of BNT162b2 (placebo crossover) and from 07FEB2022[e] to 29APR2022[f]	4	0.170 (1212)	6	0.061 (516)	76.2	(-0.5, 95.1)

Abbreviation: RVE = relative vaccine efficacy.
Note: Participants who turned 5 years of age and received BNT162b2 10 µg at Dose 2, Dose 3, or crossover Dose 1 or Dose 2 are excluded.
a. n1 = Number of participants meeting the endpoint definition.
b. 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 latest of 7 days after the third dose of BNT162b2 (original BNT162b2) or second dose of BNT162b2 (placebo crossover to BNT162b2) and 07FEB2022 to the earliest of confirmed case, death, withdrawn from the study, third dose of BNT162b2 (placebo crossover only), or 29APR2022.
c. n2 = Number of participants at risk for the endpoint.
d. Confidence interval (CI) for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.
e. Date of 7 days after the first Dose 3 BNT162b2 vaccination in original BNT162b2 participants.
f. Data cutoff date of this analysis.

Pediatric (6 Months to <5 Years of Age) Updated Interim Efficacy Data, cut-off 17.06.2022

After receiving a preliminary list of questions, the MAH submitted an updated report to present an updated efficacy analysis that was conducted in accordance with the C4591007 protocol-specified and hypothesis-testing secondary efficacy objective, which was to evaluate vaccine efficacy (VE) when at least 21 confirmed COVID-19 cases had accrued among the combined population of children 2 to <5 years and 6 months to <2 years of age following completion of the three-dose vaccination series.

This updated analysis presents observed VE against symptomatic COVID-19 for the three-dose series of BNT162b2 3-µg during blinded placebo-controlled follow-up. The analysis is based on 34 cases confirmed at least 7 days post-Dose 3 up to the data cutoff date of 17 June 2022, in the combined Dose 3 evaluable efficacy population of children 6 months to <5 years of age without evidence of prior SARS-CoV-2 infection. Analyses include post-Dose 3 VE by SARS-CoV-2 variant of concern (which were all identified from sequencing data as sub-lineages of Omicron), and analyses excluding cases involving coinfection with other respiratory pathogens.

Duration of follow-up

Table 23. Follow-Up Time After Dose 3 – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <5 Years of Age – Evaluable Efficacy (3-Dose) Population

	Vaccine Group (as Randomized)		
	BNT162b2 (3 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Time from Dose 3 to cutoff date			
6 months to <5 years			
N[b]	873	381	1254
<1 Month	148 (17.0)	59 (15.5)	207 (16.5)
≥1 to <2 Months	265 (30.4)	109 (28.6)	374 (29.8)
≥2 to <3 Months	157 (18.0)	78 (20.5)	235 (18.7)
≥3 Months	303 (34.7)	135 (35.4)	438 (34.9)
Mean (SD)	2.2 (1.34)	2.2 (1.22)	2.2 (1.31)
Median	2.1	2.3	2.2
Min, max	(0.0, 4.9)	(0.0, 4.1)	(0.0, 4.9)
2 to <5 years			
N[b]	554	224	778
<1 Month	108 (19.5)	41 (18.3)	149 (19.2)
≥1 to <2 Months	132 (23.8)	49 (21.9)	181 (23.3)
≥2 to <3 Months	98 (17.7)	41 (18.3)	139 (17.9)
≥3 Months	216 (39.0)	93 (41.5)	309 (39.7)
Mean (SD)	2.3 (1.40)	2.3 (1.28)	2.3 (1.36)
Median	2.4	2.6	2.4
Min, max	(0.0, 4.9)	(0.0, 4.1)	(0.0, 4.9)
6 months to <2 years			
N[b]	319	157	476
<1 Month	40 (12.5)	18 (11.5)	58 (12.2)
≥1 to <2 Months	133 (41.7)	60 (38.2)	193 (40.5)
≥2 to <3 Months	59 (18.5)	37 (23.6)	96 (20.2)
≥3 Months	87 (27.3)	42 (26.8)	129 (27.1)
Mean (SD)	2.1 (1.23)	2.1 (1.13)	2.1 (1.20)

Median	1.8	2.1	1.9
Min, max	(0.0, 4.9)	(0.0, 4.1)	(0.0, 4.9)

Abbreviations: 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 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (ie, negative
N-binding antibody [serum] result at Dose 1, 1-month post-Dose 2 (if available), and Dose 3 (if available) study visits, SARS- CoV-2 not detected by
NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit [prior to 7 days after
receipt of Dose 3]) and had no medical history of COVID-19 were included in the analysis.
a. n = Number of participants with the specified characteristic.
b. N = number of participants in the specified group, or the total sample. These values are the denominators for the percentage and summary statistics calculations.

Demographics

Table 24. Demographic Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <5 Years of Age – Evaluable Efficacy (3-Dose) Population

	Vaccine Group (as Randomized)		
	BNT162b2 (3 µg) (N[a]=873) n[b] (%)	**Placebo (N[a]=381) n[b] (%)**	**Total (N[a]=1254) n[b] (%)**
Sex			
Male	427 (48.9)	173 (45.4)	600 (47.8)
Female	446 (51.1)	208 (54.6)	654 (52.2)
Race			
White	666 (76.3)	296 (77.7)	962 (76.7)
Black or African American	30 (3.4)	12 (3.1)	42 (3.3)
American Indian or Alaska Native	2 (0.2)	0	2 (0.2)
Asian	87 (10.0)	38 (10.0)	125 (10.0)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.1)
Multiracial	85 (9.7)	33 (8.7)	118 (9.4)
Not reported	3 (0.3)	1 (0.3)	4 (0.3)
Ethnicity			
Hispanic/Latino	98 (11.2)	27 (7.1)	125 (10.0)
Non-Hispanic/Non-Latino	774 (88.7)	354 (92.9)	1128 (90.0)
Not reported	1 (0.1)	0	1 (0.1)
Country			
Poland	24 (2.7)	4 (1.0)	28 (2.2)
USA	849 (97.3)	377 (99.0)	1226 (97.8)
Comorbidities[c]			
Yes	76 (8.7)	37 (9.7)	113 (9.0)
No	797 (91.3)	344 (90.3)	1141 (91.0)

Abbreviations: MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at Dose 1, 1-month post-Dose 2 (if available), and Dose 3 (if available) study visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit [prior to 7 days after receipt of Dose 3]) 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. 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);1081-8 and/or obesity (BMI ≥ 95th percentile) for 2 to <5 years.

Efficacy Against Symptomatic COVID-19

This section presents results of analyses across the combined population of children 6 months to <5 years of age, conducted according to the protocol prespecified secondary efficacy objectives.

Dose 3 Evaluable Efficacy Populations – Children 6 Months to <5 Years of Age

Participants Without Evidence of Prior SARS-CoV-2 Infection

The first secondary VE hypothesis for 6 months to <5 years was evaluated in participants without evidence of prior SARS-CoV-2 infection. The observed VE from at least 7 days after Dose 3 across the total evaluable population of children 6 months to <5 years of age without evidence of prior SARS-CoV-2 infection before or during the vaccination regimen was 73.2% (2-sided 95% CI: 43.8%, 87.6%) based on 13 cases in the BNT162b2 group and 21 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine: placebo) (Table below). The predefined success criterion, lower bound of 95% CI for VE >30%, was met.

Table 25. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to <5 Years of Age – Evaluable Efficacy (3-Dose) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (3 µg) (N[a]=873)		Placebo (N[a]=381)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3						
6 months to <5 years	13	0.124 (794)	21	0.054 (351)	73.2	(43.8, 87.6)
2 to <5 years	9	0.081 (498)	13	0.033 (204)	71.8	(28.6, 89.4)
6 months to <2 years	4	0.042 (296)	8	0.020 (147)	75.8	(9.7, 94.7)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (ie, negative
N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT
[nasal swab] at Dose 1, Dose 2 and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of
Dose 3) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 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.

Participants With and Without Evidence of Prior SARS-CoV-2 Infection

Since the first secondary VE hypothesis was met, the second VE hypothesis was evaluated sequentially in participants with or without evidence of prior SARS-CoV-2 infection. The observed VE from at least 7 days after Dose 3 across the total evaluable population of children 6 months to <5 years of age with or without evidence of prior SARS-CoV-2 infection before or during the vaccination regimen was 72.5% (2-sided 95% CI: 44.3%, 86.9%) based on 14 cases in the BNT162b2 group and 23 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo). The predefined success criterion, lower bound of 95% CI for VE >30%, was met.

Dose 3 All- Available Efficacy Populations – Children 6 Months to <5 Years of Age

The observed VE from at least 7 days after Dose 3 across the total Dose 3 all-available population of children 6 months to <5 years of age was 72.3% (2-sided 95% CI: 43.7%, 86.8%) based on 14 cases in the BNT162b2 group and 23 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo) (Table below).

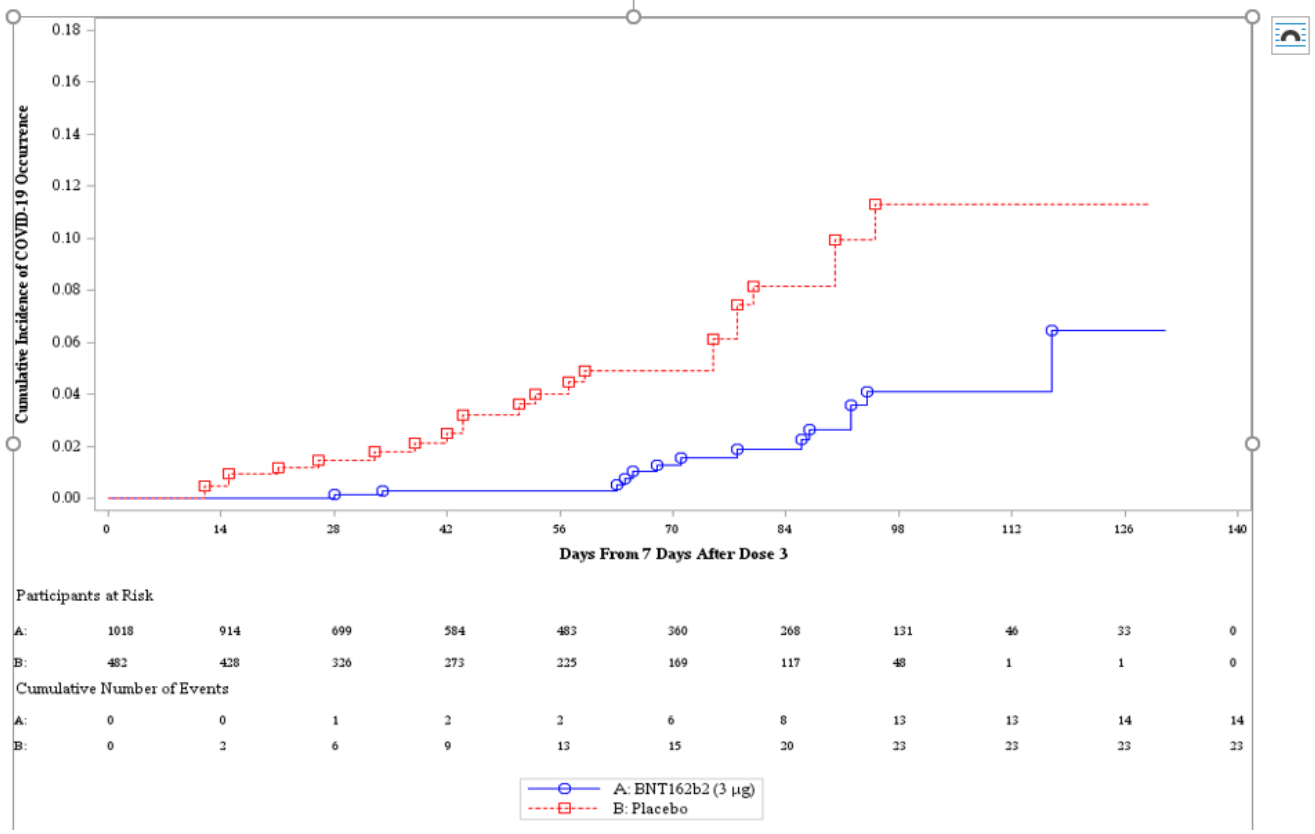
Table 26. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <5 Years of Age – Dose 3 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (3 µg) (N[a]=1351)		Placebo (N[a]=642)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3						
6 months to <5 years	14	0.153 (1018)	23	0.070 (482)	72.3	(43.7, 86.8)
2 to <5 years	10	0.104 (668)	15	0.046 (301)	70.6	(30.1, 88.2)
6 months to <2 years	4	0.049 (350)	8	0.024 (181)	75.6	(8.9, 94.6)

Abbreviations: 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 7 days after Dose 3 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.

Substantial separation of the Kaplan-Meier curves is evident very early starting from at least 7 days after Dose 3, with placebo cases steadily accruing and comparative fewer cases occurring more distantly after BNT162b2 vaccination (Figure 1).

Figure 1. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 3 – Blinded Follow-Up Period Phase 2/3 – 6 Months to <5 Years of Age – Dose 3 All-Available Efficacy Population



In the analysis by SARS-CoV-2 variant of concern in this population (Table below), the observed VE after Dose 3 was 72.6% to 82.9% against the most frequently identified variants (Omicron sublineages BA.2.12.1 and BA.2). Few cases were identified as BA.4 or BA.5, precluding meaningful interpretation of VE for these sublineages whether considered separately or combined.

Table 27. Vaccine Efficacy by Variant of Concern – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <5 Years of Age – Dose 3 All-Available Population

	Vaccine Group (as Randomized)					
	BNT162b2 (3 µg) (N[a]=1351)		Placebo (N[a]=642)			
Efficacy Endpoint Variant of Concern	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3						
Overall	14	0.153 (1018)	23	0.070 (482)	72.3	(43.7, 86.8)
Omicron	14	0.153 (1018)	22	0.070 (482)	71.0	(40.7, 86.3)
Omicron BA.1.1	0	0.153 (1018)	2	0.070 (482)	100.0	(-142.7, 100.0)
Omicron BA.2	3	0.153 (1018)	8	0.070 (482)	82.9	(28.8, 97.1)
Omicron BA.2.10	0	0.153 (1018)	1	0.070 (482)	100.0	(-1677.9, 100.0)
Omicron BA.2.12.1	6	0.153 (1018)	10	0.070 (482)	72.6	(16.9, 91.8)
Omicron BA.2.21	1	0.153 (1018)	0	0.070 (482)	UND	(NA, NA)
Omicron BA.4	2	0.153 (1018)	1	0.070 (482)	8.8	(-5279.1, 95.3)
Omicron BA.5	2	0.153 (1018)	0	0.070 (482)	UND	(NA, NA)
Unknown	0	0.153 (1018)	1	0.070 (482)	100.0	(-1677.9, 100.0)

Abbreviations: NA = not applicable; UND = Undefined; 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 7 days after Dose 3 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.

Vaccine Efficacy from Dose 1 to Cutoff Date- Children 6 Months to <5 Years of Age

The observed VE for BNT162b2 3-µg against any confirmed COVID-19 from Dose 1 onwards in the Dose 1 all-available population for children 6 months to <5 years of age was 27.9%

(2-sided 95% CI: 13.3%, 40.0%) based on 292 cases in the BNT162b2 group and 199 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine: placebo), as of the data cutoff date 17 June 2022 (Table below).

When excluding participants who had evidence of coinfection with other respiratory pathogens the observed VE after Dose 1 was 27.0% (2-sided 95% CI: 9.4%, 41.0%) based on 220 cases in the BNT162b2 group and 148 cases in the placebo group (which excluded 72 cases in the BNT162b2 group and 51 cases in the placebo group that involved coinfections).

Table 28. Vaccine Efficacy -1st CPVID-19 occurrence after dose 1-Blinded follow-up period-Phase 2/3- 6 months to < 5yo-Dose 1 all-available efficacy population

Vaccine Group (as Randomized)						
	BNT162b2 (3 µg) (N[a]=3793)		Placebo (N[a]=1891)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	292	1.307 (3407)	199	0.642 (1689)	27.9	(13.3, 40.0)
Dose 1 to before Dose 2	55	0.198 (3407)	21	0.098 (1689)	-29.4	(-125.2, 23.0)
Dose 2 to <7 days after Dose 2	12	0.058 (3072)	13	0.029 (1531)	54.0	(-9.3, 80.8)
≥7 Days after Dose 2 to before Dose 3	208	0.877 (3009)	142	0.436 (1496)	27.2	(9.3, 41.5)
Dose 3 to <7 days after Dose 3	3	0.020 (1181)	0	0.009 (510)	UND	(NA, NA)
≥7 Days after Dose 3	14	0.153 (1018)	23	0.070 (482)	72.3	(43.7, 86.8)

Abbreviations: NA = not applicable; UND = undefined; VE = vaccine efficacy.
N = number of participants in the specified group.
n1 = Number of participants meeting the endpoint definition.
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.
n2 = Number of participants at risk for the endpoint.
Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Children 2 to <5 years of age:

Disposition and Datasets Analyzed – Children 2 to <5 Years of Age

The Dose 1 all-available efficacy population of children 2 to <5 years of age included 2349 participants in the BNT162b2 group and 1173 participants in the placebo group (Table below), which reflects the 2:1 randomization. Populations of participants who received three doses of study intervention were:

- Dose 3 all-available efficacy population: 864 BNT162b2 recipients and 405 placebo recipients.
- Dose 3 evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection: 820 BNT162b2 recipients and 383 placebo recipients.
- Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection: 554 BNT162b2 recipients and 224 placebo recipients.

Exclusions from the Dose 3 evaluable efficacy population were primarily due to participants not receiving three vaccine doses prior to unblinding (63.2% of BNT162b2 group and 65.5% of placebo group).

Note that Dose 3 administration began on 31 January 2022 and the study was still actively enrolling at that time. Analysis populations included participants who received BNT162b2 3-µg or placebo, and therefore excluded participants who turned 5 years of age and received the age appropriate BNT162b2 10-µg dose level (which per protocol would have occurred after unblinding).

Table 29. Efficacy Populations – Phase 2/3 – 2 to <5 Years of Age

	Vaccine Group (as Randomized)			
	BNT162b2 (3 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)	
Randomized[b]	2349 (100.0)	1173 (100.0)		3522 (100.0)
Dose 1 all-available efficacy population	2349 (100.0)	1173 (100.0)		3522 (100.0)
Dose 3 all-available efficacy population	864 (36.8)	405 (34.5)		1269 (36.0)
Participants excluded from Dose 3 all-available efficacy population	1485 (63.2)	768 (65.5)		2253 (64.0)
Reason for exclusion[c]				
Did not receive 3 vaccinations prior to unblinding Evaluable	1485 (63.2)	768 (65.5)		2253 (64.0)
efficacy (3-dose) population	820 (34.9)	383 (32.7)		1203 (34.2)
Participants without evidence of infection prior to 7 days after Dose 3	554 (23.6)	224 (19.1)		778 (22.1)
Participants excluded from evaluable efficacy (3-dose) population Reason	1529 (65.1)	790 (67.3)		2319 (65.8)
for exclusion[c]				
Did not receive all vaccinations as randomized prior to unblinding	1485 (63.2)	768 (65.5)		2253 (64.0)
Did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	27 (1.1)	16 (1.4)	43 (1.2)	
Did not receive Dose 3 within the predefined window (at least 60 days after Dose 2 for participants enrolled before protocol amendment 6 and 54-70 days for participants enrolled after protocol amendment 6)	24 (1.0)	15 (1.3)	39 (1.1)	
Had other important protocol deviations on or prior to 7 days after Dose 3	22 (0.9)	4 (0.3)	26 (0.7)	

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

Demographics – Children 2 to <5 Years of Age

Demographic characteristics for participants 2 to <5 years of age in the Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection were generally similar in BNT162b2 and placebo groups (Table below).

Most participants were White (77.6%) and the population included 3.7% Black or African American participants, 10.0% Asian participants, 8.0% multiracial participants, with other race subgroups comprising <1%. In total, 9.8% of participants were Hispanic/Latino. The population was balanced with regard to sex with 45.9% male and 54.1% female participants. Comorbidities present at baseline that increase the risk of severe COVID-19 disease (which included obesity in this age group) were reported in similar proportions of participants in the BNT162b2 group (11.9%) and placebo group (13.8%). Obesity in this age group was reported in 6.0% of participants in the BNT162b2 group and 4.0% in the placebo group.

Among participants in the Dose 3 evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection, 13.2% in the BNT162b2 group and 17.8% in the placebo group were baseline positive for prior SARS-CoV-2 infection. Other demographic characteristics were generally similar to the

population without evidence of prior infection. The demographics of the Dose 1 all-available and Dose 3 all-available efficacy populations were also overall similar.

Table 30. Demographic Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 2 to <5 Years of Age – Evaluable Efficacy (3-Dose) Population

	Vaccine Group (as Randomized)		
	BNT162b2 (3 µg) (N[a]=554) n[b] (%)	Placebo (N[a]=224) n[b] (%)	Total (N[a]=778) n[b] (%)
Sex			
Male	262 (47.3)	95 (42.4)	357 (45.9)
Female	292 (52.7)	129 (57.6)	421 (54.1)
Race			
White	427 (77.1)	177 (79.0)	604 (77.6)
Black or African American	23 (4.2)	6 (2.7)	29 (3.7)
American Indian or Alaska Native	1 (0.2)	0	1 (0.1)
Asian	53 (9.6)	25 (11.2)	78 (10.0)
Native Hawaiian or other Pacific Islander	0	1 (0.4)	1 (0.1)
Multiracial	47 (8.5)	15 (6.7)	62 (8.0)
Not reported	3 (0.5)	0	3 (0.4)
Ethnicity			
Hispanic/Latino	60 (10.8)	16 (7.1)	76 (9.8)
Non-Hispanic/Non-Latino	493 (89.0)	208 (92.9)	701 (90.1)
Not reported	1 (0.2)	0	1 (0.1)
Country			
Poland	14 (2.5)	2 (0.9)	16 (2.1)
USA	540 (97.5)	222 (99.1)	762 (97.9)
Age group (at vaccination)			
2 Years	215 (38.8)	72 (32.1)	287 (36.9)
3 Years	218 (39.4)	97 (43.3)	315 (40.5)
4 Years	121 (21.8)	55 (24.6)	176 (22.6)
Age at vaccination (years)			
Mean (SD)	2.8 (0.76)	2.9 (0.75)	2.9 (0.76)
Median	3.0	3.0	3.0
Min, max	(2, 4)	(2, 4)	(2, 4)
Obese[c]			
Yes	33 (6.0)	9 (4.0)	42 (5.4)
No	519 (93.7)	215 (96.0)	734 (94.3)
Missing	2 (0.4)	0	2 (0.3)
Comorbidities[d]			
Yes	66 (11.9)	31 (13.8)	97 (12.5)
No	488 (88.1)	193 (86.2)	681 (87.5)

Abbreviations: MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (ie, negative

N-binding antibody [serum] result at Dose 1, 1-month post-Dose 2 (if available), and Dose 3 (if available) study visits, SARS- CoV-2 not detected by
NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit [prior to 7 days after
receipt of Dose 3]) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least

Dose 3 All-Available Efficacy Population – Children 2 to <5 Years of Age

The observed VE from at least 7 days after Dose 3 among children 2 to <5 years of age in the Dose 3 all-available population was 70.6% (2-sided 95% CI: 30.1%, 88.2%) based on 10 cases in the BNT162b2 group and 15 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo).

In the analysis by SARS-CoV-2 variant of concern in this population, the observed VE after Dose 3 was 68.5% to 82.4% against the most frequently identified Omicron sublineages (BA.2.12.1 and BA.2). Few cases were identified as BA.4 or BA.5, precluding reliable estimation of VE for these sublineages whether considered separately or combined.

Relative Vaccine Efficacy of Three vs Two Doses– Children 2 to <5 Years of Age

The RVE of BNT162b2 3-µg against symptomatic COVID-19 based on 2 cases reported at least 7 days after Dose 3 (original BNT162b2 group) compared with 4 cases reported at least 7 days after Dose 2 (original placebo group who were unblinded to receive BNT162b2) during the period of 07 February 2022 to 29 April 2022 was 84.0% (2-sided 95% CI: -11.8%, 98.6%)

Vaccine Efficacy from Dose 1 to Cutoff Date – Children 2 to <5 Years of Age Dose 1 All-Available Efficacy Population – Children 2 to <5 Years of Age

The observed VE from Dose 1 onwards in the Dose 1 all-available population of children 2 to <5 years of age was 32.3% (2-sided 95% CI: 13.8%, 46.7%) based on 169 cases in the BNT162b2 group and 121 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo) (Table below).

Clear separation of the Kaplan-Meier curves for BNT162b2 and placebo groups is evident by approximately 4 months after the first dose which generally coincides with completion of the three-dose series for this age group.

When excluding participants who had evidence of coinfection with other respiratory pathogens the observed VE after Dose 1 was 33.6% (2-sided 95% CI: 12.2%, 49.7%) based on 126 cases in the BNT162b2 group and 92 cases in the placebo group (which excluded 43 cases in the BNT162b2 group and 29 cases in the placebo group that involved coinfections).

Table 31. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Blinded Follow-Up Period – Phase 2/3 – 2 to <5 Years of Age – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (3 µg) (N[a]=2349)		Placebo (N[a]=1173)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	169	0.787 (2135)	121	0.381 (1058)	32.3	(13.8, 46.7)
Dose 1 to before Dose 2	35	0.123 (2135)	11	0.061 (1058)	-57.6	(-244.0, 21.8)
Dose 2 to <7 days after Dose 2	8	0.036 (1913)	7	0.018 (953)	43.0	(-84.6, 81.9)
≥7 Days after Dose 2 to before Dose 3	115	0.511 (1874)	88	0.251 (934)	35.9	(14.4, 51.8)
Dose 3 to <7 days after Dose 3	1	0.013 (764)	0	0.006 (324)	UND	(NA, NA)
≥7 Days after Dose 3	10	0.104 (668)	15	0.046 (301)	70.6	(30.1, 88.2)

Abbreviations: NA = not applicable; UND = undefined; VE = vaccine efficacy.
N = number of participants in the specified group.
n1 = Number of participants meeting the endpoint definition.
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.
n2 = Number of participants at risk for the endpoint.
Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Signs and Symptoms of COVID-19 – Children 2 to <5 Years of Age

Confirmed cases occurring after Dose 1 among participants 2 to <5 years of age had signs and symptoms (per protocol case criteria) consistent with mostly mild to moderate illness, similar in both groups (Table below). The most commonly reported were new or increased cough (63.4%) and fever (59.0%) from protocol-defined symptoms and including nasal congestion or runny nose (37.2%) from additional CDC-defined symptoms. Most participants in both groups reported ≤3 concurrent signs or symptoms.

The reported signs and symptoms for each age subgroup (ie, 2 years, 3 years, or 4 years of age) were generally similar.

Table 32. Signs and Symptoms for First COVID-19 Occurrence After Dose 1 – Blinded Follow-Up Period – Phase 2/3 – 2 to <5 Years of Age – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)		
Signs and Symptoms	BNT162b2 (3 µg) (N[a]=169) n[b] (%)	Placebo (N[a]=121) n[b] (%)	Total (N[a]=290) n[b] (%)
Participants with specific signs and symptoms of COVID-19	169 (100.0)	121 (100.0)	290 (100.0)
Fever	97 (57.4)	74 (61.2)	171 (59.0)
New or increased cough	116 (68.6)	68 (56.2)	184 (63.4)

New or increased shortness of breath	1 (0.6)	0 (0.0)	1 (0.3)
Chills	9 (5.3)	12 (9.9)	21 (7.2)
New or increased muscle pain	11 (6.5)	7 (5.8)	18 (6.2)
Sore throat	25 (14.8)	15 (12.4)	40 (13.8)
Diarrhea	21 (12.4)	9 (7.4)	30 (10.3)
Vomiting	16 (9.5)	12 (9.9)	28 (9.7)
Inability to eat/poor feeding	16 (9.5)	19 (15.7)	35 (12.1)
Additional CDC-defined symptoms			
Fatigue	30 (17.8)	16 (13.2)	46 (15.9)
Headache	6 (3.6)	8 (6.6)	14 (4.8)
Nasal congestion or runny nose	70 (41.4)	38 (31.4)	108 (37.2)
Nausea or abdominal pain	7 (4.1)	15 (12.4)	22 (7.6)
Lethargy	1 (0.6)	2 (1.7)	3 (1.0)
Participants with specific number of signs and symptoms			
1	34 (20.1)	33 (27.3)	67 (23.1)
2	65 (38.5)	36 (29.8)	101 (34.8)
3	38 (22.5)	33 (27.3)	71 (24.5)
4	18 (10.7)	8 (6.6)	26 (9.0)
5	11 (6.5)	8 (6.6)	19 (6.6)
>5	3 (1.8)	3 (2.5)	6 (2.1)

N = number of participants with COVID-19 occurrence from 7 days after Dose 1 in the specified group. This value is used as the denominator for the percentage calculations.
n = Number of participants with the specific criteria meeting the definition. A participant can have more than 1 symptom.

Participants with Multiple Episodes of COVID-19 During the Study – Children 2 to <5 Years of Age

As of the data cutoff date (17 June 2022), several participants in the 2 to <5 years of age group had virologically and clinically confirmed multiple episodes of COVID-19. Narratives for these participants are in Module 5.3.5.1.

