EMADOC-1700519818-1645300
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMA/VR/0000224683

Invented name: COMIRNATY

Common name: COVID-19 mRNA vaccine

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Validation	18 August 2024	14 August 2024
☐	Start date	19 August 2024	19 August 2024
☐	CHMP Rapporteur AR	23 September 2024	19 September 2024
☐	CHMP Comments	7 October 2024	7 October 2024
☐	Updated CHMP Rapporteur AR	10 October 2024	n/a
☐	Request for Supplementary Information	17 October 2024	17 October 2024
☐	Submission of Responses	22 October 2024	21 October 2024
☐	Re-start date	23 October 2024	23 October 2024
☐	CHMP Rapporteur AR	06 November 2024	06 November 2024
☐	CHMP Comments	11 November 2024	11 November 2024
☐	Updated CHMP Rapporteur AR	14 November 2024	n/a
☐	Start of Written procedure	19 November 2024	19 November 2024
☒	CHMP Outcome	21 November 2024	21 November 2024

Table of contents

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CO	Clinical Overview
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
EC	European Commission
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titre
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IRC	Independent Review Committee
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
N	number of participants in the specified group
n	number of participants with the specified characteristic
NAAT	nucleic acid amplification test
RNA	ribonucleic acid
SAE	serious adverse event
S-binding	spike protein-binding
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIIV	seasonal inactivated influenza vaccine
SOC	system organ class
US	United States
VE	vaccine efficacy

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 31 July 2024 an application for group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
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A grouped application comprised of 3 Type II Variations as follows:

C.I.4: Update of sections 4.6, 4.8 and 5.1 of the SmPC in order to update pregnancy related information based on final results from interventional study C4591015, listed as a category 3 study in the RMP. Study C4591015 is a phase 2/3, placebo controlled, randomised, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older. The Package Leaflet is updated accordingly.

C.I.4: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update information for immunocompromised individuals based on final results from interventional study C4591024, listed as a category 3 study in the RMP. Study C4591024 is a phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age. The Package Leaflet is updated accordingly.

C.I.13: Submission of the C4591030 (secondary BNT162b2 immunogenicity endpoint analysis) supplementary (post-final) clinical study report. This is a phase 3, randomised, observer-blind trial to evaluate the safety and immunogenicity of BNT162b2 when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults 18 through 64 years of age. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet

2. Overall conclusion and impact on the benefit/risk balance

Within this type II variation, the MAH wishes to update the SmPC to describe the safety and immunogenicity of the Comirnaty Original while administrated to pregnant women (study C4591015) and to immunocompromised population from 2 years old and above (study C4591024). Also, MAH submitted the final neutralising antibody data when Comirnaty Original was administrated simultaneously with seasonal inactive influenza vaccine (SIIV).

C4591015

The study C4591015 was a global Phase 2/3, randomised, placebo-controlled, observer-blind study to evaluate the safety, tolerability, and immunogenicity of Comirnaty Original (30 µg) versus placebo (saline) administered in 2 doses, 21 days apart, in approximately 350 healthy pregnant women 18 years of age or older vaccinated at 24 to 34 weeks' gestation. Participants were randomised 1:1. Enrolment in this study was terminated due to enrolment challenges as a result of universal recommendations for COVID-19 vaccination of pregnant women and the increased global availability of COVID-19 vaccines.

Efficacy

The primary immunogenicity objective was to compare neutralising antibody titres 1 months post-dose 2 in pregnant women compared to the historical control, which consisted of age matched non-pregnant women from study C4591001. The secondary objectives were to investigate vaccine efficacy (VE), describe antibody levels of mothers and their infants at different time points, up to delivery and 6 months post-delivery.

All study arms had about 110 individuals in each. The geometric mean ratio (GMR) analysis of neutralising antibodies was descriptive, but the data showed, that antibody level was higher among non-pregnant women, especially when those without earlier SARS-CoV-2 infection were compared. This is expected results and in agreement with earlier data. Section 5.1 of SmPC was updated to include a short text regarding the study design with reference to pregnant participants lower geometric mean titres (GMT) and GMR compared to non-pregnant women from historical control group.

About 110 infants born for both vaccinated and placebo arms mothers were evaluated for S-protein binding antibodies. No neutralisation assay was performed for serum from infant participants. Considering the binding and neutralising antibodies have demonstrated good agreement, this is acceptable. At the delivery, there was high level of S-protein binding antibodies in infants. This is a sign of a successful antibody transfer through placenta, which is expected results and in agreement with data from other vaccines.

Safety

The safety database constitutes of pregnant women were randomised to receive either 30 µg of Comirnaty Original (BNT162b2, n=174) or placebo (n=174) administered in 2 doses, 21 days apart at 24 to 34 weeks' gestation and their infants. The study was limited in size due to the national recommended COVID-19 vaccination of pregnant women.

The reactogenicity profile was in line with previous results from non-pregnant adult individuals. The reactions were transient and most of them were mild to moderate at intensity. The most reported local reaction was pain at injection site (83% dose 1; 75% dose 2). The most frequently reported systemic events were fatigue (50%) and headache (34-41%). Fever was reported in 1-4% (dose 1 and 2 respectively). Most reported adverse events (AEs) were related to reactogenicity. The frequency of participants reporting any serious adverse event (SAE) was low and comparable to what was reported in the placebo group (5.6% and 5.5%, respectively). Two related AEs were reported among the pregnant participants receiving BNT162b2 (tachypnoea and injection site pain). None of the infants experienced

AEs related to maternal vaccination. No new safety concern was identified in this limited study population. Sections 4.6 and 4.8 of the SmPC are updated accordingly.

C4591024

Study C4591024 was a Phase 2b study that evaluated the safety, tolerability, and immunogenicity of BNT162b2 in immunocompromised participants >2 years of age based and utilised a vaccination series of 3 doses of age adapted Comirnaty followed by a fourth dose 3-6 months after dose 3.

Efficacy

The main immunogenicity objective was to evaluate neutralising antibody titres among baseline SARS-CoV-2 negative immunosuppressed population before and after the 3rd and 4th dose. The study recruited all ages from 2 years and above. The study had also explorative objectives. Most important of those is the evaluation of neutralising antibody titre among entire evaluable immunogenicity population regardless of their baseline SARS-CoV-2 status.

Enrolment in this study was terminated due to enrolment challenges as a result of universal recommendations for COVID-19 vaccination of immunocompromised individuals and the increased global availability of COVID-19 vaccines. Altogether 124 individuals were enrolled to the study, whereas 7 participants were adults. Therefore, the entire study became descriptive.

The immunogenicity data showed that most reduced antibody response appears among those who were on immunomodulatory therapy. The immune response improved for everybody regardless of diagnosis or age after the 4th dose. The primary immunogenicity objectives were to describe the immune responses among baseline SARS-CoV-2 negative immunocompromised population. There were roughly quarter of participants with unknown baseline status because these participants did not have some baseline sample (either blood or nasal swab) or had unclear test result. Section 5.1 of SmPC was updated to include a short text describing that all studied immunocompromised groups had higher GMT after fourth dose compared to the third dose. In conclusion, the 4th dose of Comirnaty improved neutralising antibody titres among immune-compromised population. This observation is in agreement with an earlier data.

Safety

The safety database constitutes of a total of 124 immunocompromised participants aged 2 to <5 years (n=37), 5-<12 years (n=65) 12-<18 years (n=15) and ≥18 years (n=7). The dose for each of the 4 vaccinations depended on the age of participants at time of vaccination (>12 years of age: 30-µg dose, 5 to <12 years of age: 10-µg dose, 2 to <5 years: 3-µg dose).

Most of the reactogenicity evens were transient and mild to moderate at intensity. Children aged 2-<5 years old were presented with a mild reactogenicity profile with a low frequency of both local and systemic events (<21%), similar as for non-immunocompromised participants presented in other studies. Children aged 5 to <12 years that constituted the largest age group (n=65) in this limited study reported local reactions (most common pain at injection site: 53-63%) and systemic events where fatigue (46-61%). Fever was reported in 1,5-12%, none had fever >40°C. Among the participants ≥12 years old (n=22), the reactogenicity profile was in line with the data that has been presented previously for non-immunocompromised participants. The majority of AEs were in the infections and infestations SOC, and all adverse events of special interests (AESIs) were likely related to participant's underlying condition. There were no deaths, no SAEs assessed as related by the investigator, no life-threatening AEs, and no AEs leading to withdrawal. No new safety concerns were identified in this limited study population of immunocompromised individuals. Section 4.8 of the SmPC is updated accordingly.

C4591030

The study C4591030, which investigated co-administration of Comirnaty and seasonal influenza vaccine study has been part of RMP since April 2021. 1134 participants were randomised at a ratio of 1:1 into the coadministration group, or the separate administration group (placebo and SIIV)/Comirnaty, stratified by age groups (18 through 49 years and 50 through 64 years) and by history of positive SARS-CoV-2 test results by nucleic acid amplification test (NAAT) or rapid antigen test prior to randomisation (with prior history of SARS-CoV-2 and without prior history of SARS-CoV-2). Data for this study has been assessed previously in procedure II/0201.

Efficacy

The primary immunogenicity objective was to demonstrate that the immune responses elicited by Comirnaty when co-administered with SIIV are non-inferior to those elicited by Comirnaty when administered alone, as demonstrated by full-length S-binding IgG levels. The GMR met the pre specified non-inferiority criteria (lower limit of the 2-sided 95% CI for the GMR >0.67) as immunogenicity primary endpoint of this study, which was evaluated during an earlier procedure II/201.

In current update, an overview of results of the secondary BNT162b2 immunogenicity endpoint analyses of SARS-CoV-2 neutralisation titres for a subset of approximately 200 participants were presented. The neutralising assay results from this smaller selected population agree generally with the earlier presented S-protein binding antibody results from entire evaluable immunogenicity population. The antibody titre was very high for both separate and co-administration groups. The antibody concentration was numerically higher in separate administration group compared to the co-administration group according to both serology methods for this selected smaller study population. As assessed in II/0201, the GMRs of the S-protein binding antibody data from entire evaluable immunogenicity population did meet the pre specified non-inferiority criteria. The GMR coadministration vs. separate administration was 0.83 [95% CI: 0.77, 0.89]). For this post-hoc analysis for small subgroup, the GMR would not meet the pre specified non-inferiority criteria for neither of the assays (lower limit of the 2-sided 95% CI for the GMR >0.67). The result was very near to non-inferiority criteria, GMR LL 0.66 for neutralisation and 0.67 for S-binding assay. According to the applicant, this may be due to the sampling variability and smaller sample size of the neutralisation subset.

There will be no immunogenicity data presented from this co-administration study in SmPC as agreed earlier during II/201. The clinical impact for lower titre of neutralising antibodies in case of co-administration with SIIV is unknown.

The benefit-risk balance of COMIRNATY remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II
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C.I.4: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update information for immunocompromised individuals based on final results from interventional study C4591024, listed as a category 3 study in the RMP. Study C4591024 is a phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of Comirnaty (original) in immunocompromised participants ≥2 years of age. The Package Leaflet is updated accordingly.

C.I.13: Submission of the supplementary (post-final) clinical study report for study C4591030 (secondary Comirnaty immunogenicity endpoint analysis). This is a phase 3, randomised, observer-blind trial to evaluate the safety and immunogenicity of Comirnaty (original) when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults 18 through 64 years of age.

In addition, the MAH took the opportunity to introduce minor editorial changes to the Product information.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion "EMA/VR/0000224683"

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The present submission is intended to provide final immunogenicity, efficacy and safety analyses from studies C4591015 and C4591024, as well as secondary neutralisation titre data from study C4591030. As a result, the MAH has proposed update of the SmPC sections 4.4, 4.6, 4.8 and 5.1.

The phase 3 study C4591015 enrolled 348 healthy pregnant women participants ≥18 years of age and their infants, once born. This Phase 2/3 study evaluated 2 doses of BNT162b2 30 µg or placebo administered 21 days apart (Visits 1 and 2) in pregnant women vaccinated at 24 to 34 weeks' gestation.

The phase 2b study C4591024 enrolled a total of 124 immunocompromised participants aged 2 to <18 years (n=117) and ≥18 years (n=7). The study evaluated a 4-dose schedule (the first 2 doses separated by 21 days), with a third dose occurring 28 days after the second dose. The fourth dose was administered 3-6 months after Dose 3, at the discretion of the investigator. The dose for each of the 4 vaccinations depended on the age of participants at time of vaccination (>12 years of age: 30-µg dose, 5 to <12 years of age: 10-µg dose, 2 to <5 years: 3-µg dose).

Study C4591030 evaluated the safety and immunogenicity of a fourth dose of BNT162b2 30 µg administered concomitantly with SIIV compared with the vaccines given 1 month apart in adults 18 through 64 years of age who had previously received 3 doses of BNT162b2 30 µg. This study enrolled a total of 1134 participants 18 through 64 years of age who had previously received 3 doses of BNT162b2 30 µg: 568 participants in the coadministration group (BNT162b2 and SIIV)/placebo and 566 participants in the separate-administration group (placebo and SIIV)/BNT162b2. This study has been evaluated earlier during procedure II/201 and the safety data is therefore not included in this report. The MAH has here submitted the SARS-CoV-2 neutralisation assay results for a subset of participants (N= 100 in each study arm), which was a secondary immunogenicity objective of this study.

6. Clinical Efficacy aspects

6.1. Study C4591015

6.1.1. Methods – analysis of data submitted

This was a global Phase 2/3, randomised, placebo-controlled, observer-blind study to evaluate the safety, tolerability, and immunogenicity of 30 µg of BNT162b2 or placebo administered in 2 doses, 21 days apart, in approximately 350 healthy pregnant women 18 years of age or older vaccinated at 24 to 34 weeks' gestation. Participants were randomised 1:1 to receive BNT162b2 or placebo (saline).

The Phase 2 portion of the study included approximately 200 pregnant women enrolled at 27 to 34 weeks' gestation. The IRC reviewed safety data through 7 days after the second dose for all Phase 2 participants. The Phase 3 portion of this study included approximately 150 pregnant women enrolled at 24 to 34 weeks' gestation. Phase 3 proceeded after the first 200 maternal participants had been enrolled in Phase 2. Maternal participants who originally received placebo could receive BNT162b2 at the 1-month post delivery visit.

Enrolment in this study was terminated due to Enrolment challenges as a result of universal recommendations for COVID-19 vaccination of pregnant women and the increased global availability of COVID-19 vaccines.

Objectives, Estimands, and Endpoints

Table 1: Objectives, Estimands, and Endpoints

Objectives	**Estimands**	**Endpoints**
Primary Immunogenicity		
To describe the immune response to prophylactic BNT162b2 in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation and reference to the immune response in nonpregnant women 18 years of age or older from the C4591001 study without evidence of past SARS-CoV-2 infection and with and without evidence of prior SARS-CoV-2 infection	In female participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection: • GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralising titres in pregnant women to those in nonpregnant women 1 month after Dose 2	SARS-CoV-2 neutralising titres
Secondary		
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 and asymptomatic SARS-CoV-2 infection occurring from 7 days after Dose 2 through 1 month after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation without evidence of prior SARS-CoV-2 infection and with and without evidence of prior SARS-CoV-2 infection	In maternal participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection: • 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of blinded follow-up based on central laboratory or locally confirmed NAAT
To describe the immune response over time and persistence of prophylactic BNT162b2 when administered to maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation.	In maternal participants complying with the key protocol criteria (evaluable maternal participants) from each vaccine group: • GMCs/GMTs, at baseline (before Dose 1), 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery • GMFRs from baseline through 2 weeks after Dose 2, 1 month after Dose 2, at delivery, and 6 months after delivery	• Full-length S-binding IgG levels • SARS-CoV-2 neutralising titres
To describe the immune response in infants born to maternal participants vaccinated with prophylactic BNT162b2 during pregnancy	In infants born to evaluable maternal participants from each vaccine group: • GMCs and GMFRs, at birth and 6 months after deliver	• Full-length S-binding IgG levels

Exploratory		
To describe the incidence of confirmed COVID-19 among maternal participants who were vaccinated with BNT162b2.	In maternal participants who received BNT162b2 at initial randomisation: • Incidence per 1000 person-years of follow-up	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of asymptomatic SARS-CoV-2 infection through 6 months after delivery in maternal participants 18 years of age or older vaccinated at 24 to 34 weeks' gestation with BNT162b2 at initial randomisation and without evidence of prior SARS-CoV-2 infection.	In maternal participants who received BNT162b2 at initial randomisation and without evidence of prior SARS-CoV-2 infection: • Incidence per 1000 person-years of follow-up	Incidence of asymptomatic SARS-CoV-2 infection per 1000 person-years of follow-up based on N-binding antibody seroconversion
To describe the serological responses among maternal participants to the BNT162b2 vaccine candidate in cases of: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19	In each subset of evaluable maternal participants from each vaccine group with: • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection but no confirmed COVID-19 • GMCs/GMTs and GMFRs at baseline, 1 month after Dose 2, at delivery, and 6 months after delivery	• Full-length S-binding IgG levels • SARS-CoV-2 neutralising titres
To describe the immune response to prophylactic BNT162b2 between Dose 1 and Dose 2 when administered to maternal participants 18 years of age or older vaccinated at 27 to 34 weeks' gestation in the Phase 2 portion of the study	In evaluable maternal participants: • GMCs/GMTs at baseline and before Dose 2 • GMFRs from baseline to before Dose 2	• Full-length S-binding IgG levels • SARS-CoV-2 neutralising titres
To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic BNT162b2 during pregnancy.	In infants born to maternal participants from each vaccine group, based on the breastfeeding status: • GMCs and GMFRs, at birth and 6 months after delivery	Full-length S-binding IgG levels
To describe the incidence of confirmed COVID-19 in infants born to maternal participants who were vaccinated with BNT162b2 during pregnancy	In infants born to maternal participants from each vaccine group: • Incidence rate of infant	• COVID-19 incidence per 1000 person-years of follow-up based on central

	participants with confirmed COVID-19	laboratory or locally confirmed NAAT
To describe MIS-C cases in infants born to maternal participants who were vaccinated with BNT162b2 during pregnancy	In infants born to maternal participants from each vaccine group: • Incidence rate of MIS-C	MIS-C incidence per 1000 person-years of follow-up

Inclusion/Exclusion Criteria

Enrolled in this study were participants who were healthy pregnant women ≥18 years of age and their infants, once born. Enrolment was monitored to help ensure distribution of vaccination across the gestational age ranges of 27 0/7 to 34 0/7 weeks for Phase 2 and ≥24 0/7 and ≤34 0/7 weeks for Phase 3.

Allocation

All participants were centrally assigned to randomised study intervention using an IRT system.