- In the BNT162b2 group, 6 participants had multiple episodes of COVID-19; all of these cases occurred post-Dose 2 (and prior to Dose 3). Two participants had initial illness in Q3 2021 followed by subsequent illness in early 2022; all other cases occurred from early 2022 onwards (ie, after an Omicron surge had begun).
- In the placebo group, 2 participants had multiple episodes of COVID-19; one participant had both initial and subsequent illnesses post-Dose 2 (and prior to Dose 3), and the other participant had both initial and subsequent illnesses post-Dose 3. All cases occurred from early 2022 onwards.

Note, several participants had multiple PCR-positive results confirming COVID-19, for which the last reported symptom of the initial case confirmation was followed within a brief period (eg, a month or less) by a subsequent PCR-positive result and new report of associated symptoms.

Such instances are unlikely to represent separate illnesses. For participants meeting these criteria, all of the reported symptoms and PCR results were in early 2022 or later.

The reported signs and symptoms associated with the initial and the subsequent episodes generally reflected mild to moderate illness for the BNT162b2 and placebo cases, with none of the cases meeting any criteria for

severe illness. None of the participants with multiple episodes had serological and/or virological evidence of prior infection with SARS-CoV-2 at baseline.

Severe COVID-19 and MIS-C – Children 2 to <5 Years of Age

As of the data cutoff date (17 June 2022), 9 participants in the 2 to <5 years of age group had confirmed COVID-19 which met one or more of the severe case criteria, including 6 in the BNT162b2 group and 3 in the placebo group (taking into account 2:1 randomization).

As of the data cutoff date, no cases of MIS-C were reported in this age group.

Note, for all of the participants who met a single protocol defined criterion for severe illness, the symptoms were considered by the investigator as not clinically significant based on examination at the illness visit, vital signs being near normal limits, and contributing circumstances such as the child crying during examination. Note that protocol criteria were adapted from the FDA definition and designed to conservatively identify possible severe illness.

In the BNT162b2 group there were 6 cases that fulfilled severe criteria as summarized below.

Table 33. Characterization of COVID-19 Cases Assigned as Severe per FDA Criteria Among Children 2 to <5 Years of Age

Group	Age at Randomization	Timing[a]	Severity Criteria Met	Severity Range[c]	Meets CDC Criteria	Coinfection
BNT162b2	4 years	32 days	HR=132 bpm	>131	No	
BNT162b2	4 years	62 days	RR=32 breaths/min	>29	No	
BNT162b2	3 years	183 days[b]	RR=32 breaths/min	>29	No	
BNT162b2	3 years	208 days[b]	RR=32 breaths/min	>29	No	
BNT162b2	2 years	44 days	HR=150 bpm	>142	No	
BNT162b2	2 years	100 days	HR=150 bpm RR=40 breaths/min SpO_2=91% Hospitalization	>142 >38 ≤92%	Yes (Hospitalization)	Parainfluenza virus type 3
Placebo	2 years	40 days	SpO2=92%	≤92%	No	Human Rhinovirus/ Enterovirus
Placebo	4 years	92 days	HR=132 bpm	>131	No	Human Rhinovirus/ Enterovirus
Placebo[d]	2 years	162 days	SpO_2=88%	≤92%	No	

a. All cases occurred post-Dose 2.
b. COVID-19 illness was reported after the participant was unblinded.
c. Severity range was based on the participant's age at the time of the confirmed COVID-19 case.
d. Participant had evidence of prior infection with SARS-CoV-2 at Visit 1, determined by N-binding assay and NAAT.
Highlighted row (gray) presents the only case meeting >1 severity criteria including CDC criterion of hospitalization.

One case in the BNT162b2 group (identified as Omicron sublineage BA.2.3 infection) fulfilled multiple severe illness criteria including the CDC criterion of hospitalization, and notably involved parainfluenza coinfection and clinical assessment including fever, cough, shortness of breath, and wheezing requiring salbutamol administration and O_2 supplementation. All other cases met a single protocol-defined criterion for severe illness, with symptoms considered by the investigator as not clinically significant based on examination at the illness visit, vital signs near normal limits, and other contributing circumstances such as the child crying during examination.

Children 6 months to <2 years of age:

Disposition and Datasets Analyzed – 6 Months to <2 Years of Age

The Dose 1 all-available efficacy population of children 6 months to <2 years of age included 1444 participants in the BNT162b2 group and 718 participants in the placebo group (Table below), which reflects the 2:1 randomization. Populations of participants who received three doses of study intervention were

- Dose 3 all-available efficacy population: 487 BNT162b2 recipients and 237 placebo recipients
- Dose 3 evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection: 474 BNT162b2 recipients and 229 placebo recipients.
- Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection: 319 BNT162b2 recipients and 157 placebo recipients.

Exclusions from the Dose 3 evaluable efficacy population were primarily due to participants not receiving three vaccine doses prior to unblinding (66.3% of BNT162b2 group and 67.0% of placebo group).

Note that Dose 3 administration began on 31 January 2022 and the study was still actively enrolling at that time.

Table 34. Efficacy Populations – Phase 2/3 – 6 Months to <2 Years of Age

	Vaccine Group (as Randomized)		
	BNT162b2 (3 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	1444 (100.0)	718 (100.0)	2162 (100.0)
Dose 1 all-available efficacy population	1444 (100.0)	718 (100.0)	2162 (100.0)
Dose 3 all-available efficacy population	487 (33.7)	237 (33.0)	724 (33.5)
Participants excluded from Dose 3 all-available efficacy population	957 (66.3)	481 (67.0)	1438 (66.5)
Reason for exclusion[c]			
Did not receive 3 vaccinations prior to unblinding	957 (66.3)	481 (67.0)	1438 (66.5)
Evaluable efficacy (3-dose) population	474 (32.8)	229 (31.9)	703 (32.5)
Participants without evidence of infection prior to 7 days after Dose 3	319 (22.1)	157 (21.9)	476 (22.0)
Participants excluded from evaluable efficacy (3-dose) population	970 (67.2)	489 (68.1)	1459 (67.5)
Reason for exclusion[c]			
Did not receive all vaccinations as randomized prior to unblinding	957 (66.3)	481 (67.0)	1438 (66.5)
Did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	26 (1.8)	10 (1.4)	36 (1.7)
Did not receive Dose 3 within the predefined window (at least 60 days after Dose 2 for participants enrolled before protocol amendment 6 and 54-70 days for participants enrolled after protocol amendment 6)	2 (0.1)	4 (0.6)	6 (0.3)
Had other important protocol deviations on or prior to 7 days after Dose 3	12 (0.8)	3 (0.4)	15 (0.7)

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.

Demographics – 6 Months to <2 Years of Age

Demographic characteristics for participants 6 months to <2 years of age in the Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection were generally similar in BNT162b2 and placebo groups (Table below).

Most participants were White (75.2%) and the population included 2.7% Black or African American participants, 9.9% Asian participants, 11.8% multiracial participants, with other race subgroups comprising <1%. In total, 10.3% of participants were Hispanic/Latino. The population was balanced with regard to sex with 51.1% male and 48.9% female participants. Comorbidities present at baseline that increase the risk of severe COVID-19 disease were reported in similar proportions of participants in the BNT162b2 group (3.1%) and placebo group (3.8%).

Among participants in the Dose 3 evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection, 8.4% in the BNT162b2 group and 7.0% in the placebo group were baseline positive for prior SARS-CoV-2 infection. Other demographic characteristics were generally similar to the population without evidence of prior infection. The demographics of the Dose 1 all-available and Dose 3 all-available efficacy populations were also overall similar.

Table 35. Demographic Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <2 Years of Age – Evaluable Efficacy (3-Dose) Population

	Vaccine Group (as Randomized)		
	BNT162b2 (3 µg) (N[a]=319) n[b] (%)	Placebo (N[a]=157) n[b] (%)	Total (N[a]=476) n[b] (%)
Sex			
Male	165 (51.7)	78 (49.7)	243 (51.1)
Female	154 (48.3)	79 (50.3)	233 (48.9)
Race			
White	239 (74.9)	119 (75.8)	358 (75.2)
Black or African American	7 (2.2)	6 (3.8)	13 (2.7)
American Indian or Alaska Native	1 (0.3)	0	1 (0.2)
Asian	34 (10.7)	13 (8.3)	47 (9.9)
Multiracial	38 (11.9)	18 (11.5)	56 (11.8)
Not reported	0	1 (0.6)	1 (0.2)
Ethnicity			
Hispanic/Latino	38 (11.9)	11 (7.0)	49 (10.3)
Non-Hispanic/Non-Latino	281 (88.1)	146 (93.0)	427 (89.7)
Country			
Poland	10 (3.1)	2 (1.3)	12 (2.5)
USA	309 (96.9)	155 (98.7)	464 (97.5)
Age group (at vaccination)			
6 to <12 Months	87 (27.3)	45 (28.7)	132 (27.7)
12 to <18 Months	104 (32.6)	47 (29.9)	151 (31.7)
18 to <24 Months	128 (40.1)	65 (41.4)	193 (40.5)
Age at vaccination (months)			

Mean (SD)	15.3 (5.09)	15.2 (5.28)	15.3 (5.15)
Median	16.0	16.0	16.0
Min, max	(6, 23)	(6, 23)	(6, 23)
Comorbidities[c]			
Yes	10 (3.1)	6 (3.8)	16 (3.4)
No	309 (96.9)	151 (96.2)	460 (96.6)

Vaccine Efficacy from at Least 7 Days After Dose 3 to Cutoff Date – 6 Months to <2 Years of Age

Dose 3 All-Available Efficacy Population – Children 6 Months to <2 Years of Age

The observed VE from at least 7 days after Dose 3 among children 6 months to <2 years of age in the evaluable population without evidence of prior SARS-CoV-2 infection before or during the vaccination regimen was 75.8% (2-sided 95% CI: 9.7%, 94.7%) based on 4 cases in the BNT162b2 group and 8 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo). The observed VE in the evaluable population with or without evidence of prior SARS-CoV-2 infection before or during the vaccination regimen was 76.2% (2-sided 95% CI: 11.1%, 94.8%) based on 4 cases in the BNT162b2 group and 8 cases in the placebo group,

In the analysis by SARS-CoV-2 variant of concern in this population, the observed VE after Dose 3 was 83.9% against both of the most frequently identified Omicron sublineages (BA.2.12.1 and BA.2). Few cases were identified as BA.4 or BA.5, precluding reliable estimation of VE for these sublineages whether considered separately or combined.

When excluding participants who had evidence of coinfection with other respiratory pathogens the observed VE after Dose 3 was 79.3% (2-sided 95% CI: 9.2%, 96.5%) based on 3 cases in the BNT162b2 group and 7 cases in the placebo group (which excluded 1 case in the BNT162b2 group and 1 case in the placebo group that involved coinfections).

Relative Vaccine Efficacy of Three vs Two Doses – Children 6 Months to <2 Years of Age

The RVE of BNT162b2 3-µg against symptomatic COVID-19 based on 2 cases reported at least 7 days after Dose 3 (original BNT162b2 group) compared with 2 cases reported at least 7 days after Dose 2 (original placebo group who were unblinded to receive BNT162b2) during the period of 07 February 2022 to 29 April 2022 was 59.4% (2-sided 95% CI: -459.5%, 97.1%).

Vaccine Efficacy from Dose 1 to Cutoff Date – Children 6 Months to <2 Years of Age

Dose 1 All-Available Efficacy Population – Children 6 Months to <2 Years of Age

The observed VE from Dose 1 onwards in the Dose 1 all-available population of children 6 months to <2 years of age was 20.9% (2-sided 95% CI: -6.4%, 40.9%) based on 123 cases in the BNT162b2 group and 78 cases in the placebo group, adjusted for surveillance time (noting the 2:1 randomization of vaccine:placebo) (Table below).

Clear separation of the Kaplan-Meier curves for BNT162b2 and placebo groups is evident by approximately 5 months after the first dose which generally coincides with completion of the three-dose series for this age group.

When excluding participants who had evidence of coinfection with other respiratory pathogens the observed VE after Dose 1 was 15.8% (2-sided 95% CI: -19.4%, 40.2%) based on 94 cases in the

BNT162b2 group and 56 cases in the placebo group (which excluded 29 cases in the BNT162b2 group and 22 cases in the placebo group that involved coinfections).

Table 36. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <2 Years of Age – Dose 1 All- Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (3 µg) (N[a]=1444)		Placebo (N[a]=718)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	123	0.520 (1272)	78	0.261 (631)	20.9	(-6.4, 40.9)
Dose 1 to before Dose 2	20	0.076 (1272)	10	0.037 (631)	1.7	(-135.2, 56.1)
Dose 2 to <7 days after Dose 2	4	0.022 (1159)	6	0.011 (578)	66.9	(-39.6, 93.1)
≥7 Days after Dose 2 to before Dose 3	93	0.366 (1135)	54	0.185 (562)	12.9	(-24.1, 38.4)
Dose 3 to <7 days after Dose 3	2	0.007 (417)	0	0.004 (186)	UND	(NA, NA)
≥7 Days after Dose 3	4	0.049 (350)	8	0.024 (181)	75.6	(8.9, 94.6)

Abbreviations: NA = not applicable; UND = undefined; VE = vaccine efficacy.
N = number of participants in the specified group.
n1 = Number of participants meeting the endpoint definition.
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.
n2 = Number of participants at risk for the endpoint.
Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Signs and Symptoms of COVID-19 – Children 6 Months to <2 Years of Age

Confirmed cases occurring after Dose 1 among participants 6 months to <2 years of age had signs and symptoms consistent with mostly mild to moderate illness, similar in both groups (Table below). The most commonly reported were new or increased cough (69.7%) and fever (65.2%) from protocol-defined symptoms and including nasal congestion or runny nose (46.3%) from additional CDC-defined symptoms. Most participants in either group reported ≤3 concurrent signs or symptoms.

The reported signs and symptoms for each age subgroup (i.e., 6 to <12 months, 12 to <18 months, or 18 to <24 months of age) were generally similar.

Table 37. Signs and Symptoms for First COVID-19 Occurrence After Dose 1 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <2 Years of Age – Dose 1 All- Available Efficacy Population

	Vaccine Group (as Randomized)		
Signs and Symptoms	BNT162b2 (3 µg) (N[a]=123) n[b] (%)	Placebo (N[a]=78) n[b] (%)	Total (N[a]=201) n[b] (%)
Participants with specific signs and symptoms of COVID-19	123 (100.0)	78 (100.0)	201 (100.0)
Fever	80 (65.0)	51 (65.4)	131 (65.2)
New or increased cough	92 (74.8)	48 (61.5)	140 (69.7)
New or increased shortness of breath	1 (0.8)	0 (0.0)	1 (0.5)
Chills	0 (0.0)	1 (1.3)	1 (0.5)
New or increased muscle pain	2 (1.6)	1 (1.3)	3 (1.5)
Sore throat	8 (6.5)	3 (3.8)	11 (5.5)
Diarrhea	12 (9.8)	11 (14.1)	23 (11.4)
Vomiting	8 (6.5)	13 (16.7)	21 (10.4)
Inability to eat/poor feeding	14 (11.4)	9 (11.5)	23 (11.4)
Additional CDC-defined symptoms			
Fatigue	12 (9.8)	11 (14.1)	23 (11.4)
Headache	2 (1.6)	1 (1.3)	3 (1.5)
Nasal congestion or runny nose	57 (46.3)	36 (46.2)	93 (46.3)
Lethargy	2 (1.6)	2 (2.6)	4 (2.0)
Participants with specific number of signs and symptoms			
1	27 (22.0)	15 (19.2)	42 (20.9)
2	50 (40.7)	31 (39.7)	81 (40.3)
3	30 (24.4)	22 (28.2)	52 (25.9)
4	10 (8.1)	6 (7.7)	16 (8.0)
5	4 (3.3)	4 (5.1)	8 (4.0)
>5	2 (1.6)	0 (0.0)	2 (1.0)

N = number of participants with COVID-19 occurrence from 7 days after Dose 1 in the specified group. This value is used as the denominator for the percentage calculations.
n = Number of participants with the specific criteria meeting the definition. A participant can have more than 1 symptom

Participants with Multiple Episodes of COVID-19 During the Study – Children 6 Months to <2 Years of Age

As of the data cutoff date (17 June 2022), several participants in the 6 months to <2 years of age group had virologically and clinically confirmed multiple episodes of COVID-19. Narratives for these participants are available in Module 5.3.2.1.

- In the BNT162b2 group, 3 participants had multiple episodes of COVID-19; these cases occurred post-Dose 2 (and prior to Dose 3), with exception of one participant who had initial illness 180 days post-Dose 2 and subsequent illness 23 days post-Dose 3. Two participants had initial illness in Q4 2021 followed by subsequent illness in Q1 2022; the third participants had initial illness in Q1 2022 and subsequent illness after two months. All cases occurred during a period in which an Omicron surge had begun.
- In the placebo group, 3 participants had multiple episodes of COVID-19; one participant had both initial and several subsequent illnesses 3 days, 11 days, and 36 days post-Dose 1; one

participant had both initial and subsequent illnesses 21 days and 51 days post-Dose 2 (both prior to Dose 3); and the remaining participant had initial illness 18 day post-crossover Dose 1 of BNT162b2 3-µg and subsequent illness 7 days post-crossover Dose 2 of BNT162b2 3-µg.

Note, several participants had multiple PCR-positive results confirming COVID-19, for which the last reported symptom of the initial case confirmation was followed within a brief period (eg, a month or less) by a subsequent PCR-positive result and new report of associated symptoms. Such instances are unlikely to represent separate illnesses.

The reported signs and symptoms associated with the initial and the subsequent episodes generally reflected mild to moderate illness for the BNT162b2 and placebo cases, with none of the cases meeting any criteria for severe illness. None of the participants with multiple episodes had serological and/or virological evidence at baseline of prior infection with SARS-CoV-2.

Severe COVID-19 and MIS-C – Children 6 Months to <2 Years of Age

As of the data cutoff date (17 June 2022), 3 participants in the 6 months to <2 years of age group had COVID-19. Criteria for severe illness were fulfilled for 2 cases (both occurring post-Dose 2) in the BNT162b2 group and 1 case (occurring post-Dose 3) in the placebo group (taking into account 2:1 randomization), among them one case in the BNT162b2 group reported after the participant was unblinded which could have introduced potential bias (Table below). No participants with cases meeting severe criteria had evidence of prior infection with SARS-CoV-2.

One case in the BNT162b2 group (identified as Omicron sublineage BA.2.12.1 infection) fulfilled multiple severe illness criteria including CDC criteria of hospitalization and admission to the ICU, and notably involved parainfluenza coinfection and clinical assessment including wheezing, cough, fatigue, and fever. The remaining two cases (1 each in the BNT162b3 and placebo groups) fulfilled a single criterion of increased heart rate and were reported post-Dose 2. For these participants who met a single protocol-defined criterion for severe illness, symptoms were considered by the investigator as not clinically significant based on examination at the illness visit, vital signs near normal limits, and other contributing circumstances such as the child crying during examination.

Table 38. Characterization of COVID-19 cases assigned as severe per FDA criteria among children 6m to <2yo

Group	Age at Randomization	Timing	Severity Criteria Met	Severity Range[c]	Meets CDC Criteria	Coinfection
BNT162b2	21 months	293 days[a]	HR=152 bpm	>149	No	
BNT162b2	21 months	33 days	Hospitalized, admitted to ICU		Yes (Hospitalization, ICU)	Parainfluenza virus type 3
Placebo	14 months	44 days[b]	HR=172 bpm	>156	No	Human Rhinovirus/ Enterovirus

a. COVID-19 illness was reported after the participant was unblinded.
b. Case occurred post-Dose 3.
c. Severity range (Table 3) was based on the participant's age at the time of the confirmed COVID-19 case.
Highlighted row (gray) presents the only case meeting CDC criteria of hospitalization and ICU admission.

As of the data cutoff date, no cases of MIS-C were reported in this age group.

- **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 39. Children 6 months to <5 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

Study identifier	C4591007		
Design	Phase 1/2/3 randomized, observer-blind, placebo-controlled		
	Follow-up for efficacy		31.08. 2020- 29.04.2021 (immunogenicity) and 07.02.2022- 29.04.2022 (efficacy)
Hypothesis	immunobridging of antibody response younger vs. older age group (non-inferiority). Descriptive efficacy analysis		
Treatments groups	Active arm		BNT162b2 (3 µg), 3 doses, 21 days apart dose 1 and 2, and 8 weeks apart dose 2 and 3 Randomized, age groups 6m-<2y and 2y-<5y
	Control arm		Saline placebo, 3 doses, 21 days apart dose 1 and 2, and 8 weeks apart dose 2 and 3 randomized, age groups 6m-<2y and 2y-<5y
	Control arm C4591001		BNT162b2 (30 µg), 2 doses, 21 days apart, Randomized, age group 16-25
Endpoints and definitions	Immunogenicity endpoint	GMT	geometric mean titers (GMTs) at 1 month after Dose 3
	Immunogenicity endpoint	GMR	geometric mean ratio (GMR) of titers (GMTs) at 1 month after Dose 3 children vs. young adults. **Immunobridging** success was declared if the lower bound of the CI was >0.67 and GMR point estimate was ≥0.8
	Immunogenicity endpoint	Sero response rate	percentage of participants with a ≥4-fold rise in neutralizing titers from before vaccination to 1 month after Dose 3 (seroresponse rate). **Immunobridging** success was declared if the lower limit of the CI for difference in seroresponse rate was greater than -10% and provided that the GMR success criteria had been met.

	Efficacy endpoint	VE-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 3 or from Dose 1 to the data cutoff date
	Efficacy endpoint	RVE 3 doses vs 2 dose	COVID-19 incidence per 1000 person-years of follow- up in participants receiving 3 doses or 2 doses, cases confirmed ≥7 days after
Database lock	29.04.2022		

Results and Analysis

Analysis description	**Immunogenicity Analysis**			
Analysis population and time point description	1 month after dose 3 Evaluable Immunogenicity population			
Effect estimate per comparison	**Treatment group**	**2-<5 yo 3 µg 3 doses**	**16-25 yo 30 µg 2 doses**	
	Number of subject	143	170	ratio, immunobridging (Y/N)
	GMT (95% CI)	1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	GMR 1.3 (1.13, 1.5) Y
	Number of subject	141	170	% difference, immunobridging (Y/N)
	Seroresponse rate % (95% CI)	141 (100 %) (97.4, 100%)	168 (98.8 %) (95.8; 99.9%)	1.2% (-1.5, 4.2) Y
	Treatment group	**6m-<2 yo 3 µg**	**16-25 yo 30 µg**	Ratio, non-inferiority (Y/N)
	Number of subject	82	170	ratio, immunobridging (Y/N)
	GMT (95% CI)	1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	GMR 1.19 (1.00, 1.42) Y
	Number of subject	80	170	% difference, immunobridging (Y/N)

	Seroresponse rate % (95% CI)	80 (100 %) (95.5, 100%)	168 (98.8 %) (95.8; 99.9%)	1.2% (-3.4, 4.2) Y
Analysis description	**Efficacy Analysis**			
Effect estimate per comparison	Age group 6m-<5y	VE-7d-no-SARS- CoV-2 Evaluable Efficacy population	Cases in Active arm N=3/992 Cases in Placebo arm N= 7/464	
		Vaccine Efficacy VE %	80.3 %	
		95% CI	(13.9, 96.7)	
		RVE 3 doses vs 2 doses 7.02-29.04.2022	Cases in Original arm N=4/1212 Cases in Placebo cross over arm N= 6/516	
		Relative Vaccine Efficacy RVE %	76.2 %	
		95% CI	(-0.5, 95.1)	
Notes	7 participants in the 2 to <5 years of age group had confirmed severe COVID-19, including 6 in the BNT162b2 group and 1 in the placebo group. 1 participant in the 6 months to <2 years of age group, a placebo recipient, had confirmed severe COVID-19. No cases of MIS-C were reported.			

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

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 3 µg for the 6 months -<5 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 6m to <2 years old and 2 to <5 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 (EMA/H/C/005735/II/0030) and for 5 to <12 years old (EMA/H/C/005735/X/077). The reason to divide 6m-<5 year old group into younger (6m-<2 year) and older (2-<5 year old) age groups based on assumption that immunogenicity and safety of 3 µg BNT162b2 may differ even in rather narrow age range due to the developmental status of the young children.

Preliminary, immunogenicity of 2 doses of 3 µg BNT162b2 in 6m to <2 years old and 2 to <5 years of age group was compared to 2 doses of 30 µg BNT162b2 in 16 to 25 years old. The immunobridging exercise

failed for 2 to < 5 years old groups as the GMR was lower than in young adults. Therefore, MAH after consulting with EMA continued the study with comparison of 3 doses of 3 µg BNT162b2 in 6m to <2 years old and 2 to <5 years of age group as primary series compared to 2 doses of 30 µg BNT162b2 in 16 to 25 years old.

The design of the immunobridging exercise is endorsed and the use of the historical controls (16-25 yo) from study C4591001 are acceptable as these serology samples were analysed side by side with samples from 6m to <2 and 2 to <5 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 6m to <2 years of age included 82 participants in the BNT162b2 group and 49 participants in the placebo group, and for 2-<5 years old group included 143 participants in the BNT162b2 group and 59 participants in the placebo group. Study C4591001 participants 16 to 25 years of age included 170 participants in the BNT162b2 group and 38 participants in the placebo group.

According to the study protocol, approximately 250 participants (200 in the active vaccine group and 50 in the placebo group) were planned to be randomized in each younger age group (≥6 months to <2 years and ≥2 to <5 years of age). These numbers in the sample size calculation are inconsistent with the actual number of patients in the analysis. It instead seems that this part of the study was powered for immunogenicity comparison between *entire* age group of children from 6m to <5 year as altogether there was 225 subjects in entire active arm. The sample size (N=82) in active arm among younger age group is considerably smaller than in older group (N=143), but large enough for immunogenicity evaluation. The immunogenicity analyses for entire active arm of 6m-<5 year old (N= 225) vs. control arm of 16-25 yo (N=170) was not presented, but were requested at the primary round. Updated data were submitted by MAH.

The MAH also submitted supportive immunogenicity data for SARS-CoV-2 serum neutralizing titers against USA-WA1/2020 (reference), B.1.617.2 (Delta) and Omicron BA.1 variant strains. Cohorts were limited in size: 40 participants (34 in active and 4 in placebo arm) in 2 to <5 year old and 37 (32 in active and 5 in placebo arm) in 6m-<2 year old and 40 (only active arm) in 16-26 year old age groups. The sample size in this supportive analysis was small and the neutralization assay not yet validated, therefore these data are considered supportive, but important in light of the Delta and Omicron BA1 variant epidemiology. Also, additional descriptive immunogenicity analysis of neutralizing titers was conducted, to compare children with adults who received a third dose of BNT162b2 at a similar interval between Dose 2 and Dose 3.

A supportive vaccine efficacy analysis was planned to be evaluated for the combination of ≥6 months to <2 years and ≥2 to <5 years of age if immunobridging is successful, depending on accrual of a sufficient number of cases in those age groups. According to SAP, sufficient number was 21 cases from 7 days after Dose 3. In reality, for the analysis at the cut-off 29.04.2022, there were only 10 cases in study population. The statistical methods for calculating Vaccine Efficacy are considered appropriate. The efficacy analysis was based on confirmed cases among the initially enrolled N~1500 participants in the 6 months to <5 year years of age group of Study C4591007. The MAH submitted updated VE data from cut-off 17.06.2022. The MAH stated that this efficacy analysis was conducted in accordance with the C4591007 protocol-specified and hypothesis-testing secondary efficacy objective, which was to evaluate vaccine efficacy (VE) when at least 21 confirmed COVID-19 cases had accrued among the combined population of children 2 to <5 years and 6 months to <2 years of age following completion of the three-dose vaccination series. The Committee did not agree totally here with the MAH and was asked to discuss the statistical analysis plan as well as the study conduct, including the peek before the accrual of 21 cases, and justify that the VE data presently proposed

for the SmPC are type 1 error controlled. The company clarified that the first submitted analysis was descriptive and that the descriptive nature of this analysis was documented in the SAP. As a consequence, this analysis does not affect the type I error control of the hypothesis testing of the second VE analysis. The second VE analysis is therefore considered to have type I error control.

Among randomized participants, 992 participants were included in the BNT162b2 group and 464 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 appears to have been performed before the pre-defined number of cases had been accrued, but at the same cut-off date 19.04.2022 as primary immunogenicity analysis was done. As the presented data were preliminary, the final report with final analysis is requested and will be submitted when available.

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 however unlikely to impact immunogenicity or efficacy conclusions.

Assessment of paediatric data on immunogenicity and clinical efficacy

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the GMR of SARS-CoV-2 50% neutralizing titers in children 2 to <5 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.30 (2-sided 95% CI: 1.13, 1.50). GMR in children 6 months to <2 years of age compared to young adults was 1.19 (2-sided 95% CI: 1.00, 1.42). The post-hoc immunogenicity analysis for entire age group showed very similar result, as expected. GMR in children 6 months to <5 years of age compared to young adults was 1.26 (2-sided 95% CI: 1.11, 1.43).

As the lower bound of the 2-sided 95% CI for GMR was >0.67 and the GMR point estimate was >0.8 (protocol specified criterion) and >1.0 (requested by FDA), indicating the prespecified immunobridging success criterion for the GMR was met for both age groups 6 months to <2 years and 2 to <5 years old. Both of the age groups fulfilled the immunobridging criterion despite of the lower sample size than initially planned. No immunobridging results were presented for entire 6 months to <5-year-old cohort compared to the young adults. The Committee thought that this data would be suitable to be presented in SmPC instead of separate chapter for younger and older age group as it saves space and would be easier for the prescriber to gasp. Therefore, it was requested. The MAH clarified that the protocol-specified hypothesis for immunobridging was separate for the age groups 6 months to <2 years and 2 to <5 years. The results were therefore presented separately in the CSR and resulting manuscripts.

Almost equal proportions (100 % each of children 2- <5 years of age and 6m-<2 yo and 99% 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 1.2% (2-sided 95% CI: -1.5%, 4.2% for 2- <5 yo and -3.4%, 4.2% for 6m-<2 yo). The lower limit of the 95% CI for the difference in seroresponse rate were -1.5% and -3.4%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved. The post-hoc analysis showed the difference of the seroresponse rate in children 6 months to <5 years of age compared to young adults was 1.2% (2-sided 95% CI: -0.5%, 4.2%).

As immunobridging was successful, the MAH continued with VE analysis. Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for BNT162b2 3 µg against any confirmed COVID-19 from at least 7 days after Dose 3 was 80.3% (2-sided 95% CI: 13.9%,

96.7%) which included 3 cases in the BNT162b2 group and 7 cases in the placebo group. All these post-Dose 3 cases were reported in February through April 2022, when Omicron BA1. was most prevalent circulating strain in USA.

Relative Vaccine Efficacy (RVE) of three vs two doses of BNT162b2 3-µg against symptomatic COVID-19 based on 4 cases reported at least 7 days after Dose 3 (original BNT162b2 group who received three doses) compared with 6 cases reported at least 7 days after Dose 2 (original placebo group who were unblinded and received two doses of BNT162b2) during the period of 07 February 2022 to 29 April 2022 was 76.2% (2-sided 95% CI: -0.5%, 95.1%). It indicates that third dose may have a positive impact compared to only two doses.

As a response to the preliminary list of questions, the MAH submitted an updated VE analysis with cut-off date 17.06.2022. The median follow-up time for entire cohort, from 6 months to <5 year old children was 2.2 months. Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for BNT162b2 3 µg against any confirmed COVID-19 from at least 7 days after Dose 3 was 73.2% (2-sided 95% CI: 43.8%, 87.6%) which included 13 cases in the BNT162b2 group (N=873) and 21 cases in the placebo group (N=381). Similar VE was shown for both younger (6m-<2y) and older (2y-<5y) age groups and also for population with and without previous COVID-19 and for all- available efficacy population. All cases, expect one which was undefined, were caused by Omicron strain. The most common were Omicron BA.2 and Omicron BA.2.12.1.

For COVID-19 cases confirmed from Dose 1 onwards in the Dose 1 all-available (mITT) population, the observed VE for BNT162b2 3 µg for 2 to < 5 year-old was 32.6% (2-sided 95% CI: 10.8, 48.8%) based on 127 cases in the BNT162b2 group (N=1835) and 92 cases in the placebo group (N= 915). In 6 months to <2-year age group, VE from Dose 1 onwards was 14.0 % (2-sided 95% CI: -21.2, 38.4%) based on 98 cases in the BNT162b2 group (N=1178) and 58 cases in the placebo group (N= 598). As stated above, these analyses for entire 6 months to <5 years population was not presented at the submission, and it was requested. The updated analysis with cut-off 17.06.2022 showed VE for BNT162b2 3-µg against any confirmed COVID-19 from Dose 1 onwards in the Dose 1 all-available population for children 6 months to <5 years of age was 27.9% (2-sided 95% CI: 13.3%, 40.0%) based on 292 cases in the BNT162b2 group and 199 cases in the placebo group, adjusted for surveillance time. Very similar VE was observed also, when the children with respiratory coinfections were excluded from the analysis.

There were 8 severe cases of COVID-19 in age group 6m-<5-year-old in active arm after 2-doses, whereas in placebo arm 4 severe case appeared (according to FDA definition). Notably, none of the cases showed clinical signs that would suggest VAERD.

No MIS-C were reported in the 6 months to <5 years of age group, per protocol definition or per CDC definition.

Overall, BNT162b2 administered as a primary series of three doses of 3 µg given 3 weeks apart of first and second dose and at least 8 weeks apart of second and third dose for children 6 months to <5 years of age is protective against symptomatic COVID-19. The efficacy against symptomatic COVID-19 was demonstrated in the age group 6 months to <5 years. The effect size was smaller to that seen in adults preliminary due to the changed epidemiological situation (Omicron BA1. Strain prevalence). As the study is still ongoing the MAH is requested to submit the final results of the study when available. Since the submission of this application to extend the indication for Comirnaty to children 6 months to <5 years of age, updated efficacy analyses became available. Efficacy data presented in the SmPC were updated accordingly. In addition, according to the study protocol, updated efficacy analysis at the end of the blinded follow-up period is planned. The MAH

should provide complete safety and persistence-of-immunogenicity analysis after complete data are available in each age group or at the end of the study. Interim analysis, 6 months post dose 3 immunogenicity and safety data will be presented. The final report for the supportive vaccine efficacy analysis should be also submitted by the MAH when ready. The study duration for each individual is expected to be approximately 21 months.

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 duration of protection conveyed by the vaccine is unknown.

The study was conducted under Omicron wave. Majority of the confirmed cases were BA2. And BA 2.12.1. The VE against other Sars-Cov-2 virus variants is unknown.

2.5.4. Conclusions on the clinical efficacy

The immunobridging results demonstrate that 3 doses of 3 µg BNT162b2 given to children 6 months to -< 2 yo and 2-<5 years of age resulted in very similar neutralising antibody responses (GMTs, GMR, GMFR and seroresponses) compared to the efficacy population; that is, 16-25 year old subjects receiving 2 doses of 30 µg BNT162b2. Thus, efficacy may be inferred based on immunobridging. This is supported by a descriptive clinical efficacy data.

The CHMP considers the following measure necessary to address issues related to efficacy:

New REC: According to the study protocol of study C4591007, updated efficacy analysis at the end of the blinded follow-up period is planned. The MAH should provide complete safety and persistence-of-immunogenicity analysis after complete data are available in each age group or at the end of the study. Interim analysis, 6 months post dose 3 immunogenicity and safety data will be presented. The final report for the supportive vaccine efficacy analysis should be also submitted by the MAH when ready.

2.5.5. Clinical safety

Study C4591007 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 pediatric study in healthy children and young adults aged 6 months to <12 years. For these pediatric groups, the study was designed to evaluate BNT162b2 vaccination in an age de-escalation Phase 1 dose finding part and Phase 2/3 selected dose part, in protocol defined age groups: 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age. Initiation of the study with the oldest pediatric group (5 to <12 years of age) was based on acceptable safety and tolerability demonstrated in adolescents in Study C4591001. The series of BNT162b2 was initially planned as a two-dose series; however, based on emerging clinical and real-world data, the protocol was amended to add a third dose at the selected dose level for each age group.

This report summarizes interim data for participants in the 2 to <5 years and 6 months to <2 years of age groups comprised of Phase 1 dose-finding safety and immunogenicity analysis results, and Phase 2/3 selected-dose results including the primary safety objective and select secondary and exploratory immunogenicity and efficacy objectives.

Safety analyses were conducted on the safety population. Phase 1 data are based on analyses up to 1 month after Dose 2. Phase 2/3 data are based on analyses up to 1 month after Dose 3 and up to the data cutoff date of 29 April 2022. Reactogenicity and antipyretic/pain medication use were recorded daily for 7 days after

each dose administration using prompts from an electronic diary (e-diary). This allowed recording only within a fixed time window to provide an accurate representation of the participant's experience. Grading scales were based on FDA guidance.18 Events included:

Children 2 to <5 years of age:

- Local reactions: pain, redness, and swelling at the injection site
- Systemic events: fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain

Children 6 months to <2 years of age:

- Local reactions: tenderness, redness, and swelling at the injection site
- Systemic events: fever, decreased appetite, drowsiness, and irritability

Unsolicited adverse events (AEs) were collected from Dose 1 through 1 month after Dose 2 and from Dose 3 through 1 month after Dose 3, and serious AEs (SAEs) were collected from Dose 1 through 6 months after Dose 3. Deaths are recorded to the end of study.

AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention (per investigator assessment) using system organ class (SOC) and preferred term (PT) according to MedDRA. AEs were also categorized as Tier 1 (prespecified events of clinical importance; none designated at this time) and Tier 2 ('common' PTs, reported in ≥1% of participants in any vaccine group).

Myocarditis and pericarditis are designated in the C4591007 protocol as AEs of special interest (AESIs). For other events of specific clinical interest, the MAH evaluates a dynamic list of MedDRA AE terms during clinical safety data review and signal detection; these include events of interest due to association with COVID-19 and vaccines in general, taking into consideration the CDC list of AESIs for COVID-19 that include events potentially indicative of severe COVID-19 or autoimmune and neuroinflammatory disorders. Evidence of SARS-CoV-2 infection at baseline was determined by serological testing (N-binding assay) and virological testing (NAAT) on anterior nares swab at Dose 1 visit (baseline) and medical history of COVID-19.

Safety narratives were prepared for participants in cases of death, vaccine-related SAEs, safety-related withdrawals, and AEs of clinical interest including those requested by FDA.

Safety data were reported as descriptive summary statistics including counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% confidence intervals (CIs). Incidence rates per 1000 person-years are provided for safety data up to the data cutoff date to adjust for surveillance time. Missing reactogenicity e-diary data were not imputed.

2.5.5.1. Patient exposure

Phase 1

Disposition

A total of 49 participants in the **2 to <5 years of age** group were assigned into dose level groups (in a 1:1 ratio) to receive 3-µg or 10-µg BNT162b2. Of these, 48/49 were vaccinated and received both doses of BNT162b2 (N=32 in 10-µg group and N=16 in 3-µg group) and were in the safety population. For participants 2 to <5 years of age, almost all were administered study intervention as assigned. Overall, 48 (98.0%) of participants received Dose 1 and Dose 2. Most participants received Dose 2 between 19 to 23 days after Dose 1 in the 3-µg and 10-µg dose level groups (93.8% and 97.0%, respectively).

A total of 16 participants in the **6 months to <2 years** of age group were assigned to receive 3 µg BNT162b2. Of these, 16/16 were vaccinated and received both doses of BNT162b2 and were in the safety population. For participants 6 months to <2 years of age, all were administered study intervention as assigned. Overall, 16 (100.0%) of participants received Dose 1 and Dose 2. All participants received Dose 2 between 19 to 23 days after Dose 1 (100.0%).

No important protocol deviations occurred, and no participants were withdrawn from the Phase 1 part of the study.

Demographics

Most participants **2 to <5 years** of age were White (79.2%), the median age was 3.0 years and 58.3% of participants were male. Most **6 months to <2 years** of age were White (87.5%), the median age was 15.5 months and 62.5% of participants were male.

Participants in the safety population had a medical history profile consistent with that of individuals in the general population in the same age group. There were no participants with a history of any cardiac disorder. No participants received concomitant vaccines after Dose 1.

Phase 2/3 –2 to <5 years of age

Disposition of participants

Most participants 2 to <5 years of age randomized to either group (>99%) received two doses, and 32.2% received the third dose of study intervention prior to unblinding, as of the data cutoff date (29 April 2022). The safety population constitutes of 2750 phase 2/3 participants e BNT162b2 (N=1835) and placebo (N=915) groups. No participants in the safety population were excluded from the study. No participants included in the safety population were HIV+.

Few participants, who were all in the placebo group, discontinued from the vaccination period due to AEs. Few participants were withdrawn from the study (1.6%). The most common reason was due to withdrawal by parent/guardian.

Among participants originally randomized to the BNT162b2 group, unblinding (per protocol, at 6-months post-Dose 2 or when turning 5 years of age) occurred for 1 child (0.1%) who received open-label Dose 2 and for 435 children (51.7%) who received open-label Dose 3.

Among participants originally randomized to the placebo group, unblinding during the vaccination period occurred for 370 children (87.3%) who received the first, 350 children (82.5%) who received the second dose, and for 98 children (23.1%) who received a third dose of open-label BNT162b2.

Few participants (5.0%) from the original placebo group reached the 1-month post-Dose 3 visit after unblinding and initiating the series of BNT162b2. For this age group, BNT162b2 administered after unblinding was at the age-appropriate dose level at the time of vaccination (3-µg if <5 years of age, 10-µg if 5 years of age); see below regarding children who turned 5 years and received the higher dose. Data from participants who were unblinded are included in safety endpoint analyses up to the point at which they were unblinded. Safety endpoint analyses are focused on blinded placebo-controlled follow-up. Separate analyses that include safety data obtained after participant unblinding are additionally provided for reactogenicity and AEs.

Table 40. Disposition of al randomized participants prior to unblinding -phase 2/3 2 to <5 yo

	Vaccine Group (as Randomized)		
	BNT162b2 (3 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	1835 (100.0)	915 (100.0)	2750 (100.0)
Not vaccinated	0	0	0
Vaccinated	1835 (100.0)	915 (100.0)	2750 (100.0)
Dose 1	1835 (100.0)	915 (100.0)	2750 (100.0)
Dose 2	1819 (99.1)	907 (99.1)	2726 (99.1)
Dose 3	606 (33.0)	280 (30.6)	886 (32.2)
Completed 1-month post–Dose 2 visit (vaccination period)	1814 (98.9)	907 (99.1)	2721 (98.9)
Completed 1-month post–Dose 3 visit (vaccination period)	503 (27.4)	274 (29.9)	777 (28.3)
Discontinued from vaccination period but continued in the study	0	3 (0.3)	3 (0.1)
Discontinued after Dose 1 and before Dose 2	0	2 (0.2)	2 (0.1)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	1 (0.1)	1 (0.0)
Discontinued after Dose 3 and before 1-month post–Dose 3 visit	0	0	0
Reason for discontinuation from vaccination period			
Adverse event	0	1 (0.1)	1 (0.0)
Withdrawal by participant	0	1 (0.1)	1 (0.0)
Other	0	1 (0.1)	1 (0.0)
Withdrawn from study	24 (1.3)	21 (2.3)	45 (1.6)
Withdrawn after Dose 1 and before Dose 2	6 (0.3)	4 (0.4)	10 (0.4)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	0	0	0
Withdrawn on or after 1-month post–Dose 2 visit and before Dose 3	14 (0.8)	16 (1.7)	30 (1.1)
Withdrawn after Dose 3 and before 1-month post–Dose 3 visit	2 (0.1)	1 (0.1)	3 (0.1)
Withdrawn on or after 1-month post–Dose 3 visit	2 (0.1)	0	2 (0.1)
Reason for withdrawal from study			
Adverse event	1 (0.1)	0	1 (0.0)
Lost to follow-up	4 (0.2)	3 (0.3)	7 (0.3)
Protocol deviation	2 (0.1)	3 (0.3)	5 (0.2)
Withdrawal by participant	4 (0.2)	2 (0.2)	6 (0.2)
Withdrawal by parent/guardian	13 (0.7)	13 (1.4)	26 (0.9)

a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.

Important protocol deviations

Important protocol deviations were reported for 41 participants (2.2%) in the BNT162b2 group and 16 participants (1.7%) in the placebo group. Most protocol deviations in the BNT162b2 group were related to investigational product (23 [1.3%] compared with 9 [1.0%] in the placebo group), which included dosing errors, vaccination delay criteria related to non-study vaccine administration, or being deemed unsuitable for use (as BNT162b2 must be thawed/diluted prior to administration, whereas saline placebo does not).

Duration of follow-up

The median duration of blinded follow-up for after Dose 3 was 1.4 months (range: 0.0 to 3.2 months) (Table below).

Table 41. Follow up time after dose 2 or dose 3-phase 2/3 2 to <5yo-Safety population

	Vaccine Group (as Administered)		
	BNT162b2 (3 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Original blinded placebo-controlled follow-up period			
Time from Dose 2 to Dose 3 or cutoff date			
N[b]	1819	907	2726
<1 Month	162 (8.9)	75 (8.3)	237 (8.7)
≥1 -<2 Months	116 (6.4)	67 (7.4)	183 (6.7)
≥2 -<3 Months	427 (23.5)	203 (22.4)	630 (23.1)
≥3 -<4 Months	204 (11.2)	103 (11.4)	307 (11.3)
≥4 -<5 Months	158 (8.7)	79 (8.7)	237 (8.7)
≥5 -<6 Months	78 (4.3)	41 (4.5)	119 (4.4)
≥6 -<7 Months	655 (36.0)	329 (36.3)	984 (36.1)
≥7 -<8 Months	12 (0.7)	7 (0.8)	19 (0.7)
≥8 -<9 Months	4 (0.2)	3 (0.3)	7 (0.3)
≥9 -<10 Months	1 (0.1)	0	1 (0.0)
≥10 Months	2 (0.1)	0	2 (0.1)
Mean (SD)	4.1 (2.07)	4.1 (2.06)	4.1 (2.07)
Median	4.0	4.0	4.0
Min, max	(0.0, 10.4)	(0.3, 8.8)	(0.0, 10.4)
Time from Dose 3 to cutoff date			
N[c]	606	280	886
<1 Month	143 (23.6)	64 (22.9)	207 (23.4)
≥1-<2 Months	252 (41.6)	117 (41.8)	369 (41.6)
≥2-<3 Months	115 (19.0)	62 (22.1)	177 (20.0)
≥3 Months	96 (15.8)	37 (13.2)	133 (15.0)
Mean (SD)	1.7 (0.95)	1.7 (0.95)	1.7 (0.95)
Median	1.4	1.6	1.4
Min, max	(0.0, 3.2)	(0.0, 3.2)	(0.0, 3.2)
Blinded and open-label period			
Time from Dose 2 to Dose 3 or cutoff date			
N[b]	1820	907	2727
<1 Month	157 (8.6)	74 (8.2)	231 (8.5)
≥1 -<2 Months	112 (6.2)	67 (7.4)	179 (6.6)
≥2 -<3 Months	410 (22.5)	198 (21.8)	608 (22.3)
≥3 -<4 Months	167 (9.2)	102 (11.2)	269 (9.9)
≥4 -<5 Months	129 (7.1)	82 (9.0)	211 (7.7)
≥5 -<6 Months	61 (3.4)	43 (4.7)	104 (3.8)
≥6 -<7 Months	256 (14.1)	285 (31.4)	541 (19.8)
≥7 -<8 Months	175 (9.6)	35 (3.9)	210 (7.7)

≥8 -<9 Months	205 (11.3)	17 (1.9)	222 (8.1)
≥9 -<10 Months	56 (3.1)	2 (0.2)	58 (2.1)
≥10 Months	92 (5.1)	2 (0.2)	94 (3.4)
Mean (SD)	4.9 (2.92)	4.2 (2.20)	4.7 (2.72)
Median	4.4	4.1	4.3
Min, max	(0.0, 10.4)	(0.3, 10.4)	(0.0, 10.4)
Time from Dose 3 to cutoff date			
N[c]	1041	280	1321
<1 Month	173 (16.6)	63 (22.5)	236 (17.9)
≥1-<2 Months	272 (26.1)	113 (40.4)	385 (29.1)
≥2-<3 Months	470 (45.1)	66 (23.6)	536 (40.6)
≥3 Months	126 (12.1)	38 (13.6)	164 (12.4)
Mean (SD)	2.0 (0.87)	1.7 (0.95)	1.9 (0.90)
Median	2.2	1.6	2.1
Min, max	(0.0, 3.2)	(0.0, 3.2)	(0.0, 3.2)

Note: "Original blinded placebo-controlled follow-up period" is defined as period from the first dose of study vaccination to before the participant was unblinded. If the unblinding date is missing, consider the cutoff date as the period end date.

"Blinded and open-label period" is defined as the period from the first dose of study vaccination to the cutoff date (original BNT162b2 group) or before the first dose of open-label BNT162b2 (original placebo group).

If the date of open-label BNT162b2 is missing for original placebo group, consider the cutoff date as the period end date.

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

b. N = number of participants who received Dose 2 in the specified group, or the total sample. These values are the denominators for the percentage and summary statistics calculations.

c. N = number of participants who received Dose 3 in the specified group, or the total sample. These values are the denominators for the percentage and summary statistics calculations.

Vaccine administration and timing

Data on vaccine administration and timing in phase 2/3, children 2 to <5 Years of Age as of the data cutoff date (29 April 2022) are presented in the table below.

All participants in the original placebo group received Dose 1 of placebo as randomized, and 99.1% and 30.6% received Dose 2 and Dose 3, respectively, during blinded follow-up. After unblinding (per protocol) to receive active vaccination with BNT162b2, 305 children (33.3%) received a first active dose of BNT162b2 at the 3-µg dose level and 65 (7.1%) received the 10-µg dose level.

Table 42. Vaccine as administered- phase 2/3 2 to <5yo-all randomized participants

Vaccine (as Administered)	Vaccine Group (as Randomized) BNT162b2 (3 µg) (N[a]=1835) n[b] (%)	Placebo (N[a]=915) n[b] (%)
Original placebo-controlled period		
Vaccinated	1835 (100.0)	915 (100.0)
Dose 1		
BNT162b2 (3 µg)	1835 (100.0)	0
Placebo	0	915 (100.0)
Dose 2[c]		
BNT162b2 (3 µg)	1819 (99.1)	0
BNT162b2 (10 µg)	1 (0.1)	0
Placebo	0	907 (99.1)
Dose 3		
BNT162b2 (3 µg)	920 (50.1)	0
BNT162b2 (10 µg)	121 (6.6)	0
Placebo	0	280 (30.6)
Open-label BNT162b2 vaccination for original placebo recipients		
First crossover dose		
BNT162b2 (3 µg)		305 (33.3)
BNT162b2 (10 µg)		65 (7.1)
Second crossover dose		
BNT162b2 (3 µg)		284 (31.0)
BNT162b2 (10 µg)		66 (7.2)
Third crossover dose		
BNT162b2 (3 µg)		89 (9.7)
BNT162b2 (10 µg)		9 (1.0)

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. Participants who turned 5 years of age received the age appropriate dose of BNT162b2 10 µg.

Demographic and other baseline characteristics

Demographic characteristics for phase 2/3 pediatric participants 2 to <5 years of age were similar in BNT162b2 and placebo groups in the safety population (Table below).

Comorbidities present at baseline that increase the risk of severe COVID-19 disease19 (excluding obesity) were present in similar proportions of participants in the BNT162b2 group (6.4%) and placebo group (9.7%). The most common baseline comorbidities (BNT162b2 vs placebo) were:

- Asthma (2.8% vs 4.7%)
- Disabilities (0.9% vs 1.4%)
- Premature birth (1.1% vs 1.0%)

One participant who was in the BNT162b2 group had an immunocompromised condition reported at baseline (neutropenia). Demographics of participants in the original placebo group who were unblinded to receive active vaccination with BNT162b2 were generally similar to those of the blinded vaccine groups.

Table 43. Demographic characteristics -phase 2/3- 2 to <5yo-Safety population

	Vaccine Group (as Administered)		
	BNT162b2 (3 µg) (N[a]=1835) n[b] (%)	Placebo (N[a]=915) n[b] (%)	Total (N[a]=2750) n[b] (%)
Sex			
Male	901 (49.1)	471 (51.5)	1372 (49.9)
Female	934 (50.9)	444 (48.5)	1378 (50.1)
Race			
White	1469 (80.1)	720 (78.7)	2189 (79.6)
Black or African American	94 (5.1)	41 (4.5)	135 (4.9)
American Indian or Alaska Native	3 (0.2)	4 (0.4)	7 (0.3)
Asian	127 (6.9)	76 (8.3)	203 (7.4)
Native Hawaiian or other Pacific Islander	2 (0.1)	1 (0.1)	3 (0.1)
Multiracial	131 (7.1)	69 (7.5)	200 (7.3)
Not reported	9 (0.5)	4 (0.4)	13 (0.5)
Ethnicity			
Hispanic/Latino	264 (14.4)	120 (13.1)	384 (14.0)
Non-Hispanic/Non-Latino	1568 (85.4)	795 (86.9)	2363 (85.9)
Not reported	3 (0.2)	0	3 (0.1)
Country			
Finland	63 (3.4)	30 (3.3)	93 (3.4)
Poland	205 (11.2)	103 (11.3)	308 (11.2)
Spain	73 (4.0)	35 (3.8)	108 (3.9)
USA	1494 (81.4)	747 (81.6)	2241 (81.5)
Age at vaccination (years)			
Mean (SD)	3.0 (0.79)	3.0 (0.79)	3.0 (0.79)
Median	3.0	3.0	3.0
Min, max	(2, 4)	(2, 4)	(2, 4)
Obese[c]			
Yes	120 (6.5)	45 (4.9)	165 (6.0)
No	1712 (93.3)	870 (95.1)	2582 (93.9)
Missing	3 (0.2)	0	3 (0.1)
Baseline SARS-CoV-2 status			
Positive[d]	233 (12.7)	125 (13.7)	358 (13.0)
Negative[e]	1597 (87.0)	783 (85.6)	2380 (86.5)
Missing	5 (0.3)	7 (0.8)	12 (0.4)
Comorbidities[f]			
Yes	222 (12.1)	130 (14.2)	352 (12.8)
No	1613 (87.9)	785 (85.8)	2398 (87.2)

Abbreviations: CDC = Centers for Disease Control and Prevention; 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 1 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep.2020;69(32):1081-8 and/or obesity (BMI ≥ 95th percentile).

Medical History

The safety population included children with medical histories consistent with the general population. The SOCs with the most reported medical history PTs, and other select SOCs, were:

Immune system disorders: 13.6% in BNT162b2 and 16.5% in placebo mostly consisting of a variety of non-drug allergies, also including drug hypersensitivity (1.7% in BNT162b2 and 2.8% in placebo) and anaphylactic reaction (0.1% in BNT162b2 and 0.2% in placebo).

Infections and infestations: 10.6% in BNT162b2 and 12.0% in placebo including a variety of viral and bacterial infections commonly seen in this age group. History of COVID-19 was reported in 0.9% of participants each in BNT162b2 and placebo groups (17 vs 8).

Skin and subcutaneous tissue disorders: 9.0% in BNT162b2 and 10.1% in placebo mostly consisting of eczema (5.1% in BNT162b2 and 5.9% in placebo) and various types of rashes and dermatitis that may be commonly seen in this age group.

Nervous system disorders: 2.8% in BNT162b2 and 2.2% in placebo including various types of epilepsy and sensory or developmental disorders that may be commonly seen in this age group.

Psychiatric disorders: 1.4% in BNT162b2 and 1.2% in placebo including autism spectrum disorder (0.5% in BNT162b2 and 0.7% in placebo), attention deficit hyperactivity disorder (0.2% in BNT162b2), and a variety of behavioural disorders that may be commonly seen in this age group.

Cardiac disorders: reported in 6 (0.3%) participants in the BNT162b2 and 4 (0.4%) participants in the placebo group including bradycardia, tachycardia, supraventricular tachycardia (n=1 each in the BNT162b2 group) and pulmonary valve stenosis (n=2 in the BNT162b2 group and n=1 each in the placebo group). Additionally, congenital cardiac conditions (e.g., atrial or ventricular septal defects, pulmonary valve disorder, patent ductus arteriosus, cardiomyopathy, Prader-Willi syndrome) were reported in both the BNT162b2 and placebo groups at low frequencies (<1%).

Concomitant vaccines were administered in 13.1% in BNT162b2 and 11.6% in placebo group.

Phase 2/3 – 6 months to <2 years of age

Disposition

Disposition of children 6 months to <2 years of age until cutoff date (29APR2022) is presented in the table below. The safety population of 1776 Phase 2/3 participants 6 months to <2 years of age was: BNT162b2 (N=1178) and placebo (N=598) groups. No participants in the safety population were excluded from the study. No participants included in the safety population were HIV+.

Table 44. Disposition of all randomised participants prior to unblinding-phase 2/3 6m to <5yo

	Vaccine Group (as Randomized)		
	BNT162b2 (3 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	1178 (100.0)	598 (100.0)	1776 (100.0)
Not vaccinated	0	0	0
Vaccinated	1178 (100.0)	598 (100.0)	1776 (100.0)
Dose 1	1178 (100.0)	598 (100.0)	1776 (100.0)
Dose 2	1166 (99.0)	596 (99.7)	1762 (99.2)
Dose 3	386 (32.8)	184 (30.8)	570 (32.1)
Completed 1-month post–Dose 2 visit (vaccination period)	1165 (98.9)	596 (99.7)	1761 (99.2)
Completed 1-month post–Dose 3 visit (vaccination period)	262 (22.2)	179 (29.9)	441 (24.8)
Discontinued from vaccination period but continued in the study	1 (0.1)	0	1 (0.1)
Discontinued after Dose 1 and before Dose 2	1 (0.1)	0	1 (0.1)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	0	0
Discontinued after Dose 3 and before 1-month post–Dose 3 visit	0	0	0
Reason for discontinuation from vaccination period			
Adverse event	1 (0.1)	0	1 (0.1)
Withdrawn from study	9 (0.8)	4 (0.7)	13 (0.7)
Withdrawn after Dose 1 and before Dose 2	5 (0.4)	0	5 (0.3)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	0	0	0
Withdrawn on or after 1-month post–Dose 2 visit and before Dose 3	3 (0.3)	3 (0.5)	6 (0.3)
Withdrawn after Dose 3 and before 1-month post–Dose 3 visit	0	0	0
Withdrawn on or after 1-month post–Dose 3 visit	1 (0.1)	1 (0.2)	2 (0.1)
Reason for withdrawal from study			
Adverse event	1 (0.1)	0	1 (0.1)
Lost to follow-up	1 (0.1)	0	1 (0.1)
Withdrawal by participant	2 (0.2)	0	2 (0.1)
Withdrawal by parent/guardian	5 (0.4)	4 (0.7)	9 (0.5)

a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.