Blinding

The study was observer-blinded, as the physical appearance of the investigational vaccine and the placebo may differ. The participant, investigator, study coordinator, and other site staff were blinded through the 1-month postdelivery visit for each maternal participant, at which point maternal participants who originally received placebo could receive BNT162b2.

Immunogenicity

The below assays were performed for immunogenicity analyses, which were all based on samples analysed at the central laboratory.

- SARS-CoV-2 neutralisation assay;
- Full-length S-binding IgG levels;
- N-binding antibody assay

For the primary immunogenicity objective, the GMR at 1 month after Dose 2 was calculated as the difference in means of logarithmically transformed assay results (SARS-CoV-2 neutralising titres in pregnant women minus those in nonpregnant women) and exponentiating the difference. Two-sided CIs were obtained by calculating CIs using Student t distribution for the difference of the means of the logarithmically transformed assay results and exponentiating the confidence limits. The primary immunogenicity analysis included participants without evidence of prior SARS-CoV-2 infection and with and without evidence of prior SARS-CoV-2 infection. The nonpregnant participants were randomly selected from Study C4591001 female participants based on 1:1 age matching to the maternal participants within each vaccine group.

Efficacy

Efficacy was assessed throughout a maternal and infant participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a maternal or infant participant developed acute respiratory illness, for the purposes of the study he or she was considered to potentially have COVID-19 illness. The assessments included a nasal (midturbinate) swab, which was tested at a central laboratory using an approved and validated RT-PCR test, or other equivalent nucleic acid amplification–based test (i.e., NAAT) to detect SARS-CoV-2. In addition, clinical information and results from local

standard-of-care tests were assessed. The central laboratory NAAT result was used for the case definition, unless no result was available from the central laboratory, in which case a local NAAT result could be used.

Statistics general consideration

All of the immunogenicity analyses were based on the evaluable immunogenicity populations. An additional analysis was performed based on the all-available immunogenicity populations as there was over 10% difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations.

Participants were summarized according to the vaccine group to which they (or their mothers) were randomised.

The efficacy analyses were based on the evaluable efficacy populations. In addition, VE was also analysed by the all-available efficacy (mITT) populations.

Due to early Enrolment termination and reduced sample size, all endpoints were analysed descriptively without formal hypothesis tests.

Subgroup analyses based on race and ethnicity were performed on all primary safety and immunogenicity endpoints (as supplemental analyses).

Analyses among HIV-positive women and their infants were provided separately, as these were considered special populations for this study.

Exploratory analyses of the serological response at baseline, 1 month after Dose 2, delivery, and 6 months after delivery were planned for maternal participants with confirmed COVID- 19, confirmed severe COVID-19, or SARS-CoV-2 infection, based on both protocol and CDC definitions; however, since there were no maternal participants who reported severe COVID-19 and a limited number of confirmed COVID-19 cases, these analyses were not conducted as the sample sizes would have been too small for any meaningful interpretation.

Assessor´s comment: The methodology of the Study C4591015 is similar to the Comirnaty studies reported earlier and is approvable. There were plenty of exploratory objectives for this study, which were not all calculated due to limited sample size. Also, not all of the calculated explorative results are presented in current AR due to non-conclusive results from the limited number of participants.

In immunological comparison, age matched historical control group consisting of non-pregnant women was used. This is not the ideal control group as the time and place for the control is not the same as for the active arm. The study C4591015 recruited since 16.02.2021, whereas C4591001 phase 3 recruited in summer 2020. The time gap between studies was at least 6 months.

Still, we have to accept it as it was not feasible and ethical to conduct a clinical trial on a group, to whom the vaccination with Comirnaty was officially recommended.

The issues of postponement of the study results has been assessed during an earlier procedure EMEA/H/C/005735/MEA/012.2. It was agreed, that due to the high burden in neutralisation assay laboratory, the study results were delayed.

6.1.2. Results

Immunogenicity population- Maternal Participants

Exclusions from the evaluable immunogenicity population were balanced across BNT162b2 and placebo groups among C4591015 participants and among C4591001 participants; the most common reason for exclusion for C4591015 participants was due to a lack of at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2. The proportions of participants without evidence of prior infection for the C4591015 (ca. 33%) and C4591001 (86%) study participants reflect varying conditions of the COVID-19 pandemic, as the studies were conducted in different times and countries.

Table 2: Immunogenicity Populations – Maternal Participants (Study C4591015) and Nonpregnant Female Participants (Study C4591001) – All Randomized Participants

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	C4591015 (Maternal)	C4591001 (Nonpregnant Women)	C4591015 (Maternal)	C4591001 (Nonpregnant Women)
	n[a] (%)	n[a] (%)	n[a] (%)	n[a] (%)
Randomized[b]	174 (100.0)	123 (100.0)	174 (100.0)	133 (100.0)
All-available immunogenicity population	171 (98.3)	120 (97.6)	170 (97.7)	129 (97.0)
HIV-positive	12 (6.9)	0	9 (5.2)	0
Participants excluded from all-available immunogenicity population	3 (1.7)	3 (2.4)	4 (2.3)	4 (3.0)
Reason for exclusion				
Did not receive at least 1 dose of the study intervention	1 (0.6)	0	1 (0.6)	0
Did not have at least 1 valid and determinate immunogenicity result after vaccination	2 (1.1)	N/A	3 (1.7)	N/A
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	N/A	3 (2.4)	N/A	4 (3.0)
Evaluable immunogenicity population	111 (63.8)	114 (92.7)	115 (66.1)	124 (93.2)
HIV-positive	10 (5.7)	0	9 (5.2)	0
Without evidence of infection up to 1 month after Dose 2[c]	59 (33.9)	107 (87.0)	58 (33.3)	113 (85.0)
Participants excluded from evaluable immunogenicity population	63 (36.2)	9 (7.3)	59 (33.9)	9 (6.8)
Reason for exclusion[d]				
Not eligible for the study at randomization	7 (4.0)	0	4 (2.3)	0
Did not receive 2 doses of the vaccine to which they were randomized	4 (2.3)	1 (0.8)	4 (2.3)	4 (3.0)
Did not receive Dose 2 within 19-42 days after Dose 1	3 (1.7)	3 (2.4)	3 (1.7)	1 (0.8)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2	59 (33.9)	6 (4.9)	57 (32.8)	8 (6.0)
Had other protocol deviation(s) as determined by the clinician	8 (4.6)	0	5 (2.9)	0

Abbreviation: N/A = not applicable.
Note: Participants from C4591001 are a selected subset of age matched nonpregnant female Phase 3 participants.
Note: Blood samples for immunogenicity assessment drawn at the delivery visit but within 1 month after Dose 2 visit window were also included in this analysis.
a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Participants who had no serological or virological evidence (prior to the 1 month after Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Dose 1 and 1 month after Dose 2 and no positive result between visits, negative NAAT [nasal swab] at Dose 1, Dose 2, and any unscheduled visit prior to the 1 month after Dose 2 blood sample collection) were included in the analysis.
d. Participants may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 01MAR2024 (02:39)
(Data cutoff date : C4591001 [31Aug2021]) Output File: ./nda3/C4591015 Bridging/adva s008 imm pop brdg

Demographics

A greater proportion of C4591015 participants identified as Black or African American (≥27.0% compared with ≥5.3% in C4591001) and a higher percentage were enrolled from South African sites (≥24.3% compared with ≥0.8% in C4591001). Additionally, the proportion of C4591015 maternal participants with positive baseline SARS-CoV-2 status (≥37.8%) was higher than what was observed among C4591001 participants (≥3.5%), which could have been due to the different timepoints at which participants were enrolled in each study relative to the progression of the COVID-19 pandemic. The majority of participants identified as non-Hispanic/non-Latino (≥62.2%). The median age of participants at Dose 1 was 30.0 years, and the median gestational age at Dose 1 for the BNT162b2 and placebo groups was 28.9 weeks and 29.1 weeks, respectively. Both groups were similar with regards to HIV status. Pre-pregnancy BMIs for C4591015 maternal participants were generally higher than those observed in C4591001 nonpregnant female participants.

Table 3: Demographic Characteristics – Maternal Participants (Study C4591015) and Nonpregnant Female Participants (Study C4591001) – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	C4591015 (Maternal) (N[a]=111) n[b] (%)	C4591001 (Nonpregnant Women) (N[a]=114) n[b] (%)	C4591015 (Maternal) (N[a]=115) n[b] (%)	C4591001 (Nonpregnant Women) (N[a]=124) n[b] (%)
Race				
White	77 (69.4)	94 (82.5)	77 (67.0)	94 (75.8)
Black or African American	30 (27.0)	6 (5.3)	32 (27.8)	14 (11.3)
American Indian or Alaska Native	0	2 (1.8)	0	2 (1.6)
Asian	2 (1.8)	7 (6.1)	6 (5.2)	8 (6.5)
Multiracial	0	5 (4.4)	0	6 (4.8)
Not reported	2 (1.8)	0	0	0
Ethnicity				
Hispanic/Latino	42 (37.8)	39 (34.2)	40 (34.8)	45 (36.3)
Non-Hispanic/non-Latino	69 (62.2)	75 (65.8)	75 (65.2)	79 (63.7)
Country				
Argentina	0	24 (21.1)	0	27 (21.8)
Brazil	11 (9.9)	16 (14.0)	10 (8.7)	11 (8.9)
Germany	0	5 (4.4)	0	5 (4.0)
South Africa	27 (24.3)	2 (1.8)	31 (27.0)	1 (0.8)
Spain	16 (14.4)	0	11 (9.6)	0
Turkey	0	2 (1.8)	0	1 (0.8)
United Kingdom	5 (4.5)	0	4 (3.5)	0
United States	52 (46.8)	65 (57.0)	59 (51.3)	79 (63.7)
HIV-Positive				
No	101 (91.0)	114 (100.0)	106 (92.2)	124 (100.0)
Yes	10 (9.0)	0	9 (7.8)	0
Age at Dose 1 (years)				
Mean (SD)	30.0 (6.04)	30.1 (6.24)	30.0 (5.93)	29.8 (5.88)
Median	30.0	30.0	30.0	30.0
Min, max	(18, 44)	(18, 44)	(18, 44)	(18, 44)
Gestational age at Dose 1 (weeks)				
n	111	N/A	115	N/A
Mean (SD)	29.2 (2.49)	N/A	29.3 (2.34)	N/A
Median	28.9	N/A	29.1	N/A
Min, max	(24.0, 34.9)	N/A	(24.1, 35.6)	N/A
Gestational age at Dose 2 (weeks)				
n	111	N/A	115	N/A
Mean (SD)	32.2 (2.46)	N/A	32.4 (2.36)	N/A
Median	32.0	N/A	32.3	N/A
Min, max	(27.0, 37.7)	N/A	(27.0, 38.6)	N/A
Baseline SARS-CoV-2 status				
Positive	42 (37.8)	4 (3.5)	49 (42.6)	6 (4.8)
Negative	67 (60.4)	109 (95.6)	63 (54.8)	118 (95.2)
Missing	2 (1.8)	1 (0.9)	3 (2.6)	0
Body mass index (BMI)				
Underweight (<18.5 kg/m^2)	0	2 (1.8)	0	5 (4.0)
Normal weight (≥18.5 kg/m^2 - 24.9 kg/m^2)	27 (24.3)	51 (44.7)	27 (23.5)	49 (39.5)
Overweight (≥25.0 kg/m^2 - 29.9 kg/m^2)	41 (36.9)	30 (26.3)	42 (36.5)	32 (25.8)
Obese (≥30.0 kg/m^2)	43 (38.7)	31 (27.2)	46 (40.0)	38 (30.6)

Abbreviations: N/A = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Gestational age at Dose 2 (weeks) = gestational age at Dose 1 (weeks) + (date of Dose 2 - date of Dose 1)/7.
Note: Participants from C4591001 are a selected subset of age matched nonpregnant female Phase 3 participants.
Note: As per inclusion criteria 10 for weight in C4591015 protocol, the BMI included is pre-pregnancy and if unavailable, the BMI recorded from the first obstetric visit was used. The weight categories included in the table were created as per these records.
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.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 01MAR2024 (02:39)
(Data cutoff date : C4591001 [31Aug2021]) Output File: ./nda3/C4591015_Bridging/adsl_s005_demo_p3_saf17

Assessor´s comment: the study pregnancy study recruited mainly in USA (47%), South Africa (24%) and Spain (14%), whereas the historical control population was from USA (57%), Argentina (21%), Brazil (14%) and Germany(4%). The geographical origin of study population may influence the antibody levels among baseline seropositives as different SARS-COV-2 were spread in different locations. Also it is unknown, how many different SARS-CoV-2 infections every seropositive participant have had. As the historical control was recruited early in the pandemic, much higher proportion was still seronegative (95%) compared to the pregnancy study population (55-60 %).

Immunogenicity population – Infant Participants

The proportions of infant participants included in the immunogenicity populations were balanced between the BNT162b2 and placebo groups. The evaluable immunogenicity population for infant participants included 109 participants in the BNT162b2 group and 105 participants in the placebo group.
The proportion of participants excluded from the evaluable immunogenicity population was 34.7% and 37.5% for the BNT162b2 group and the placebo group, respectively. The most frequent reason for exclusion of infant participants from the evaluable immunogenicity populations was because the mother was not considered to be an evaluable immunogenicity maternal participant.

Table 4: Immunogenicity Populations (infant)

	Maternal Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	167 (100.0)	168 (100.0)	335 (100.0)
All-available immunogenicity population (infant)	163 (97.6)	156 (92.9)	319 (95.2)
HIV-positive maternal	11 (6.6)	9 (5.4)	20 (6.0)
Participants excluded from all-available immunogenicity population (infant)	4 (2.4)	12 (7.1)	16 (4.8)
Reason for exclusion[c]			
Were born to maternal participants who were not all-available immunogenicity maternal participants	0	1 (0.6)	1 (0.3)
Did not have at least 1 valid and determinate immunogenicity result	4 (2.4)	12 (7.1)	16 (4.8)
Evaluable immunogenicity population (infant)	109 (65.3)	105 (62.5)	214 (63.9)
HIV-positive maternal	10 (6.0)	9 (5.4)	19 (5.7)
Participants excluded from evaluable immunogenicity population (infant)	58 (34.7)	63 (37.5)	121 (36.1)
Reason for exclusion[c]			
Were born to maternal participants who were not evaluable immunogenicity maternal participants	58 (34.7)	54 (32.1)	112 (33.4)
Did not have at least 1 valid and determinate immunogenicity result	4 (2.4)	12 (7.1)	16 (4.8)
Had other protocol deviation(s) as determined by the clinician	0	1 (0.6)	1 (0.3)

a. n = Number of participants with the specified characteristic, or the total sample.
b. Infants were not randomized and vaccinated but are summarized according to the vaccine group to which their mothers were randomized. These values are the denominators for the percentage calculations .
c. Participants may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (08:47) Source Data: adsl Table Generation: 19FEB2024 (04:02)
(Database snapshot date: Safety [29Mar2023], Immunogenicity [09Jan2024]) Output File: ./nda3/C4591015 CSR/adva s008 imm pop inf

Demographics

Demographics and baseline characteristics for the safety population of infant participants were balanced for the BNT162b2 and placebo groups. The majority of participants were White (67%), non-Hispanic/non-Latino (64%), and located in the US (48%) or South Africa (27%). The majority of infants were born ≥37 weeks to 41 weeks 6 days, and 89% of infant participants were breastfed. Both groups were similar with regards to HIV status.

Table 5: Demographic Characteristics – Evaluable Immunogenicity Population (Infant)

	Maternal Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=109) n[b] (%)	Placebo (N[a]=105) n[b] (%)	Total (N[a]=214) n[b] (%)
Sex			
Male	50 (45.9)	57 (54.3)	107 (50.0)
Female	59 (54.1)	48 (45.7)	107 (50.0)
Race			
White	76 (69.7)	67 (63.8)	143 (66.8)
Black or African American	29 (26.6)	29 (27.6)	58 (27.1)
Asian	1 (0.9)	5 (4.8)	6 (2.8)
Multiracial	0	1 (1.0)	1 (0.5)
Not reported	3 (2.8)	3 (2.9)	6 (2.8)
Ethnicity			
Hispanic/Latino	40 (36.7)	35 (33.3)	75 (35.0)
Non-Hispanic/non-Latino	67 (61.5)	69 (65.7)	136 (63.6)
Not reported	2 (1.8)	1 (1.0)	3 (1.4)
Country			
Brazil	11 (10.1)	8 (7.6)	19 (8.9)
South Africa	27 (24.8)	31 (29.5)	58 (27.1)
Spain	16 (14.7)	10 (9.5)	26 (12.1)
United Kingdom	5 (4.6)	4 (3.8)	9 (4.2)
United States	50 (45.9)	52 (49.5)	102 (47.7)
Mother HIV-Positive			
Yes	10 (9.2)	9 (8.6)	19 (8.9)
No	99 (90.8)	96 (91.4)	195 (91.1)
Breast Feeding Status			
Yes	96 (88.1)	94 (89.5)	190 (88.8)
No	13 (11.9)	8 (7.6)	21 (9.8)
Missing	0	3 (2.9)	3 (1.4)
Gestational age at birth (weeks)			
<37 weeks 0 days	1 (0.9)	4 (3.8)	5 (2.3)
≥37 weeks - 41 weeks 6 days	107 (98.2)	99 (94.3)	206 (96.3)
≥42 weeks	1 (0.9)	2 (1.9)	3 (1.4)

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (08:47) Source Data: adsl Table Generation: 19FEB2024 (03:17)
(Database snapshot date: Safety [29Mar2023], Immunogenicity [09Jan2024]) Output File: ./nda3/C4591015 CSR/adsl s005 evalim inf

Efficacy population- maternal participants

The evaluable efficacy population included 161 participants in the BNT162b2 group and 163 participants in the placebo group.

Exclusions from the evaluable efficacy population were similar across groups; the most common reason was due to other protocol deviation(s) as determined by the clinician.

The evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2 included 91 participants in the BNT162b2 group and 94 participants in the placebo group.

Efficacy population- infant participants

The evaluable efficacy population included 167 participants in the BNT162b2 group and 168 participants in the placebo group.

For infants born to mothers in the BNT162b2 and placebo groups, most (88.0% and 90.5%,respectively) were breastfed and few (6.6% and 5.4%, respectively) were born to mothers who were HIV-positive.

Primary immunogenicity – Maternal GMR of Neutralising Titres

- Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 (evaluable immunogenicity population), the ratio of the neutralising GMT (GMR) in Study C4591015 maternal participants in the BNT162b2 (30 µg) group to that of Study C4591001 nonpregnant females who received BNT162b2 30 µg was 0.67 (95% CI: 0.50, 0.90). See the table below, which is the version MAH intends to be added to the SmPC.
- For participants with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 (evaluable immunogenicity population), the model-adjusted ratio of the neutralising GMT (adjusted GMR) in Study C4591015 maternal participants in the BNT162b2 (30 µg) group to that of Study C4591001 nonpregnant females who received BNT162b2 30 µg was 0.95 (95% CI: 0.69, 1.30).