Important protocol deviations

Important protocol deviations were reported in 22 participants in the BNT162b2 group and 8 participants in the placebo group. Most protocol deviations in the BNT162b2 group were related to investigational product (17 compared with 4 in the placebo group), such as dosing errors, vaccination delay criteria related to non-study vaccine administration, or being deemed unsuitable for use.

Duration of follow-up

Duration of Follow-Up – Phase 2/3 – Children 6 Months to <2 Years of Age until cutoff date (29APR2022) is presented in the table below.

Table 45. Follow up time after dose 2 or dose 3-phase 2/3 6m to <5yo-Safety population

Table 23. Follow-Up Time After Dose 2 or Dose 3 – Phase 2/3 – 6 Months to <2 Years of Age – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (3 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Original blinded placebo-controlled follow-up period			
Time from Dose 2 to Dose 3 or cutoff date			
N[b]	1166	596	1762
<1 Month	68 (5.8)	36 (6.0)	104 (5.9)
≥1 -<2 Months	51 (4.4)	27 (4.5)	78 (4.4)
≥2 -<3 Months	160 (13.7)	77 (12.9)	237 (13.5)
≥3 -<4 Months	86 (7.4)	50 (8.4)	136 (7.7)
≥4 -<5 Months	102 (8.7)	42 (7.0)	144 (8.2)
≥5 -<6 Months	63 (5.4)	39 (6.5)	102 (5.8)
≥6 -<7 Months	615 (52.7)	317 (53.2)	932 (52.9)
≥7 -<8 Months	18 (1.5)	6 (1.0)	24 (1.4)
≥8 -<9 Months	3 (0.3)	1 (0.2)	4 (0.2)
≥10 Months	0	1 (0.2)	1 (0.1)
Mean (SD)	4.8 (1.96)	4.8 (1.98)	4.8 (1.97)
Median	6.3	6.3	6.3
Min, max	(0.2, 8.6)	(0.1, 10.4)	(0.1, 10.4)
Time from Dose 3 to cutoff date			
N[c]	386	184	570
<1 Month	64 (16.6)	29 (15.8)	93 (16.3)
≥1-<2 Months	196 (50.8)	100 (54.3)	296 (51.9)
≥2-<3 Months	86 (22.3)	36 (19.6)	122 (21.4)
≥3 Months	40 (10.4)	19 (10.3)	59 (10.4)
Mean (SD)	1.6 (0.87)	1.6 (0.82)	1.6 (0.85)
Median	1.3	1.3	1.3
Min, max	(0.0, 3.2)	(0.0, 3.2)	(0.0, 3.2)
Blinded and open-label period			
Time from Dose 2 to Dose 3 or cutoff date			
N[b]	1167	596	1763
<1 Month	67 (5.7)	36 (6.0)	103 (5.8)
≥1 -<2 Months	51 (4.4)	27 (4.5)	78 (4.4)
≥2 -<3 Months	160 (13.7)	77 (12.9)	237 (13.4)

≥3 -<4 Months	85 (7.3)	50 (8.4)	135 (7.7)
≥4 -<5 Months	102 (8.7)	41 (6.9)	143 (8.1)
≥5 -<6 Months	63 (5.4)	39 (6.5)	102 (5.8)
≥6 -<7 Months	249 (21.3)	276 (46.3)	525 (29.8)
≥7 -<8 Months	158 (13.5)	34 (5.7)	192 (10.9)
≥8 -<9 Months	152 (13.0)	10 (1.7)	162 (9.2)
≥9 -<10 Months	33 (2.8)	4 (0.7)	37 (2.1)
≥10 Months	47 (4.0)	2 (0.3)	49 (2.8)
Mean (SD)	5.5 (2.66)	5.0 (2.14)	5.4 (2.51)
Median	6.3	6.3	6.3
Min, max	(0.2, 10.4)	(0.1, 10.4)	(0.1, 10.4)
Time from Dose 3 to cutoff date			
N[a]	758	184	942
<1 Month	101 (13.3)	28 (15.2)	129 (13.7)
≥1-<2 Months	196 (25.9)	88 (47.8)	284 (30.1)
≥2-<3 Months	388 (51.2)	46 (25.0)	434 (46.1)
≥3 Months	73 (9.6)	22 (12.0)	95 (10.1)
Mean (SD)	2.1 (0.83)	1.7 (0.85)	2.0 (0.85)
Median	2.2	1.5	2.1
Min, max	(0.0, 3.2)	(0.0, 3.2)	(0.0, 3.2)

Note: "Original blinded placebo-controlled follow-up period" is defined as period from the first dose of study vaccination to before the participant was unblinded. If the unblinding date is missing, consider the cutoff date as the period end date.

"Blinded and open-label period" is defined as the period from the first dose of study vaccination to the cutoff date (original BNT162b2 group) or before the first dose of open-label BNT162b2 (original placebo group).

If the date of open-label BNT162b2 is missing for original placebo group, consider the cutoff date as the period end date.

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

b. N = number of participants who received Dose 2 in the specified group, or the total sample. These values are the denominators for the percentage and summary statistics calculations

c. N = number of participants who received Dose 3 in the specified group, or the total sample. These values are the denominators for the percentage and summary statistics calculations.

Vaccine administration and timing

Vaccine Administration and timing in phase 2/3 in children 6 months to <2 Years of age until cutoff date (29APR2022) is presented in the table below.

All participants in the original placebo group received Dose 1 of placebo as randomized, and 99.7% and 30.8% received Dose 2 and Dose 3, respectively, during blinded follow-up. After unblinding (per protocol) to receive active vaccination with BNT162b2, as of the data cutoff date, 344 children (57.5%) received a first active dose, 296 children (49.5%) received a second active dose, and 77 children (12.9%) received a third active dose of open-label BNT162b2.

Table 46. Vaccine as administered- phase 2/3- 6m to <5yo-all randomized participants

Vaccine (as Administered)	Vaccine Group (as Randomized) BNT162b2 (3 µg) (N[a]=1178) n[b] (%)	Placebo (N[a]=598) n[b] (%)
Original placebo-controlled period		
Vaccinated	1178 (100.0)	598 (100.0)
Dose 1		
BNT162b2 (3 µg)	1178 (100.0)	0
Placebo	0	598 (100.0)
Dose 2		
BNT162b2 (3 µg)	1167 (99.1)	0
Placebo	0	596 (99.7)
Dose 3		
BNT162b2 (3 µg)	758 (64.3)	0
Placebo	0	184 (30.8)
Open-label BNT162b2 vaccination for original placebo recipients		
First crossover dose		
BNT162b2 (3 µg)		344 (57.5)
Second crossover dose		
BNT162b2 (3 µg)		296 (49.5)
Third crossover dose		
BNT162b2 (3 µg)		77 (12.9)

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.

Demographic and other baseline characteristics

Demographic characteristics for phase 2/3 pediatric participants 6 months to <2 years of age were similar in BNT162b2 and placebo groups in the safety population (Table below).

Comorbidities present at baseline that increase the risk of severe COVID-19 disease19 were present in similar proportions of participants in the BNT162b2 group (4.2%) and placebo group (5.7%). The most common baseline comorbidities (BNT162b2 vs placebo) were:

- Premature birth (1.6% vs 2.0%)
- Asthma (0.8% vs 0.8%)
- Congenital heart disease (0.8% vs 1.8%)

No participants in this age group reported having an immunocompromised condition at baseline. Demographics of participants in the original placebo group who were unblinded to receive active vaccination with BNT162b2 were generally similar to those of the blinded vaccine groups.

Table 47. Demographic characteristics -phase 2/3- 6m to <5yo-Safety population

	Vaccine Group (as Administered)		
	BNT162b2 (3 µg) (N[a]=1178) n[b] (%)	Placebo (N[a]=598) n[b] (%)	Total (N[a]=1776) n[b] (%)
Sex			
Male	589 (50.0)	291 (48.7)	880 (49.5)
Female	589 (50.0)	307 (51.3)	896 (50.5)
Race			
White	922 (78.3)	480 (80.3)	1402 (78.9)
Black or African American	42 (3.6)	24 (4.0)	66 (3.7)
American Indian or Alaska Native	3 (0.3)	1 (0.2)	4 (0.2)
Asian	91 (7.7)	40 (6.7)	131 (7.4)
Multiracial	117 (9.9)	49 (8.2)	166 (9.3)
Not reported	3 (0.3)	4 (0.7)	7 (0.4)
Ethnicity			
Hispanic/Latino	161 (13.7)	64 (10.7)	225 (12.7)
Non-Hispanic/Non-Latino	1014 (86.1)	530 (88.6)	1544 (86.9)
Not reported	3 (0.3)	4 (0.7)	7 (0.4)
Country			
Brazil	0	2 (0.3)	2 (0.1)
Finland	54 (4.6)	26 (4.3)	80 (4.5)
Poland	125 (10.6)	63 (10.5)	188 (10.6)
Spain	42 (3.6)	22 (3.7)	64 (3.6)
USA	957 (81.2)	485 (81.1)	1442 (81.2)
Age at vaccination (months)			
Mean (SD)	15.2 (4.97)	15.4 (5.06)	15.3 (5.00)
Median	16.0	16.0	16.0
Min, max	(6, 23)	(6, 23)	(6, 23)
Baseline SARS-CoV-2 status			
Positive[c]	89 (7.6)	44 (7.4)	133 (7.5)
Negative[d]	1078 (91.5)	541 (90.5)	1619 (91.2)
Missing	11 (0.9)	13 (2.2)	24 (1.4)
Comorbidities[e]			
Yes	50 (4.2)	34 (5.7)	84 (4.7)
No	1128 (95.8)	564 (94.3)	1692 (95.3)

Abbreviations: MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.

d. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

e. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR Morb Mortal Wkly Rep.2020;69(32):1081-8.

Medical history

The safety population included children 6 months to <2 years of age with a medical history profile consistent with the general population. The SOCs with the most reported medical history PTs, and other select SOCs, were:

Immune system disorders: 9.8% in BNT162b2 and 8.7% in placebo mostly consisting of a variety of non-drug allergies, also including drug hypersensitivity (0.8% in BNT162b2 and 0.8% in placebo).

Skin and subcutaneous tissue disorders: 9.3% in BNT162b2 and 11.5% in placebo mostly consisting of eczema (5.5% in BNT162b2 and 6.9% in placebo) and various types of rashes and dermatitis that may be commonly seen in this age group.

Infections and infestations: 9.3% in BNT162b2 and 10.2% in placebo including a variety of viral and bacterial infections that may be commonly seen in this age group. History of COVID-19 (including asymptomatic COVID-19) was reported in 8 participants (0.7%) in BNT162b2 group and 8 participants in the placebo group (1.3%).

Respiratory, thoracic, and mediastinal disorders: 3.3% in BNT162b2 and 3.2% in placebo consisting of asthma and other respiratory illnesses that may be commonly seen in this age group.

Nervous system disorders: 1.1% in BNT162b2 and 0.7% in placebo including seizures and developmental disorders that may be commonly seen in this age group.

Cardiac disorders: reported in 6 participants (0.5%) in the BNT162b2 group including aortic valve stenosis, cardiac valve disease, coronary artery disease, left ventricular hypertrophy, long QT syndrome, and pulmonary valve stenosis (n=1 each); and 1 participant (0.2%) in the placebo group with history of cardiac disorder (not unspecified). Additionally, congenital cardiac conditions (e.g., atrial or ventricular septal defects, aorta or aortic valve defects, cardiomyopathy, Fallot's tetralogy) were reported in both BNT162b2 and placebo groups at low frequencies (≤1%).

A similar percentage of participants in either group (27.2% in BNT162b2 and 28.8% in placebo) received any concomitant vaccine after Dose 1. Most concomitant vaccines received were for influenza and other routine pediatric immunizations.

2.5.5.2. Adverse events

Reactogenicity- Phase 1

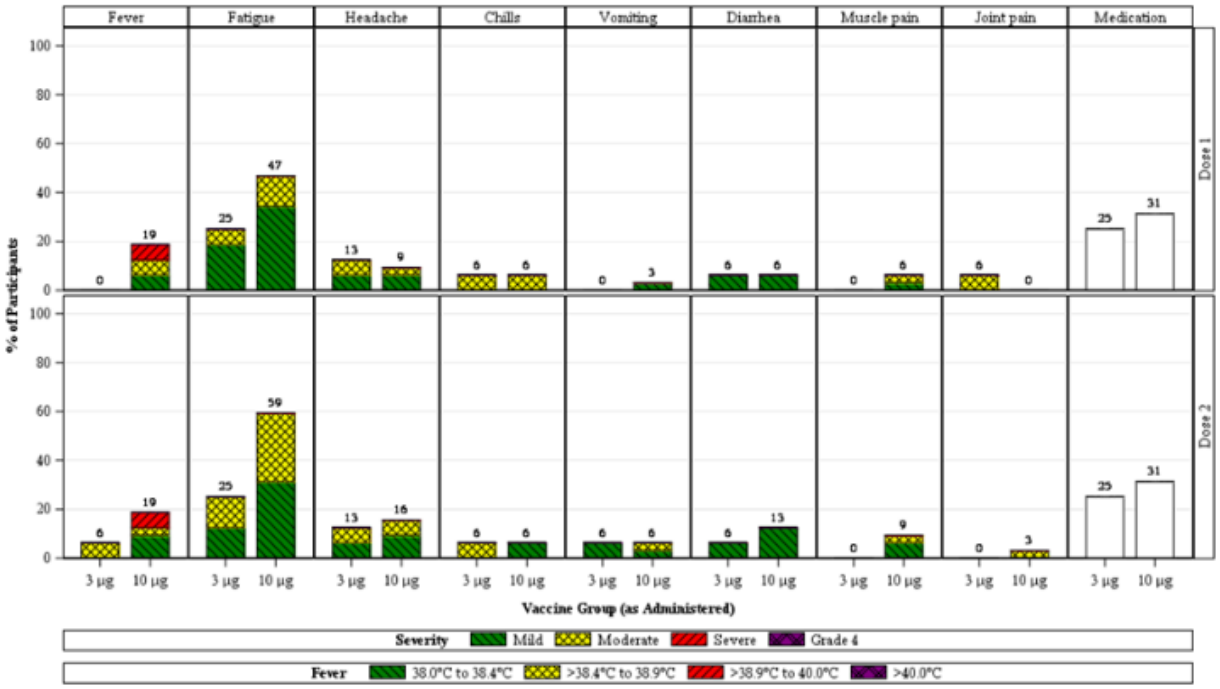
Local reactions

In the **2 to <5 years of age group**, pain at the injection site was the most commonly reported local reaction within 7 days, incidence after any dose was 65.6% in the 10-µg group compared with 43.8% in the 3-µg group; redness was reported after any dose in 28.1% versus 0.0%; and swelling after any dose was reported in 12.5% versus 0.0%, in the 10-µg and 3-µg groups, respectively. All local reactions were mild or moderate in severity. No Grade 4 events were reported at any dose levels. Across dose levels, the median onset for most local reactions was 1 to 2 days after Dose 1 or Dose 2, and most events resolved within 1 or 2 days of onset.

Based on the reactogenicity profile observed in the 2 to <5 years of age group, BNT162b2 at the 3-µg dose level was the only dose level tested in the **6 months to <2 years** of age group. After Dose 1, the only reported local reactions in children 6 months to <2 years of age were mild redness and swelling at the injection site (18.8% and 6.3%, respectively). After Dose 2, the only reported local reaction was mild tenderness at the injection site (6.3%). All local reactions were mild in severity. No moderate, severe, or Grade 4 events were reported. The median onset for most local reactions was within 1 day after Dose 1 or Dose 2, and most events resolved within 1 to 4 days of onset.

Systemic events

Figure 2. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 – 2 to <5 Years of Age Group – 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.

In the **2 to <5 years of age group**, fever was reported in 6 participants in the 10-µg dose group after either dose. Of these, 2 participants reported fever >38.9 °C to 40 °C after each dose. Fever was reported in only 1 participant in the 3-µg dose level group (>38.4 °C to 38.9 °C), after Dose 2. All systemic events were mild or moderate in severity. No Grade 4 events were reported at any dose levels. Across dose levels, the median onset for most systemic events was 1 to 2 days after Dose 1 or Dose 2, and most events resolved within 1 to 2 days of onset.

In the **6 months to <2 years** of age group reported incidences of systemic events (Dose 1 vs Dose 2) were:
- Irritability: 43.8% vs 31.3%
- Drowsiness: 25.0% vs 6.3%
- Decreased appetite: 6.3% vs 12.5%
- Fever: 6.3% vs 12.5%

Fever was reported in 1 participant after Dose 1, and in 2 participants after Dose 2; all of the reported fevers were <38.4 °C. Antipyretic or pain medication use was dose number dependent, reported by 18.8% of participants after Dose 1 with no reported use after Dose 2. All systemic events were mild or moderate in

severity within 7 days after Dose 1 and Dose 2. No severe or Grade 4 events were reported. The median onset for most systemic events was 1 to 2 days after Dose 1 or Dose 2, and most events resolved within 1 to 3 days of onset.

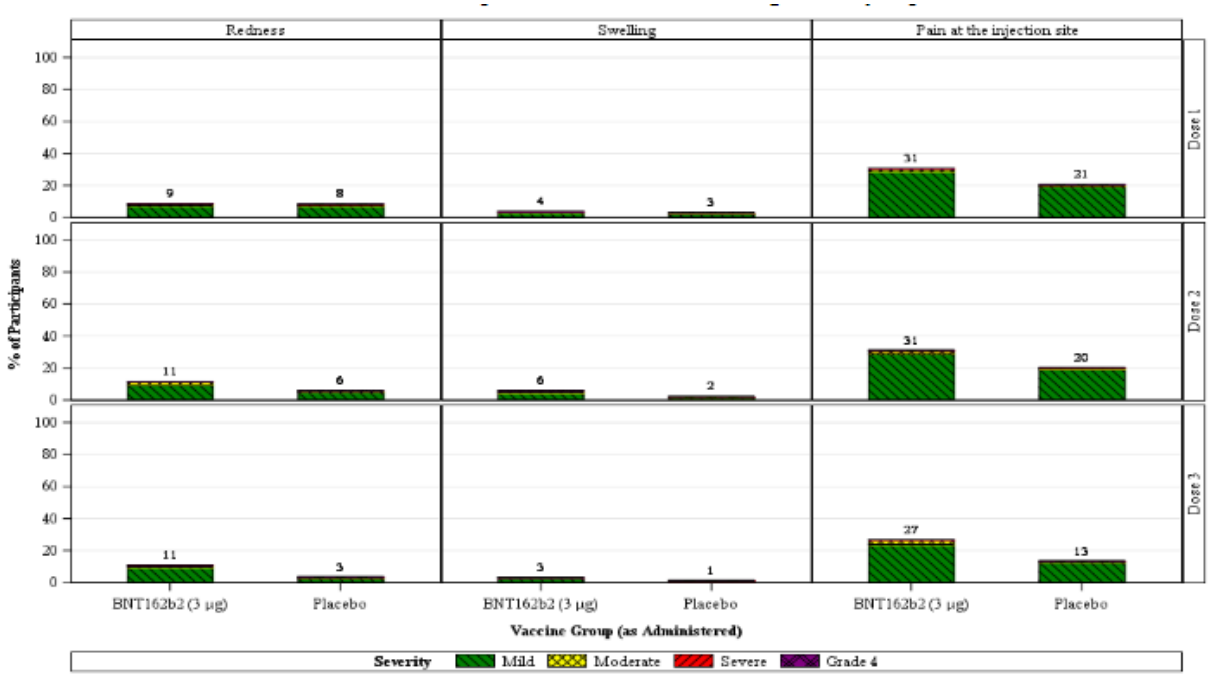
Reactogenicity – Phase 2/3

Local reactions

Among children aged **2 to <5 Years**, local reactions and systemic events were assessed for Phase 2/3 participants 2 to <5 years of age for 7 days after each dose, with e-diary data from N=1825 after Dose 1, N=1779 after Dose 2, and N=552 after Dose 3 of BNT162b2 3-µg; and N=909 after Dose 1, N=878 after Dose 2, and N=262 after Dose 3 of placebo.

Most local reactions were mild or moderate, with severe local reactions reported infrequently after any dose (≤0.1%). No Grade 4 local reactions were reported after any dose. The median onset for all local reactions after any dose of BNT162b2 3-µg was 1 to 2 days, and all events resolved within a median duration of 1 day after onset.

Figure 3. Participants reporting local reactions by maximum severity within 7d after each dose-phase 2/3-blinded placebo-controlled follow up period 2 to <5yo-safetu population.



Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2022 (08:23) Source Data: adfacevd
Table Generation: 12MAY2022 (22:59) (Cutoff Date: 29APR2022, Snapshot Date: 11MAY2022) Output File: .
/nda2_ubped/C4591007_6M_LT5Y_SAF_IMM_EUA_MAY2022/adce_f001_lr_p2_5

A separate analysis was performed for 120 participants with e-diary data who received Dose 1 and Dose 2 at the randomized dose level of BNT162b2 3-µg, and then turned 5 years of age prior to Dose 3 and therefore received Dose 3 at the age-appropriate 10-µg dose level in an open-label manner. For these participants, local reactions showed a dose level-dependent increase after Dose 3 compared to after Dose 2.

After any of three doses of BNT162b2 3-µg, the frequency and pattern of local reactions in baseline positive children was similar to those who were baseline negative and did not suggest any clinically meaningful

difference based on prior infection status. Subgroup analyses were performed based on sex, race and ethnicity, and there were no meaningful differences in the overall patterns of local reactions across these subgroups.

Among children aged **6 Months to <2 Years**, local reactions and systemic events were assessed for Phase 2/3 participants 6 months to <2 years of age for 7 days after each dose, with e-diary data from N=1173 after Dose 1, N=1147 after Dose 2, and N=365 after Dose 3 of BNT162b2 3-µg; and N=595 after Dose 1, N=591 after Dose 2, and N=170 after Dose 3 of placebo.

Incidences of any local reactions at the injection site after each dose in children aged **6 Months to <2 Years** were:

	Dose 1		Dose 2		Dose 3	
	BNT162b2	Placebo	BNT162b2	Placebo	BNT162b2	Placebo
• Tenderness:	16.6%	11.2%	15.0%	8.5%	16.0%	11.8%
• Redness:	10.6%	7.4%	9.3%	6.6%	7.1%	5.3%
• Swelling:	3.9%	2.5%	3.9%	1.5%	2.7%	1.8%

Most local reactions were mild or moderate, with severe local reactions reported infrequently after any dose (≤0.3%). No Grade 4 local reactions were reported after any dose. The median onset for all local reactions after any dose of BNT162b2 3-µg was 1 to 2 days, and most events resolved within a median duration of 1 day after onset.

Subgroup analyses were performed based on sex, race and ethnicity, and there were no meaningful differences in the overall patterns of local reactions across these subgroups.

Systemic events

Among children aged **2 to <5 Years**, Fatigue was the most frequently reported systemic event reported within 7 days after each dose, at similar frequencies in the BNT162b2 and placebo group. Most systemic events were mild or moderate, with severe systemic events reported infrequently after any dose (≤0.6%). No Grade 4 events were reported after any dose. The median onset for most systemic events after any dose of BNT162b2 3-µg was 2 days (noting that some events had median onset of up to 6 days post-dose, which was similar in BNT162b2 and placebo groups), and most events resolved within a median duration of 1 day after onset.

Incidences of any systemic events after each dose and antipyretic/pain medication use were:

	Dose 1		Dose 2		Dose 3	
	BNT162b2	Placebo	BNT162b2	Placebo	BNT162b2	Placebo
• Fatigue:	29.7%	30.6%	25.7%	22.9%	24.5%	21.8%
• Diarrhea:	7.7%	8.0%	6.7%	7.3%	5.1%	5.0%
• Fever:	5.2%	5.3%	4.9%	5.2%	5.1%	4.2%
• Headache:	4.5%	4.9%	4.6%	4.1%	4.9%	4.2%
• Vomiting:	3.0%	2.7%	3.4%	3.3%	1.6%	3.8%
• Chills:	2.3%	2.4%	3.0%	2.6%	3.3%	2.7%
• Muscle pain:	2.4%	1.7%	2.6%	2.4%	2.0%	1.5%
• Joint pain:	0.8%	2.0%	1.4%	1.0%	1.3%	0.8%
• Medication use:	10.8%	9.1%	9.9%	8.4%	8.5%	6.9%

Fever 38.9 °C to 40 °C was reported by ≤1.1% of participants in the BNT162b2 group and ≤1.1% in the placebo group, after each of the three doses. The overall median onset for fevers in either group was 4 to 5 days post-dose, and fevers all resolved in a median duration of 1 to 1.5 days. Three participants, all in the BNT162b2 group, reported a fever >40.0 °C after Dose 1 or Dose 2, one of whom had a clinical presentation suggestive of viral exanthem. These include:

- A participant reported a fever of 40.8 °C on Day 2 post-Dose 1 and persisting through Day 5 (temperatures on Days 3 to 5 were: 40.7 °C, 40.5 °C, 38.4 °C) and returned to normal body temperature (37.7 °C) on Day 6 with reported antipyretic/pain medication use. The fever was also reported as a nonserious AE of pyrexia considered by the investigator as related to study intervention and led to withdrawal. This participant reported no other AEs or Grade 3 systemic events.
- A participant reported fever starting on Day 3 post-Dose 2 and persisting through Day 7 (temperatures on Days 3 to 7 were: 39.5 °C, 40.3 °C, 39.6 °C, 39.1 °C, 38.0 °C). The fever was also reported as a severe SAE of pyrexia, with a concurrent SAE of pain in extremity (calf pain) with onset 6 days post-Dose 2 and nonserious AE of rash (chest, upper back, and ear) with onset 7 days post-Dose 2, all considered by the investigator as related to study intervention and resolved within 2 to 4 days of onset. This participant reported no other AEs or Grade 3 systemic events. Antipyretic/pain medication use was reported for the event(s). The events are described with severe AEs, SAEs and AESI of rash. The clinical presentation, (i.e., defervescence and development of a rash on the face and chest) is suggestive of a viral exanthem such as roseola as a possible diagnosis (based on sponsor assessment).
- A participant reported fever of 39.9 °C on Day 5 post-Dose 2, persisting to Day 7 (temperatures on Days 6 and 7 were: 40.3 °C 38.7 °C). This participant reported no other Grade 3 systemic events or any AEs. No antipyretic/pain medication use was reported

A separate analysis was performed for 120 participants with e-diary data who received Dose 1 and Dose 2 at the randomized dose level of BNT162b2 3-µg, and then turned 5 years of age prior to Dose 3 and therefore received Dose 3 at the age-appropriate 10-µg dose level in an open-label manner. For these participants, events of fever, fatigue, headache, and chills showed a dose level-dependent increase after Dose 3 compared to after Dose 2, whereas other events remained similar or showed no clear pattern after each subsequent dose.

Subgroup analyses were performed based on sex, race, ethnicity and baseline SARS-CoV-2 status, and there were no meaningful differences in the overall patterns of systemic events across these subgroups.

Among children **6 Months to <2 Years of Age**, irritability was the most frequently reported systemic event reported within 7 days after each dose, followed by drowsiness and decreased appetite.

Incidences of any systemic events and antipyretic/pain medication use after each dose in children aged **6 Months to <2 Years** were:

	Dose 1		Dose 2		Dose 3	
	BNT162b2	Placebo	BNT162b2	Placebo	BNT162b2	Placebo
• Irritability:	51.2%	47.2%	47.4%	40.7%	43.6%	37.6%
• Drowsiness:	27.0%	29.3%	23.8%	21.2%	19.9%	12.9%
• Decreased appetite:	22.2%	21.2%	22.2%	18.0%	20.2%	13.5%
• Fever:	7.2%	7.2%	7.4%	6.1%	6.8%	5.9%
• Medication use:	24.0%	19.7%	21.2%	18.8%	19.2%	16.5%

Most systemic events were mild or moderate, with severe systemic events reported infrequently after any dose (≤1.1%). No Grade 4 events were reported after any dose. The median onset for most systemic events after any dose of BNT162b2 3-µg was 2 days (noting that some events had median onset of up to 4.5 days post-dose, which was similar in BNT162b2 and placebo groups), and all events resolved within a median duration of 1 to 2 days after onset. Fever 38.9 °C to 40 °C was reported by ≤2.0% of participants in the BNT162b2 group and ≤1.2% in the placebo group, after each of the three doses. The overall median onset for fevers in either group was 2 to 4.5 days post-dose, and all reported fevers resolved in a median duration of 1 day. Three participants in the BNT162b2 group reported a fever >40.0 °C (n=1 each post-Dose 1, Dose 2, Dose 3), two of whom had a concurrent viral infection (roseola or unknown). These were:

- A participant reported fever of 40.6 °C on Day 2 post-Dose 1 that persisted through Day 4 (temperatures on Days 3 to 4 were: 39.0 °C, 38.1 °C) and returned to normal body temperature (37.2 °C) on Day 5 with reported antipyretic medication use. The fever was also reported as a nonserious AE of severe pyrexia considered by the investigator as related to study intervention and leading to withdrawal; this participant had a concurrent nonserious AE of exanthema subitum (attributed to a viral infection) considered as not related to study intervention that resolved in 4 days. This participant reported no other AEs or Grade 3 systemic events.
- A participant reported fever starting on Day 1 post-Dose 2 and persisting through Day 5 (temperatures on Days 1 to 5 were: 39.2 °C, 39.5 °C, 40.5 °C, 38.4 °C, 39.1 °C) and returned to normal body temperature (37.1 °C) on Day 6 with reported antipyretic/pain medication use. Other reported Grade 3 systemic events, all of which were post-Dose 2, were drowsiness on Days 1-2 and Days 5-6 and irritability on Day 2 and Day 5. Based on clinical presentation at an unscheduled illness visit, the participant was diagnosed with roseola. This participant reported no AEs in blinded follow-up; after unblinding, an unrelated AE of vomiting (attributed to food exposure) was reported post-Dose 2 (prior to open-label Dose 3).
- A participant reported fever of 40.5 °C starting on Day 3 post-Dose 3 and persisting through Day 4 (temperatures on Day 3 and Day 4 were: 40.5 °C and 39.5 °C, with no temperature reported on Day 5) and returned to normal body temperature on Day 6 (37.8 °C). The fever was also reported as an AE leading to withdrawal and is included in severe AE analysis. The event was considered by the investigator as related to study intervention. This participant reported no other AEs or Grade 3 systemic events. No antipyretic/pain medication use was reported.

One participant in the placebo group had fever >40.0 °C (post-Dose 1). This was:

- A participant reported fever of 40.4 °C on Day 5 post-Dose 1 that returned to normal on Day 6 (37.5 °C). This participant reported no AEs or other Grade 3 systemic events.

Due to an anomaly in the eCRF data collection on symptom resolution for events of fever in the 6 months to <2 years of age group, if a fever was ongoing on Day 7 of the reactogenicity period, duration was considered 'unknown'. This data collection issue was documented as a quality event expected to be resolved by the time of the future licensure application for this age group. Additional analyses of systemic events that included any e-diary data reported after a participant was unblinded did not suggest any meaningful differences in the reactogenicity profile.

Subgroup analyses were performed based on sex, race, ethnicity and baseline SARS-CoV-2 status, and there were no meaningful differences in the overall patterns of systemic events across these subgroups.

Adverse events

Phase 1 –2 to <5 Years of Age

All AEs through the data cutoff date of 16 July 2021 were mild to moderate. Immediate AEs reported within 30 minutes post-dose included injection site pain in 1 participant each in the 3-µg and 10-µg dose groups after Dose 1, and in 1 participant in the 10-µg dose group after Dose 2 (Table below).

No SAEs, deaths, or AEs leading to withdrawal were reported in Phase 1 participants 2 to <5 years of age as of the data cutoff date of 16 July 2021, which represents up to approximately 3 months of follow-up.

Table 48. Number (%) of participants reporting at least 1 adverse event from dose 1 through cutoff date - 16JUL2021-phase 1- 2 to <5yo-safety population.

	Vaccine Group (as Administered)	
	3 µg (N[a]=16)	10 µg (N[a]=32)
Adverse Event	n[b] (%)	n[b] (%)
Any adverse event	4 (25.0)	12 (37.5)
Related[c]	2 (12.5)	7 (21.9)
Severe	0	0
Life-threatening	0	0
Any serious adverse event	0	0
Related[c]	0	0
Severe	0	0
Life-threatening	0	0
Any nonserious adverse event	4 (25.0)	12 (37.5)
Related[c]	2 (12.5)	7 (21.9)
Severe	0	0
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

a. N = number of 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 vaccine.

Number of participants reporting at least 1 AE from Dose 1 through 1 months after Dose 2, by SOC and PT is described in supplemental table below. No Phase 1 participants 2 to <5 years of age had any cases reported of anaphylaxis, appendicitis, Bell's palsy, myocarditis/pericarditis, or MIS-C.

Table 49. Number (%) of participants reporting at least 1 adverse event from dose 1 through 1month after dose 2, by system Orgam class and preferred term -phase 1- 2 to <5yo-safety population.

System Organ Class Preferred Term	Vaccine Group (as Administered) 3 µg (N[a]=16) n[b] (%)	 (95% CI[c])	 10 µg (N[a]=32) n[b] (%)	 (95% CI[c])
Any adverse event	4 (25.0)	(7.3, 52.4)	12 (37.5)	(21.1, 56.3)
Blood and lymphatic system disorders	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Lymphadenopathy	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Gastrointestinal disorders	0	(0.0, 20.6)	3 (9.4)	(2.0, 25.0)
Abdominal pain	0	(0.0, 20.6)	2 (6.3)	(0.8, 20.8)
Abdominal discomfort	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
General disorders and administration site conditions	2 (12.5)	(1.6, 38.3)	4 (12.5)	(3.5, 29.0)
Injection site pain	2 (12.5)	(1.6, 38.3)	3 (9.4)	(2.0, 25.0)
Injection site bruising	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Injury, poisoning and procedural complications	2 (12.5)	(1.6, 38.3)	3 (9.4)	(2.0, 25.0)
Contusion	1 (6.3)	(0.2, 30.2)	1 (3.1)	(0.1, 16.2)
Animal bite	1 (6.3)	(0.2, 30.2)	0	(0.0, 10.9)
Foreign body ingestion	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Skin laceration	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Musculoskeletal and connective tissue disorders	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Costochondritis	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Skin and subcutaneous tissue disorders	1 (6.3)	(0.2, 30.2)	2 (6.3)	(0.8, 20.8)
Dermatitis diaper	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Rash	0	(0.0, 20.6)	1 (3.1)	(0.1, 16.2)
Rash papular	1 (6.3)	(0.2, 30.2)	0	(0.0, 10.9)

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.

AEs that were considered related to study intervention included 2 subjects in the 3µg and 4 subjects in the 10 µg with pain at injection site, 2 subjects in the 10µg group with abdominal pain. One event of lymphadenopathy was reported in the 10µg group. Physical examinations were performed at baseline and after vaccination, with any abnormal findings reported per protocol.

Phase 1- 6 months to <2 years of age

Adverse Events in Phase 1, in children 6 months to <2 years of age until cutoff date (16Jul2022) which represents up to approximately 3 months of follow-up is presented in the table below.

Table 50. Number (%) of participants reporting at least 1 adverse event from dose 1 through cutoff date - 16JUL2021-phase 1- 6m to <5yo-safety population.

	Vaccine Group (as Administered)
Adverse Event	3 µg (N[a]=16) n[b] (%)
Any adverse event	2 (12.5)
Related[c]	1 (6.3)
Severe	0
Life-threatening	0
Any serious adverse event	0
Related[c]	0
Severe	0
Life-threatening	0
Any nonserious adverse event	2 (12.5)
Related[c]	1 (6.3)
Severe	0
Life-threatening	0
Any adverse event leading to withdrawal	0
Related[c]	0
Severe	0
Life-threatening	0
Death	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 vaccine.

Number of participants reporting at least 1 AE from Dose 1 through 1 months after Dose 2, by SOC and PT is described in the supplemental table below. No Phase 1 participants had any cases reported of lymphadenopathy, anaphylaxis, appendicitis, Bell's palsy, myocarditis/pericarditis, or MIS-C.

Table 51. Number (%) of participants reporting at least 1 adverse event from dose 1 through 1month after dose 2, by system organ class and preferred term -phase 1- 6m to <5yo-safety population.

	Vaccine Group (as Administered)	
	3 µg (N[a]=16)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any adverse event	2 (12.5)	(1.6, 38.3)
Respiratory, thoracic and mediastinal disorders	1 (6.3)	(0.2, 30.2)
Rhinorrhoea	1 (6.3)	(0.2, 30.2)
Skin and subcutaneous tissue disorders	1 (6.3)	(0.2, 30.2)
Urticaria	1 (6.3)	(0.2, 30.2)

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.

Physical examinations were performed at baseline and after vaccination, with any abnormal findings reported per protocol.

Phase 2/3 –2 to <5 Years of Age

An overview of AEs reported in the 2 to <5 years of age group from Dose 1 to 1 month after Dose 3 of BNT162b2 3-µg or placebo is shown in the table below.

Table 52. Number (%) of participants reporting at least 1 adverse event from dose 1 through 1month after dose 3, phase 2/3 -blinded placebo-controlled follow -up period – 2 to <5yo-safety population.

	Vaccine Group (as Administered)	
	BNT162b2 (3 µg) (N[a]=1835)	Placebo (N[a]=915)
Adverse Event	n[b] (%)	n[b] (%)
Any adverse event	344 (18.7)	171 (18.7)
Related[c]	37 (2.0)	18 (2.0)
Severe	9 (0.5)	6 (0.7)
Life-threatening	0	0
Any serious adverse event	12 (0.7)	8 (0.9)
Related[c]	1 (0.1)	0
Severe	5 (0.3)	3 (0.3)
Life-threatening	0	0

Any nonserious adverse event	339 (18.5)	169 (18.5)
Related[c]	37 (2.0)	18 (2.0)
Severe	4 (0.2)	3 (0.3)
Life-threatening	0	0
Any adverse event leading to withdrawal	3 (0.2)	1 (0.1)
Related[c]	2 (0.1)	1 (0.1)
Serious	1 (0.1)	0
Severe	1 (0.1)	1 (0.1)
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 the study intervention.

Subgroup Analyses on AEs from Dose 1 to 1 Month After Dose 3, Phase 2/3, 2 to <5 years

Subgroups of Phase 2/3 pediatric participants 2 to <5 years of age had similar AE profiles from Dose 1 to 1 month after Dose 3, overall and categorically (i.e., related, or severe events) across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status.

Subgroups of race (Black or African American, Asian, multiracial), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. While there were some numerical differences between subgroups, there were no meaningful differences in the overall patterns of AEs by category across these subgroups. There were some higher frequencies reported in females compared to males. However, in the BNT162b2 group, the overall incidences of participants 2 to <5 years of age reporting at least 1 AE were 18.5% for male participants and 19.0% for female participants.

Adverse Events from Dose 1 to Data Cutoff Date

From Dose 1 to the data cutoff date, the proportions of participants with any AE up to the cutoff date were similar in the BNT162b2 (18.8%) and placebo (18.9%) groups. To events already reported up to 1 month after Dose 3 (Table below), a limited number of additional events were reported up to the data cutoff date. As of the data cutoff date, any related or any SAEs were reported across the BNT162b2 and placebo groups by 2.0% or ≤0.7% of participants, respectively. No additional SAEs or withdrawals due to AEs were reported in either group beyond 1-month post-Dose 3. No study participants died.

Table 53. Number (%) and incidence rate of participants reporting at least 1 adverse event from dose 1 through cutoff (29APR2022) -phase 2/3 blinded placebo controlled follow- up period, 2 to <5yo-safety population.

	Vaccine Group (as Administered)							
	BNT162b2 (3 µg) (N[a]=1835, TE[b]=7.6)				Placebo (N[a]=915, TE[b]=3.8)			
Adverse Event	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])
Any adverse event	345	18.8 (17.0, 20.7)	45.5	(40.8, 50.6)	173	18.9 (16.4, 21.6)	45.9	(39.3, 53.3)
Related[g]	37	2.0 (1.4, 2.8)	4.9	(3.4, 6.7)	18	2.0 (1.2, 3.1)	4.8	(2.8, 7.5)
Severe	9	0.5 (0.2, 0.9)	1.2	(0.5, 2.3)	6	0.7 (0.2, 1.4)	1.6	(0.6, 3.5)
Life-threatening	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Any serious adverse event	12	0.7 (0.3, 1.1)	1.6	(0.8, 2.8)	8	0.9 (0.4, 1.7)	2.1	(0.9, 4.2)
Related[g]	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Severe	5	0.3 (0.1, 0.6)	0.7	(0.2, 1.5)	3	0.3 (0.1, 1.0)	0.8	(0.2, 2.3)
Life-threatening	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Any nonserious adverse event	340	18.5 (16.8, 20.4)	44.8	(40.2, 49.9)	171	18.7 (16.2, 21.4)	45.4	(38.8, 52.7)
Related[g]	37	2.0 (1.4, 2.8)	4.9	(3.4, 6.7)	18	2.0 (1.2, 3.1)	4.8	(2.8, 7.5)
Severe	4	0.2 (0.1, 0.6)	0.5	(0.1, 1.4)	3	0.3 (0.1, 1.0)	0.8	(0.2, 2.3)
Life-threatening	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Any adverse event leading to withdrawal	3	0.2 (0.0, 0.5)	0.4	(0.1, 1.2)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Related[g]	2	0.1 (0.0, 0.4)	0.3	(0.0, 1.0)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Severe	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Life-threatening	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Death	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years (PY) across all participants in the specified group. Exposure time for a participant is the time from dose 1 through unblinding or cutoff date. This value is the denominator for the incidence rate (IR) calculation.
c. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any event.
d. 2-Sided CI based on Clopper-Pearson.
e. IR is calculated as number of participants reporting the event/total exposure time in 100 PY across all participants in the specified group.
f. 2-Sided CI based on Poisson distribution.
g. Assessed by the investigator as related to the study intervention.

Analysis of Adverse Events from Dose 1 to 1 Month After Dose 3

Table 54. Number (%) of participants reporting at least 1 adverse event from dose 1 to 1month after dose 3, by system Orgam class and preferred term -phase 2/3- blinded placebo- controlled follow- up period - 2 to <5yo-safety population.

	Vaccine Group (as Administered)			
	BNT162b2 (3 µg) (N[a]=1835)		Placebo (N[a]=915)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	344 (18.7)	(17.0, 20.6)	171 (18.7)	(16.2, 21.4)
Blood and lymphatic system disorders	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Anaemia	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Lymphadenopathy	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Congenital, familial and genetic disorders	4 (0.2)	(0.1, 0.6)	1 (0.1)	(0.0, 0.6)
Ankyloglossia congenital	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Dermoid cyst	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Familial mediterranean fever	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Pectus excavatum	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Phimosis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Ear and labyrinth disorders	11 (0.6)	(0.3, 1.1)	2 (0.2)	(0.0, 0.8)
Ear pain	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.4)
Cerumen impaction	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Deafness bilateral	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Ear disorder	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Ear inflammation	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
External ear inflammation	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Hypoacusis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Motion sickness	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Noninfective myringitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Otorrhoea	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Eye disorders	2 (0.1)	(0.0, 0.4)	2 (0.2)	(0.0, 0.8)
Astigmatism	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Corneal erosion	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Papilloedema	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Strabismus	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Swelling of eyelid	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Gastrointestinal disorders	83 (4.5)	(3.6, 5.6)	53 (5.8)	(4.4, 7.5)
Vomiting	50 (2.7)	(2.0, 3.6)	30 (3.3)	(2.2, 4.6)
Diarrhoea	26 (1.4)	(0.9, 2.1)	18 (2.0)	(1.2, 3.1)
Constipation	2 (0.1)	(0.0, 0.4)	4 (0.4)	(0.1, 1.1)
Abdominal pain	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Dyspepsia	0	(0.0, 0.2)	2 (0.2)	(0.0, 0.8)
Nausea	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Umbilical hernia	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Abdominal distension	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Anal incontinence	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Coeliac disease	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Defaecation disorder	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)

Gastroenteritis viral	2 (0.1)	(0.0, 0.4)	2 (0.2)	(0.0, 0.8)
Otitis media acute	3 (0.2)	(0.0, 0.5)	1 (0.1)	(0.0, 0.6)
Urinary tract infection	3 (0.2)	(0.0, 0.5)	1 (0.1)	(0.0, 0.6)
Croup infectious	2 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.6)
Impetigo	3 (0.2)	(0.0, 0.5)	0	(0.0, 0.4)
Otitis externa	1 (0.1)	(0.0, 0.3)	2 (0.2)	(0.0, 0.8)
Sinusitis	2 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.6)
Viral upper respiratory tract infection	1 (0.1)	(0.0, 0.3)	2 (0.2)	(0.0, 0.8)
Appendicitis	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Cellulitis	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Gastroenteritis rotavirus	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Nasopharyngitis	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Tonsillitis	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Acute sinusitis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Body tinea	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Bronchitis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Focal peritonitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Gastroenteritis adenovirus	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Gianotti-Crosti syndrome	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Hordeolum	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Infection	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Laryngitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Lower respiratory tract infection	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Molluscum contagiosum	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Oral herpes	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Periorbital cellulitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Pharyngitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Pharyngitis streptococcal	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Pharyngotonsillitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Pneumonia	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Pyelonephritis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Roseola	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Skin bacterial infection	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)

Tooth abscess	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Viral infection	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Vulvovaginal mycotic infection	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Injury, poisoning and procedural complications	17 (0.9)	(0.5, 1.5)	11 (1.2)	(0.6, 2.1)
Fall	6 (0.3)	(0.1, 0.7)	5 (0.5)	(0.2, 1.3)
Skin laceration	4 (0.2)	(0.1, 0.6)	5 (0.5)	(0.2, 1.3)
Head injury	3 (0.2)	(0.0, 0.5)	1 (0.1)	(0.0, 0.6)
Arthropod bite	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Animal bite	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Animal scratch	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Clavicle fracture	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Foreign body	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Humerus fracture	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Limb injury	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Lip injury	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Mouth injury	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Scratch	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Skin abrasion	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Stress fracture	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Thermal burn	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Tooth fracture	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Investigations	3 (0.2)	(0.0, 0.5)	2 (0.2)	(0.0, 0.8)
Body temperature increased	2 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.6)
Anti-transglutaminase antibody increased	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Cardiac murmur functional	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Metabolism and nutrition disorders	5 (0.3)	(0.1, 0.6)	2 (0.2)	(0.0, 0.8)
Decreased appetite	1 (0.1)	(0.0, 0.3)	2 (0.2)	(0.0, 0.8)
Dehydration	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Failure to thrive	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Hypoglycaemia	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Musculoskeletal and connective tissue disorders	7 (0.4)	(0.2, 0.8)	4 (0.4)	(0.1, 1.1)
Pain in extremity	3 (0.2)	(0.0, 0.5)	1 (0.1)	(0.0, 0.6)

Arthralgia	2 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.6)
Myalgia	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Neck pain	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Synovitis	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Nervous system disorders	7 (0.4)	(0.2, 0.8)	5 (0.5)	(0.2, 1.3)
Febrile convulsion	2 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.6)
Headache	2 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.6)
Epilepsy	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Speech disorder developmental	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Paraesthesia	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Somnolence	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Status epilepticus	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Psychiatric disorders	3 (0.2)	(0.0, 0.5)	6 (0.7)	(0.2, 1.4)
Irritability	3 (0.2)	(0.0, 0.5)	3 (0.3)	(0.1, 1.0)
Attention deficit hyperactivity disorder	0	(0.0, 0.2)	2 (0.2)	(0.0, 0.8)
Insomnia	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Renal and urinary disorders	1 (0.1)	(0.0, 0.3)	2 (0.2)	(0.0, 0.8)
Dysuria	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Pollakiuria	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Urinary incontinence	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Respiratory, thoracic and mediastinal disorders	72 (3.9)	(3.1, 4.9)	30 (3.3)	(2.2, 4.6)
Cough	32 (1.7)	(1.2, 2.5)	12 (1.3)	(0.7, 2.3)
Rhinorrhoea	19 (1.0)	(0.6, 1.6)	11 (1.2)	(0.6, 2.1)
Nasal congestion	9 (0.5)	(0.2, 0.9)	1 (0.1)	(0.0, 0.6)
Oropharyngeal pain	3 (0.2)	(0.0, 0.5)	4 (0.4)	(0.1, 1.1)
Tonsillar hypertrophy	5 (0.3)	(0.1, 0.6)	0	(0.0, 0.4)
Asthma	3 (0.2)	(0.0, 0.5)	1 (0.1)	(0.0, 0.6)
Rhinitis allergic	2 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.6)
Adenoidal hypertrophy	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Allergic cough	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Bronchial hyperreactivity	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Obstructive sleep apnoea syndrome	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)

Paranasal sinus hypersecretion	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Productive cough	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Respiratory disorder	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Sneezing	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Upper-airway cough syndrome	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Skin and subcutaneous tissue disorders	20 (1.1)	(0.7, 1.7)	7 (0.8)	(0.3, 1.6)
Urticaria	6 (0.3)	(0.1, 0.7)	3 (0.3)	(0.1, 1.0)
Rash	4 (0.2)	(0.1, 0.6)	0	(0.0, 0.4)
Dermatitis atopic	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Dermatitis contact	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Erythema	2 (0.1)	(0.0, 0.4)	0	(0.0, 0.4)
Miliaria	1 (0.1)	(0.0, 0.3)	1 (0.1)	(0.0, 0.6)
Dermatitis	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Dermatitis diaper	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Eczema	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Rash erythematous	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Rash macular	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Rash maculo-papular	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Surgical and medical procedures	3 (0.2)	(0.0, 0.5)	3 (0.3)	(0.1, 1.0)
Adenoidectomy	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Circumcision	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Nail operation	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Orchidopexy	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Removal of foreign body	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Tongue tie operation	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Tonsillectomy	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Tooth extraction	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.6)
Vascular disorders	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)
Haematoma	1 (0.1)	(0.0, 0.3)	0	(0.0, 0.4)

Three participants in the BNT162b2 group experienced nonserious AEs of **pain in extremity**. Two were considered by the investigator as not related to study intervention and they resolved within 2 days. Arthralgia was reported in 2 participants in the BNT162b2 group, both cases was related to fall from coach or tree.

Two cases of febrile convulsion were reported in the BNT162b2 group, one participant who experienced **fever and febrile convulsions** 43 days after dose2 which resolved within 1 day, and one participant that experienced febrile convulsions 21 days post dose1 which resolved within 1 day (both cases are further described in section SAE). Two events of **epilepsy/status epilepticus** were reported, one in a participant who was hospitalized 47 days after receiving dose2 and 3 days after receiving influenza vaccine, one event was reported 18 days after dose1 in the setting of a urinary tract infection. Both events were reported as unrelated SAEs.

One case with **anaphylactic reaction** was reported in a participant the BNT162b2 group 5 days after dose. The participant did not have shortness of breath or hypotension. The participant developed a pruritic rash around the mouth as well as a generalized rash on the body along with abdominal pain and wheezing. The participant was seen at an urgent care clinic and the reaction resolved. The event was considered by the investigator as not related to study intervention. A participant experienced hypoacusis (**hearing**

impairment) 65 and 153 days after dose 2. According to otolaryngologist, the first episode of hypoacusis was due to adenoid hypertrophy, and the second episode of hypoacusis was probably due to multiple episodes of secretory otitis media. On Day 210, the hypoacusis resolved. The events were considered by the investigator as not related to study intervention.

Related Adverse Events – Dose 1 to 1 Month After Dose 3 – 2 to <5 Years of Age

From Dose 1 to 1 month after Dose 3, AEs assessed by the investigator as related to study intervention were reported with similar frequencies in the BNT162b2 (2.0%) and placebo (2.0%) groups. Most related AEs were consistent with reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 1.4% of participants in the BNT162b2 group compared with 1.2% of participants in the placebo group.

Immediate Adverse Events – After Each Dose – 2 to <5 Years of Age

Immediate AEs reported within 30 minutes of vaccination were low in frequency after any dose (≤0.3%) of BNT162b2 or placebo. No immediate events of anaphylaxis were reported after any vaccination. After Dose 1, immediate AEs in the BNT162b2 group were skin abrasion, erythema, injection site bruising, and injury associated with device (0.1% each); and in the placebo group were injection site pain (0.2%), injection site erythema, and injection site swelling (0.1% each). After Dose 2, immediate AEs in the BNT162b2 group were injection site pain, injection site erythema, rash erythematous, and urticaria (0.1% each); and in the placebo group were injection site erythema and injection site swelling (0.1% each).No immediate AEs were reported after Dose 3 in either group.

Severe or Life-Threatening Adverse Events – Dose 1 to 1 Month After Dose 3 – 2 to <5 Years of Age

AEs were reported by ≤0.7% of participants in both the BNT162b2 and placebo groups. Most of the events considered as severe were unrelated SAEs. No life-threatening (i.e., Grade 4) AEs were reported from Dose 1 to 1 month after Dose 3. In the BNT162b2 group, severe AEs included pyrexia, bilateral deafness, appendicitis, viral gastroenteritis, skin laceration, epilepsy, status epilepticus, and adenoidal hypertrophy (0.1% each).

The status epilepticus was reported as an unrelated SAE that led to study withdrawal.

The events of epilepsy, appendicitis, and viral gastroenteritis were also reported as unrelated SAEs.

The event of pyrexia was reported as a related SAE and recorded in the e-diary as a systemic event. The unrelated bilateral deafness is discussed above in AE analysis by SOC/PT. Epilepsy and appendicitis events are also included in the AESI analysis.

In the **placebo group**, severe AEs were macular rash, bronchial hyperreactivity, epilepsy, febrile convulsion, fall, and conjunctivitis (0.1% each). The events of bronchial hyperreactivity, epilepsy, and febrile convulsion were reported as unrelated SAEs. The events of febrile convulsions or epilepsy are also included in the AESI analysis.

Adverse Events from Dose 1 to Data Cutoff Date

Few additional AEs were reported from Dose 1 to the data cutoff date (29 April 2022). Overall, frequencies of any AEs reported after Dose 1 up the data cutoff date were similar in the BNT162b2 and placebo groups (18.8% vs 18.9%). Many of the AEs were consistent with reactogenicity events (e.g., vomiting, pyrexia, and fatigue). Overall, most of the additional AEs reported after 1-month post-Dose 3 up to the data cutoff date consisted of unrelated viral infections, fevers, and other minor illnesses and injuries typical for this age group in the general pediatric population. Additional analyses of AEs from Dose 1 to the data cutoff that included events reported after a participant was unblinded, or that were reported for the original placebo group after unblinding to receive active vaccination with BNT162b2, did not suggest any meaningful differences in safety profile.

Adverse Events of Special Interest (AESI) There were no cases reported in the 2 to <5 years of age group as of the data cutoff date (29 April 2022) of myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), or vaccine-related anaphylaxis. AEs of clinical interest that were identified in the safety database as of the data cutoff date included lymphadenopathy and appendicitis, which are summarized below.

Lymphadenopathy: Lymphadenopathy is considered an adverse reaction to this vaccine and is noted as such in the product labelling. Based on AE analysis during blinded follow-up from Dose 1 to 1-month post-Dose 3, 1 case of lymphadenopathy was reported by 1 participant (0.1%) in the BNT162b2 group and none in the placebo group. The case of lymphadenopathy occurred 2 days post dose 2 and resolved within 6 days. The event was considered related to study intervention. Lymphadenopathy is included in section 4.8 in the product information.

Appendicitis: Two events of appendicitis were reported, both in the BNT162b2 group and both reported as unrelated SAEs. In one case, the participant had acute appendicitis and localized peritonitis with onset 105 days post-Dose 2 and both resolved the next day. In the other case, the participant had appendicitis with onset 11 days post-Dose 2 that resolved the same day (see details section SAE).

MedDRA Standardized MedDRA Query (SMQ) Analysis: Based on previous FDA requests for AEs of clinical interest in prior submissions, the following MedDRA Standardized MedDRA Query (SMQ) searches were performed on the safety data: *Angioedema, Arthritis, Convulsions, Demyelination, Hypersensitivity, Peripheral Neuropathy and Vasculitis.* No events were identified consistent with demyelination, peripheral neuropathy, or vasculitis. Additional notable pertinent negatives from safety review (i.e., no cases reported in this population as of the data cutoff date) included but were not limited to thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune events, meningitis, encephalitis, neuritis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome. Events that were identified in the search were in the angioedema, hypersensitivity, arthritis, and convulsions SMQs which are summarized below and, in the following table. The incidence of *angioedema* (SMQ) events was similar in the BNT162b2 and placebo groups (0.4%), and the incidence of hypersensitivity (SMQ) events was higher in the BNT162b2 group (0.9%) compared to the placebo group (0.4%).Rash is considered an adverse reaction to this vaccine and is noted as such in the product labelling. *Rashes* were reported infrequently in the SMQ analysis for children 2 to <5 years of age, but at a slightly higher incidence in the BNT162b2 group (0.4%) than placebo (0.1%).

Other events from this SMQ analysis reported in the BNT162b2 group included 6 events of *urticaria* (n=6), *contact or atopic dermatitis* (n=2 each), eczema (n=1), *eyelid swelling* (n=1), and *allergic cough or rhinitis* (n=2 each). Of these, 4 cases of urticaria were considered as related to study intervention and all others were considered as not related.

Convulsions were reported at the same incidence (0.2%) in the BNT162b2 and placebo groups and are further described in section of SAE.