Table 6: Geometric mean ratios – participants without or with or without evidence of infection up to 1 month after Dose 2 – maternal participants (study 9) and nonpregnant female participants (Study 2) – evaluable immunogenicity population*

Participants without evidence of infection*						
		Comirnaty				
		Study 9 Pregnant women		Study 2 Nonpregnant women		Pregnant/ nonpregnant
Assay	Dose/ Sampling time point[b]	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	GMR[e] (95% CI)[e]
SARS-CoV-2 neutralization assay - NT50 (titre)[a]	2/1 month	58	1 109.2 (849.2, 1 448.9)	107	1 663.7 (1 411.5, 1 960.8)	0.67 (0.50, 0.90)
Participants with or without evidence of infection						
		Comirnaty				
		Study 9 Pregnant women		Study 2 Nonpregnant women		Pregnant/ nonpregnant
Assay	Dose/ Sampling time point[b]	n[f]	GMT[g] (95% CI[g])	n[f]	GMT[g] (95% CI[g])	GMR[h] (95% CI)[h]
SARS-CoV-2 neutralization assay - NT50 (titre)[a]	2/1 month	99	1 900.0 (1 518.2, 2 377.7)	113	2 005.7 (1 627.0, 2 472.6)	0.95 (0.69, 1.30)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants from Study 2 are a selected subset of age matched nonpregnant female Phase 3 participants.

* Participants who had no serological or virological evidence (prior to the 1 month after Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Dose 1 and 1 month after Dose 2 and no positive result between visits, negative NAAT [nasal swab] at Dose 1, Dose 2, and any unscheduled visit prior to the 1 month after Dose 2 blood sample collection) were included in the analysis.

a. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020]).
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
e. GMR and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
f. n = Number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point.
g. GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed NT50 titres using a regression model with group, age at Dose 1 in years (continuous), and baseline log transformed NT50 titres.
h. GMR (ratio of GMTs of pregnant women to nonpregnant women) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Assessor´s comment: the GMR analysis was descriptive, but the data shows, that antibody level was higher among non-pregnant women, especially among those without earlier SARS-CoV-2 infection. This is expected results and in agreement with earlier data. We suggested to use short text instead of the table to describe that pregnant woman had lower GMT and GMR than non-pregnant women from historical control group (OC), which the Applicant has followed in an updated SmPC.

Secondary Immunogenicity Analyses- Maternal participants

Neutralising GMTs and Full-length S-binding IgG GMCs

In maternal participants in the BNT162b2 group, GMTs of neutralising antibodies and full-length S-binding IgG GMTs were substantially increased, compared to the placebo group, peaked at 2 weeks after Dose 2 and remained elevated through the 6-month postdelivery visit. See the results in Table below. Results for participants in the evaluable immunogenicity population with or without evidence of infection followed a similar trend.

Table 7: Geometric Mean Titres and Concentrations of Participants Without Evidence of Infection – Evaluable Immunogenicity Population (Maternal)

		Vaccine Group (as Randomized)			
		BNT162b2 (30 µg)		Placebo	
Assay	Dose/Sampling Time Point[a]	n[b]	GMT/GMC[c] (95% CI[c])	n[b]	GMT/GMC[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	65	43.5 (43.5, 43.5)	59	44.8 (42.3, 47.5)
	2/2 Weeks	58	1901.8 (1472.9, 2455.5)	54	44.5 (42.5, 46.5)
	2/1 Month	50	1099.4 (820.6, 1473.0)	49	43.5 (43.5, 43.5)
	Delivery	55	678.3 (526.4, 874.0)	47	43.5 (43.5, 43.5)
	6-Month postdelivery	26	492.8 (219.6, 1105.7)	N/A	
Full-length S-binding IgG level assay (U/mL)	1/Prevax	65	2.1 (1.5, 2.8)	59	2.0 (1.3, 3.0)
	2/2 Weeks	58	7639.0 (6403.0, 9113.6)	54	1.7 (1.2, 2.6)
	2/1 Month	50	4336.9 (3456.0, 5442.4)	49	1.6 (1.1, 2.3)
	Delivery	55	2894.2 (2370.8, 3533.1)	47	1.5 (1.0, 2.2)
	6-Month postdelivery	26	1603.3 (887.8, 2895.5)	N/A	

Abbreviations: GMC = geometric mean concentration; GMT = geometric mean titer; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; N/A = not applicable; NT50 = 50% neutralizing titer; S = spike protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Human immunodeficiency virus (HIV)-positive participants are not included in this summary.
Note: Participants who had no serological or virological evidence (up to the reporting timepoints) of past SARS-CoV-2 infection (ie, a negative N-binding antibody [serum] result at all planned visits up to the reporting timepoints, a negative NAAT [nasal swab] result at the study vaccination visit and at any unscheduled visit up to the reporting timepoints) and 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, GMCs, and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers or concentrations and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 12JAN2024 (03:07) Source Data: adva Table Generation: 22FEB2024 (01:04)
(Database snapshot date: Safety [29Mar2023], Immunogenicity [09Jan2024]) Output File: ./nda3/C4591015 CSR/adva s001 eval wo

Assessor´s comment: the neutralising and binding antibody levels show agreement, so that the highest levels were measured 2 weeks post dose 2. The levels then started to lower reaching 3-4x lower levels at 6 months post-delivery timepoint in comparison to the 2 weeks post dose 2. This antibody kinetics is in agreement with an earlier data.

The placebo group demonstrated about the same low antibody level than at the baseline during entire study period.

GFMRs

GMFRs of neutralising and binding antibodies at 1 month after Dose 2 was substantially higher in the BNT162b2 group compared to the placebo group. In maternal participants in the BNT162b2 group, the GMFR for neutralising and full- length S- binding antibodies peaked at 2 weeks after Dose 2 and remained elevated through the delivery visit and 6-month postdelivery timepoints. See the results below. Results for participants in the overall evaluable immunogenicity population followed a similar trend.

Table 8: Geometric Mean Fold Rise From Before Vaccination to Each Subsequent Time Point (Evaluable Immunogenicity Population, All-Available Immunogenicity Population [Maternal])

		Vaccine Group (as Randomized)			
		BNT162b2 (30 µg)		Placebo	
Assay	Dose/Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/2 Weeks	100	46.8 (34.8, 62.9)	106	1.1 (0.9, 1.2)
	2/1 Month	87	34.7 (26.0, 46.1)	97	1.4 (1.1, 1.7)
	Delivery	92	17.8 (12.9, 24.7)	90	1.2 (1.0, 1.5)
	6-Month postdelivery	85	28.8 (18.2, 45.6)	N/A	
Full-length S-binding IgG level assay (U/mL)	2/2 Weeks	100	770.0 (445.2, 1331.8)	106	1.2 (0.9, 1.5)
	2/1 Month	88	562.2 (349.5, 904.5)	97	1.3 (1.0, 1.6)
	Delivery	92	382.2 (229.0, 637.9)	91	1.0 (0.8, 1.4)
	6-Month postdelivery	85	252.2 (127.0, 500.7)	N/A	

Abbreviations: GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; N/A = not applicable; NT50 = 50% neutralizing titer; S = spike protein; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Human immunodeficiency virus (HIV)-positive participants are not included in this summary.
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.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 12JAN2024 (03:07) Source Data: adva Table Generation: 22FEB2024 (01:04)
(Database snapshot date: Safety [29Mar2023], Immunogenicity [09Jan2024]) Output File: ./nda3/C4591015_CSR/adva_s002_gmfr_evl

Subgroup Analyses

GMTs at prevaccination (Dose 1) and 1 month after Dose 2 were evaluated by race, ethnicity, and baseline SARS-CoV-2 status in Study C4591015 maternal participants and Study C4591001 nonpregnant females, see table below. Among participants with or without evidence of infection, higher baseline and post-vaccination titres were observed in Black/African American participants as compared to other race groups. Higher GMTs were also observed in participants with positive baseline SARS-CoV-2 status at both baseline and 1 month after Dose 2 timepoints compared to those observed in participants with negative baseline status.

Overall, GMTs for the BNT162b2 groups for both studies were generally similar and did not identify any clinically meaningful differences for any other race subgroup or ethnicity. As several subgroups included a limited number of participants, these results should be interpreted with caution

Table 9: Geometric Mean Titres, by Subgroup – Participants With or Without Evidence of Infection – Maternal Participants (Study C4591015) and Nonpregnant Female Participants (Study C4591001) – Evaluable Immunogenicity Population

Assay	Dose/Sampling Time Point[a]	Subgroup	Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			C4591015 (Maternal)		C4591001 (Nonpregnant Women)		C4591015 (Maternal)		C4591001 (Nonpregnant Women)	
			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	All	100	70.4 (57.7, 85.9)	113	45.4 (43.2, 47.6)	106	72.9 (59.7, 89.0)	124	46.4 (43.4, 49.6)
		Race								
		White	76	59.3 (49.1, 71.7)	94	43.5 (43.5, 43.5)	77	63.6 (52.8, 76.6)	94	46.4 (42.9, 50.3)
		Black or African American	20	148.5 (79.7, 276.7)	5	82.9 (26.7, 257.3)	23	122.5 (63.5, 236.3)	14	43.5 (43.5, 43.5)
		All others	4	43.5 (43.5, 43.5)	14	48.4 (38.5, 60.8)	6	57.9 (27.8, 120.8)	16	48.9 (38.1, 62.6)
		Ethnicity								
		Hispanic/Latino	41	65.0 (50.2, 84.1)	39	43.5 (43.5, 43.5)	40	77.2 (56.3, 105.8)	45	49.9 (42.2, 58.9)
		Non-Hispanic/non-Latino	59	74.4 (55.6, 99.6)	74	46.4 (43.1, 49.9)	66	70.5 (54.2, 91.7)	79	44.5 (42.5, 46.7)
		Baseline SARS-CoV-2 status								
		Positive	34	179.2 (114.4, 280.8)	4	141.3 (37.8, 528.6)	44	145.3 (97.5, 216.3)	6	165.7 (47.6, 577.2)
		Negative	65	43.5 (43.5, 43.5)	109	43.5 (43.5, 43.5)	59	44.8 (42.3, 47.5)	118	43.5 (43.5, 43.5)
	2/1 Month	All	100	2198.7 (1618.5, 2987.0)	114	1732.0 (1469.4, 2041.5)	106	98.4 (74.3, 130.4)	124	44.7 (43.0, 46.5)
		Race								
		White	76	1685.1 (1214.9, 2337.3)	94	1615.8 (1354.5, 1927.5)	77	65.5 (53.4, 80.4)	94	44.3 (42.7, 46.0)
		Black or African American	20	8016.9 (4356.2, 14753.8)	6	2688.4 (750.2, 9634.0)	23	336.6 (140.3, 808.1)	14	48.9 (38.0, 62.9)
		All others	4	535.0 (103.9, 2754.0)	14	2286.5 (1390.8, 3759.2)	6	162.6 (16.7, 1587.1)	16	43.5 (43.5, 43.5)
		Ethnicity								
		Hispanic/Latino	40	1940.1 (1140.7, 3299.8)	39	1850.8 (1425.2, 2403.5)	40	76.6 (54.4, 107.8)	45	45.3 (41.8, 49.0)
		Non-Hispanic/non-Latino	60	2390.0 (1635.0, 3493.8)	75	1673.3 (1351.5, 2071.6)	66	114.5 (76.4, 171.6)	79	44.4 (42.6, 46.3)
		Baseline SARS-CoV-2 status								
		Positive	34	8728.0 (5441.3, 14000.0)	4	7062.2 (2589.4, 19261.0)	44	253.5 (151.2, 425.2)	6	76.8 (30.4, 193.8)
		Negative	64	1124.8 (861.3, 1469.0)	109	1663.2 (1415.4, 1954.4)	59	50.6 (41.7, 61.6)	118	43.5 (43.5, 43.5)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
Note: Blood samples for immunogenicity assessment drawn at the delivery visit but within 1 month after Dose 2 visit window were also included in this analysis.
Note: Human immunodeficiency virus (HIV)-positive participants are not included in this summary.
Note: Participants from C4591001 are a selected subset of age matched nonpregnant female Phase 3 participants.
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.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 01MAR2024 (02:12)
(Data cutoff date : C4591001 [31Aug2021]) Output File: ./nda3/C4591015_Bridging/adva_s001_gmtc_sub_eval

Assessor´s comment: the highest impact for antibody level after 1 month post dose 2 is the baseline SARS-COV-2 baseline status. Priming with natural infection results with 5-8 fold higher antibody titres compared to SARS-CoV-2 naïve population. The other factors such as race and ethnicity have less impact. This is expected results and in agreement with an earlier data.

Secondary Immunogenicity Analyses – Infant Participants

Full-length S-binding IgG GMCs

- Maternal vaccination with BNT162b2 30 µg yielded substantially higher GMCs of full-length S-binding IgG in infants compared to placebo. For the evaluable immunogenicity population, at birth and 6 months of age GMCs were 5576.4 (95% CI: 4246.2, 7323.2) and 311.1 (95% CI: 235.8, 410.5) respectively for infants whose mothers received BNT162b2, compared to 19.4 (95% CI: 10.2, 37.0) and 22.0 (95% CI: 11.4, 42.7) for infants whose mothers received placebo, see the results in the table below.

Table 10: Geometric Mean Concentrations – Evaluable Immunogenicity Population (Infant)

		Maternal Vaccine Group (as Randomized)			
		BNT162b2 (30 µg)		Placebo	
Assay	Sampling Time Point[a]	n[b]	GMC[c] (95% CI[c])	n[b]	GMC[c] (95% CI[c])
Full-length S-binding IgG level assay (U/mL)	Birth	91	5576.4 (4246.2, 7323.2)	92	19.4 (10.2, 37.0)
	6 Months of age	83	311.1 (235.8, 410.5)	69	22.0 (11.4, 42.7)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; S = spike protein.
Note: Infants born to human immunodeficiency virus (HIV)-positive participants are not included in this summary.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMCs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 12JAN2024 (03:07) Source Data: adva Table Generation: 22FEB2024 (01:04)
(Database snapshot date: Safety [29Mar2023], Immunogenicity [09Jan2024]) Output File: ./nda3/C4591015_CSR/adva_s001_eval_infant

Assessor´s comment: no neutralising test was performed in infant participants, but the binding antibodies were evaluated. Anyhow, as binding and neutralising antibodies have demonstrated good agreement, this is acceptable. These data show successful antibody transfer through placenta, which is expected results and in agreement with data from other vaccines.

It is noted, that in infants, the binding antibody levels were about double as high as in their mothers at the delivery, but lowered much more than in their mothers. While in their mothers, the antibody level was about half reduced 6 months after the delivery, then in infants, the levels were reduced 20- fold. Anyhow, these data show, that maternal immunisation results in high antibody level in their infants and is most likely protective several months post-delivery.

The MAH wishes to present this data in SmPC as a text as following:

In an additional descriptive immunogenicity analysis, infants born to maternal participants who received Comirnaty had higher geometric mean concentrations (GMCs) of full-length S-binding immunoglobulin G (IgG) concentrations at birth and at 6 months after delivery [5 576.4 (95% CI: 4 246.2, 7 323.2); n=91 and 311.1 (95% CI: 235.8, 410.5); n=83], respectively, compared to infants born to maternal participants from the placebo group [19.4 (95% CI: 10.2, 37.0); n=92 and 22.0 (95% CI: 11.4, 42.7); n=69].

Despite that the immunogenicity evaluation in newborns was a secondary objective, the MAH removed this part from 5.1 following a request in an RSI.

GMFRs

- In infants in the evaluable immunogenicity population whose mothers received BNT162b2, the GMFR of full-length S-binding IgG from birth to 6 months of age was 0.1 [95% CI: 0.0, 0.1], indicating a decline in antibody titres during this period.

Exploratory Subgroup Analyses

GMCs of full-length S-binding IgG in infants in the evaluable immunogenicity population were evaluated by breastfeeding status, see the table below. GMCs for breastfed infants were generally higher than those observed for infants who were not breastfed. GMCs for breastfed or not breastfed infants whose mothers received BNT162b2 were substantially higher at birth compared to infants whose mothers received placebo, and remained elevated at 6 months of age. As the not breasted subgroup included a limited number of participants, these results should be interpreted with caution.

Table 11: Geometric Mean Concentrations, by Breastfeeding Status – Evaluable Immunogenicity Population (Infant)

			Maternal Vaccine Group (as Randomized)			
			BNT162b2 (30 µg)		Placebo	
Assay	Sampling Time Point[a]	Breastfeeding Status	n[b]	GMC[c] (95% CI[c])	n[b]	GMC[c] (95% CI[c])
Full-length S-binding IgG level assay (U/mL)	Birth	Overall[d]	91	5576.4 (4246.2, 7323.2)	92	19.4 (10.2, 37.0)
		Breastfed	81	5810.9 (4305.5, 7842.8)	84	20.6 (10.4, 40.8)
		Not breastfed	7	4858.4 (2218.3, 10640.4)	6	10.3 (0.5, 201.8)
	6 Months of age	Overall[d]	83	311.1 (235.8, 410.5)	69	22.0 (11.4, 42.7)
		Breastfed	62	358.5 (254.0, 505.8)	48	26.6 (11.9, 59.5)
		Not breastfed	21	204.8 (138.0, 303.9)	20	9.9 (3.6, 27.4)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; S = spike protein.
Note: Infants born to human immunodeficiency virus (HIV)-positive participants are not included in this summary.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMCs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Participants with unknown breastfeeding status are included in the 'Overall' category as well.
PFIZER CONFIDENTIAL SDTM Creation: 12JAN2024 (03:07) Source Data: adva Table Generation: 22FEB2024 (01:01)
(Database snapshot date: Safety [29Mar2023], Immunogenicity [09Jan2024]) Output File: ./nda3/C4591015 CSR/adva s001 eval brstfd inf

Assessor´s comment: these data show that breastfed babies have somewhat higher level of binding antibodies against SARS-CoV-2 than babies, who have got antibodies through placental transfer only. This means that antibodies from vaccinated mothers milk are stable enough to survive passage through

gastrointestinal tract and baby is immunized passively through breastmilk. This is expected results and in agreement with earlier data from other vaccines.

The clinical impact of this antibody level difference between breastfed and not breastfed babies is unknown. There is no data of levels of neutralising antibodies in breastmilk compared to serum in vaccinated mothers.

Immunogenicity Conclusions

The immunogenicity outcomes for evaluable maternal participants in this study are as follows:

- The observed SARS-CoV-2 50% neutralising GMT 1 month after Dose 2 was lower in the maternal participants without evidence of prior SARS-CoV-2 infection, when compared to similar nonpregnant female participants from Study C4591001, which is consistent with what has been observed in other maternal COVID vaccine studies across the wider literature.
- In the group inclusive of participants with prior evidence of SARS-CoV-2 infection, maternal participants had higher antibody levels than nonpregnant participants from Study C4591001. This observation is due to the higher prior SARS-CoV-2 infection rate in the maternal participants. After accounting for the baseline neutralising titres, the model-adjusted SARS-CoV-2 50% neutralising GMT in maternal participants was numerically lower than nonpregnant comparators.
- The SARS-CoV-2 50% neutralising GMTs and full-length S-binding IgG GMCs for both participants without prior infection and those with or without prior infection were substantially higher in groups vaccinated with BNT162b2 versus the placebo group for all post-vaccination timepoints.
- The SARS-CoV-2 50% neutralising GMT and full-length S-binding IgG GMC responses for both participants without prior infection and those with or without prior infection were highest 2 weeks after Dose 2 and dropped at the 6 month after Dose 2 timepoint. Antibody levels remained elevated in participants vaccinated with BNT162b2 at the 6 month timepoint compared to those observed in the placebo group at any previous timepoint.
- There was an increase in SARS-CoV-2 50% neutralising GMTs and GMCs of full-length S-binding IgG from the Dose 1 prevaccination to the Dose 2 prevaccination time points; however, this increase was not as substantial as the increase observed after post-Dose 2.

The immunogenicity outcomes for evaluable infant participants in this study are as follows:

- Full-length S-binding IgG GMC levels at birth were higher in the infants born to vaccinated maternal participants than those born to participants in the placebo group. These concentrations dropped over the following 6 months but remained higher in infants born to vaccinated participants compared to those born to participants in the placebo group, even at the 6 month post-birth timepoint.
- Comparing the maternal and infant full-length S-binding IgG GMCs [4336.9 (95% CI: 3456.0, 5442.4) at 1-month post-dose 2 and 5576.4 (95% CI: 4246.2, 7323.2) at birth respectively] indicates effective transplacental transfer of antibody.

C4591015 – Efficacy

Secondary Efficacy Analyses – Maternal Participants

Vaccine Efficacy Against Confirmed COVID-19

Due to the very small sample size resulting from early termination of Enrolment the number of COVID-19 cases are low and VE results are uninterpretable.

Table 12: . Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy Population (Maternal)

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=88)		Placebo (N[a]=90)			
Efficacy Endpoint	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**
First COVID-19 occurrence from 7 days after Dose 2	2	0.155 (86)	2	0.149 (89)	3.8	(-1227.8, 93.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1, not positive at Visit 2, NAAT [nasal swab] negative at Visits 1, 2, and any unscheduled visit prior to 7 days after Dose 2) 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 100 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (09:10) Source Data: adc19ef Table Generation: 12DEC2023 (23:13) Output File: ./nda3/C4591015_EFF/adc19ef_ve_cov_7pd2_wo_evlm

Assessor´s comment: the efficacy population was small, below 100 in each arm and in both arms had equal number of cases (n=2). This results in very wide 95 % CI and no conclusions can be made.

Vaccine Efficacy Against Asymptomatic SARS-CoV-2 Infection Based on Seroconversion (N-Binding)

For asymptomatic infection, based on N-binding antibody seroconversion, in the evaluable efficacy population of maternal participants without evidence of SARS-CoV-2 infection prior to the first post-Dose 2 N-binding test, the VE had wide 95% CI due to the limited number of participants and these results should be interpreted with caution.

Table 13: Vaccine Efficacy – Asymptomatic Infection Based on N-Binding Antibody Seroconversion – Blinded Follow-up Period – Participants Without Evidence of Infection Prior to the First Post–Dose 2 N-Binding Test –Evaluable Efficacy Population (Maternal)

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=84)		Placebo (N[a]=89)			
Efficacy Endpoint	**n[b]**	**Surveillance Time[c]**	**n[b]**	**Surveillance Time[c]**	**VE (%)**	**(95% CI[d])**
Asymptomatic infection based on N-binding antibody seroconversion after Dose 2	4	0.099	10	0.147	40.9	(-104.9, 86.5)

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 (before Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Dose 1 and no positive before Dose 2, negative NAAT [nasal swab] at Dose 1, Dose 2, and at any unscheduled visit before Dose 2) and had at least one post-dose 2 N-binding Test in the blinded follow up period were included in the analysis.
a. N = number of participants in the specified group.
b. n = Number of participants meeting the endpoint definition.
c. Total surveillance time in 100 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for case accrual is from Dose 2 to the end of the surveillance period.
d. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (09:10) Source Data: adc19asm Table Generation: 12DEC2023 (23:18) Output File: ./nda3/C4591015_EFF/adc19ef_ve_cov_d2_wo_evlm

Assessor´s comment: due to the low sample size, the uncertainty of the VE estimate is large, but in placebo group there were more cases of asymptomatic infections (10/89) than in vaccinated arm (4/84).

6.1.3. Discussion

The study C4591015 was a global Phase 2/3, randomised, placebo-controlled, observer-blind study to evaluate the safety, tolerability, and immunogenicity of 30 µg of BNT162b2 or placebo administered in 2 doses, 21 days apart, in approximately 350 healthy pregnant women 18 years of age or older vaccinated at 24 to 34 weeks' gestation. Participants were randomised 1:1 to receive BNT162b2 or placebo (saline).

Enrolment in this study was terminated due to enrolment challenges as a result of universal recommendations for COVID-19 vaccination of pregnant women and the increased global availability of COVID-19 vaccines. The original study protocol was amended 5 times mainly to adapt the protocol to the requests from the authorities and to the reduced sample size.

The methodology of the Study C4591015 was similar to the Comirnaty studies reported earlier and is acceptable. The primary immunogenicity endpoints were evaluated using neutralising assay and secondary endpoints S-protein binding antibodies. The primary immunogenicity objective was to compare neutralising antibody titres in pregnant women compared to the age matched non-pregnant women 1 months post- dose 2. The secondary objectives were to investigate VE, describe antibody levels of mothers and their infants at different time points, up to delivery and 6 months post-delivery. There were also plenty of exploratory objectives for this study, which not all gave meaningful results due to the limited sample size.

In immunological comparison, about 110 individuals in each study arm in pregnant cohort were age matched with the historical control group consisting of non- pregnant woman from study C4591001. Both studies were randomised, placebo-controlled and observer-blind. Anyhow, this was not the ideal control group as the time and place for the control is not the same as for the active arm. The study C4591015 recruited since 16.02.2021, whereas C4591001 phase 3 recruited in summer 2020. The time gap between studies was at least 6 months. The pregnancy study recruited mainly in USA (47%), South Africa (24%) and Spain (14%), whereas the historical control population was from USA (57%), Argentina (21%), Brazil (14%) and Germany (4%). The geographical origin of study population may influence the antibody levels among baseline seropositives as different SARS-COV2 were spread in different locations. Also it is unknown, how many different SARS-Cov2 infections every seropositive participant have had. As the historical control was recruited early in the pandemic, much higher proportion was still seronegative (95%) compared to the pregnancy study population (55-60%). Still, we have to accept this kind of historical control as it was not feasible and ethical to conduct a placebo controlled clinical trial on a group, to whom the vaccination with Comirnaty was officially recommended.

The GMR analysis of neutralising antibodies was descriptive, but the data shows, that antibody level was higher among non-pregnant women, especially when those without earlier SARS-CoV-2 infection were compared. This is expected results and in agreement with earlier data. The MAH wishes to add a table including immunogenicity information from pregnant and non-pregnant women to the SmPC. We suggested to use a short text instead of a table describing that GMT and GMR was lower among pregnant compared to the non-pregnant from historical control (OC), which the Applicant has followed in an updated SmPC.

The neutralising and S protein binding antibody levels show agreement. The highest levels of both kind of antibodies were measured 2 weeks post dose 2. The levels then started to lower reaching 3-4x lower levels at 6 months post- delivery timepoint in comparison to the 2 weeks post dose 2. This kind of

antibody kinetics is in agreement with an earlier data. The placebo group demonstrated about the same low antibody level than at the baseline during entire study period.

Subgroup analysis show that the highest impact for antibody level after 1 month post dose 2 is the baseline SARS-CoV-2 baseline status. Priming with natural infection results with 5-8 fold higher antibody titres compared to SARS-CoV-2 naïve population. This is expected results and in agreement with an earlier data.

About 110 infants born for both vaccinated and placebo arm mothers were evaluated for S-protein binding antibodies. No neutralisation assay was performed for serum from infant participants. Anyhow, as binding and neutralising antibodies have demonstrated good agreement, this is acceptable. At the delivery, there was high level of S-protein binding antibodies in infants. This is a sign of a successful antibody transfer through placenta, which is expected results and in agreement with data from other vaccines. The MAH wishes to add immunogenicity data in newborns to the SmPC despite that the immunogenicity evaluation in newborns was a secondary objective. Still we agree that this information is important to be presented in SmPC.

It is noted, that in infants, the binding antibody levels were about double as high as in their mothers at the delivery, but lowered much more than in their mothers. While in their mothers, the antibody level was about half reduced 6 months after the delivery, then in infants, the levels were reduced 20- fold. Anyhow, these data show, that maternal immunisation results in high antibody level in their infants and is most likely protective several months post-delivery.

One of the explorative objectives were to compare the antibody levels 6 months post delivery among breastfed babies in comparison for those who were not. These data show that breastfed babies had somewhat higher level of binding antibodies against SARS-CoV-2 than babies, who have got antibodies through placental transfer only. This means that antibodies from vaccinated mothers milk are stable enough to survive passage through gastrointestinal tract and baby is immunized passively through breastmilk. This is expected results and in agreement with earlier data from other vaccines. There is no data of levels of neutralising antibodies in breastmilk compared to serum in vaccinated mothers. The clinical impact of this antibody level difference between breastfed and not breastfed babies is unknown.

Vaccine efficacy evaluation in pregnant women compared to non-pregnant women was a secondary objective for this study. Due to the very small sample size resulting from early termination of Enrolment the number of COVID-19 cases was also low and VE results were uninterpretable. In VE evaluation for symptomatic Covid-19, there was equal number of cases (N=2) in both study arms (ca N=90). In VE evaluation for asymptomatic COVID-19 placebo group there were more cases of asymptomatic infections (10/89) than in vaccinated arm (4/84).

In conclusion, this descriptive study demonstrated that antibody titres were somewhat lower in pregnant women compared to the non-pregnant women in historical control group. These antibodies were transferred through placenta and the newborns had high levels of antibodies in their blood at the delivery. After 6 months the antibody titres in babies was strongly reduced, but still higher that in the placebo group. Breastfeeding helps to maintain higher antibody titres. These observations are in agreement with earlier data.

6.2. Study C4591024

6.2.1. Methods – analysis of data submitted

Study C4591024 was a Phase 2b study that evaluated the safety, tolerability, and immunogenicity of BNT162b2 in participants >2 years of age based on representative medical conditions and utilized a vaccination series of 3 doses (the first 2 doses separated by 21 days, with a third dose occurring 28 days after the second dose) followed by a fourth dose 3-6 months after dose 3. The dose for each of the 4 vaccinations depended upon the age of the participant at the time of vaccination.

- For the 22 participants who were >12 years of age, a 30 µg dose level was used.
- For the 65 participants who were 5 to <12 years of age, a 10 µg dose level was used.
- For the 37 participants who were 2 to <5 years of age, a 3 µg dose level was used.

Enrolment in this study was terminated due to enrolment challenges as a result of universal recommendations for COVID-19 vaccination of immunocompromised individuals and the increased global availability of COVID-19 vaccines.

Objectives, Estimands, and Endpoints

Table 14: Primary and exploratory Immunogenicity Objectives, Estimands and Endpoints (modified)

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To describe the immune response to prophylactic BNT162b2 in participants ≥18 years of age without serological or virological evidence of past SARS-CoV-2 infection and with: • Asymptomatic CLL without treatment and undergoing observation, or CLL on BTK inhibitor or anti-CD20 monoclonal antibodies • Diagnosed with NSCLC and on chemotherapy, checkpoint inhibitors, or targeted agents for oncogene-driven tumors • Maintenance hemodialysis treatment due to end-stage renal disease • Immunomodulator therapy for an autoimmune inflammatory disorder	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each disease subset: • GMTs at 1 month after Dose 3 and Dose 4	• SARS-CoV-2 neutralizing titers
To describe the immune response to prophylactic BNT162b2 in participants ≥2 to <18 years of age without serological or virological evidence of past SARS-CoV-2 infection and either: • Are on immunomodulator therapy for an autoimmune inflammatory disorder • Are on immunosuppression therapy after solid organ transplant • Underwent bone marrow or stem cell transplant at least 6 months before enrollment	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each age group (≥2 to <5, ≥5 to <12, and ≥12 to <18 years) and disease subset: • GMTs at 1 month after Dose 3 and Dose 4	• SARS-CoV-2 neutralizing titers
Exploratory:	**Exploratory:**	**Exploratory:**
To further describe the immune response to prophylactic BNT162b2 in participants ≥18 years of age without serological or virological evidence of past SARS-CoV-2 infection and with: • Asymptomatic CLL without treatment and undergoing observation, or CLL on BTK inhibitor or anti-CD20 monoclonal antibodies • Diagnosed with NSCLC and on chemotherapy, checkpoint inhibitors, or targeted agents for oncogene-driven tumor • Maintenance hemodialysis treatment due to end-stage renal disease • Immunomodulator therapy for an autoimmune inflammatory disorder	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each disease subset: • GMTs at all immunogenicity blood draws • GMFRs from baseline to 1 month after Dose 2[a], from baseline 1 month after Dose 3, and from Dose 4 to 1 month and 6 months after Dose 4 • Percentages of participants with seroresponse at 1 month after Dose 2[a], 1 month after Dose 3, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers
To further describe the immune response to prophylactic BNT162b2 in participants ≥2 to <18 years of age without serological or virological evidence of past SARS-CoV-2 infection and either: • Are on immunomodulator therapy for an autoimmune inflammatory disorder • Are on immunosuppression therapy after solid organ transplant • Underwent bone marrow or stem cell transplant at least 6 months before enrollment	In participants complying with the key protocol criteria (evaluable participants) and no serological or virological evidence of past SARS-CoV-2 infection in each age group (≥2 to <5; ≥5 to <12; ≥12 to <18) and disease subset: • GMTs at all immunogenicity blood draws • GMFRs from baseline to 1 month after Dose 2[a], baseline 1 month after Dose 3, and from Dose 4 to 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers
To further describe the immune response to prophylactic BNT162b2 in participants with and without serological or virological evidence of past SARS-CoV-2 infection	• GMTs at all immunogenicity blood draws • GMFRs from baseline to 1 month after Dose 2[a], from baseline to 1 month after Dose 3, and from Dose 4 to 1 month and 6 months after Dose 4 • Percentages of participants with seroresponse at 1 month after Dose 2[a], 1 month after Dose 3, and 1 month and 6 months after Dose 4	• SARS-CoV-2 neutralizing titers
To describe the incidence of confirmed COVID-19 among immunocompromised participants	• Incidence rate of confirmed COVID-19 per 1000 person-years of follow-up	• COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To describe the incidence of MIS-C cases	• Incidence rate of confirmed MIS-C cases	• Confirmed cases as per CDC symptom criteria

a. Serology testing at 1 month after Dose 2 was not conducted because a full primary series in immunocompromised individuals is 3 doses
b. Only 1 participant had enrolled in the PBMC subset due to the challenges with study enrollment overall; with too few participants to make a meaningful analysis, further collection of blood for PBMC assessment and HLA typing was not required.
c. Due to the challenges with study enrollment overall and with too few cases to make a meaningful analysis, sequencing analyses were not conducted.
Source: Appendix 16.1.1, Protocol Section 3

Assessor´s comment: the main immunogenicity objective was to evaluate neutralising antibody titre among baseline SARS-CoV-2 negative immunosuppressed population before and after the 3rd and 4th dose. The study recruited all ages from 2 years and above. The study had also explorative objectives, most important of those is the evaluate neutralising antibody titre among entire evaluable immunogenicity population regardless of their baseline SARS-CoV-2 status.

Inclusion/Exclusion Criteria

Participants must have met all the inclusion criteria and not met the exclusion criteria specified for the protocol. Key criteria are summarized below.

Eligible study participants were healthy male or female individuals ≥2 years of age who were immunocompromised by virtue of the following:

- Had known NSCLC and were ≥18 years of age with at least 1 of the following:
    - Who received chemotherapy at least 2 weeks (14 days) before Enrolment (or is treatment naïve), and were not expected to receive chemotherapy within at least 2 weeks (14 days) after dose administration; and/or
    - Was receiving checkpoint inhibitor treatment (PD-1/PD-L1 inhibitor, CTLA-4 inhibitor) and had undergone at least 1 treatment cycle prior to enrolment (at Visit 1); or
    - Was receiving targeted drug therapy treatment (EGFR, ALK, ROS1, BRAF, RET, MET, NTRK inhibitors) and had undergone at least 1 treatment cycle prior to Enrolment (at Visit 1); or
- Had known CLL and were ≥18 years of age with at least 1 of the following:
    - Had asymptomatic disease (e.g., Rai stage <3, Binet stage A or B) and was undergoing observation and was not receiving any treatment for CLL; or
    - Was receiving B-cell inhibitory monoclonal antibody treatment (anti-CD20) and had received at least 3 cycles prior to Enrolment; and/or
    - Was receiving a BTK inhibitor, PI3K inhibitor, or BCL-2 inhibitor

OR

- Was currently undergoing maintenance haemodialysis treatment secondary to end- stage renal disease and was ≥18 years of age

OR

- Was on active immunomodulator therapy (e.g., TNFα inhibitor, tofacitinib or MTX) for an autoimmune inflammatory disorder (e.g., inflammatory arthritis, such as rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, and inflammatory bowel disease, such as ulcerative colitis and Crohn's disease) at a stable dose defined as receiving the same dose for at least 3 months (84 days) with no changes in the 28 days prior to Visit 1.

OR

- Was receiving a solid organ transplant at least 3 months (84 days) prior to enrolment (Visit 1) and with no acute rejection episodes within 2 months (60 days) prior to Enrolment (Visit 1), and is 2 to <18 years of age

OR

- Has had an autologous or allogenic bone marrow or stem cell transplant at least 6 months (182 days) prior to Enrolment (Visit 1), with adequate immune reconstitution for immunisation, in the investigator's opinion, and was 2 to <18 years of age

Individuals were excluded from the study if they had a past clinical or microbiological diagnosis of COVID-19, or a past clinical diagnosis of MIS-C. Individuals were also excluded from the study if they had active GVHD, transplant rejection, or PTLD, or were treated for one of these conditions within 3 months before Enrolment. A bleeding diathesis or condition associated with prolonged bleeding that would contraindicate an IM injection, a medical or psychiatric condition including recent (within past year) or active suicidal ideation/behaviour and pregnant or breastfeeding individuals were also excluded. Individuals were also excluded if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention.