Table 55. Selected standardised MedDRA queries from dose 1 to 1 month after dose 3- 2 to <5yo-Phase 2/3 blinded placebo- controlled follow-up period-safety population

SMQ	Overall SMQ System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (3 µg) (N[a]=1835) n[b] (%)	Vaccine Group (as Administered) Placebo (N[a]=915) n[b] (%)
	Participants with any unsolicited adverse events within SMQ	27 (1.47)	9 (0.98)
Angioedema (SMQ)	Any unsolicited adverse events within Angioedema (SMQ)	7 (0.38)	4 (0.44)
	Eye disorders	1 (0.05)	0
	Swelling of eyelid	1 (0.05)	0
	General disorders and administration site conditions	0	1 (0.11)
	Swelling face	0	1 (0.11)
	Skin and subcutaneous tissue disorders	6 (0.33)	3 (0.33)
	Urticaria	6 (0.33)	3 (0.33)
Arthritis (SMQ)	Any unsolicited adverse events within Arthritis (SMQ)	1 (0.05)	0
	Musculoskeletal and connective tissue disorders	1 (0.05)	0
	Synovitis	1 (0.05)	0
Convulsions (SMQ)	Any unsolicited adverse events within Convulsions (SMQ)	4 (0.22)	2 (0.22)
	Nervous system disorders	4 (0.22)	2 (0.22)
	Epilepsy	1 (0.05)	1 (0.11)
	Febrile convulsion	2 (0.11)	1 (0.11)
	Status epilepticus	1 (0.05)	0
Demyelination (SMQ)	Any unsolicited adverse events within Demyelination (SMQ)	0	0
Hypersensitivity (SMQ)	Any unsolicited adverse events within Hypersensitivity (SMQ)	16 (0.87)	4 (0.44)
	General disorders and administration site conditions	1 (0.05)	0
	Injection site rash	1 (0.05)	0
	Immune system disorders	0	1 (0.11)
	Hypersensitivity	0	1 (0.11)
	Respiratory, thoracic and mediastinal disorders	4 (0.22)	1 (0.11)
	Allergic cough	2 (0.11)	0
	Rhinitis allergic	2 (0.11)	1 (0.11)
	Skin and subcutaneous tissue disorders	11 (0.60)	2 (0.22)
	Dermatitis	0	1 (0.11)
	Dermatitis atopic	2 (0.11)	0
	Dermatitis contact	2 (0.11)	0
	Eczema	1 (0.05)	0
	Rash	4 (0.22)	0
	Rash erythematous	1 (0.05)	0
	Rash macular	0	1 (0.11)
	Rash maculo-papular	1 (0.05)	0
Peripheral neuropathy (SMQ)	Any unsolicited adverse events within Peripheral neuropathy (SMQ)	0	0
Vasculitis (SMQ)	Any unsolicited adverse events within Vasculitis (SMQ)	0	0

Abbreviation: SMQ = standardised MedDRA query.
Note: MedDRA (v25.0) 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.

Physical examinations were performed at baseline and after vaccination, with any abnormal findings reported per protocol.

Phase 2/3 Safety –6 Months to <2 Years of Age

An overview of AEs reported in the 6 months to <2 years of age group from Dose 1 to 1 month after Dose 3 is shown in the table below.

Table 56. Number (%) of participants reporting at least 1 adverse event from dose 1 to 1month after dose 3-phase 2/3- blinded placebo- controlled follow- up period – 6m to <5yo-safety population.

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (3 µg) (N[a]=1178) n[b] (%)	Placebo (N[a]=598) n[b] (%)
Any adverse event	355 (30.1)	162 (27.1)
Related[c]	55 (4.7)	21 (3.5)
Severe	12 (1.0)	10 (1.7)
Life-threatening	0	1 (0.2)
Any serious adverse event	17 (1.4)	14 (2.3)
Related[c]	0	1 (0.2)
Severe	8 (0.7)	9 (1.5)
Life-threatening	0	1 (0.2)
Any nonserious adverse event	343 (29.1)	157 (26.3)
Related[c]	55 (4.7)	20 (3.3)
Severe	5 (0.4)	1 (0.2)
Life-threatening	0	0
Any adverse event leading to withdrawal	3 (0.3)	0
Related[c]	3 (0.3)	0
Serious	0	0
Severe	1 (0.1)	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 the study intervention.

Subgroup Analyses

Subgroups of Phase 2/3 paediatric participants 6 months to <2 years of age had similar AE profiles from Dose 1 to 1 month after Dose 3, overall and categorically (i.e., related or severe events) across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American, Asian, multiracial), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. While there were some numerical differences between subgroups, there were no meaningful differences in the overall patterns of AEs by category across these subgroups.

Adverse Events from Dose 1 to Data Cutoff Date

AEs reported from Dose 1 to the data cutoff date (29 April 2022) is presented in the table below.

Table 57. Number (%) and incidence of participants reporting at least 1 adverse event from dose 1 to 1 month though cutoff date (29APR2022)-phase 2/3- blinded placebo- controlled follow- up period – 6m to <5yo-safety population.

	Vaccine Group (as Administered)							
	BNT162b2 (3 µg) (N[a]=1178, TE[b]=5.5)				Placebo (N[a]=598, TE[b]=2.8)			
Adverse Event	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])
Any adverse event	357	30.3 (27.7, 33.0)	64.5	(58.0, 71.6)	163	27.3 (23.7, 31.0)	58.3	(49.7, 68.0)
Related[g]	55	4.7 (3.5, 6.0)	9.9	(7.5, 12.9)	21	3.5 (2.2, 5.3)	7.5	(4.7, 11.5)
Severe	12	1.0 (0.5, 1.8)	2.2	(1.1, 3.8)	10	1.7 (0.8, 3.1)	3.6	(1.7, 6.6)
Life-threatening	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Any serious adverse event	17	1.4 (0.8, 2.3)	3.1	(1.8, 4.9)	14	2.3 (1.3, 3.9)	5.0	(2.7, 8.4)
Related[g]	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Severe	8	0.7 (0.3, 1.3)	1.4	(0.6, 2.8)	9	1.5 (0.7, 2.8)	3.2	(1.5, 6.1)
Life-threatening	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Any nonserious adverse event	345	29.3 (26.7, 32.0)	62.4	(56.0, 69.3)	158	26.4 (22.9, 30.1)	56.5	(48.1, 66.1)
Related[g]	55	4.7 (3.5, 6.0)	9.9	(7.5, 12.9)	20	3.3 (2.1, 5.1)	7.2	(4.4, 11.1)
Severe	5	0.4 (0.1, 1.0)	0.9	(0.3, 2.1)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Life-threatening	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Any adverse event leading to withdrawal	3	0.3 (0.1, 0.7)	0.5	(0.1, 1.6)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Related[g]	3	0.3 (0.1, 0.7)	0.5	(0.1, 1.6)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Severe	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Life-threatening	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Death	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years (PY) across all participants in the specified group. Exposure time for a participant is the time from dose 1 through unblinding or cutoff date. This value is the denominator for the incidence rate (IR) calculation.
c. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any event.
d. 2-Sided CI based on Clopper-Pearson.
e. IR is calculated as number of participants reporting the event/total exposure time in 100 PY across all participants in the specified group.
f. 2-Sided CI based on Poisson distribution.
g. Assessed by the investigator as related to the study intervention.

Adverse Events from Dose 1 to 1 Month After Dose 3

AEs reported from Dose 1 to 1 month after Dose 3 for participants 6 months to <2 years are presented in the table below.

Infections and illnesses typical of this age group were also reported with no clinically meaningful imbalance between groups. This AE profile is generally consistent with that observed for other age groups, that is, most events are either reactogenicity or age-appropriate occurrences expected in the general population.

Analysis of AEs from Dose 1 to 1-month post-Dose 2 and from Dose 3 to 1-month post-Dose 3 overall and by Tier 2 events did not suggest any safety concerns.

Table 58. Number (%) of participants reporting at least 1 adverse event from dose 1 to 1month after dose 3, by system Orgam class and preferred term -phase 2/3- blinded placebo- controlled follow- up period – 6m to <5yo-safety population.

	Vaccine Group (as Administered)			
	BNT162b2 (3 µg) (N[a]=1178)		Placebo (N[a]=598)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	355 (30.1)	(27.5, 32.8)	162 (27.1)	(23.6, 30.8)
Blood and lymphatic system disorders	7 (0.6)	(0.2, 1.2)	0	(0.0, 0.6)
Iron deficiency anaemia	3 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Lymphadenopathy	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Leukopenia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Neutropenia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Pancytopenia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Thrombocytopenia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Congenital, familial and genetic disorders	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Dermoid cyst	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Familial mediterranean fever	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Ear and labyrinth disorders	2 (0.2)	(0.0, 0.6)	5 (0.8)	(0.3, 1.9)

Ear pain	0	(0.0, 0.3)	2 (0.3)	(0.0, 1.2)
Ear inflammation	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Eustachian tube dysfunction	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Otorrhoea	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Tympanic membrane perforation	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Vertigo	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Eye disorders	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Eye swelling	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Swelling of eyelid	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Gastrointestinal disorders	105 (8.9)	(7.3, 10.7)	52 (8.7)	(6.6, 11.2)
Vomiting	47 (4.0)	(2.9, 5.3)	29 (4.8)	(3.3, 6.9)
Diarrhoea	39 (3.3)	(2.4, 4.5)	17 (2.8)	(1.7, 4.5)
Teething	12 (1.0)	(0.5, 1.8)	8 (1.3)	(0.6, 2.6)
Dyspepsia	3 (0.3)	(0.1, 0.7)	1 (0.2)	(0.0, 0.9)
Constipation	3 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Faeces discoloured	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Abdominal pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Abdominal pain upper	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Anal erythema	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Bowel movement irregularity	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Inguinal hernia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Oral mucosal eruption	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Stomatitis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Toothache	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
General disorders and administration site conditions	67 (5.7)	(4.4, 7.2)	33 (5.5)	(3.8, 7.7)
Pyrexia	54 (4.6)	(3.5, 5.9)	28 (4.7)	(3.1, 6.7)
Fatigue	8 (0.7)	(0.3, 1.3)	2 (0.3)	(0.0, 1.2)
Injection site erythema	9 (0.8)	(0.3, 1.4)	1 (0.2)	(0.0, 0.9)
Injection site pain	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Adverse food reaction	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Chills	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Gait disturbance	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)

Injection site haemorrhage	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Injection site swelling	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Injection site warmth	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Irritability postvaccinal	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Vessel puncture site rash	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Immune system disorders	7 (0.6)	(0.2, 1.2)	3 (0.5)	(0.1, 1.5)
Seasonal allergy	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Anaphylactic reaction	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Allergy to arthropod sting	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Drug hypersensitivity	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Food allergy	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Hypersensitivity	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Serum sickness	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Infections and infestations	116 (9.8)	(8.2, 11.7)	58 (9.7)	(7.4, 12.4)
Otitis media	19 (1.6)	(1.0, 2.5)	13 (2.2)	(1.2, 3.7)
Hand-foot-and-mouth disease	18 (1.5)	(0.9, 2.4)	13 (2.2)	(1.2, 3.7)
Ear infection	12 (1.0)	(0.5, 1.8)	8 (1.3)	(0.6, 2.6)
Rhinitis	10 (0.8)	(0.4, 1.6)	5 (0.8)	(0.3, 1.9)
Conjunctivitis	11 (0.9)	(0.5, 1.7)	2 (0.3)	(0.0, 1.2)
Otitis media acute	6 (0.5)	(0.2, 1.1)	3 (0.5)	(0.1, 1.5)
Upper respiratory tract infection	3 (0.3)	(0.1, 0.7)	3 (0.5)	(0.1, 1.5)
Gastroenteritis	5 (0.4)	(0.1, 1.0)	0	(0.0, 0.6)
Respiratory syncytial virus bronchiolitis	4 (0.3)	(0.1, 0.9)	1 (0.2)	(0.0, 0.9)
Fungal skin infection	4 (0.3)	(0.1, 0.9)	0	(0.0, 0.6)
Sinusitis	2 (0.2)	(0.0, 0.6)	2 (0.3)	(0.0, 1.2)
Gastroenteritis viral	3 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Impetigo	3 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Nasopharyngitis	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Urinary tract infection	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Viral upper respiratory tract infection	3 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Bronchiolitis	0	(0.0, 0.3)	2 (0.3)	(0.0, 1.2)
Gastroenteritis rotavirus	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Genital candidiasis	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)

Hordeolum	0	(0.0, 0.3)	2 (0.3)	(0.0, 1.2)
Oral herpes	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Otitis media chronic	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Pneumonia	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Roseola	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Viral infection	0	(0.0, 0.3)	2 (0.3)	(0.0, 1.2)
Anal abscess	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Body tinea	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Boston exanthema	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Cellulitis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Coxsackie viral infection	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Enterobiasis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Enterovirus infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Erythema infectiosum	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Exanthema subitum	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Furuncle	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Gastroenteritis norovirus	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Large intestine infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Lower respiratory tract infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Lower respiratory tract infection viral	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Mastoiditis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Metapneumovirus infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Molluscum contagiosum	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Oral candidiasis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Penile infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Pharyngitis streptococcal	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Respiratory syncytial virus infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Rhinovirus infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Staphylococcal skin infection	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Subcutaneous abscess	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Tinea infection	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Tinea versicolour	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Tonsillitis	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)

Viral rash	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Injury, poisoning and procedural complications	22 (1.9)	(1.2, 2.8)	15 (2.5)	(1.4, 4.1)
Fall	5 (0.4)	(0.1, 1.0)	4 (0.7)	(0.2, 1.7)
Head injury	1 (0.1)	(0.0, 0.5)	4 (0.7)	(0.2, 1.7)
Thermal burn	3 (0.3)	(0.1, 0.7)	1 (0.2)	(0.0, 0.9)
Limb injury	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Skin laceration	3 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Upper limb fracture	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Accidental overdose	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Animal bite	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Animal scratch	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Arthropod bite	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Burns second degree	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Contusion	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Craniocerebral injury	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Environmental exposure	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Exposure to lead	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Eye abrasion	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Femur fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Foreign body ingestion	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Joint dislocation	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Ligament sprain	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Lip injury	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Periorbital haematoma	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Post procedural discomfort	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Radial head dislocation	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Scratch	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Skin abrasion	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Tibia fracture	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Wound	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Investigations	1 (0.1)	(0.0, 0.5)	3 (0.5)	(0.1, 1.5)
Body temperature increased	0	(0.0, 0.3)	3 (0.5)	(0.1, 1.5)
Electrocardiogram abnormal	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)

Metabolism and nutrition disorders	7 (0.6)	(0.2, 1.2)	3 (0.5)	(0.1, 1.5)
Decreased appetite	4 (0.3)	(0.1, 0.9)	1 (0.2)	(0.0, 0.9)
Feeding disorder	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Feeding intolerance	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Hypoglycaemia	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Lactose intolerance	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Musculoskeletal and connective tissue disorders	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Hypermobility syndrome	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Muscular weakness	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Haemangioma of breast	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Nervous system disorders	14 (1.2)	(0.7, 2.0)	3 (0.5)	(0.1, 1.5)
Somnolence	5 (0.4)	(0.1, 1.0)	1 (0.2)	(0.0, 0.9)
Seizure	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Febrile convulsion	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Headache	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Lethargy	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Hypoglossal nerve disorder	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Hypotonia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Product issues	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Device dislocation	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Psychiatric disorders	17 (1.4)	(0.8, 2.3)	5 (0.8)	(0.3, 1.9)
Irritability	16 (1.4)	(0.8, 2.2)	5 (0.8)	(0.3, 1.9)
Staring	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Renal and urinary disorders	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Pollakiuria	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Reproductive system and breast disorders	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Balanoposthitis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Respiratory, thoracic and mediastinal disorders	59 (5.0)	(3.8, 6.4)	21 (3.5)	(2.2, 5.3)
Rhinorrhoea	26 (2.2)	(1.4, 3.2)	10 (1.7)	(0.8, 3.1)

Cough	19 (1.6)	(1.0, 2.5)	6 (1.0)	(0.4, 2.2)
Nasal congestion	12 (1.0)	(0.5, 1.8)	3 (0.5)	(0.1, 1.5)
Sneezing	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Asthma	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Bronchial hyperreactivity	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Childhood asthma	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Choking	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Dysphonia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Pneumomediastinum	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Respiratory distress	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Tonsillar hypertrophy	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Upper-airway cough syndrome	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Skin and subcutaneous tissue disorders	35 (3.0)	(2.1, 4.1)	17 (2.8)	(1.7, 4.5)
Rash	8 (0.7)	(0.3, 1.3)	3 (0.5)	(0.1, 1.5)
Urticaria	8 (0.7)	(0.3, 1.3)	3 (0.5)	(0.1, 1.5)
Eczema	5 (0.4)	(0.1, 1.0)	4 (0.7)	(0.2, 1.7)
Dermatitis diaper	3 (0.3)	(0.1, 0.7)	3 (0.5)	(0.1, 1.5)
Rash macular	1 (0.1)	(0.0, 0.5)	2 (0.3)	(0.0, 1.2)
Rash maculo-papular	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Rash papular	1 (0.1)	(0.0, 0.5)	2 (0.3)	(0.0, 1.2)
Alopecia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Dermatitis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Dermatitis atopic	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Dermatitis contact	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Drug eruption	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Ecchymosis	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Erythema	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Petechiae	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Rash erythematous	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Rash pruritic	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Vascular disorders	1 (0.1)	(0.0, 0.5)	4 (0.7)	(0.2, 1.7)
Cyanosis	0	(0.0, 0.3)	3 (0.5)	(0.1, 1.5)
Flushing	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)

Select AEs that were reported from Dose 1 to 1-month post-Dose 3 that according to the MAH merit additional detail to provide a fuller clinical picture are summarized below.

Leukopenia/Thrombocytopenia

A participant with a medical history of long QT syndrome, received Dose 1 BNT162b2 (3 µg) in Q2 2021 and Dose 2 BNT162b2 (3 µg) on Day 28. Fourteen days after receiving Dose 1 clinical laboratory tests showed leukocytes 2400/mm^3 (RR: 4500-13,000/mm^3) (reported as leukocytopenia, non-SAE, grade 2) and thrombocyte platelets count 113,000/mm^3 (RR: 227,000-550,000/mm^3) (reported as thrombocytopenia, non-SAE, Grade 2). COVID-19 test was negative. The participant developed a fever, loss of appetite, and drowsiness, was less active on Day 15, and a diagnosis of stomatitis was made on Day 16 (reported as herpetic stomatitis, non-SAE, grade 1, resolved on Day 18). Laboratory tests on Day 27, were within the RRs

(leukocytes 6500/mm^3 and platelets 289,000/mm^3) and thrombocytopenia and leukocytopenia considered resolved (in summary by the assessor with information from safety narrative) In the opinion of the investigator, there was a reasonable possibility that the leukopenia and thrombocytopenia were related to the study intervention. Thrombocytopenia and leukocytopenia are not described as AEs in the SmPC but nor thrombocytopenia or leukocytopenia presented in this case were profound and both events fully resolved. Stomatitis, fever and loss of appetite may indicate other infection(s), and this could also have caused this transient and small affection on thrombocytes and leucocytes. At rechallenge (dose 2 on Day 28) no new AEs were reported.

Neutropenia

further discussed also including other reported AE (gastroenteritis) in section SAEs

Gait disturbance

A participant developed nonserious mild right leg limping of unknown origin in 6 days post-Dose 1 of BNT162b2 that resolved the next day The event was considered by the investigator as not related to study intervention and did not recur with the second dose and agreed.

Vertigo

A participant had vertigo 12 days post-Dose 1 of BNT162b2 (reported as non-SAE, Grade 1) and was assessed by the investigator as attributed to motion 12 days post-Dose 1 of BNT162b2. The vertigo resolved and is assessed by the investigator as not related and this is agreed.

Seizure/febrile seizure

2 events of seizure were reported in the BNT162b2 group

A participant with no pertinent medical history, received Dose 1 BNT162b2 (3 µg) in Q1 2022 and Dose 2 BNT162b2 (3 µg) on Day 55. The participant experienced a febrile convulsion (reported as SAE, Grade 2), 38 days after receiving Dose 1, and was admitted to the hospital. This case is further described in Section SAE.

A participant with no pertinent medical history, received Dose 1 BNT162b2 (3 µg) in Q3 2021 and Dose 2 BNT162b2 (3 µg) on Day 22. The participant experienced a seizure (reported as non-SAE, Grade 3), 163 days after receiving Dose 2 and was unresponsive for approximately 60 seconds, with no jerking movements and some blue discoloration of skin. After gaining consciousness, the participant experienced a period of lethargy and fussiness for 10 to 15 minutes. Blood glucose was normal (84 mg/dL), but the participant was noted to have chest congestion. Laboratory testing detecting rotavirus in a stool sample and 2 electrocardiograms (ECGs) that showed possible borderline left ventricular hypertrophy. The participant was discharged from the hospital with a diagnosis of rotavirus infection. Approximately seven months after receiving dose 1, the participant was evaluated by a neurologist and neurological examination results were normal. The results of the EEG performed were normal. Later that month, the participant was evaluated by a cardiologist: echocardiogram (normal) and ECG (normal).

Both cases described above occurred >30 days after vaccination and were considered by the investigator and the MAH as not related to study intervention and is agreed.

A participant in the BNT162b2 group had an SAE of seizure (Grade 1) with unknown cause, with onset 3 days post-Dose 2 and resolved. This case is further described in Section SAE.

Serum sickness

A participant who had mild serum sickness (described as full body rash) (reported as non-SAE, Grade 1) with onset 31 days post-Dose 2 of BNT162b2 and was according to the investigator attributed to antibiotic treatment and resolved in 6 days. It is noted that the MAH informs that this case included in AESI analysis but no further information is found.

Pyrexia

A participant experienced pyrexia (reported as non-SAE, Grade 2), 2 days after receiving Dose 3, duration 3 days with maximum temp 104.9°F (40.5°C). In the opinion of the investigator, there was a reasonable possibility that the pyrexia was related to the study intervention and led to withdrawal. This case is further described (in section discontinuation due to AEs).

A participant who developed pyrexia (reported as non-SAE, Grade 3, related). A diagnosis of exanthema subitum was made on 1 day after receiving Dose 1. The participant was withdrawn from the study because of the pyrexia. This case is further described in section discontinuation due to AEs.

Anaphylactic reaction

One participant in the BNT162b2 group and 1 participant in the placebo group each had unrelated SAEs of anaphylaxis (both attributed to food allergic reactions), with the events resolving within a day of onset. These cases are detailed in the section for SAE.

Cyanosis

A participant in the placebo group had a severe SAE of cyanosis with onset 5 days post-Dose 1 and resolved the same day. The event was considered by the investigator as related to study intervention. An extensive medical work-up was performed in the Emergency Room with normal findings, and the child was discharged home with no further abnormalities noted.

One participant was reported with cyanosis 172 days post-Dose 2 placebo, assessed by the investigator as caused by abdominal pain, and resolved.

Related Adverse Events – Dose 1 to 1 Month After Dose 3 – 6 Months to <2 Years of Age

AEs assessed by the investigator as related to study intervention were reported at a slightly higher frequency in the BNT162b2 group (4.7%) than in the placebo group (3.5%). Most related AEs were consistent with reactogenicity events, most reported in both the BNT162b2 and placebo groups from the SOCs of general disorders and administration site conditions (1.6% and 0.7%) and gastrointestinal disorders (1.4% and 1.3%) (Table below).

Table 59. Number (%) of participants reporting at least 1 adverse event from dose 1 to 1month after dose 3, by system Orgam class and preferred term -phase 2/3- blinded placebo- controlled follow- up period – 6m to <5yo-safety population.

	Vaccine Group (as Administered)			
	BNT162b2 (3 µg) (N[a]=1178)		Placebo (N[a]=598)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	55 (4.7)	(3.5, 6.0)	21 (3.5)	(2.2, 5.3)
Blood and lymphatic system disorders	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Leukopenia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Lymphadenopathy	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Thrombocytopenia	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Gastrointestinal disorders	17 (1.4)	(0.8, 2.3)	8 (1.3)	(0.6, 2.6)
Diarrhoea	9 (0.8)	(0.3, 1.4)	5 (0.8)	(0.3, 1.9)
Vomiting	8 (0.7)	(0.3, 1.3)	4 (0.7)	(0.2, 1.7)
Abdominal pain upper	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Faeces discoloured	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
General disorders and administration site conditions	19 (1.6)	(1.0, 2.5)	4 (0.7)	(0.2, 1.7)
Injection site erythema	9 (0.8)	(0.3, 1.4)	1 (0.2)	(0.0, 0.9)
Fatigue	6 (0.5)	(0.2, 1.1)	2 (0.3)	(0.0, 1.2)
Pyrexia	6 (0.5)	(0.2, 1.1)	0	(0.0, 0.6)
Chills	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Injection site haemorrhage	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Injection site pain	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Injection site swelling	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Injection site warmth	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Irritability postvaccinal	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Infections and infestations	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Sinusitis	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Investigations	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Body temperature increased	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Metabolism and nutrition disorders	5 (0.4)	(0.1, 1.0)	1 (0.2)	(0.0, 0.9)
Decreased appetite	3 (0.3)	(0.1, 0.7)	1 (0.2)	(0.0, 0.9)
Feeding disorder	2 (0.2)	(0.0, 0.6)	0	(0.0, 0.6)
Nervous system disorders	6 (0.5)	(0.2, 1.1)	1 (0.2)	(0.0, 0.9)
Somnolence	5 (0.4)	(0.1, 1.0)	1 (0.2)	(0.0, 0.9)
Headache	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Psychiatric disorders	11 (0.9)	(0.5, 1.7)	4 (0.7)	(0.2, 1.7)
Irritability	11 (0.9)	(0.5, 1.7)	4 (0.7)	(0.2, 1.7)

Respiratory, thoracic and mediastinal disorders	2 (0.2)	(0.0, 0.6)	2 (0.3)	(0.0, 1.2)
Cough	2 (0.2)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Rhinorrhoea	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Skin and subcutaneous tissue disorders	6 (0.5)	(0.2, 1.1)	3 (0.5)	(0.1, 1.5)
Rash	3 (0.3)	(0.1, 0.7)	0	(0.0, 0.6)
Rash macular	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Urticaria	1 (0.1)	(0.0, 0.5)	1 (0.2)	(0.0, 0.9)
Eczema	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Rash erythematous	1 (0.1)	(0.0, 0.5)	0	(0.0, 0.6)
Rash papular	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Vascular disorders	0	(0.0, 0.3)	2 (0.3)	(0.0, 1.2)
Cyanosis	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)
Flushing	0	(0.0, 0.3)	1 (0.2)	(0.0, 0.9)

Note: MedDRA (v25.0) 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.

Immediate Adverse Events

Immediate AEs reported within 30 minutes of vaccination were low in frequency after any dose (≤0.5%) of BNT162b2 or placebo. No immediate events of anaphylaxis were reported after any vaccination. After Dose 1, immediate AEs in the BNT162b2 group were vomiting, injection site erythema, and hematoma (0.1% each); and none in the placebo group.

After Dose 2, immediate AEs in the BNT162b2 group were injection site erythema (0.2%) and injection site swelling and rash (0.1% each); and in the placebo group were vomiting, injection site erythema, scratch, and flushing (0.2% each). No immediate AEs were reported after Dose 3 in either group.

Severe or Life-Threatening Adverse Events – Dose 1 to 1 Month After Dose 3

Severe (Grade 3) AEs reported from Dose 1 to 1-month post-Dose 3 were reported at similar incidences in the BNT162b2 (1.0%) and placebo (1.8%) groups. Most severe AEs were gastrointestinal or respiratory infections/illnesses reported as unrelated SAEs, with no imbalance between groups.

One life-threatening (i.e., Grade 4) AEs was reported from Dose 1 to 1 month after Dose 3, by a participant in the placebo group who had a thermal burn that was reported as a non-related SAE.

In the BNT162b2 group, notable severe events included:

- 1 participant had severe, non-serious neutropenia (as described in section SAE).
- 1 participant had pyrexia 2 days after Dose 1 that led to withdrawal (see section discontinuation) and was assessed by the investigator as severe and related to study intervention; a concurrent AE of exanthema subitum (attributed to a viral infection) considered not related to study intervention; both events resolved within 4 days.

- 1 participant with a history of nut allergy reported had an unrelated event of severe anaphylactic reaction caused by a nut allergy, also reported as an SAE (see section SAE) and included in the AESI analysis.
- 1 participant was reported having an anaphylactoid reaction that resolved (reported as SAE, grade 3) directly after eating nut. The participant had received dose 1 BNT162b2 (3µg) 15 days before this event and was assessed as by the investigator and MAH as not related to the study intervention or clinical trial procedures but was considered related to a nut allergy, that is agreed by the assessor (for details see section SAE).
- 2 participants had unrelated severe events of febrile convulsion or seizure (n=1 each), (for details see section SAE).

In the placebo group, 2 severe events of cyanosis were reported as SAEs (described above), one attributable to 'abdominal pain' and one of unknown aetiology both assessed as unrelated.

Subgroup Analyses

Subgroups had similar AE profiles from Dose 1 to 1 month after Dose 3, across the BNT162b2 and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American, Asian, multiracial), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. In general, the AE profiles within each subgroup were similar to the overall AE profile for the safety population as whole, reflecting events consistent with reactogenicity and other childhood illnesses and injuries that are commonly reported in the general pediatric population. While there were some numerical differences between subgroups, there were no meaningful differences in the overall patterns of AEs by category across these subgroups.