Blinding

This was an open-label study.

Immunogenicity Endpoints and Analysis

For all the immunogenicity endpoints, the analysis were based on the evaluable immunogenicity population. An additional analysis was performed based on the corresponding all-available immunogenicity population. Participants were summarized according to the vaccine group to which they were assigned.

Geometric Means

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.

Geometric Mean Fold Rises

GMFRs were defined as ratios of the results after vaccination to the results before vaccination. GMFRs were limited to participants with nonmissing 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 limits.

Reverse Cumulative Distribution Curves

Empirical RCDCs plotted proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points were joined by a step function with data points on the left side of the step.

6.2.2. Results

Changes in study conduct

There have been 5 protocol amendments during the study. Some changes were purely administrative clarifications initially reported in PACLs. Other more important changes are listed below:

- Removal of the requirement to conduct a potential COVID-19/MIS-C convalescent visit following each COVID-19/MIS-C illness visit.
- Removal of the exploratory objective looking into viral shedding in line with the removal of the convalescent visit.
- Addition of primary and exploratory safety, tolerability, and immune response objectives for the expanded cohort of participants on active immunomodulator therapy.

- Updated Visit 5 window to allow its occurrence as early as 28 days after Visit 2 and updated wording to allow subgroup analysis of immunogenicity endpoints based on various timing of Dose 3. These changes were made to be in line with Regulatory recommendations for providing a 3rd dose of BNT162b2 to immunocompromised individuals.
- Updated procedures to allow a fourth dose (booster), reducing the window for provision of Dose 3, and allowing vaccination with the age-appropriate dose.
- Updated the number of participants in each group based on actual recruitment figures.
- Removed further blood draws for participants who have consented to PBMC sampling.

Assessor´s comment: the changes of the study protocol has been assessed earlier during procedures PAM MEA/016.0-0.16.6.

Study population

This study was conducted at 18 sites in Brazil, Germany, Mexico, and the USA.

Please see the Safety population section for study population characteristics. The numbers included into each group in evaluable immunogenicity population are presented below.

Table 15: Evaluable immunogenicity population (assessors table)

		3 µg 2 to < 5 y	**10 µg 5 to < 12 y**	**30 µg 12 to < 18 y**	**30 µg ≥ 18 y**	**Total N (%)**
All patients N	Dose 3 Dose 4	26 16	56 31	11 6	4 4	97 57
Immuno modulatory therapy N	Dose 3 Dose 4	8 7	17 8	5 2	3+1 haemodialysis 3+1 NSCLC	34 21
Solid organ transplant N	Dose 3 Dose 4	11 4	19 13	1 1	0 0	31 18
Stem cell transplant N	Dose 3 Dose 4	7 5	20 10	5 3	0 0	32 18
Dose 3 population baseline characteristics						
Sex N (%)	Male female	15 (57.7) 11 (42.3)	34 (60.7) 22 (39.3)	7 (63.6) 4 (36.4)	1 (25.0) 3 (75.0)	57 (59) 40 (41)
Median age (years) at vaccination		3.0	8.5	12.0	50.5	
Baseline SARS-Cov-2 status N (%)	Positive negative missing	1 (3.8) 22 (84.6) 3 (11.5)	1 (1.8) 41 (73.2) 14 (25.0)	2 (18.2) 6 (54.5) 3 (27.3)	0 4 (100.0) 0	4 (4.1) 73 (75.3) 20 (20.6)
Country	Brazil Germany USA	3 (11.5) 8 (30.8) 15 (57.7)	7 (12.5) 24 (42.9) 25 (44.6)	2 (18.2) 8 (72.7) 1 (9.1)	1 (25.0) 1 (25.0) 2 (50.0)	13 (13.4) 41 (42.3) 43 (44.3)

Assessor´s comment: The MAH faced problems to recruit the desired sample size for the planned study among immunocompromised population. The study started to recruit subjects in October 2021, which is

already 10 months since CMA for Comirnaty 30 µg for adults in EU. Indeed, all countries provided vaccine against COVID-19 after the authorisation at first to the most vulnerable population, which includes the immunocompromised individuals. Therefore, it is not surprising, that the desired sample size was unreachable. Therefore, it was considered acceptable to stop recruiting subjects during procedure PAM 016.4 September 2022 and continue with the available study population.

The largest sample size was achieved among age group 5-<12 years, who received 10 µg Comirnaty. Older cohorts, which received adult dose 30 µg Comirnaty, recruited very low number as for older than 12, the vaccine was officially recommended at the time of the study.

The majority of study population was from USA and Germany and was SARS-CoV-2 negative at the baseline. There was rather large proportion, about 20% of participants in age group 5-<18 with unknown baseline SARS-CoV-2 status. This is strange and need a clarification (OC). The MAH answered that these participants did not have some baseline sample (either blood or nasal swab) or had unclear test result.

GMTs- 1 months post dose 3 or 4

Participants without evidence of infection

Participants 2 to <5 Years of Age
In total, GMTs were higher at 1 month after Dose 3 (741.6) and 1 month after Dose 4 (2219.5) compared to levels observed before study vaccination across all disease subsets. At 6 months after Dose 4, GMTs were reduced across all disease subsets (293.2). No participants in the stem cell transplant group had a valid and determinate assay result at any time point.

Between disease subsets, GMTs were generally similar between participants in the immunomodulatory therapy group and the solid organ transplant group at 1 month after Dose 3 (600.2 and 884.7, respectively) and before Dose 4 (266.3 and 870.6, respectively). At 1 month after Dose 4, GMTs were higher in the solid organ transplant group (9576.3) than in the immunomodulatory therapy group (837.5).

Table 16: Summary of Geometric Mean Titres – Participants Without Evidence of Infection by Age Group – Dose 3 or Dose 4 Evaluable Immunogenicity Population Age Group: 2–<5 Years

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Assigned) BNT162b2 (3 µg) Immunomodulatory Therapy n[b]	GMT[c] (95% CI[c])	Solid Organ Transplant n[b]	GMT[c] (95% CI[c])	Stem Cell Transplant n[b]	GMT[c] (95% CI[c])	Total n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1/Prevax[d]	5	43.5 (43.5, 43.5)	6	43.5 (43.5, 43.5)	0	NE (NE, NE)	11	43.5 (43.5, 43.5)
	3/1 Month[e]	5	600.2 (77.8, 4629.8)	6	884.7 (176.7, 4430.6)	0	NE (NE, NE)	11	741.6 (267.6, 2055.4)
	4/Pre-Dose 4[d]	3	266.3 (4.0, 17892.6)	2	870.6 (0.4, 1819648.5)	0	NE (NE, NE)	5	427.7 (72.7, 2515.7)
	4/1 Month[f]	3	837.5 (1.4, 518774.5)	2	9576.3 (0.0, 2070132632.7)	0	NE (NE, NE)	5	2219.5 (117.6, 41883.5)
	4/6 Months[f]	1	43.5 (NE, NE)	1	1976.0 (NE, NE)	0	NE (NE, NE)	2	293.2 (0.0, 9911056113277.4)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NE = not estimable; NT50 = 50% neutralizing titer; Prevax = before vaccination; 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 or 1 month post Dose 4 study blood sample collection. Participants who had no serological or virological evidence (prior to the subsequent blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at any visit prior to subsequent time point, SARS-CoV-2 not detected by NAAT [nasal swab] until prior vaccination, and negative NAAT [nasal swab] result at any unscheduled visit prior to the subsequent blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Dose 3 evaluable immunogenicity population or Dose 4 evaluable immunogenicity population.
e. Dose 3 evaluable immunogenicity population.
f. Dose 4 evaluable immunogenicity population.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2024 (16:15) Source Data: adva Table Generation: 29MAR2024 (03:12)
(Database snapshot date : 10AUG2023, 23FEB2024) Output File: ./nda3/C4591024_CSR_SERO/adva_s001_gmt_wo_evl

Assessor´s comment: the sample size in this age group was small, especially when dividing into subgroups and therefore conclusions should be drawn carefully. Anyhow, the data shows, that most reduced antibody response appears among those who are on immunomodulatory therapy. The immune response improved for all after the 4th dose.

Participants 5 to <12 Years of Age

In total, GMTs were higher at 1 month after Dose 3 (1612.0) and 1 month after Dose 4 (3270.8) compared to levels observed before study vaccination across all disease subsets. At 6 months after Dose 4, GMTs were reduced across all disease subsets (296.7).

Between disease subsets, GMTs were lowest in participants in the immunomodulatory therapy group before Dose 4 (258.3), 1 month after Dose 4 (754.2), and 6 months after Dose 4 (135.5). At 1 month after Dose 3, GMTs were higher in the stem cell transplant group (4592.3) than in the immunomodulatory therapy group (758.4) and the solid organ transplant group (741.2). At 1 month after Dose 4, GMTs in the solid organ transplant group (5335.3) and the stem cell transplant group (5330.8) were both higher than those in the immunomodulatory therapy group (754.2).

Table 17: Summary of Geometric Mean Titres – Participants Without Evidence of Infection by Age Group – Dose 3 or Dose 4 Evaluable Immunogenicity Population Age Group: 5–<12 Years

		Vaccine Group (as Assigned) BNT162b2 (10 µg)							
		Immunomodulatory Therapy		Solid Organ Transplant		Stem Cell Transplant		Total	
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 - reference strain - NT50 (titer)	1/Prevax[d]	6	43.5 (43.5, 43.5)	9	43.5 (43.5, 43.5)	11	43.5 (43.5, 43.5)	26	43.5 (43.5, 43.5)
	3/1 Month[e]	6	758.4 (123.7, 4650.4)	9	741.2 (150.6, 3647.0)	11	4592.3 (1989.5, 10600.4)	26	1612.0 (763.0, 3405.3)
	4/Pre-Dose 4[d]	5	258.3 (23.4, 2849.1)	6	453.1 (118.5, 1732.5)	7	1040.1 (202.9, 5333.1)	18	535.5 (232.7, 1232.5)
	4/1 Month[f]	2	754.2 (0.0, 351878145.2)	4	5335.3 (517.0, 55061.8)	2	5330.8 (0.0, 113927797661576.0)	8	3270.8 (760.5, 14067.2)
	4/6 Months[f]	2	135.5 (129.3, 142.0)	3	490.9 (2.4, 99303.5)	1	314.0 (NE, NE)	6	296.7 (62.0, 1419.9)

Assessor´s comment: the data shows, that most reduced antibody response appears among those who are on immunomodulatory therapy. The immune response improved for all after the 4th dose. As this age group had the largest sample size in this study, these results are the most trustable.

Participants 12 to <18 Years of Age

At 1 month after Dose 3, GMTs in the immunomodulatory therapy group, solid organ transplant group, and stem cell transplant group were 7330.0, 43.5 and 2368.1, respectively Only 1 participant in the solid organ transplant group had a valid and determinate assay result at 1 month after Dose 4 (2845.0).

Table 18: Summary of Geometric Mean Titres – Participants Without Evidence of Infection by Age Group – Dose 3 or Dose 4 Evaluable Immunogenicity Population Age Group: 12–<18 Years

		Vaccine Group (as Assigned) BNT162b2 (30 µg)							
		Immunomodulatory Therapy		Solid Organ Transplant		Stem Cell Transplant		Total	
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 - reference strain - NT50 (titer)	1/Prevax[d]	1	43.5 (NE, NE)	1	43.5 (NE, NE)	2	43.5 (43.5, 43.5)	4	43.5 (43.5, 43.5)
	3/1 Month[e]	1	7330.0 (NE, NE)	1	43.5 (NE, NE)	2	2368.1 (1679.9, 3338.3)	4	1156.4 (32.2, 41553.3)
	4/Pre-Dose 4[d]	0	NE (NE, NE)	1	4534.0 (NE, NE)	0	NE (NE, NE)	1	4534.0 (NE, NE)
	4/1 Month[f]	0	NE (NE, NE)	1	2845.0 (NE, NE)	0	NE (NE, NE)	1	2845.0 (NE, NE)

Assessor´s comment: the sample size is too low to make separate analysis for subgroups. The immune response improved for all after the 4th dose.

Participants ≥18 Years of Age

GMTs were only able to be determined for participants in the immunomodulatory therapy group at all 4 time points and for 1 participant in the haemodialysis group at prevaccination and at 1 month after Dose 3. In total, GMTs were higher at 1 month after Dose 3 (344.6) and elevated 1 month after Dose 4 (1474.0) compared to levels observed before study vaccination.

Table 19: Summary of Geometric Mean Titres – Participants Without Evidence of Infection by Age Group – Dose 3 or Dose 4 Evaluable Immunogenicity Population Age Group: ⩾18 Years

		Vaccine Group (as Assigned) BNT162b2 (30 µg)							
		Immunomodulatory Therapy		Non-Small Cell Lung Cancer		Haemodialysis		Total	
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 - reference strain - NT50 (titer)	1/Prevax[d]	2	43.5 (43.5, 43.5)	0	NE (NE, NE)	1	43.5 (NE, NE)	3	43.5 (43.5, 43.5)
	3/1 Month[e]	2	596.5 (0.1, 3699753.4)	0	NE (NE, NE)	1	115.0 (NE, NE)	3	344.6 (18.7, 6348.0)
	4/Pre-Dose 4[d]	2	202.3 (49.3, 828.9)	0	NE (NE, NE)	0	NE (NE, NE)	2	202.3 (49.3, 828.9)
	4/1 Month[f]	1	1474.0 (NE, NE)	0	NE (NE, NE)	0	NE (NE, NE)	1	1474.0 (NE, NE)

Assessor´s comment: the sample size is too low to make separate analysis for subgroups. The immune response improved for all after the 4th dose.

Participants with or without evidence of infection

GMTs were observed to be higher across all timepoints in participants with or without evidence of prior infection compared to those without evidence of infection, see the table below, which MAH wishes to be added to the SmPC.

Table 20: Summary of geometric mean titres – participants with or without evidence of infection by age group – all available immunogenicity population

		Comirnaty							
		3 mcg Age group: 2 to < 5 years		10 mcg Age group: 5 to < 12 years		30 mcg Age group: 12 to < 18 years		30 mcg Age group: ≥ 18 years	
Assay	Dose/ Sampling time point[b]	n[c]	GMT[c] (95% CI[d])	n[c]	GMT[c] (95% CI[d])	n[c]	GMT[c] (95% CI[d])	n[c]	GMT[c] (95% CI[d])
SARSCoV2 neutralization assay – reference strain - NT50 (titre)[a]	1/Prevax	32	44.8 (42.2, 47.7)	62	44.5 (42.5, 46.5)	14	54.2 (33.7, 87.0)	6	82.2 (16.0, 422.5)
	3/1 month	32	942.3 (537.1, 1 653.4)	60	1 566.5 (1 019.9, 2 405.9)	14	2 940.6 (1 175.5, 7 356.0)	6	787.1 (66.5, 9 321.5)
	4/Pre-dose 4	29	487.8 (269.0, 884.9)	57	922.2 (586.7, 1 449.3)	11	3 284.5 (1 609.8, 6 701.3)	3	606.2 (5.3, 68 756.0)
	4/1 month	26	3 447.0 (1 851.0, 6 419.2)	50	6 463.4 (4 319.7, 9 670.9)	9	13 457.1 (5 270.1, 34 362.4)	4	1 031.3 (56.9, 18 681.7)
	4/6 months	25	1 296.7 (674.2, 2 494.0)	49	2 382.3 (1 554.3, 3 651.2)	8	5 776.1 (2 801.4, 11 909.2)	3	1 605.6 (28.5, 90 614.9)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020]).
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Assessor´s comment: the primary immunogenicity objectives were to describe the immune responses among immunosuppressed baseline SARS-CoV-2 negative population. The MAH wishes to update the SmPC with a table presenting immune responses regardless of the baseline SARS-CoV-2 status, which was an exploratory objective. There were roughly quarter of participants with unknown baseline status and the sample size is small even for entire evaluable immunogenicity population. The data shows mainly, that the 4th dose improves the antibody titre in all studied age groups including immunosuppressed individuals from 2 years and older. This observation is in agreement with an earlier data. We suggested to replace the table above with a short text describing that all groups had higher GMT after fourth dose (OC), which the Applicant has followed in an updated SmPC.

GMFRs From Before Dose 1 to Each Subsequent Timepoint

Participants Without Evidence of Infection

Similar to the pattern observed in GMTs, the GMFRs in participants without evidence of prior infection in the evaluable immunogenicity population were observed to be higher at 1 month after Dose 3 and 1 month after Dose 4 across all age groups.

Participants With or Without Evidence of Infection

In the evaluable immunogenicity population, GMFRs were observed to be generally higher across all timepoints in participants with or without evidence of prior infection compared to those without evidence of infection.

GMFRs From Before Dose 4 to Each Subsequent Timepoint

Participants Without Evidence of Infection

Participants 2 to<5 Years of Age

In the evaluable immunogenicity population, no participants in the stem cell transplant group had valid and determinate assay results at both prevaccination time points and at the given dose/ sampling time points. In total, the GMFRs 1 month after Dose 4 were 5.2 (95% CI: 1.4, 18.7) and 2.0 (95% CI: 0.0, 16990.4) at 6 months after Dose 4.

Participants 5 to <12 Years of Age

In the evaluable immunogenicity population, the GMFRs 1 month after Dose 4 were 9.4 (95% CI: 7.1, 12.3) and 1.5 (95% CI: 0.7, 3.2) at 6 months after Dose 4.

Participants 12 to <18 Years of Age

In the evaluable immunogenicity population, only the solid organ transplant group had 1 participant with valid and determinate assay results at both prevaccination time points and 1 month after Dose 4. The fold-rise for this participant was 0.6.

Participants ≥18 Years of Age

In the evaluable immunogenicity population, only the immunomodulatory therapy group had 1 participant with valid and determinate assay results at both prevaccination time points and 1 month after Dose 4. The fold-rise for this participant was 8.1.

Participants With or Without Evidence of Infection

GMFRs were observed to be generally higher across all timepoints in participants with or without evidence of prior infection in the evaluable immunogenicity population compared to those without evidence of infection.

Seroresponse – 1 Month Post-Dose 3 or Post-Dose 4

Participants Without Evidence of Infection

Participants 2 to<5 Years of Age

In the evaluable immunogenicity population, there were no participants in the stem cell transplant group with a valid and determinate assay result at both the prevaccination timepoint and subsequent sampling timepoints.