Adverse Events from Dose 1 to Data Cutoff Date

Few additional AEs were reported from Dose 1 to the data cutoff date (29 April 2022) for participants 6 months to <2 years. Overall, frequencies of any AEs reported after Dose 1 up to the data cutoff date were similar in the BNT162b2 and placebo groups (30.3% vs 27.3%).

Many of the AEs were consistent with reactogenicity events (e.g., vomiting, pyrexia, and fatigue). Overall, most of the additional AEs reported after 1-month post-Dose 3 up to the data cutoff date consisted of unrelated viral infections, fevers, and other minor illnesses and injuries typical for this age group in the general pediatric population. Additional analyses of AEs from Dose 1 to the data cutoff that included events reported after a participant was unblinded, or that were reported for the original placebo group after unblinding to receive active vaccination with BNT162b2, did not suggest any meaningful differences in the safety profile.

- One nonserious case of **anaphylactic reaction** was reported in the BNT162b2 group, considered not related to study intervention, by a participant after they were unblinded in the study (therefore not included in summary tables of blinded placebo-controlled AEs). This participant had a pertinent medical history of eczema, multiple food allergies, and eczema coxsackium, received Dose 1 BNT162b2 (3 µg) in Q2 2021, Dose 2 BNT162b2 (3 µg) on Day 22, and Dose 3 BNT162b2 (3 µg) on Day 246. The participant experienced an anaphylactic reaction, 64 days after receiving Dose 3 BNT162b2 (3 µg) (reported as non-SAE grade). The trigger for this event was unknown. The participant presented with vomiting and

pruritus, which are the same symptoms that the participant experienced during prior allergic episodes. The participant got treatment at home and at the hospital. All symptoms lasted no more than 1 hour, and the event resolved the same day. In the opinion of the investigator, there was no reasonable possibility that the anaphylactic reaction was related to the study intervention, and this is agreed.

Adverse Events of Special Interest (AESI)

There were no cases reported in the 6 months to <2 years of age group as of the data cutoff date (29 April 2022) of myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), appendicitis, or vaccine-related anaphylaxis.

AEs of clinical interest that were identified in the safety database as of the data cutoff date included lymphadenopathy as summarized below.

Lymphadenopathy

Lymphadenopathy is considered an adverse reaction to this vaccine and is noted as such in the product labelling. Based on AE analysis from Dose 1 to 1-month post-Dose 3 during blinded follow-up , lymphadenopathy was reported in 2 participants (0.2%) in theBNT162b2 group and none in the placebo group. Lymphadenopathy is already included in section 4,8 of the product information.

Details of these cases are as follows:

- A participant was noted to have a neck mass of unspecified size 24 days post-Dose 2 of BNT162b2 (administered in the left thigh), considered as not related to study intervention. The participant was seen in Q1 2022 by an ear nose and throat specialist who conducted an ultrasound and diagnosed the mass as a swollen lymph node of unknown etiology, with no other symptoms reported; follow-up with the specialist and with the pediatrician was scheduled.
- A participant, had a mild enlarged left leg lymph node (groin) on 2 days post-Dose 2 of BNT162b2 (administered in the left thigh), resolved in 3 days, and was considered by the investigator as related to study intervention and this assessment is agreed.

SMQ Analysis Based on previous FDA requests for AEs of clinical interest in prior submissions, the following MedDRA Standardized MedDRA Query (SMQ) searches were performed on the safety data: *Angioedema, Arthritis, Convulsions, Demyelination, Hypersensitivity, Peripheral Neuropathy and Vasculitis.* No events were identified consistent with arthritis, demyelination, peripheral neuropathy, or vasculitis. Additional notable pertinent negatives from safety review (ie, no cases reported in this population as of the data cutoff date) included but were not limited to thrombocytopenic events, thromboembolic or intravascular coagulation events, autoimmune events, meningitis, encephalitis, neuritis, Kawasaki disease, MIS-C, or acute respiratory distress syndrome.

Events that were identified in the search were in the angioedema, hypersensitivity, and convulsions SMQs which are summarized below. The safety review using SMQs was based on AEs reported from Dose 1 to 1-month post-Dose 3 during blinded and placebo-controlled follow-up.

Angioedema/Hypersensitivity

The incidence of angioedema (SMQ) events was similar in the BNT162b2 (0.8%) and placebo (0.7%) groups, and the incidence of hypersensitivity (SMQ) events was similar in the BNT162b2 group (2.1%) compared to the placebo group (2.0%). Rash is considered an adverse reaction to this vaccine and is noted as such in the product labelling. Rashes were reported infrequently in the SMQ analysis for children 6 months to <2 years of age and at similar incidences in the BNT162b2 (1.1%) and placebo (1.2%) groups. In the BNT162b2 group, these included 13 events (including PTs of vessel puncture site rash, rash, rash erythematous, rash macular, rash maculo-papular) of which 7 events were considered by the investigator as related to vaccination. Rashes assessed as related to vaccination were typically mild to moderate, occurred in anatomical locations of extremities (upper and lower), torso, or face with typical onset of 1 to 5 days post-dose, and most resolved within 6 days of onset.

- One participant in the BNT162b2 group had a rash (generalized rash on face and trunk) on 6 days post-Dose 1 resolving in 4 days, that led to withdrawal (described in section withdrawal).

Other events from this SMQ analysis reported in the BNT162b2 group included events of urticaria (n=8), dermatitis or dermatitis atopic/contact (n=1 each), eczema (n=5), eyelid swelling (n=1), Of these, 1 case of urticaria was considered as related to study intervention and all others were considered as not related.

- Two unrelated severe anaphylactic reactions (attributed to food allergic reactions) were reported (n=1 each in the BNT162b2 and placebo groups) in participants with medical histories of pre-existing food allergies; both were reported as SAEs.
- One unrelated event of mild serum sickness (full body rash) was reported in 1 participant in the BNT162b2 group (attributed to amoxicillin treatment), with onset 31 days post-Dose 2 and resolved in 6 days
- One unrelated event of drug eruption (attributed to Amoxicillin allergy) was reported by a participant in the BNT162b2 group with onset on Day 30 post-Dose 2 and resolved in 3 days.
- One unrelated event of hypersensitivity (unknown cause) was reported by a participant in the BNT162b2 group with onset 59 days post-Dose 2 and resolved the same day.
- One unrelated event of mild drug hypersensitivity (attributed to a new drug allergy to penicillin) was reported in a participant in the placebo group with onset 15 days post-Dose 1 who also had concurrent urticaria (rash on trunk, face, and bilateral extremities) that was reported as resolved 5 days later.

Convulsions

Convulsions were reported at the similar incidences in the BNT162b2 (0.3%) and placebo (0.2%) groups. The two events are described at section SAE.

Table 60. Selected standardised MedDRA queries from dose 1 to 1 month after dose 3- 6m to <5yo-Phase 2/3 blinded placebo- controlled follow-up period-safety population

SMQ	Overall SMQ System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (3 µg) (N[a]=1178) n[b] (%)	Vaccine Group (as Administered) Placebo (N[a]=598) n[b] (%)
	Participants with any unsolicited adverse events within SMQ	38 (3.23)	16 (2.68)
Angioedema (SMQ)	Any unsolicited adverse events within Angioedema (SMQ)	9 (0.76)	4 (0.67)
	Eye disorders	1 (0.08)	1 (0.17)
	Eye swelling	0	1 (0.17)
	Swelling of eyelid	1 (0.08)	0
	Skin and subcutaneous tissue disorders	8 (0.68)	3 (0.50)
	Urticaria	8 (0.68)	3 (0.50)
Arthritis (SMQ)	Any unsolicited adverse events within Arthritis (SMQ)	0	0
Convulsions (SMQ)	Any unsolicited adverse events within Convulsions (SMQ)	4 (0.34)	1 (0.17)
	Nervous system disorders	4 (0.34)	1 (0.17)
	Febrile convulsion	2 (0.17)	0
	Seizure	2 (0.17)	1 (0.17)
Demyelination (SMQ)	Any unsolicited adverse events within Demyelination (SMQ)	0	0
Hypersensitivity (SMQ)	Any unsolicited adverse events within Hypersensitivity (SMQ)	25 (2.12)	12 (2.01)
	General disorders and administration site conditions	1 (0.08)	0
	Vessel puncture site rash	1 (0.08)	0
	Immune system disorders	3 (0.25)	2 (0.33)
	Anaphylactic reaction	1 (0.08)	1 (0.17)
	Drug hypersensitivity	0	1 (0.17)
	Hypersensitivity	1 (0.08)	0
	Serum sickness	1 (0.08)	0
	Skin and subcutaneous tissue disorders	21 (1.78)	10 (1.67)
	Dermatitis	1 (0.08)	0
	Dermatitis atopic	1 (0.08)	0
	Dermatitis contact	1 (0.08)	0
	Drug eruption	1 (0.08)	0
	Eczema	5 (0.42)	4 (0.67)
	Rash	8 (0.68)	3 (0.50)
	Rash erythematous	1 (0.08)	0
	Rash macular	1 (0.08)	2 (0.33)
	Rash maculo-papular	2 (0.17)	1 (0.17)
	Rash pruritic	0	1 (0.17)
Peripheral neuropathy (SMQ)	Any unsolicited adverse events within Peripheral neuropathy (SMQ)	0	0
Vasculitis (SMQ)	Any unsolicited adverse events within Vasculitis (SMQ)	0	0

Abbreviation: SMQ = standardised MedDRA query.
Note: MedDRA (v25.0) 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.

Other Safety Evaluations

Physical examinations were performed at baseline and after vaccination, with any abnormal findings reported per protocol.

2.5.5.3. Serious adverse event/deaths/other significant events

Phase 2/3 - 2 to <5 Years of Age

Deaths

No deaths were reported in the Phase 2/3 pediatric population of children 2 to <5 years of age up to the data cutoff date.

Serious Adverse Events from Dose 1 to Data Cutoff Date

Few SAEs were reported during blinded placebo-controlled follow-up in BNT162b2 3-µg (0.7%) and placebo (0.9%) groups from Dose 1 to the data cutoff date.

Few SAEs were during blinded placebo-controlled follow-up in BNT162b2 3-µg (0.7%) and placebo (0.9%) groups from Dose 1 to the data cutoff date. Most SAEs were gastrointestinal or respiratory infections/illnesses, with no imbalance between groups (considering 2:1 randomization). SAEs are summarized by the assessor below.

Pyrexia, pain in extremity, rash

Two SAEs reported by the same participant in the BNT162b2 group were considered by the investigator as related to study intervention, which included pyrexia accompanied by viral exanthem after receiving the second dose. This concerned a participant without a pertinent medical history who had pyrexia (40.3°C) (reported as SAE, Grade 2) 2 days post-Dose 2 that resolved in 5 days (also reported as a systemic event).The participant was seen in the hospital for the pyrexia and discharged home the same day in good condition. The fever was followed 3 days later by a pain in extremity (reported as SAE, Grade 2), characterized by limping while walking, that resolved in 3 days. The participant was hospitalized where his physical examinations, X-rays and ultrasound of lower extremity were normal. Clinical laboratory showed blood creatine kinase of 491, 1878 and 1503 IU/L (RR not reported), erythrocyte sedimentation rate of 17 and 20 mm/h (RR: 0-15 mm/h), C-reactive protein of 11, white blood cell count of 3.1, 2.9 and 1.8 (RR:4.5-13.5 × 10^9/L), thrombocytes 137 × 10^9/L (RR: 180-400 × 10^9/L). On the day pyrexia resolved, a nonserious AE of rash (Grade 2) on his chest, upper back, and ear developed that was also assessed as related and resolved in 2 days. In the opinion of the investigator, there was a reasonable possibility that the pyrexia and pain in extremity were related to the study intervention but not related to clinical trial procedures. The MAH concurred with the investigator's causality assessment about pyrexia but assessed that the pain in extremity could reasonably be of muscular origin and related to the second dose of blinded study intervention but also be due to an unspecified viral infection. Assessment by the MAH is agreed.

Status epilepticus and hypoglycaemia

A participant with a pertinent medical history including e.g., Miller-Dieker syndrome and seizure, urinary tract infection (UTI), with several concomitant medications. The participant received Dose 1 BNT162b2 (3 µg) in Q2 2021. The participant developed status epilepticus (reported as SAE, Grade 3, 3 days duration), 17 days after receiving Dose 1. On Day 13, the participant was diagnosed with UTI, and treated with Levofloxacin. The participant initially improved, but after 48 hours started to have sporadic episodes of severe pain, manifesting as crying and grimacing with an increase in seizures from baseline (5 to 10 times) to more than 20 seizures during that time. On Day18, the participant's highest recorded temperature was 99.3°F (37.4°C).

Respiratory panel tests (incl. SARS-CoV-2) were negative. On Day 18, the participant was diagnosed with hypoglycaemia (reported as non-SAE, Grade 1) as well as seizures. On Day 19, the hypoglycaemia resolved, and on Day 20, the status epilepticus was considered resolved. On Day 22, a urine culture showed normal urogenital flora. The events of status epilepticus led to study withdrawal (Section discontinuation due to AEs) and the participant did not receive Dose 2. In the opinion of the investigator, there was no reasonable possibility that the status epilepticus was related to the study intervention or clinical trial procedures but was related to the UTI. The MAH concurred with the investigator's causality assessment and stated that the status epilepticus was most likely due to hypoglycemia or a complication secondary to the intercurrent infectious condition and this assessment is agreed.

Two unrelated SAEs of clinical interest (epilepsy, febrile convulsion) were reported in the BNT162b2 group:

Epilepsy

A participant with a pertinent family medical history of febrile seizures, received Dose 1 BNT162b2 (3 µg) in Q3 2021 and Dose 2 BNT162b2 (3 µg) on Day 21. The participant received influenza vaccine (*Influvacc Tetra*) on Day 65. The participant seizures reported as suspected epilepsy (SAE, Grade 3), 47 days after receiving Dose 2 and 3 days after receiving the influenza vaccine. On Day 68, the participant presented to the emergency department after experiencing a seizure, including an episode of vomiting, followed by trembling of the left hand, mimic movements of half of the face, and disturbed consciousness without fainting. The participant was hospitalized in good general condition. Laboratory test results showed thrombocyte platelet count 472 g/L (reference range [RR]: 150-420 g/L) and thyroid -stimulating hormone of 6.3 IU/mL (RR: 0.4-6.0 IU/mL). During hospitalization, no symptoms were observed; a COVID-19 test result was negative. A computed tomography scan of the head revealed no signs of pathology, and electroencephalogram (EEG) results were not reported. The participant was treated with paracetamol and a solution for infusion, no further seizures were observed, the participant was discharged from the hospital on Day 70, and there were no seizures reported after the discharge. EEG performed while the participant was drowsy on Day 98 showed abnormal results. On Day 126, the neurologist verified the EEG result and reported that the diagnosis was still suspicion of epilepsy, since the seizure did not repeat. In the opinion of the investigator and MAH, there was no reasonable possibility that the epilepsy was related to the study intervention or clinical trial procedures, but it was suspected as being related to the influenza vaccine. Due to limited medical data and inconclusive EEG, epilepsy cannot be confirmed but the assessor agrees with the investigator and MAH that this reported SAE is, due to long time to onset after dose and that other concomitant factors were obvious, probably not related to study intervention.

Febrile convulsions

A participant with no pertinent medical history, was reported having a seizure during fever (39.3°C) that occurred 20 days after dose 1 BNT162b2 (3 µg) vaccine that lasted for 10 minutes (reported as febrile convulsions, SAE, Grade 2, resolved). Thereafter no new seizures and at revaccination with second dose no other AE/SAE was reported. Due to long time to onset after dose the assessor agrees that there was no reasonable possibility that the febrile convulsion was related to the study intervention.

Furthermore, one case in the Placebo and thereafter crossover group receiving BNT162b2 (3 µg) vaccine after unblinding was reported with febrile convulsion.

A participant with a pertinent medical history of a neurodevelopmental disorder for which prior febrile seizures occurred, received 2 doses of Placebo. The participant received the first crossover dose of BNT162b2

on Day 157 and the second crossover dose of BNT162b2 on Day 177. The participant experienced a febrile convulsion (reported as non-SAE, grade 1), 1 day after receiving the second crossover dose of BNT162b2. The seizure lasted 2 minutes and the temperature of the participant was 38°C with no other symptoms or concomitant vaccinations reported. In the opinion of the investigator, there was a reasonable possibility that the febrile convulsion was related to BNT162b2. This participant had one episode of 2-minute-long convulsion during low fever. Since the fever was below 38.5 °C, it is not conclusive for febrile convulsions. It is possible that this participant, with a medical history of a neurodevelopmental disorder for which prior febrile seizures occurred, had a convulsion caused by low grade fever after vaccination and thereby no new safety concern detected.

Appendicitis

Two unrelated SAEs of clinical interest were reported in the BNT162b2 group:

- A participant who had SAEs of acute appendicitis (Grade 2) and localized peritonitis (Grade 1), both with onset 105 days post-Dose 2.
- A participant with no pertinent medical history was diagnosed with appendicitis, 11 days after receiving Dose 2 BNT162b2 (3 µg) reported as SAE, grade 3 and resolved.

In the opinion of the investigator and MAH there was no reasonable possibility that the two cases of appendicitis were related to the study intervention, concomitant medications, or clinical trial procedures and this assessment is agreed by the assessor. Furthermore, after this event on Day 218 the latter participant received Dose 3 BNT162b2 (3 µg), and no AEs/SAEs reported after rechallenging.

Viral gastroenteritis:

One participant is described / in participants 2 to <5 Years of Age in the in the BNT162b2 (3 µg) group reported with viral gastroenteritis (reported as an SAE, Grade 3), 23 days after Dose 2 and resolved. This case was assessed by the investigator as unrelated to study intervention and related to viral infection. This assessment is agreed.

Table 61. Number (%) and incidence rate of participants reporting at least 1 serious adverse event from dose 1 through cutoff date (29APR2022), by system Orgam class and preferred term -phase 2/3- blinded placebo- controlled follow- up period – 2 to <5yo-safety population.

	Vaccine Group (as Administered)							
	BNT162b2 (3 µg) (N[a]=1835, TE[b]=7.6)				Placebo (N[a]=915, TE[b]=3.8)			
System Organ Class Preferred Term	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])
Any adverse event	12	0.7 (0.3, 1.1)	1.6	(0.8, 2.8)	8	0.9 (0.4, 1.7)	2.1	(0.9, 4.2)
EYE DISORDERS	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Papilloedema	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
GASTROINTESTINAL DISORDERS	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Diarrhoea	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Pyrexia	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
INFECTIONS AND INFESTATIONS	6	0.3 (0.1, 0.7)	0.8	(0.3, 1.7)	3	0.3 (0.1, 1.0)	0.8	(0.2, 2.3)
Appendicitis	2	0.1 (0.0, 0.4)	0.3	(0.0, 1.0)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Focal peritonitis	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Gastroenteritis	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Gastroenteritis adenovirus	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Gastroenteritis rotavirus	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Gastroenteritis viral	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Lower respiratory tract infection	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Upper respiratory tract infection	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Foreign body	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
METABOLISM AND NUTRITION DISORDERS	2	0.1 (0.0, 0.4)	0.3	(0.0, 1.0)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Dehydration	2	0.1 (0.0, 0.4)	0.3	(0.0, 1.0)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
Pain in extremity	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)

NERVOUS SYSTEM DISORDERS	3	0.2 (0.0, 0.5)	0.4	(0.1, 1.2)	2	0.2 (0.0, 0.8)	0.5	(0.1, 1.9)
Epilepsy	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Febrile convulsion	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Status epilepticus	1	0.1 (0.0, 0.3)	0.1	(0.0, 0.7)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)
Bronchial hyperreactivity	0	0.0 (0.0, 0.2)	0.0	(0.0, 0.5)	1	0.1 (0.0, 0.6)	0.3	(0.0, 1.5)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years (PY) across all participants in the specified group. Exposure time for a participant is the time from dose 1 through unblinding or cutoff date. This value is the denominator for the incidence rate (IR) calculation.
c. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any event.
d. 2-Sided CI based on Clopper-Pearson.
e. IR is calculated as number of participants reporting the event/total exposure time in 100 PY across all participants in the specified group.
f. 2-Sided CI based on Poisson distribution.

Phase 2/3 - 6 Months to <2 Years of Age

Deaths

No deaths were reported in the Phase 2/3 pediatric population of children 6 months to <2 years of age up to the data cutoff date.

Serious Adverse Events from Dose 1 to Data Cutoff Date

Few SAEs were reported during blinded follow-up in BNT162b2 3-µg (1.4%) and placebo (2.3%) groups from Dose 1 to the data cutoff date (Table below).

Most SAEs were gastrointestinal or respiratory infections/illnesses, with no imbalance between groups.

SAEs of potential clinical interest reported in the BNT162b2 group are further discussed below.

A participant with a pertinent medical history of food allergy (mild perioral rash in response to nuts; now regularly eats nut following desensitization) was reported having an **anaphylactoid reaction** (reported as SAE, Grade 3) directly after eating nut. The participant had received dose 1 BNT162b2 (3 µg) 15 days before this event and was assessed as by the investigator and MAH as not related to the study intervention or clinical trial procedures but was considered related to a nut allergy, and this is agreed.

A participant with no pertinent medical history, received Dose 1 BNT162b2 (3 µg) in Q1 2022 and Dose 2 BNT162b2 (3 µg) on Day 55. The participant experienced a **febrile convulsion** (reported as SAE, Grade 2), fever (up to 40°C), 38 days after receiving Dose 1, and was admitted to the hospital. The febrile convulsion resolved without antiseizure medication. The participant's physical examination on admission included good general condition, restlessness, and tiredness, with otherwise no abnormalities and otitis media was confirmed by a laryngologist. On Day 39 CRP was 10.6 mg/L (RR: 0-5 mg/L). In the opinion of the investigator, and MAH there was no reasonable possibility that the febrile convulsion was related to the study

intervention, concomitant medications, or clinical trial procedures. The assessor agrees based on long time to onset, other concomitant factors and at rechallenge no new AEs were reported.

A participant with no pertinent medical history. Two days after receiving Dose 2, episodes of the participant's eyes rolling back, along with an elevated temperature (38.0°C) and symptoms of a respiratory tract infection were noticed, and these symptoms were reported as **seizure** (SAE, grade 1). On Day 4, the participant was admitted to the hospital, eyeball turning upward once without deviations but otherwise the physical and neurological examinations, were normal. Laboratory test not conclusive for other diseases and brain ultrasound examination were normal. The participant was discharged and a few episodes per day of his eyes rolling back were noticed. Symptoms resolved on Day 42. The participant was withdrawn from the study because of an unblinding request. Summary of EEGs examinations at acute phase and follow up has been provided but are inconclusive for diagnosis of seizure. The participant was seen in the neurological clinic and the final diagnosis was convulsions, not elsewhere classified. In the opinion of the investigator and MAH, there was no reasonable possibility that the seizure was related to the study intervention or clinical trial procedures.

According to the CHMP the symptoms are not conclusive for epilepsy, nor results from EEG. Furthermore, the follow-up EEG was normalized. The symptoms of eyes rolling back could have had other causes such as pain or gastroesophageal reflux. There were other concomitant symptoms such as respiratory tract infection and elevated temperature, however, the symptoms were not typical for seizures and temperature not above 38.5°C and thereby the event cannot be assessed as febrile seizure. The assessment that there was no reasonable possibility that the seizure was related to the study intervention or clinical trial procedures, is agreed with the investigator and MAH.

A participant had **neutropenia** (reported as non-SAE, Grade 3) of unknown etiology with onset 20 days post-Dose 2 of BNT162b2, resolved 36 days after onset, and considered by the investigator as not related to study intervention. This was reported after a routine screening with complete blood count conducted by her pediatrician. Clinical laboratory tests showed a white blood cell count of 3.2 x 10^3/µL (RR not specified) and ANC of 230 cells/µL (RR not specified). The participant was asymptomatic at the time with no fever, chills, oral lesions, diarrhea, cough, vomiting, or any other symptoms and no further diagnostic work-up was performed.

The participant also had another SAE reported of viral gastroenteritis 30 days post-Dose 2 that resolved in 4 days (reported as SAE, Grade 3); and considered by the investigator as not related to study intervention; this event is included in the SAE analysis.

Further information is available that this participant is evaluated for potential 'cyclical' neutropenia due to an additional event reported after the submission cutoff date (hospitalization 166 days post-Dose 2 for RSV infection with clinical laboratory evidence of neutropenia).

None of the events are considered by the investigator as not related to study intervention This assessment is agreed and the event of neutropenia could have been confounded by infection. It is noted that only whole blood cell count without definition of RR but this does not change the assessment. No new safety concern detected.

SAEs of potential clinical interest reported in the placebo group included anaphylactic reaction 111 days post dose 1, severe cyanosis 5 days post dose 1, and viral bronchiolitis and pneumomediastinum 83 days post dose 2.

Table 62. Number (%) and incidence rate of participants reporting at least 1 serious adverse event from dose 1through cutoff date (29APR2022), by system Orgam class and preferred term -phase 2/3- blinded placebo- controlled follow- up period – 6m to <5yo-safety population.

	Vaccine Group (as Administered)							
	BNT162b2 (3 µg) (N[a]=1178, TE[b]=5.5)				Placebo (N[a]=598, TE[b]=2.8)			
System Organ Class Preferred Term	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])
Any adverse event	17	1.4 (0.8, 2.3)	3.1	(1.8, 4.9)	14	2.3 (1.3, 3.9)	5.0	(2.7, 8.4)
GASTROINTESTINAL DISORDERS	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Vomiting	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
IMMUNE SYSTEM DISORDERS	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Anaphylactic reaction	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
INFECTIONS AND INFESTATIONS	13	1.1 (0.6, 1.9)	2.4	(1.3, 4.0)	6	1.0 (0.4, 2.2)	2.1	(0.8, 4.7)
Anal abscess	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Bronchiolitis	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	2	0.3 (0.0, 1.2)	0.7	(0.1, 2.6)
Enterovirus infection	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Gastroenteritis	2	0.2 (0.0, 0.6)	0.4	(0.0, 1.3)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Gastroenteritis norovirus	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Gastroenteritis rotavirus	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Gastroenteritis viral	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Large intestine infection	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Lower respiratory tract infection	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Lower respiratory tract infection viral	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Metapneumovirus infection	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Pneumonia	2	0.2 (0.0, 0.6)	0.4	(0.0, 1.3)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Respiratory syncytial virus bronchiolitis	4	0.3 (0.1, 0.9)	0.7	(0.2, 1.9)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Respiratory syncytial virus infection	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Rhinovirus infection	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Tonsillitis	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Viral infection	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	3	0.5 (0.1, 1.5)	1.1	(0.2, 3.1)
Accidental overdose	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Burns second degree	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Head injury	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Thermal burn	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
METABOLISM AND NUTRITION DISORDERS	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	2	0.3 (0.0, 1.2)	0.7	(0.1, 2.6)
Feeding intolerance	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)

Hypoglycaemia	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
NERVOUS SYSTEM DISORDERS	2	0.2 (0.0, 0.6)	0.4	(0.0, 1.3)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Febrile convulsion	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
Seizure	1	0.1 (0.0, 0.5)	0.2	(0.0, 1.0)	0	0.0 (0.0, 0.6)	0.0	(0.0, 1.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Pneumomediastinum	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
Respiratory distress	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	1	0.2 (0.0, 0.9)	0.4	(0.0, 2.0)
VASCULAR DISORDERS	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	2	0.3 (0.0, 1.2)	0.7	(0.1, 2.6)
Cyanosis	0	0.0 (0.0, 0.3)	0.0	(0.0, 0.7)	2	0.3 (0.0, 1.2)	0.7	(0.1, 2.6)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years (PY) across all participants in the specified group. Exposure time for a participant is the time from dose 1 through unblinding or cutoff date. This value is the denominator for the incidence rate (IR) calculation.
c. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any event.
d. 2-Sided CI based on Clopper-Pearson.
e. IR is calculated as number of participants reporting the event/total exposure time in 100 PY across all participants in the specified group.
f. 2-Sided CI based on Poisson distribution.

Phase 2/3 – 2-<5 Years of Age

Among participants 2 to <5 years of age, AEs leading to withdrawal during blinded follow-up from Dose 1 to the data cutoff date (29 April 2022) were reported by 0.2% in the BNT162b2 group and 0.1% in the placebo group. These included events of pyrexia, status epilepticus, or urticaria reported by 1 participant each in the BNT162b2 group and swelling face/macular rash both reported by 1 participant in the placebo group.

A participant and withdrew due to a nonserious (Grade 2) AE of **pyrexia** with onset 2 days post-Dose 1 and resolution in 5 days (recorded in the e-diary as a systemic event Section 5.2.3.1.1.2). The participant developed a temperature of 40.8°C 1 day after receiving Dose 1 BNT162b2 (3 µg) and reported as pyrexia, non-SAE, grade 2. No other reactogenicity symptoms were reported. On Day 3, the participant had a temperature of 40.7°C. On Day 4, the pyrexia continued with a temperature of 40.5°C and had mild fatigue. On Day 5, the temperature was 38.4°C and the mild fatigue continued. On Day 5; SARS-CoV-2 PCR, was negative. On Day 6, the pyrexia resolved and considered by the investigator as related to vaccine and agreed.

A participant and withdrew due to an event of **status epilepticus** 18 days post-Dose 1 that was reported as an unrelated SAE (section SAE).

A participant who experienced **urticaria** (reported as non-SAE, grade 1), specifically pruritic maculopapular rash located on the chest, back of thighs, and arms, 1 day after receiving Dose 1. On Day 5, the urticaria resolved. In the opinion of the investigator, there was a reasonable possibility that the urticaria was related to the study intervention leading to withdrawal. Urticaria described as a rare event in the SmPC.

The following subject did not receive dose 3, since withdrawal was requested by the parent(s)/legal guardian:

This concerns a participant who received Dose 1 BNT162b2 (3 µg) in Q3 2021 and Dose 2 BNT162b2 (3 µg) on Day 23, who was diagnosed with bilateral **deafness** (reported as non-SAE, Grade 3) during a primary

care audiometric evaluation in Q3 2021 (exact day not reported). The bilateral deafness resolved after tympanostomy tube placement on Day 92. The participant's parent(s)/legal guardian requested withdrawal from the study. In the opinion of the investigator, there was no reasonable possibility that the bilateral deafness was related to the study intervention.

In the placebo group, 1 participant had a nonserious AE of swelling face and macular rash 1-day post-Dose 1 that resolved the same day, leading to withdrawal from vaccination.

Phase 2/3 – 6 Months to <2 years of Age

Three AEs leading to withdrawal were reported during blinded follow-up from Dose 1 to the data cutoff date (29 April 2022), all in theBNT162b2 group; these include 2 cases of pyrexia and one case of rash, all considered by the investigator as related to study intervention.

Two participants in the BNT162b2 group were withdrawn due to events of pyrexia (>40 °C), which were both also recorded in the e-diary as a systemic event and considered by the investigator as related to study intervention. Both cases reported as pyrexia had concomitant causality factors. Nevertheless, pyrexia is already described in the SmPC and thereby no new safety concern detected.

One participant with previous history of eczema developed generalized rash 6 days after Dose 1 which resolved after 3 days. The participant discontinued from study intervention but remained in the study and Dose 2 was administered on Day 268. Rash is already included in section 4.8 of the product information.

2.5.6. Discussion on clinical safety

This report concerns interim data for participants included the two age groups 6 months to <2 years and 2-<5 years in study C4591007. Safety data from the Phase 1 studies where the two doses of 3µg (n=16) and 10µg (n=32) was evaluated in children aged 2-<5 years and two doses of 3µg dose (n=16) was evaluated in children aged 6 months to <2 years. The main safety data base constitutes of two Phase 2/3 studies where three doses of either 3µg BNT162b2 or placebo was administered. The age group 2-<5 years included 2,750 subjects (3µg n=1,835; placebo n=915) and the age group 6 months to<2 years included 1,776 subjects (3µg n=1,178; placebo n=598). Reactogenicity was recorded daily for 7 days after each dose by using e-diary. AEs were collected from Dose 1 through 1 month after Dose 2 and from Dose 3 through 1 month after Dose 3, and serious AEs (SAEs) were collected from Dose 1 through 6 months after Dose 3. In both groups >99% received dose1 and 2, and dose 3 had been administered to 32-33% of the subjects in both age groups at the cutoff date (29APR2022).

Reactogenicity

The results from the Phase 1 study suggest that the selected dose of 3µg is associated with a clearly lower frequency of both local and systemic reactions compared to a dose of 10µg among children aged 2 - <5 years. In the phase 1 study for children aged 6 months to <2 years where only 3µg was administered, the results do not suggest another reactogenicity profile to what was seen in children 2-<5 years.

In the Phase 2/3 study, children **aged 2 - <5 years** were randomized to receive three doses of either 3µg BNT162b2 (n=1832) or placebo (n=915). Pain at injection site was the most common local reaction, reported

at a higher frequency in the 3µg BNT162b2 group (dose1 31%; dose2 31%; dose3 27%) compared to placebo group (dose1 21%; dose2 20%; dose3 13%). The difference between the two groups were smaller for redness (9-11% vs 3-9%) and swelling (3-6% vs 1-3%), and the frequency was overall lower for dose 3 compared to the first two doses.

Fatigue was the most common systemic event, reported at an almost similar frequency in the 3µg BNT162b2 group (dose1 30%; dose2 26%; dose3 25%) and in the placebo group (dose1 31%; dose2 23%; dose3 22%). Fever was reported at a similar frequency between the two groups (5% vs 4-5%). Fever 38.9°C to 40°C was reported by ≤1.1% in both groups after each of the three doses. Three participants, all in the BNT162b2 group, reported a fever >40.0°C after Dose 1 or Dose 2. No other differences in terms of systemic events were noted between the groups and the use of antipyretic/pain medication was also similar (9-11% vs 7-10%).

In the Phase 2/3 study children **aged 6 months to <2 years** of age were randomized to receive three doses of either 3µg BNT162b2 (n=1178) or placebo (n=598). Pain at injection site was the most common local reaction, reported at a higher frequency in the 3µg BNT162b2 group (dose1 17%; dose2 15%; dose3 16%) compared to placebo group (dose1 11%; dose2 9%; dose3 12%). The difference between the two groups were smaller for redness (7-11% vs 5-7%) and swelling (3-4% vs 2-3%).

Irritability was the most common systemic event, reported at almost similar frequency in the 3µg BNT162b2 group (dose1 51%; dose2 47%; dose3 44%) and in the placebo group (dose1 47%; dose2 41%; dose3 38%). Fever was reported at a similar frequency between the two groups (7% vs 6-7%), and fever 38.9°C to 40°C was reported by ≤2.0% of participants in the BNT162b2 group and ≤1.2% in the placebo group, after each of the three doses. Three participants in the BNT162b2 group reported a fever >40.0°C (n=1 each post-Dose 1, Dose 2, Dose 3), two of whom had a concurrent viral infection (roseola or unknown). Drowsiness was reported in 20-27% in the 3µg BNT162b2 group vs 13-30% in the placebo group. Decreased appetite was reported in 20-22% in the 3µg BNT162b2 group and in 14-21% in the placebo group. For both drowsiness and decreased appetite, the lowest frequency reported after dose 3. Use of antipyretic/pain medication was reported in 20-24% vs 17-20% in both groups, the lowest frequency was reported after dose 3. It is noted that drowsiness was reported at a frequency of >20%, which is not reflected in the SmPC. Therefore, applicant was asked to update the SmPC section 4.8 accordingly**.**

In the Phase 2/3 studies, no Grade 4 local or systemic reactions were reported after any dose, and the subgroup analysis did not show any clinically meaningful differences in terms of sex, race, ethnicity or baseline SARS-CoV-2 status.

Overall, the reactogenicity profile in the Phase 2/3 studies seems acceptable for children aged 6 months-<5 years, it was noted that for several of the systemic events, a similar frequency events were reported for the vaccine and the placebo group. There was no clear difference in reactogenicity profile between the three administered doses. It is however noted that only 30% of the subjects had received dose 3 at cutoff date.

AEs

From Dose 1 to the data cutoff date (29 April 2022), the proportions of participants **2 to <5 years of age** with any AE were similar in the 3µg BNT162b2 (18.8%) and placebo (18.9%) groups. To events already reported up to 1 month after Dose 3, a limited number of additional events were reported up to the data cutoff date. Many of the AEs were consistent with reactogenicity events (e.g., vomiting, pyrexia, and fatigue). Overall, most of the additional AEs reported after 1-month post-Dose 3 up to the data cutoff date consisted of unrelated viral infections, fevers, and other minor illnesses and injuries typical for this age group in the

general paediatric population. In the general disorders and administration site conditions SOC, AEs were reported at numerically higher incidence in the BNT162b2 group than the placebo group (4.3% vs 3.9%), largely attributable to injection site reactions and fatigue.

Few SAEs were reported among participants 2 to <5 years of age during blinded placebo-controlled follow-up in BNT162b2 3-µg (0.7%) and placebo (0.9%) groups from Dose 1 to the data cutoff date. Most SAEs were gastrointestinal or respiratory infections/illnesses, with no imbalance between groups. Most of the events considered as severe were unrelated SAEs. No life-threatening (i.e., Grade 4) AEs were reported from Dose 1 to 1 month after Dose 3.

Two SAEs reported by the same participant in the BNT162b2 group were considered by the investigator as related to study intervention, which included pyrexia accompanied by viral exanthem after receiving the second dose.

One participant with pertinent medical history including seizure, was reported with SAEs of status epilepticus 17 days after receiving Dose 1 of BNT162b probably due to a urinary tract infection and hypoglycemia.

Two unrelated SAEs of epilepsy and febrile convulsion, 47 days after receiving Dose 2 and 3 days after receiving the influenza vaccine, were reported.

One case of 10 min seizure during fever (39.3°C) 20 days after dose 1 of 3µg BNT162b2. was reported. Two unrelated SAEs of appendicitis were reported in the BNT162b2 group.

From Dose 1 to the data cutoff date, the proportions of participants in the **6 months to <2 years of age** group reported at least one AE were similar in the BNT162b2 (30.3%) and placebo (27.3%) groups. In addition to events already reported up to 1 month after Dose 3, a limited number of additional events were reported up to the data cutoff date. Many of the AEs were consistent with reactogenicity events that were reported as AEs (e.g., vomiting, diarrhea, and pyrexia).

Few SAEs were reported among subjects aged 6 months to <2 years during blinded follow-up BNT162b2 3-µg (1.4%) and placebo (2.3%) groups from Dose 1 to the data cutoff date. Most severe AEs were gastrointestinal or respiratory infections/illnesses reported as unrelated SAEs, with no imbalance between groups. One life-threatening (i.e., Grade 4) AE was reported from Dose 1 to 1 month after Dose 3, by a participant in the placebo group who had a thermal burn that was reported as an SAE.

One SAE of anaphylactoid reaction was reported directly after eating nut, the first dose of BNT162b2 was received 15 days before. One case of neutropenia (reported as non-SAE, Grade 3) and viral gastroenteritis was reported 30 days post-Dose 2.

One case of febrile convulsion was reported 38 days after receiving Dose 1. One SAE of seizure (Grade 1) was reported 3 days post-Dose 2 and resolved 17 days later. These cases were assessed by the CHMP as not related to study vaccine.

In total three participants in the BNT162b2 group and none in the placebo group reported lymphadenopathy. Lymphadenopathy is already included in section 4,8 of the product information.

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 no cases of myocarditis/pericarditis, Kawasaki disease,

peripheral neuropathy, MIS-C, 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 both age groups. Three subjects in the BNT162 arm 2 to <5 years of age discontinued due to AEs or SAEs (pyrexia, status epilepticus, or urticaria), and three subjects 6 months to <2 years in the BNT162b2 discontinued due to AEs (pyrexia, rash).

Overall, in both age groups most 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 these age groups respectively. No imbalance between the vaccine and placebo groups was noted. Furthermore, SAEs occurred at a very low frequency in both placebo and vaccine arm in both study age groups.

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.

There are still limited data available on interaction with other vaccines given concomitantly (missing information), and limited data regarding long term safety (missing information).

2.5.7. Conclusions on the clinical safety

The safety evaluation is mainly based on the still ongoing Phase 2/3 study that at the cutoff (29APR2022) included 2,750 subjects (3µg n=1,835; placebo n=915) aged 2-<5 years of age and 1,776 subjects (3µg n=1,178; placebo n=598) aged 6 months to <2 months of age.

Overall, the reactogenicity profile are in line with what can be anticipated from a vaccine with mostly mild to moderate reaction. For several of the systemic reaction, a similar frequency was reported in both the vaccine and the placebo group.

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

2.6. Risk Management Plan

2.6.1. Safety concerns

Important Identified Risks	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

2.6.2. 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.	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.	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long term safety data.	Final CSR submission:	03-Dec-2024

Category 3					
C4591009 *Ongoing*	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	Protocol submission:	31-Aug-2021
				Protocol amendment submission:	11-Jul-2022
				Monitoring report 1 submission:	31-Oct-2022
				Monitoring report 2 submission:	31-Oct-2024
				Interim Analysis submission:	31-Oct-2023
				Final CSR submission:	31-Mar-2026
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 AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Sep-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 including the bivalent Omicron modified vaccine, if feasible.	Myocarditis and pericarditis 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.	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 *Ongoing*	US	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction.	Not Applicable.	Final CSR submission:	30-Jun-2023
				Protocol amendment (for bivalent Omicron-modified vaccine) submission:	31-Dec-2022
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
WI235284 *Ongoing*	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 *Ongoing*	Ex-EU[a,b]	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection and to assess the	Not Applicable.	Final CSR submission:	30-Jun-2023

		effectiveness of bivalent Omicron-modified vaccines following their introduction.		Protocol amendment (for bivalent Omicron-modified vaccine) submission:	31-Dec-2022
				Final CSR (for bivalent Omicron-modified vaccine) submission:	30-Jun-2024
BNT162-01 Cohort 13 *Ongoing*	EU	To assess potentially protective immune responses in immunocompromised adults.	Use in immunocompromised patients.	IA submission:	30-Sep-2021
				Final CSR submission:	31-Oct-2023
C4591024 (former Safety and immunogenicity in high-risk adults) *Ongoing*	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:	30-Jun-2021
				Final CSR submission:	30-Jun-2023
C4591021 (former ACCESS/VAC 4EU) *Ongoing*	EU	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine including bivalent Omicron modified vaccine, if feasible. 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 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:	31-Jan-2022
				Final CSR submission:	30-Sep-2024
C4591022 *Ongoing*	US/CA	To assess whether pregnant women receiving BNT162b2	Use in pregnancy.		31-Jan-2022

		experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.		Interim reports submission:	31-Jan-2023
					31-Jan-2024
				Final CSR submission:	31-Dec-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 including myocarditis after the bivalent Omicron modified vaccine, if feasible	Myocarditis/pericarditis Long term safety data.	Protocol submission:	30-Nov-2021
				Final CSR submission:	31-Dec-2029
C4591030 (Co-administration study with seasonal influenza vaccine) *Ongoing*	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:	17 Aug 2021
				Final CSR submission:	31-Dec-2022
C4591031 Substudy E *Ongoing*	Global	To describe the safety and tolerability profile of BNT162b2 (30 and 60 µg), BNT162b2 OMI (30 and 60 µg), and bivalent BNT162b2 and BNT162b2 OMI (30 µg or 60 µg) given as a fourth dose to BNT162b2-experienced participants >55 years of age. To obtain data on bivalent BNT162b2 and BNT162b2 OMI at 60 µg (30 µg each), bivalent BNT162b2 and BNT162b2 OMI at 30 µg (15 µg each), and BNT162b2 OMI at 60 µg in participants 18 to 55 years of age.	Not applicable[c] Reactogenicity as partial proxy to the general safety profile	Interim reports submission (> 55 y):	31-Aug-2022
				Interim reports submission (18 - to 55 y):	31-Oct-2022
				6M Final CSR submission (>55 y):	31-Jan-2023
				6M Final CSR submission (18- to 55 y):	30-Mar 2023
C4591044 *Ongoing*	US	To describe the safety/tolerability and immune response to BNT162b5 Bivalent and BNT162b2 Bivalents given as a 2nd booster dose to COVID-19-vaccine-experienced participants ≥12 years of age.	Not applicable[c] Reactogenicity as partial proxy to the general safety profile	Protocol Submission:	14-Jun-2022
				Protocol amendment 1 submission:	28-Jul-2022
				Final CSR submission:	30-Sep-2023

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

2.6.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis and pericarditis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: DHCP letter and communication plan (see **Error! Reference source not found.** and Annex 6).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date) C4591009 (31-Mar-2026) 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-Dec-2029).
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 (03-Dec-2024) C4591009 (31-Mar-2026) C4591011[b] (31-Dec-2023) C4591012[b] (31-Dec-2023) C4591021 (former ACCESS/VAC4EU) (30 Sep-2024)[b].
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) C4591009 (31-Mar-2026) C4591010[a](30-Sep-2024) C4591011[a] (31-Dec-2023) C4591015 (30-Apr-2023) C4591021 (former ACCESS/VAC4EU)[a] (30-Sep-2024). C4591022[a] (31-Dec-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-Oct-2023) C4591010[c] (30-Sep-2024) C4591011 (31-Dec-2023)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		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) 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)**Error! Bookmark not defined.**
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: Studies (Final CSR Due Date) 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.**
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. 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) 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) C4591001 (31-Dec-2023) C4591007 (03-Dec-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-Dec-2029)

a. Please note that studies C4591009, C4591010, C4591011, C4591021 (former ACCESS/VAC4EU) and C4591022 address only "Use in pregnancy" and not "Breast feeding".
b. Addresses AESI-based safety events of interest including vaccine associated enhanced disease
c. Addresses AESI-based safety events of interest.

2.6.4. Conclusion

The CHMP considered that the risk management plan version 8.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. 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.

2.8. Product information

2.8.1. User consultation

A user consultation with target patient groups on the package information leaflet has been performed on the basis of a bridging report making reference to Comirnaty 30 micrograms/dose concentrate for dispersion for injection, EMEA/H/C/005735. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.1, from 16 December 2020)5 document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

Outer and immediate labelling (from start of supply to end February 2023).

The following exemptions are temporarily agreed for the labelling. These exemptions are justified on the necessity to label batches ahead of time.

Outer carton

- Age range information: No range age information initially proposed, instead of children 6 months to 4 years' (age range agreed during evaluation).
- "(After dilution, each vial contains 10 doses of 0.2 mL.)" (initially proposed with brackets), instead of "After dilution, each vial contains 10 doses of 0.2 mL." (without brackets, agreed during evaluation).
- MA number with 'XXX' placeholder, instead of MA number will be used after approval.

2.8.3. Quick Response (QR) code

The review of the QR code request submitted by the MAH is discussed separately with the QRD group and is based on previous discussions and assessment for other Comirnaty presentations.

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Comirnaty (tozinameran) is included in the additional monitoring list as New active substance and new biological.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

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).

COVID-19 in children is mostly a mild disease. Severe cases occur rarely, and predominantly in subjects with underlying conditions. The Applicant is seeking an indication for Comirnaty (BNT162b2) 3 µg formulation to children 6 months to <5 years of age.

COVID-19 is mostly a mild disease in children although severe cases rarely occur, predominantly in subjects with underlying conditions.

3.1.2. Available therapies and unmet medical need

There are currently no vaccines against COVID-19 approved in EU for the use in children below 5 years of age.

3.1.3. Main clinical studies

The application is based on a placebo-controlled, observer-blinded study in children 6 Months to <5 Years of Age. Participants were randomized 2:1 to receive vaccine or placebo at sites in the US, Finland, Poland, Spain, and Brazil.

The applicant selected to develop 3-dose regimen, since a two-dose regimen showed inferior immunogenicity in the 2-5 years old stratum, compared to young adults.

There was approximately 21-day interval between dose 1 and dose 2, and at least 8 weeks between dose 2 and dose 3.

The primary endpoint was non-inferior immunogenicity 1 month after dose three, in two strata, 6 months-2 year, and 2-5 years. The reference for non-inferiority was neutralizing titres 1 month after dose 2 in participants 16 to 25 years of age from Phase 2/3 of the C4591001 study, who had received 2 doses of BNT162b2 (30 µg) with 21-day interval.

Vaccine efficacy was de facto managed as an exploratory endpoint: confirmed COVID-19 incidence from 7 days after Dose 3 per 1000 person-years of blinded follow-up.

The main safety data base constitutes of two Phase 2/3 studies where three doses of either 3µg BNT162b2 or placebo was administered. The age group 2-<5 years included 2,750 subjects (3µg n=1,835; placebo n=915) and the age group 6 months to<2 years included 1,776 subjects (3µg n=1,178; placebo n=598). Reactogenicity was recorded daily for 7 days after each dose by using e-diary.

3.2. Favourable effects

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection, the GMR of SARS-CoV-2 50% neutralizing titers in children 2 to <5 years of age (at 1-month post-Dose 3 of BNT162b2 3-µg) compared to young adults 16 to 25 years of age (at 1-month post-Dose 2 of BNT162b2 30-µg) was 1.30 (2-sided 95% CI: 1.13, 1.50). GMR in children 6 months to <2 years of age compared to young adults was 1.19 (2-sided 95% CI: 1.00, 1.42).

As the lower bound of the 2-sided 95% CI for GMR was >0.67 and the GMR point estimate was >0.8 (protocol specified criterion) and >1.0 (requested by FDA), indicating the prespecified immunobridging success criterion for the GMR was met for both age groups 6 months to <2 years and 2 to <5 years old.

Almost equal proportions (100 % each of children 2- <5 years of age and 6m-<2 yo and 99% 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 1.2% (2-sided 95% CI: -1.5%, 4.2% for 2- <5 yo and -3.4%, 4.2% for 6m-<2 yo). The lower limit of the 95% CI for the difference in seroresponse rate were -1.5% and -3.4%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved. The difference of the seroresponse rate in children 6 months to <5 years of age compared to young adults was 1.2% (2-sided 95% CI: -0.5%, 4.2%.

In support of the immunobridging a preliminary analysis of efficacy was submitted with cut-off date 29.04.2022 and was updated along the procedure

Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for BNT162b2 3 µg against any confirmed COVID-19 from at least 7 days after Dose 3 was

80.3% (2-sided 95% CI: 13.9%, 96.7%) which included 3 cases in the BNT162b2 group and 7 cases in the placebo group. All these post-Dose 3 cases were reported in February through April 2022, when Omicron BA1. was most prevalent circulating strain in USA.

The MAH submitted an updated VE analysis with cut-off date 17.06.2022. The median follow-up time for entire cohort, from 6 months to <5 year old children was 2.2 months. Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for BNT162b2 3 µg against any confirmed COVID-19 from at least 7 days after Dose 3 was 73.2% (2-sided 95% CI: 43.8%, 87.6%) which included 13 cases in the BNT162b2 group (N=873) and 21 cases in the placebo group (N=381). All cases, expect one which was undefined, were caused by Omicron strain. The most common were Omicron BA.2 and Omicron BA.2.12.1.

There were 8 severe cases of COVID-19 in age group 6m-<5-year-old in active arm after 2-doses, whereas in placebo arm 4 severe case appeared. Notably, none of the cases showed clinical signs that would suggest VAERD.

A descriptive immunogenicity analysis of Omicron neutralizing titers was conducted using the FFRNT unvalidated assay, to compare children (2 to <5Y) with adults (18 to 50Y) who received a third dose of BNT162b2 at a similar interval between Dose 2 and Dose 3. Results showed the Omicron specific neutralization titers are very similar across pediatric population (GMT 128.8 and 114.3 respectively in children 6 months to <2 years and 2 to <5 years) and an 18 to 50 years adult comparator group (GMT 164.2) for whom high efficacy was observed.

No MIS-C were reported in the 6 months to <5 years of age group, per protocol definition or per CDC definition.

3.3. Uncertainties and limitations about favourable effects

The duration of protection in the target population is unknown. Indeed, the median duration of blinded follow-up for after Dose 3 was only 1.4 months.

The efficacy against Omicron BA.5 has not been studied.

Vaccine efficacy in special groups among children, such as immunocompromised or those at high-risk of severe disease were not assessed. A study in immunocompromised children is included in the PIP.

3.4. Unfavourable effects

The main safety data of Comirnaty 3µg in children 6 months to <5 years of age has been evaluated in a still ongoing Phase 2/3 study (C4591007); the study includes two safety groups based on age. The group of children 6 months to-<2 years constitutes of 1,776 subjects (3µg n=1,178; placebo n=598), and the group of children aged 2-<5 years included 2,750 subjects (3µg n=1,835; placebo n=915). The cutoff date is 29 April 2022.

Among the children aged 2-<5 years, pain at injection site was the most common local reaction, reported at a higher frequency in the 3µg BNT162b2 group (dose1 31%; dose2 31%; dose3 27%) compared to placebo group (dose1 21%; dose2 20%; dose3 13%).

Fatigue was the most common systemic event, reported at an almost similar frequency in the 3µg BNT162b2 group (dose1 30%; dose2 26%; dose3 25%) and in the placebo group (dose1 31%; dose2 23%; dose3 22%).

Fever was reported at a similar frequency between the two groups (5% vs 4-5%). Fever 38.9°C to 40°C was reported by ≤1.1% in both groups after each of the three doses.

No other differences in terms of systemic events were noted between the groups and the use of antipyretic/pain medication was also similar (9-11% vs 7-10%).

Among the children aged 6 months to <2 years, tenderness at injection site was the most common local reaction, reported at a higher frequency in the 3µg BNT162b2 group (dose1 17%; dose2 15%; dose3 16%) compared to placebo group (dose1 11%; dose2 9%; dose3 12%).

Irritability was the most common systemic event, reported at almost similar frequency in the 3µg BNT162b2 group (dose1 51%; dose2 47%; dose3 44%) and in the placebo group (dose1 47%; dose2 41%; dose3 38%).

Fever was reported at a similar frequency between the two groups (7% vs 6-7%), and fever 38.9°C to 40°C was reported by ≤2.0% of participants in the BNT162b2 group and ≤1.2% in the placebo group, after each of the three doses.

Most of the local and systemic events resolved within two 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.

Among the children aged 6 months to <2 years**,** Drowsiness was also frequently reported after administration of BNT162b2 3µg vaccine. Therefore, such information is reflected in the adverse reaction table in section 4.8 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

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.

There are limited data available on interaction with other vaccines given concomitantly.

3.6. Effects Table

Effects Table for Comirnaty 3µg (data cut-off:29 April 2022).

Effect	Short Description	Unit	BNT 162 b2 (3 µg)3 doses	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Vaccine efficacy	• First COVID-19 occurrence from 7days after Dose 3, **without** prior SARS-COV-2,	**% (95% CI)**	**80.3 % (**13.9; 96.7)			
		Cases/ Number of subjects at risk for the endpoint	**3/** 992	**7/**464	Few cases, small sample size, short follow-up	Evaluable efficacy population (7 days post dose 2) - Study C4951007
Immunogenicity	**Endpoint**	**Treatment group**	**2-<5 yo 3 µg 3 doses**	**16-25 yo 30 µg 2 doses**	Smaller sample size than planned, but sufficient number of subjects to evaluate immunogenicity	1 month after dose 2 Evaluable Immunogenicity population C4951001
	GMT (95% CI)	**GMR (Ratio)** 1.30 (1.13, 1.50)	**1535.2** (1388.2, 1697.8) N=143	**1180.0** (1066.6, 1305.4) N=170	**Noninferior**	
	Seroresponse rate % (95% CI)	• Difference% (95% CI) **-1.2**% (-1.5, 4.2)	**141/ 141 (100 %)** (97.4, 100.0%)	**168/170 (99.2%)** (98.8; 99.9%)	**Noninferior**	
	Endpoint	**Treatment group**	**6m-<2 yo 3 µg 3 doses**	**16-25 yo 30 µg 2 doses**	Smaller sample size than planned, but sufficient number of subjects to evaluate immunogenicity	1 month after dose 2 Evaluable Immunogenicity population C4951001
	GMT (95% CI)	**GMR (Ratio)** 1.19 (1.00, 1.42)	**1406.5** (1211.3, 1633.1) N=82	**1180.0** (1066.6, 1305.4) N=170	**Noninferior**	
	Seroresponse rate % (95% CI)	Difference % (95% CI) **-1.2**% (-3.4, 4.2)	**80/80 (100 %)** (95.5, 100.0%)	**168/170 (99.2%)** (98.8; 99.9%)	**Noninferior**	
Unfavourable Effects						

Effect	Short Description	Unit	BNT 162 b2 (3 µg)3 doses	Placebo	Uncertainties/ Strength of evidence	References
Pain at injection site	2-<5 years	%	Dose1 31% Dose2 31% Dose3 27%	Dose1 21% Dose2 20% Dose3 13%	Transient events, majority mild to moderate intensity	Phase 2/3 N=2,750 (3µg n=1,835; placebo n=915)
Fatigue	2-<5 years	%	Dose1 30% Dose2 26% Dose3 25%	Dose1 31% Dose2 26% Dose3 25%		
Fever	2-<5 years	%	Dose1 5% Dose2 5% Dose3 5%	Dose1 5% Dose2 5% Dose3 4%		
Tenderness at injection site	6 months to <2 years	%	Dose1 17% Dose2 15% Dose3 16%	Dose1 11% Dose2 9% Dose3 12%		Phase 2/3 N=1,776 (3µg n=1,178; placebo n=598)
Irritability	6 months to <2 years	%	Dose1 51% Dose2 47% Dose3 44%	Dose1 47% Dose2 41% Dose3 38%		
Fever	6 months to <2 years	%	Dose1 7% Dose2 7% Dose3 7%	Dose1 7% Dose2 6% Dose3 6%		
Severe COVID-19	2-<5 years		6 in active arm, post dose 2	1 in placebo arm		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There are currently no vaccines against COVID-19 approved in EU for the use in children below 5 years of age. The benefit of the vaccine in this age group is protection against symptomatic Covid-19. The known unfavourable effects are considered acceptable in terms of reactogenicity. No cases of myocarditis were observed in 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 such identified.

3.7.2. Balance of benefits and risks

The favourable effects outweigh the unfavourable effects for Comirnaty 3µg in the sought indication.

3.8. Conclusions

The overall benefit /risk balance of Comirnaty 0.1 mg/ml is positive, subject to the conditions stated in the "Recommendations" section

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 3 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 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.