The proportion of participants without evidence of infection in the Dose 3 or Dose 4 evaluable immunogenicity population who achieved seroresponse to the reference strain was 63.6% (95% CI: 30.8, 89.1) at 1 month after Dose 3 and 80.0% (95% CI: 28.4, 99.5) at before Dose 4 and 1 month after Dose 4. At 6 months after Dose 4, 1 (50.0%) out of the 2 participants with assay results at 6 months after Dose 4 achieved seroresponse to the reference strain.

Participants 5 to <12 Years of Age

In total, the proportion of participants without evidence of infection in the Dose 3 or Dose 4 evaluable immunogenicity population who achieved seroresponse to the reference strain at 1 month after Dose 3 was 80.8% (95% CI: 60.6, 93.4) and 66.7% (95% CI: 41.0, 86.7) before Dose 4. Seroresponse rate was 87.5% (95% CI: 47.3, 99.7) at 1 month after Dose 4 and 33.3% (95% CI: 4.3, 77.7) at 6 months after Dose 4.

Participants 12 to <18 Years of Age

In the evaluable immunogenicity population, the solid organ transplant group was the only group that had a participant with a valid and determinate assay result at both the prevaccination timepoint and all subsequent sampling timepoints.

The proportion of participants without evidence of infection in the Dose 3 or Dose 4 evaluable immunogenicity population who achieved seroresponse to the reference strain at 1 month after Dose 3 was 75.0% (95% CI: 19.4, 99.4). At before Dose 4 and 1 month after Dose 4, 1 participant had valid assay result and the participant had seroresponse.

Participants ≥18 Years of Age

In the evaluable immunogenicity population, the immunomodulatory therapy group was the only group that had a participant with a valid and determinate assay result at both the prevaccination timepoint and all subsequent sampling timepoints.

The proportion of participants without evidence of infection in the Dose 3 or Dose 4 evaluable immunogenicity population who achieved seroresponse to the reference strain at 1 month after Dose 3 was 33.3% (95% CI: 0.8, 90.6). Two participants had valid assay results at before Dose 4 and none had seroresponse. At 1 month after Dose 4, 1 participant had a valid assay result and the participant had seroresponse.

Participants With or Without Evidence of Infection

The proportion of participants with or without evidence of prior infection in the Dose 3 or Dose 4 evaluable immunogenicity population who achieved seroresponse to the reference strain was observed to be higher compared to those without evidence of prior infection.

Table 21: GMFRs and Seroresponse for Participants With or Without Evidence of Infection - Evaluable immunogenicity population. Assessor´s table.

Dose/ Timepoint	**Endpoint**	**3 µg 2 to < 5 y**	**10 µg 5 to < 12 y**	**30 µg 12 to < 18 y**	**30 µg ≥ 18 y**
3/1 month	Number of observations GMFR (95% CI)	N= 26 20.7 (11, 38)	N= 56 38.2 (25, 60)	N= 11 65.2 (20, 208)	N= 4 4.7 (1, 45)
	N Seroresponse % (95% CI)	N= 19 73.1 (52, 88)	N= 46 82.1 (70, 91)	N= 10 90.9 (59, 100)	N= 1 25 (1, 81)
4/pre vacc.	N GMFR (95% CI)	N= 24 11.3 (6, 23)	N= 55 20.7 (13., 33.)	N= 10 63.4 (29, 138)	N=3 3.9 (2, 9)
	N Seroresponse % (95% CI)	N= 16 66.7 (45, 84)	N= 39 70.9 (57, 82)	N=10 100 (69, 100)	N=0 0 (0, 71)
4/1 month	N GMFR (95% CI)	N= 16 89.5 (40, 201)	N=31 143 (85, 24)	N= 6 141.4 (48, 417)	N= 4 9.1 (2, 54)
	N Seroresponse % (95% CI)	N= 15 93.9 (70, 84)	N= 30 96.8 (83, 100)	N= 6 100 (54, 100)	N= 3 75 (19, 99)
4/6 month	N GMFR (95% CI)	N= 15 34.6 (16, 76)	N= 28 51.1 (26, 99)	N= 5 62.5 (13, 292)	N= 3 10.3 (0, 1748)
	N Seroresponse % (95% CI)	N= 14 93.3 (68, 100)	N= 23 82.1 (63, 94)	N=5 100 (48, 100)	N= 1 33 (1, 91)

Assessor´s comment: highest seroresponse was achieved 1 month post 4th dose.

Immunogenicity Conclusions

Analysis of immunogenicity data at 1 month after Dose 3 (26 participants 2 to <5 years of age, 56 participants 5 to <12 years of age, 11 participants 12 to <18 years of age, and 4 participants ≥18 years of age) and 1 month after Dose 4 (16 participants 2 to <5 years of age, 31 participants 5 to <12 years of age, 6 participants 12 to <18 years of age, and 4 participants ≥18 years of age) in the evaluable immunogenicity population without evidence of prior infection demonstrated a vaccine-elicited immune response.

GMTs

GMTs were observed to be higher at 1 month after Dose 3 and 1 month after Dose 4 compared to levels observed before study vaccination across age groups and disease subsets.

GMFRs

Similar to the pattern observed in GMTs, the GMFRs were observed to be higher 1 month after Dose 3 and 1 month after Dose 4 across age groups and disease subsets.

Seroresponse

The proportion of participants achieving seroresponse to the reference strain was observed to be highest at 1 month after Dose 4 across age groups and disease subsets.

6.2.3. Discussion

Study C4591024 was a Phase 2b study that evaluated the safety, tolerability, and immunogenicity of BNT162b2 in immunocompromised participants >2 years of age based and utilized a vaccination series of 3 doses of age adapted Comirnaty followed by a fourth dose 3-6 months after dose 3.

The main immunogenicity objective was to evaluate neutralising antibody titre among baseline SARS-COV-2 negative immunosuppressed population before and after the 3rd and 4th dose. The study recruited all ages from 2 years and above. The study had also explorative objectives, most important of those is the evaluate neutralising antibody titre among entire evaluable immunogenicity population regardless of their baseline SARS-COV-2 status.

Enrolment in this study was terminated due to enrolment challenges as a result of universal recommendations for COVID-19 vaccination of immunocompromised individuals and the increased global availability of COVID-19 vaccines. The MAH faced problems to recruit the desired sample size for the planned study among immunocompromised population. The study started to recruit subjects in October 2021, which is already 10 months since CMA for Comirnaty 30 µg for adults in EU. Indeed, all countries provided vaccine against COVID-19 after the authorisation at first to the most vulnerable population, which includes the immunocompromised individuals. Therefore, it is not surprising, that the desired sample size was unreachable. Therefore, it was considered acceptable to stop recruiting subjects during procedure PAM 016.4 September 2022 and continue with the available study population. Altogether 124 individuals were enrolled to the study, whereas 7 participants were adults. Therefore entire study became descriptive.

The largest sample size was achieved among age group 5-<12 years, who received 10 µg Comirnaty. Older cohorts, which received adult dose 30 µg Comirnaty, recruited very low number as for older than 12, the vaccine was officially recommended at the time of the study.

The majority of study population was from USA and Germany and was SARS-CoV-2 negative at the baseline. There was rather large proportion, about 25% of participants in age group 5-<18 with unknown

baseline SARS-CoV-2 status. The reason was unknown and needed a clarification from the MAH (OC). The Applicant explained that absence of the baseline sample (either blood or nasal swab) or unclear test result caused the "unknown baseline Covid-19 status" label for about 20% of participants.

The immunogenicity data shows, that most reduced antibody response appears among those who were on immunomodulatory therapy. The immune response improved for everybody regardless of diagnosis or age after the 4th dose.

The primary immunogenicity objectives were to describe the immune responses among baseline SARS-CoV-2 negative immunocompromised population. The MAH wishes to update the SmPC with a table presenting immune responses regardless of the baseline SARS-CoV-2 status, which was an exploratory objective. There were roughly 20 % of participants with unknown baseline status and the sample size is small even for entire evaluable immunogenicity population. The data shows mainly, that the 4th dose improves the antibody titre in all studied age groups including immunosuppressed individuals from 2 years and older. We suggest to replace the table with a short text describing improved immunogenicity after the 4th dose for all studies groups (OC), which the Applicant has followed in an updated SmPC.

In conclusion, the 4th dose of Comirnaty improved neutralising antibody titres among immunocompromised population. This observation is in agreement with an earlier data.

6.3. Study C4591030

6.3.1. Methods – analysis of data submitted

Study C4591030 was a Phase 3, multicentre, randomised, observer-blind, 2-arm, parallel-design study conducted in Australia and New Zealand. The purpose of this study was to assess the safety and immunogenicity of a fourth dose of BNT162b2 administered concomitantly with SIIV compared with the vaccines given 1 month apart in adults 18 through 64 years of age who had previously received 3 doses of BNT162b2. Approximately 1126 participants were planned to be randomised at a ratio of 1:1 into the coadministration group (BNT162b2 and SIIV)/placebo, or the separate-administration group (placebo and SIIV)/BNT162b2, stratified by age groups (18 through 49 years and 50 through 64 years) and by history of positive SARS-CoV-2 test results by NAAT or rapid antigen test prior to randomisation (with prior history of SARS-CoV-2 and without prior history of SARS-CoV-2).

Results pertaining to the primary, secondary, and exploratory objectives for Study C4591030 were previously described in the C4591030 Final CSR (dated 29 June 2023), which was submitted, reviewed and approved via EMEA/H/C/005735/II/0201 (CHMP Opinion: 30 May 2024, EC decision: 03 July 2024). As requested in the EMEA/H/C/005735/II/0201 final assessment report, an overview of results of the secondary BNT162b2 immunogenicity endpoint analyses of SARS-CoV-2 neutralisation titres for a subset of approximately 200 participants.

6.3.2. Results

Immunogenicity Population

The evaluable BNT162b2 immunogenicity population of the SARS-CoV-2 neutralisation assay subset included 100 (100%) participants in the coadministration group and 100 (100%) in the separate-administration group. No participants were excluded from the evaluable BNT162b2 immunogenicity population of the SARS-CoV-2 neutralisation assay subset.

Participants without evidence of infection up to 1 month after BNT162b2 vaccination included 60 (60.0%) in the coadministration group and 60 (60.0%) in the separate-administration group.

Table 22: Demographic Characteristics – SARS-CoV-2 Neutralisation Assay Subset – Evaluable BNT162b2 Immunogenicity Population

	Vaccine Group (as Administered)		
	Coadministration Group (N^a=100) n^b (%)	Separate-Administration Group (N^a=100) n^b (%)	Total (N^a=200) n^b (%)
Sex			
Male	35 (35.0)	41 (41.0)	76 (38.0)
Female	65 (65.0)	59 (59.0)	124 (62.0)
Race			
White	86 (86.0)	78 (78.0)	164 (82.0)
Black or African American	0	1 (1.0)	1 (0.5)
Asian	10 (10.0)	13 (13.0)	23 (11.5)
Native Hawaiian or other Pacific Islander	2 (2.0)	6 (6.0)	8 (4.0)
Not reported	2 (2.0)	1 (1.0)	3 (1.5)
Unknown	0	1 (1.0)	1 (0.5)
Country			
New Zealand	80 (80.0)	78 (78.0)	158 (79.0)
Australia	20 (20.0)	22 (22.0)	42 (21.0)
Age at first study vaccination (years)[c]			
Mean (SD)	38.8 (12.89)	40.3 (13.77)	39.5 (13.33)
Median	37.0	40.5	38.0
Min, max	(19, 65)	(19, 64)	(19, 65)
Age group (at first study vaccination)			
18-49 Years	74 (74.0)	69 (69.0)	143 (71.5)
50-64 Years	26 (26.0)	31 (31.0)	57 (28.5)
Baseline SARS-CoV-2 status			
Positive[d]	40 (40.0)	40 (40.0)	80 (40.0)
Medical history of COVID-19	35 (35.0)	33 (33.0)	68 (34.0)
Positive N-binding antibody	39 (39.0)	39 (39.0)	78 (39.0)
Negative[e]	60 (60.0)	60 (60.0)	120 (60.0)
Timing of the third dose of BNT162b2 prior to BNT162b2 vaccination received during the study (days)			
n	100	100	200
Mean (SD)	135.8 (28.14)	163.6 (25.79)	149.7 (30.30)
Median	132.5	159.5	147.0
Min, max	(92, 191)	(119, 227)	(92, 227)
≥ 90 to < 180 Days	91 (91.0)	74 (74.0)	165 (82.5)
≥ 180 to < 270 Days	9 (9.0)	26 (26.0)	35 (17.5)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: The coadministration group received BNT162b2 (30 µg) in the left deltoid and SIIV in the right deltoid at the first vaccination visit, and placebo in the left deltoid at the second vaccination visit. The separate-administration group received placebo in the left deltoid and SIIV in the right deltoid at the first vaccination visit, and BNT162b2 (30 µg) in the left deltoid at the second vaccination visit.
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. For New Zealand participants, date of birth was entered as "01 Jan Year" as per local regulations.
d. Positive N-binding antibody result at Visit 1 or medical history of COVID-19.
e. Negative N-binding antibody result at Visit 1 and no medical history of COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2023 (22:27) Source Data: adsl Table Generation: 05MAR2024 (01:36)
(Database snapshot date: 29Feb2024) Output File: ./nda3/C4591030_NeuCSR2024/adsl_s005_nt

Secondary Immunogenicity Analyses

SARS-CoV-2 Neutralising Geometric Mean Titres and Geometric Mean Fold-rises

In the evaluable BNT162b2 immunogenicity population of the SARS-CoV-2 neutralisation assay subset, reference strain neutralising GMTs were increased from baseline to 1 month after BNT162b2 vaccination among both the coadministration and separate-administration groups. GMTs were slightly lower in the coadministration group compared with the separate- administration group at 1 month after vaccination. SARS-CoV-2 neutralising titre GMFRs for the reference strain from before vaccination to 1 month after BNT162b2 vaccination were 2.5 (95% CI: 2.1, 2.9) in the coadministration group and 3.3 (95% CI: 2.7, 3.9) in the separate-administration group.

Table 23: Geometric Mean Titres/Concentrations and Geometric Mean Fold Rises Overall and by Baseline SARS-CoV-2 Status – SARS-CoV-2 Neutralisation Assay Subset – Evaluable BNT162b2 Immunogenicity

Population

			Sampling Time Point								
			Baseline			1 Month After BNT162b2 Vaccination					
Assay	Subgroup	Vaccine Group (as Randomized)	n[a]	GMT/ GMC[b]	(95% CI[b])	n[a]	GMT/ GMC[b]	(95% CI[b])	n[c]	GMFR[d]	(95% CI[d])
SARS-CoV-2 neutralization assay - reference strain - NT50 (Titer)	All	Coadministration group	100	2755.9	(2107.6, 3603.4)	100	6773.9	(5545.0, 8275.3)	100	2.5	(2.1, 2.9)
		Separate-administration group	100	2421.2	(1780.1, 3293.3)	100	7886.6	(6264.9, 9928.2)	100	3.3	(2.7, 3.9)
	Baseline SARS-CoV-2 status										
	Positive[e]	Coadministration group	40	8980.2	(6548.2, 12315.5)	40	13070.5	(9687.5, 17634.8)	40	1.5	(1.2, 1.7)
		Separate-administration group	40	8385.7	(5990.8, 11738.1)	40	17012.4	(12963.0, 22326.7)	40	2.0	(1.6, 2.6)
	Negative[e]	Coadministration group	60	1253.8	(989.0, 1589.5)	60	4370.6	(3554.5, 5374.0)	60	3.5	(2.8, 4.3)
		Separate-administration group	60	1057.7	(766.1, 1460.2)	60	4724.0	(3597.0, 6204.1)	60	4.5	(3.5, 5.7)
Full-length S-binding IgG (U/mL)	All	Coadministration group	100	5607.5	(4539.1, 6927.3)	100	13396.5	(11378.4, 15772.6)	100	2.4	(2.1, 2.7)
		Separate-administration group	100	4878.9	(3854.0, 6176.3)	100	16035.9	(13549.6, 18978.3)	100	3.3	(2.9, 3.8)
	Baseline SARS-CoV-2 status										
	Positive[e]	Coadministration group	40	12263.0	(9280.2, 16204.5)	40	20305.4	(15956.9, 25839.0)	40	1.7	(1.3, 2.1)
		Separate-administration group	40	12379.1	(9510.3, 16113.4)	40	26970.9	(22144.8, 32848.8)	40	2.2	(1.8, 2.6)
	Negative[e]	Coadministration group	60	3328.2	(2677.1, 4137.8)	60	10152.6	(8360.2, 12329.4)	60	3.1	(2.6, 3.6)
		Separate-administration group	60	2622.6	(2041.4, 3369.5)	60	11338.6	(9202.5, 13970.5)	60	4.3	(3.7, 5.1)

Abbreviations: GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgG = immunoglobulin G;
LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ for all GMT/GMC and GMFR calculations.
Note: The baseline was defined as Visit 1 for the coadministration group and Visit 2 for the separate-administration group.
a. n = Number of participants in the vaccine group with valid and determinate assay results for the specified assay at the specified sampling time point.
b. GMT/GMC and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the titers/concentrations and the corresponding CIs (based on the Student t distribution).
c. n = Number of participants with valid and determinate assay results for the specified assay at both the given sampling time points.
d. GMFRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises (later time point over earlier time point) and the corresponding CIs (based on the Student t distribution).
e. Positive = positive N-binding antibody result at Visit 1 or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1 and no medical history of COVID-19.
PFIZER CONFIDENTIAL SDTM Creation: 04MAR2024 (02:51) Source Data: adva Table Generation: 12MAR2024 (02:58)
(Database snapshot date: 29Feb2024) Output File: ./nda3/C4591030_NeuCSR2024/adva_gmfr_s001_ref_bnt

An ad hoc analysis of model-based GMR (coadministration group to separate-administration group), which was not prespecified, was also conducted for the SARS-CoV-2 neutralisation assay subset. The model-based GMR for the SARS-CoV-2 neutralisation assay (reference strain) in the subset was 0.80 (95% CI: 0.66, 0.96), very similar to that observed for the full- length S-binding IgG assay in the same subset of participants. The model-based GMR for the full-length S-binding IgG assay (coadministration group to separate-administration group) was 0.83 (95% CI: 0.77, 0.89) in the overall study population in the primary analysis, while in the neutralisation assay subset the GMR was 0.77 (95% CI: 0.67, 0.89).

Table 24: Model-Based Geometric Mean Ratio for SARS-CoV-2 Neutralization Titres and Full-Length S-Binding IgG Levels (U/mL) at 1 Month After BNT162b2 Vaccination – SARS-CoV-2 Neutralization Assay Subset – Evaluable BNT162b2 Immunogenicity Population

	Vaccine Group (as Randomized)				
	Coadministration Group		Separate-Administration Group		Coadministration Group/Separate-Administration Group
Assay	n[a]	GMT/ GMC[b] (95% CI[b])	n[a]	GMT/ GMC[b] (95% CI[b])	GMR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (Titer)	100	6565.8 (5701.4, 7561.2)	100	8241.2 (7177.3, 9462.8)	0.80 (0.66, 0.96)
Full-length S-binding IgG (U/mL)	100	13092.5 (11748.7, 14590.0)	100	16949.5 (15242.5, 18847.6)	0.77 (0.67, 0.89)

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; GMT = geometric mean titer; IgG = immunoglobulin G;
LLOQ = lower limit of quantitation; LSMeans = least squares means; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: The baseline was defined as Visit 1 for the coadministration group and Visit 2 for the separate-administration group.
a. n = Number of participants with valid and determinate assay results for the specified assay at both baseline and the given sampling time point.
b. GMTs/GMCs and the 2-sided 95% CIs were calculated by exponentiating the LSMeans of the titers/concentrations and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with terms of vaccine group, age group, and the corresponding baseline assay results (log scale). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in LSMeans and the corresponding CIs based on the same linear regression model as that for GMTs/GMCs.
PFIZER CONFIDENTIAL SDTM Creation: 04MAR2024 (02:51) Source Data: adva Table Generation: 14MAR2024 (04:55)
(Database snapshot date: 29Feb2024) Output File: ./nda3/C4591030_NeuCSR2024/adva_gmr_nt_mode_bnt

Assessor´s comment: the result assessed during II/201

Table 2. Model-Based Geometric Mean Ratio for Full-Length S-Binding IgG Levels (U/mL) at 1 Month After BNT162b2 Vaccination – Evaluable BNT162b2 Immunogenicity Population

	Vaccine Group (as Randomized)				
	Coadministration Group		Separate-Administration Group		Coadministration Group/Separate-Administration Group
Assay	n[a]	GMC[b] (95% CI[b])	n[a]	GMC[b] (95% CI[b])	GMR[c] (95% CI[c])
Full-length S-binding IgG (U/mL)	499	13767.8 (13110.0, 14458.6)	413	16644.5 (15774.7, 17562.3)	0.83 (0.77, 0.89)

The neutralising assay results from this smaller selected population agree with the earlier presented S-protein binding antibody results from entire evaluable immunogenicity population. The antibody titre was very high for both separate and co-administration groups. The antibody concentration was numerically higher in separate administration group compared to the co-administration group according to both

serology method. For this post- hoc analysis for small subgroup, the GMR would not meet the pre specified non-inferiority criteria (lower limit of the 2-sided 95% CI for the GMR >0.67) There will be no immunogenicity data presented from this co-administration study in SmPC as agreed earlier during II/201. The clinical impact for lower neutralising antibody titre in case of separate administration is unknown.

Immunogenicity Conclusions

Secondary BNT162b2 Immunogenicity – SARS-CoV-2 Neutralisation Assay Subset

- SARS-CoV-2 reference strain GMTs were increased from baseline to 1 month after BNT162b2 vaccination among both the coadministration and separate-administration groups. GMTs were slightly lower in the coadministration group compared with the separate-administration group at 1 month after vaccination.
- GMFRs for the reference strain from before study vaccination to 1 month after BNT162b2 vaccination were slightly lower in the coadministration group (2.5 [95% CI: 2.1, 2.9]) compared with the separate-administration group (3.3 [95% CI: 2.7, 3.9]).
- Due to the sampling variability and smaller sample size of the neutralisation subset, the lower bounds of the 95% CI of the model-based GMRs were lower than seen for the full-length S-binding IgG assay in the overall study population in the primary analysis; however, the point estimates of GMRs for the SARS-CoV-2 neutralisation assay and full-length S-binding IgG assay were similar: 0.77 (95% CI: 0.67, 0.89) and 0.80 (95% CI: 0.66, 0.96) for the full-length S-binding IgG assay and the SARS- CoV-2 neutralisation assay (reference strain) in the neutralisation subset respectively, compared to 0.83 (95% CI: 0.77, 0.89) in the overall study population in the primary analysis for the full-length S-binding IgG.

6.3.3. Discussion

The primary results were evaluated during procedure II/201, but are repeated here to put the new results into the context.

Because the recommendations for COVID-19 vaccination and influenza vaccination have a considerable overlap, including recommended age groups, at-risk populations, and timing, both vaccines may need to be administered at the same time. Such guidance is already provided in the USA and European Union, and by the World Health Organization (WHO) since autumn 2022.

The study C4591030, which investigates co-administration of Comirnaty and seasonal influenza vaccine study has been part of RMP since April 2021.

1134 participants were randomised at a ratio of 1:1 into the coadministration group, or the separate administration group (placebo and SIIV)/Comirnaty, stratified by age groups (18 through 49 years and 50 through 64 years) and by history of positive SARS-CoV-2 test results by NAAT or rapid antigen test prior to randomisation (with prior history of SARS CoV-2 and without prior history of SARS-CoV-2).

The primary immunogenicity objective was to demonstrate that the immune responses elicited by Comirnaty when co-administered with SIIV are noninferior to those elicited by Comirnaty when administered alone, as demonstrated by full-length S-binding IgG levels. The full-length S-binding IgG measurement results showed that binding antibody concentration was numerically higher in separate administration group compared to the co-administration group (non-overlapping GMC 95% CI). The GMR coadministration vs. separate administration was 0.83 [95% CI: 0.77, 0.89]). The GMR met the pre specified non-inferiority criteria (lower limit of the 2-sided 95% CI for the GMR >0.67) as immunogenicity

primary endpoint of this study. S-binding IgG levels has not been used earlier as a primary immunogenicity endpoint in Comirnaty studies. Neutralisation assay is seen as the most relevant to demonstrate protection against infection.

Already during the study report evaluation (MEA 018) we noted that the primary SARS-CoV-2 Immunogenicity endpoint for this study is full-length S-binding IgG levels and not the neutralising antibodies. At the same time, SARS-CoV-2 neutralising antibody titre is a secondary endpoint and was planned to be evaluated for a subset of approximately 200 participants. The approach of choosing binding antibodies as a primary endpoint could be acceptable if a good correlation of binding IgG and Neutralisation assays would be demonstrated. Therefore, the MAH had to show the correlation between neutralising and binding antibodies to ensure clinical relevance of the binding antibody data. The MAH has submitted the requested method correlation analysis and the result is acceptable as demonstrating a good correlation (R^2 = 0.97) between the values measured using Neutralisation and Binding assay.

In current update, an overview of results of the secondary BNT162b2 immunogenicity endpoint analyses of SARS-CoV-2 neutralisation titres for a subset of approximately 200 participants were presented.

The evaluable BNT162b2 immunogenicity population of the SARS-CoV-2 neutralisation assay subset included 100 (100%) participants in the coadministration group and 100 (100%) in the separate-administration group. The neutralising assay results from this smaller selected population agree generally with the earlier presented S-protein binding antibody results from entire evaluable immunogenicity population. The antibody titre was very high for both separate and co-administration groups. The antibody concentration was numerically higher in separate administration group compared to the co-administration group according to both serology method for this selected smaller study population. For this post-hoc analysis for small subgroup, the GMR would not meet the pre specified non-inferiority criteria for neither of the assays (lower limit of the 2-sided 95% CI for the GMR >0.67). The result was very near to non-inferiority criteria, GMR LL 0.66 for neutralisation and 0.67 for S-binding assay. The GMRs of the S- protein binding antibody data from entire evaluable immunogenicity population did meet the pre specified non-inferiority criteria.

There will be no immunogenicity data presented from this co-administration study in SmPC as agreed earlier during II/201. The clinical impact for lower titre of neutralising antibodies in case of co-administration with SIIV is unknown.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

7.1.1. C4591015

Study C4591015 was a global Phase 2/3, randomised, placebo-controlled, observer-blind study to evaluate the safety, tolerability, and immunogenicity of 30 µg of BNT162b2 or placebo administered in 2 doses, 21 days apart, in healthy pregnant women 18 years of age or older vaccinated at 24 to 34 weeks' gestation.

The Phase 2 portion of the study included approximately 200 pregnant women enrolled at 27 to 34 weeks' gestation. The IRC reviewed safety data through 7 days after the second dose for all Phase 2 participants.

The Phase 3 portion of this study included approximately 150 pregnant women enrolled at 24 to 34 weeks' gestation. Phase 3 proceeded after the first 200 maternal participants had been enrolled in Phase 2. Maternal participants who originally received placebo could receive BNT162b2 at the 1-month post-delivery visit.

Subjects with known HIV infection could be included if the participant had a viral load <50 copies/mL and CD4count >200 cells/mm3 within 6 months before Enrolment, and on stable antiretroviral therapy for at least 6 months.

Enrolment in this study was terminated on 25 October 2021 due to Enrolment challenges as a result of universal recommendations for COVID-19 vaccination of pregnant women and the increased global availability of COVID-19 vaccines.

7.1.2. C4591024

This was a Phase 2b, open-label study with BNT162b2 in immunocompromised participants ≥18 years of age treated for NSCLC or CLL, receiving haemodialysis treatment secondary to end-stage renal disease, or receiving immunomodulator therapy for an autoimmune inflammatory disorder, and in immunocompromised participants 2 to <18 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to Enrolment.

The study evaluated a 4-dose schedule (the first 2 doses separated by 21 days), with a third dose occurring 28 days after the second dose. The fourth dose (booster) occurred 3-6 months after Dose 3*.

The dose for each of the 4 vaccinations depended upon the age of the participant at the time of vaccination, as follows:

- For participants who were >12 years of age (on the day of vaccination): at a 30-µg dose level
- For participants who were 5 to <12 years of age (on the day of vaccination): at a 10-µg dose level
- For participants who were 2 to <5 years of age (on the day of vaccination): at a 3-µg dose level
- In each of the cohorts <18 years of age (at Visit 1), participants with the following immunocompromising conditions were recruited/enrolled:
    - Immunomodulator treatment for an autoimmune inflammatory disorder (≥10 participants in each age cohort)
    - Immunomodulator treatment after solid organ transplant (≥10 participants in each age cohort)
    - Underwent bone marrow or stem cell transplant ≥6 months (182 days) before Enrolment (≥10 participants in each age cohort)
- In the cohort that was ≥18 years of age (at Visit 1), participants with the following immunocompromising conditions were recruited/enrolled:
    - Treated for NSCLS or CLL (no participants who were receiving treatment or under observation for CLL were enrolled in Study C4591024.)
    - Were receiving haemodialysis treatment secondary to end-stage renal disease
    - Immunomodulatory treatment for an autoimmune inflammatory disorder

*Note that the timing of the fourth dose was determined by the investigator's discretion, taking into account factors such as the participant's underlying condition and level of immunosuppression, the evolving clinical literature, the COVID-19 incidence in the participant's geographic area, and the potential for increased reactogenicity with Dose 4 occurring earlier. Additionally, although more data are needed for COVID-19 vaccines, there is a risk of reduced immunogenicity and antibody persistence with a shorter interval between Dose 3 and Dose 4. Investigators were encouraged to weigh the risks and benefits for each participant and make an individualized decision on the timing of the third dose, provided it falls within the minimum and maximum time frames detailed above. Depending on the timing of Dose 3 and Dose 4, participants were expected to participate for up to 14 months, with a maximum of approximately 15 months

There have been 5 protocol amendments during the study. Some changes were purely administrative clarifications initially reported in PACLs. Other more important changes are listed below:

- Removal of the requirement to conduct a potential COVID-19/MIS-C convalescent visit following each COVID-19/MIS-C illness visit.
- Removal of the exploratory objective looking into viral shedding in line with the removal of the convalescent visit.
- Addition of primary and exploratory safety, tolerability, and immune response objectives for the expanded cohort of participants on active immunomodulator therapy.
- Updated Visit 5 window to allow its occurrence as early as 28 days after Visit 2 and updated wording to allow subgroup analysis of immunogenicity endpoints based on various timing of Dose 3. These changes were made to be in line with Regulatory recommendations for providing a 3rd dose of BNT162b2 to immunocompromised individuals.
- Updated procedures to allow a fourth dose (booster), reducing the window for provision of Dose 3, and allowing vaccination with the age-appropriate dose.
- Updated the number of participants in each group based on actual recruitment figures.
- Removed further blood draws for participants who have consented to PBMC sampling.

7.2. Results

7.2.1. C4591015

The study was not able to enrol the intended number of participants due to real-world use of the vaccine in this population.

Disposition

Maternal population

Table 25: Disposition of All Randomized Participants – Maternal – Prior to Unblinding

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N^a=174) n^b (%)	Placebo (N^a=174) n^b (%)	Total (N^a=348) n^b (%)
Randomized	174 (100.0)	174 (100.0)	348 (100.0)
Not vaccinated	1 (0.6)	1 (0.6)	2 (0.6)
Vaccinated			
Dose 1	173 (99.4)	173 (99.4)	346 (99.4)
Dose 2	170 (97.7)	170 (97.7)	340 (97.7)
Completed 1-month postdelivery visit	161 (92.5)	159 (91.4)	320 (92.0)
Withdrawn from the study	7 (4.0)	12 (6.9)	19 (5.5)
Withdrawn before Dose 1	1 (0.6)	1 (0.6)	2 (0.6)
Withdrawn after Dose 1 and before Dose 2	2 (1.1)	2 (1.1)	4 (1.1)
Withdrawn after Dose 2	4 (2.3)	9 (5.2)	13 (3.7)
Reason for withdrawal			
Withdrawal by subject	4 (2.3)	9 (5.2)	13 (3.7)
Protocol deviation	2 (1.1)	2 (1.1)	4 (1.1)
Lost to follow-up	1 (0.6)	1 (0.6)	2 (0.6)

Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but analyzed and reported separately.
a. N = number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (09:53) Source Data: adds Table Generation: 12MAY2023 (12:05) Output File: ./nda3/C4591015_BR/adds_s002_all_p3_rand

Infant population:

A total of 167 infants were born to maternal participants in the BNT162b2 group and 168 were born to maternal participants in the placebo group. Most (86.9%) infant participants completed the 6-months-of-age follow-up visit. Withdrawal from the study was more frequently reported among infants whose mothers were randomised to placebo (17.3%) than those whose mothers were randomised to BNT162b2 (9.0%); the most frequent reasons for withdrawal during the study was withdrawal by parent/guardian and lost to follow-up. Two infant participants (1 in the BNT162b2 [pneumonia, mother was HIV positive]and 1 in the placebo group [neonatal pneumonia]) died during the study due to SAEs that were assessed as unrelated to study vaccination, and were subsequently withdrawn from the study.

The safety population for maternal participants included 173 participants in the BNT162b2 group and 173 participants in the placebo group; 2 maternal participants were excluded from the safety population because they did not receive the study intervention. Most maternal participants included in the safety population were breastfeeding, and 12 in the BNT162b2 group and 10 in the placebo group were HIV-positive.

Demographics

Maternal population:

Table 26: Demographic Characteristics – Safety Population (Maternal)

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=173) n[b] (%)	Placebo (N[a]=173) n[b] (%)	Total (N[a]=346) n[b] (%)
Race			
White	117 (67.6)	118 (68.2)	235 (67.9)
Black or African American	47 (27.2)	43 (24.9)	90 (26.0)
American Indian or Alaska Native	1 (0.6)	1 (0.6)	2 (0.6)
Asian	5 (2.9)	9 (5.2)	14 (4.0)
Native Hawaiian or other Pacific Islander	0	1 (0.6)	1 (0.3)
Multiracial	1 (0.6)	0	1 (0.3)
Not reported	2 (1.2)	1 (0.6)	3 (0.9)
Ethnicity			
Hispanic/Latino	70 (40.5)	63 (36.4)	133 (38.4)
Non-Hispanic/Non-Latino	103 (59.5)	110 (63.6)	213 (61.6)
Country			
Brazil	24 (13.9)	19 (11.0)	43 (12.4)
South Africa	40 (23.1)	42 (24.3)	82 (23.7)
Spain	21 (12.1)	18 (10.4)	39 (11.3)
United Kingdom	7 (4.0)	8 (4.6)	15 (4.3)
United States	81 (46.8)	86 (49.7)	167 (48.3)
HIV-positive			
Yes	12 (6.9)	10 (5.8)	22 (6.4)
No	161 (93.1)	163 (94.2)	324 (93.6)
Age at Dose 1 (years)			
Mean (SD)	29.6 (6.27)	29.6 (5.79)	29.6 (6.03)
Median	30.0	30.0	30.0
Min, max	(18, 44)	(18, 44)	(18, 44)
Gestational age at Dose 1 (weeks)			
n	173	173	346
Mean (SD)	30.0 (2.74)	30.2 (2.64)	30.1 (2.69)
Median	30.1	30.4	30.4
Min, max	(24.0, 34.9)	(24.1, 36.1)	(24.0, 36.1)
Gestational age at Dose 2 (weeks)			
n	170	170	340
Mean (SD)	33.1 (2.68)	33.4 (2.72)	33.2 (2.70)
Median	33.3	33.4	33.4
Min, max	(27.0, 37.7)	(27.0, 39.6)	(27.0, 39.6)
Baseline SARS-CoV-2 status confirmed			
Positive	63 (36.4)	64 (37.0)	127 (36.7)
Negative	102 (59.0)	105 (60.7)	207 (59.8)
Missing	8 (4.6)	4 (2.3)	12 (3.5)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	0	1 (0.6)	1 (0.3)
Normal weight (≥18.5 kg/m^2 - 24.9 kg/m^2)	43 (24.9)	39 (22.5)	82 (23.7)
Overweight (≥25.0 kg/m^2 - 29.9 kg/m^2)	65 (37.6)	62 (35.8)	127 (36.7)
Obese (≥30.0 kg/m^2)	65 (37.6)	70 (40.5)	135 (39.0)
Missing	0	1 (0.6)	1 (0.3)

Abbreviations: HIV = human immunodeficiency virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Gestational age at Dose 2 (weeks) = gestational age at Dose 1 (weeks) + (date of Dose 2 – date of Dose 1)/7.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (09:47) Source Data: adsl Table Generation: 10MAY2023 (10:21) Output File: ./nda3/C4591015_BR/adsl_s005_demo_p3_saf

Most (≥97.7%) maternal participants were administered Dose 1 and Dose 2 as randomised. For participants who were originally randomised to placebo, 87.4% and 85.1% received a first dose and second dose of BNT162b2, respectively, following unblinding at the 1-month postdelivery visit.
In all randomised maternal participants, the majority (≥87.9%) in the BNT162b2 and placebo groups received Dose 2 in the protocol-defined window of 19 to 23 days after Dose 1. For the 152 (87.4%) maternal participants who were originally randomised to placebo and received a first dose of BNT162b2 after unblinding, the majority (127 [73.0%]) received a second dose of BNT162b2 in the protocol-defined window of 19 to 23 days after the first dose.

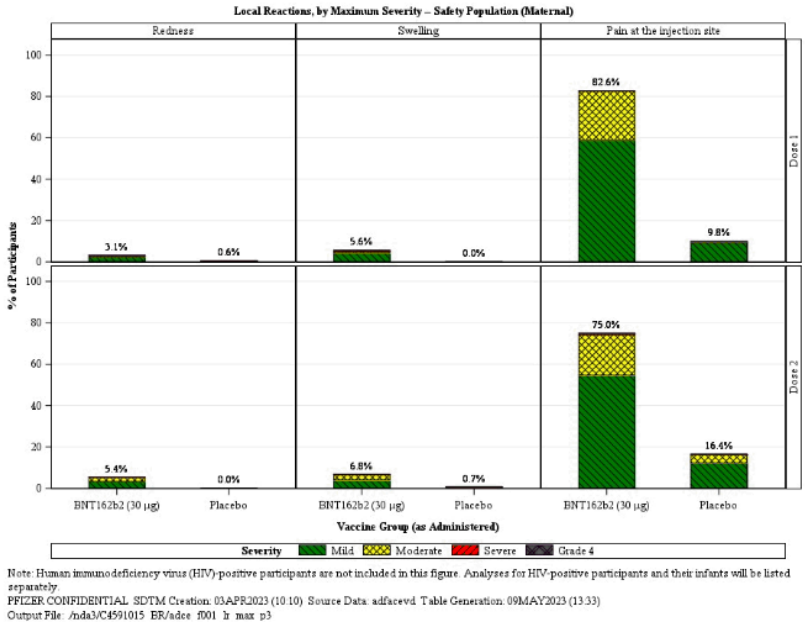
Infant population:

The majority of participants were White (65.4%), non-Hispanic/non-Latino (60.3%), and located in the US (48.7%) or South Africa (23.9%). The majority of infants were born ≥37 weeks to 41 weeks 6 days, and 89.3% of infant participants were breastfed. Both groups were similar with regards to HIV status (mother positive in 6-7%).

Reactogenicity

Local reactions

Figure 1: Local Reactions, by Maximum Severity - Safety Population (Maternal)



Note: Human immunodeficiency virus (HIV)-positive participants are not included in this figure. Analyses for HIV-positive participants and their infants will be listed separately.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (10:10) Source Data: adfacevd Table Generation: 09MAY2023 (13:33)
Output File: /nda3/C4591015_ER/adce_f001_lr_max_p3

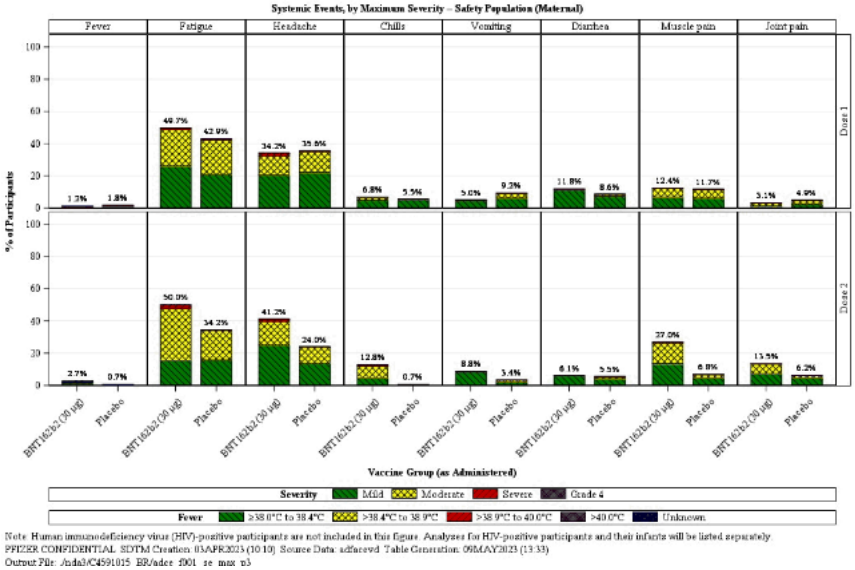
Most local reactions were mild or moderate in severity. A severe event of swelling was reported in 1 participant in the BNT162b2 group after Dose 1, and a severe event of pain at the injection site was reported in 1 participant in the same group after Dose 2. No Grade 4 local reactions were reported in either group.

Across both groups, median onset for all local reactions was between Day 1 and Day 2.5 after Dose 1 or Dose 2, and all events resolved with median durations between 1 to 2 days.

Subgroup analysis: Local reactions reported within 7 days after vaccination were evaluated by race, ethnicity, and baseline SARS-CoV-2 status. Overall, for these subgroups, local reactions were reported at higher frequencies among participants in the BNT162b2 group after both doses compared to those in the placebo group. Among vaccinated participants, no clinically meaningful differences were observed by race or ethnicity in either group. For participants with baseline negative SARS-CoV-2 status, higher frequencies of pain at the injection site were reported after each dose in both the BNT162b2 and placebo groups as compared to baseline positive participants. As several subgroups included a limited number of participants, these results should be interpreted with caution.

Systemic Events

Figure 2: Local Reactions, by Maximum Severity - Safety Population (Maternal)



Note: Human immunodeficiency virus (HIV)-positive participants are not included in this figure. Analyses for HIV-positive participants and their infants will be listed separately.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (10:10) Source Data: adfacevd Table Generation: 09MAY2023 (13:33)
Output File: /tda3/C4591015_BR/adce_f001_se_mix_n3

Most systemic events were mild or moderate in severity. In both the BNT162b2 and placebo groups, the most frequently reported severe events after any dose were fatigue (2.0% and 0.6%, respectively) and headache (1.9% and 0.6%, respectively). No Grade 4 systemic events were reported in either group.

Across both groups, median onset for all systemic events was between Day 1 and Day 4 after Dose 1 or Dose 2, and all events resolved with median durations between 1 to 4.5 days.

The reported frequencies of participants with baseline systemic events were similar for the BNT162b2 and placebo groups, with the baseline fatigue most frequently reported (29.7% and 33.8%, respectively).

Subgroup analyses: Systemic events reported within 7 days after vaccination were evaluated by race, ethnicity, and baseline SARS-CoV-2 status. Among vaccinated participants, no clinically meaningful differences were observed by race, ethnicity, or SARS-CoV-2 status in either group. As several subgroups included a limited number of participants, these results should be interpreted with caution.

Adverse Events

Table 27: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Follow-Up Period – Safety Population (Maternal)

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N^a=161) n^b (%)	Placebo (N^a=163) n^b (%)
Any adverse event	38 (23.6)	37 (22.7)
Related[c]	1 (0.6)	1 (0.6)
Severe	7 (4.3)	8 (4.9)
Life-threatening	0	3 (1.8)
Any serious adverse event	9 (5.6)	9 (5.5)
Related[c]	0	0
Severe	5 (3.1)	4 (2.5)
Life-threatening	0	3 (1.8)
Any nonserious adverse event	33 (20.5)	33 (20.2)
Related[c]	1 (0.6)	1 (0.6)
Severe	2 (1.2)	4 (2.5)
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

Note: Human immunodeficiency virus (HIV)-positive participants are not included in this summary. Analyses for HIV-positive participants and their infants will be summarized separately.
Note: Nonserious adverse events related to study intervention with onset within 7 days (excluding immediate adverse event and adverse events leading to withdrawal) after vaccination and identified as reactogenicity events were excluded from the analysis of adverse events. These events were included in the analysis of reactogenicity events.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (10:10) Source Data: adae Table Generation: 03MAY2023 (10:32) Output File: ./nda3/C4591015_BR/adae_s091_all_pd2_p3_saf

Participants Randomised to Placebo and Who Received BNT162b2 After Unblinding

Note that these participants did not use an e-diary to record local reactions or systemic events occurring within 7 days of vaccination after receipt of BNT162b2 after unblinding at 1 month postdelivery, and all such events were reported as AEs.

The frequency of AEs reported among participants who originally received placebo and then received BNT162b2 after unblinding (22.2%) was similar to that in the BNT162b2 group during the blinded follow-up period (23.6%), and overall the results did not suggest any meaningful differences in types of AEs reported. From vaccination with BNT162b2 to 1 month after the second dose of BNT162b2 for original placebo participants who then received BNT162b2 after unblinding, there were no reported SAEs, life-threatening AEs, AEs leading to withdrawal, or deaths. Except for 1 participant, all AEs were mild or moderate in severity. Related AEs were reported in 12.5% of participants. The most frequently reported AEs in these participants unblinded at 1-month postdelivery were reactogenicity events. The frequency of AEs reported among participants who originally received placebo and then received BNT162b2 after unblinding (22.2%) was similar to that in the BNT162b2 group during the blinded follow-up period (23.6%). From vaccination with BNT162b2 to 1 month after the second dose of BNT162b2 for original placebo participants who then received BNT162b2 after unblinding, there were no reported SAEs, life-threatening AEs, AEs leading to withdrawal, or deaths. Except for 1 participant, all AEs were mild or moderate in severity. Related AEs were reported in 12.5% of participants. The most frequently reported AEs in these participants unblinded at 1-month postdelivery were reactogenicity events.

Infant Participants

The proportions of infant participants with any AEs reported from birth to 1 month of age were similar in the BNT162b2 (35.3%) and placebo (37.1%) groups. Most AEs were mild or moderate in severity (≤6.3% were severe between both groups), and none were assessed by the investigator as related. Between both groups, SAEs were reported in ≤13.8% and life-threatening AEs were reported in and ≤3.1% of infants. One infant participant in the placebo group was withdrawn due to a fatal SAE of neonatal pneumonia that was assessed by the investigator as unrelated to study intervention. Additionally, 1 infant born to an HIV-positive maternal participant in the BNT162b2 group was withdrawn due to a fatal SAE of pneumonia that was also assessed as unrelated to study intervention by the investigator.

Adverse Events by System Organ Class and Preferred Term

Maternal Participants

AEs in maternal participants from Dose 1 to 1 month after Dose 2 that were most frequently reported for the BNT162b2 group were in the SOCs of pregnancy, puerperium and perinatal conditions (9.3%), infections and infestations (5.0%), and gastrointestinal disorders (4.3%); in the placebo group, AEs were reported in these SOCs for pregnancy, puerperium and perinatal conditions (9.2%), gastrointestinal disorders (6.1%), infections and infestations (2.5%), and blood and lymphatic system disorders (2.5%), respectively. The frequency of AEs reported by PT was generally similar between the BNT162b2 and placebo groups. Few Tier 2 AEs[1] were reported in maternal participants from Dose 1 to 1 month after Dose 2. In the BNT162b2 group, most Tier 2 AEs were reported in 2 participants each.

Participants Randomised to Placebo and Who Received BNT162b2 After Unblinding

In maternal participants originally randomised to placebo, who received BNT162b2 after unblinding at 1-month postdelivery, AEs reported from the first dose of BNT162b2 to 1 month after the second dose of BNT162b2 were most frequently in the SOCs of general disorders and administration site conditions (13.2%), infections and infestations (6.9%), and nervous system disorders (5.6%). The few AEs reported in >1 participant was primarily reactogenicity events; the most frequently reported were injection site pain (9.0%) and headache (4.9%).

Infant Participants

AEs in infant participants from birth to 1 month of age that were most frequently reported for the BNT162b2 group were in the SOCs of pregnancy, puerperium and perinatal conditions (16.7%) and congenital, familial and genetic disorders (10.3%); in the placebo group, AEs were reported in these SOCs for 19.5% and 5.0%, respectively. In the BNT162b2 group, most AEs were reported in 1 participant each. The most frequently reported AE in the BNT162b2 group was jaundice neonatal (12.2%), which was reported similarly in the placebo group (10.7%).

Tier 2 AEs were reported at similar frequencies between the BNT162b2 and placebo groups (53 and 61 participants, respectively). In the BNT162b2 group, most Tier 2 AEs were reported in 1 to 3 participants each.

Infants Born to HIV-Positive Participants

There were few infants born to HIV-positive maternal participants with AEs reported during the study; most were born to mothers in the placebo group. None of the AEs were assessed as related. One infant born to an HIV-positive participant maternal participant in the BNT162b2 group had a fatal SAE of pneumonia that was assessed by the investigator as not related.

Related Adverse Events

[1] A MedDRA PT is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event

Maternal Participants

Table 28: Number (%) of Participants Reporting at Least 1 Related Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Follow-Up Period – Safety Population (Maternal)

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=161) n[b] (%)	 (95% CI[c])	 Placebo (N[a]=163) n[b] (%)	 (95% CI[c])
Any event	1 (0.6)	(0.0, 3.4)	1 (0.6)	(0.0, 3.4)
General disorders and administration site conditions	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Injection site pain	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Tachypnoea	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)

Note: MedDRA (v25.1) coding dictionary applied.
Note: Human immunodeficiency virus (HIV)-positive participants are not included in this summary. Analyses of HIV-positive participants and their infants will be listed separately.
Note: Nonserious adverse events related to study intervention with onset within 7 days (excluding immediate adverse event and adverse events leading to withdrawal) after vaccination and identified as reactogenicity events were excluded from the analysis of adverse events. These events were included in the analysis of reactogenicity events.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "Any 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.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (10:10) Source Data: adae Table Generation: 03MAY2023

Neither of the two related AEs were SAEs or AEs which led to withdrawal.

In infant participants, none of the AEs reported from birth to 1 month of age were assessed as related to study intervention by the investigator.

Immediate Adverse Events

Maternal Participants

In maternal participants, there were no immediate AEs reported within 30 minutes after receiving Dose 1. After Dose 2, 1 participant in the placebo group reported an immediate AE of injection site pain.

Participants Randomised to Placebo and Who Received BNT162b2 After Unblinding

In maternal participants who were originally randomised to placebo and then received BNT162b2 after unblinding at 1-month postdelivery, there were no immediate AEs reported after the first or second dose of BNT162b2.

Severe and Life-Threatening Adverse Events

Maternal Participants

Severe AEs were reported by 7 participants (4.3%) in the BNT162b2 group and 8 participants (4.9%) in the placebo group from Dose 1 to 1 month after Dose 2. In the BNT162b2 group, severe AEs were mostly reported by 1 participant each and were most frequently reported (≤2 participants) in the SOCs of pregnancy, puerperium and perinatal conditions and infections and infestations. The few severe AEs that were SAEs were similar in frequency between groups (5 [3.1%] participants in the BNT162b2 group, 4 [2.5%] participants in the placebo group), and none were assessed by the investigator as related.

Infant Participants

Severe AEs were reported by 5 participants (3.2%) in the BNT162b2 group and 10 participants (6.3%) in the placebo group from birth to 1 month of age. In the BNT162b2 group, severe AEs were reported in 1 participant each and were most frequently reported (≤3 participants) in the SOCs of congenital, familial and genetic disorders and pregnancy, puerperium and perinatal conditions. The few severe AEs that were

SAEs were similar in frequency between groups (5 [3.2%] participants in the BNT162b2 group, 8 [5.0%] participants in the placebo group), and none were assessed by the investigator as related.

Deaths

Maternal Participants

There were no deaths in maternal participants.

Infant Participants

One infant born at 32 weeks and 3 days gestational age, to a maternal participant in the placebo group, died at 7 days of age due to an SAE of neonatal pneumonia; the event duration was 7 days, and was assessed as not related by the investigator. Additionally, one infant born at 40 weeks gestational age, to an HIV-positive maternal participant in the BNT162b2 group, died at 124 days of age due to an SAE of pneumonia; the event duration was 6 days, and was investigator-assessed as not related.

Serious Adverse Events

Maternal Participants

For SAEs reported in maternal participants from Dose 1 to 1 month after Dose 2, the proportions were similar in the BNT162b2 (5.6%) and placebo (5.5%) groups; none were assessed by the investigator as related.

Table 29: Number (%) of Participants Reporting at Least 1 Serious Adverse Event From Dose 1 Through 1 Month After Delivery, by System Organ Class and Preferred Term – Blinded Follow-Up Period – Safety Population (Maternal)

System Organ Class Preferred Term	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=161) n[b] (%)	(95% CI[c])	Placebo (N[a]=163) n[b] (%)	(95% CI[c])
Any event	21 (13.0)	(8.3, 19.2)	23 (14.1)	(9.2, 20.4)
Cardiac disorders	1 (0.6)	(0.0, 3.4)	2 (1.2)	(0.1, 4.4)
Nonreassuring foetal heart rate pattern	0	(0.0, 2.3)	2 (1.2)	(0.1, 4.4)
Bradycardia foetal	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Gastrointestinal disorders	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Abdominal wall haematoma	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Hepatobiliary disorders	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Cholelithiasis	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Infections and infestations	3 (1.9)	(0.4, 5.3)	2 (1.2)	(0.1, 4.4)
Endometritis	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Lower respiratory tract infection	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Pneumonia	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Pyelonephritis	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Urinary tract infection	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Injury, poisoning and procedural complications	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Urinary tract procedural complication	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Investigations	0	(0.0, 2.3)	2 (1.2)	(0.1, 4.4)
Foetal heart rate abnormal	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Ultrasound foetal abnormal	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Musculoskeletal and connective tissue disorders	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Osteoarthritis	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Pregnancy, puerperium and perinatal conditions	13 (8.1)	(4.4, 13.4)	17 (10.4)	(6.2, 16.2)
Pre-eclampsia	4 (2.5)	(0.7, 6.2)	2 (1.2)	(0.1, 4.4)
Foetal distress syndrome	3 (1.9)	(0.4, 5.3)	2 (1.2)	(0.1, 4.4)
Cephalo-pelvic disproportion	1 (0.6)	(0.0, 3.4)	3 (1.8)	(0.4, 5.3)
Premature separation of placenta	0	(0.0, 2.3)	3 (1.8)	(0.4, 5.3)
Foetal hypokinesia	1 (0.6)	(0.0, 3.4)	1 (0.6)	(0.0, 3.4)
Gestational hypertension	1 (0.6)	(0.0, 3.4)	1 (0.6)	(0.0, 3.4)
Postpartum haemorrhage	0	(0.0, 2.3)	2 (1.2)	(0.1, 4.4)
Arrested labour	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Breech presentation	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Failed induction of labour	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Foetal growth restriction	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Haemorrhage in pregnancy	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Meconium in amniotic fluid	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Meconium stain	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Omphalorrhexis	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Placental insufficiency	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Preterm premature rupture of membranes	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Prolonged rupture of membranes	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.4)
Retained placenta or membranes	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Reproductive system and breast disorders	2 (1.2)	(0.2, 4.4)	0	(0.0, 2.2)
Uterine disorder	2 (1.2)	(0.2, 4.4)	0	(0.0, 2.2)
Skin and subcutaneous tissue disorders	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Pruritus	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Vascular disorders	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)
Deep vein thrombosis	1 (0.6)	(0.0, 3.4)	0	(0.0, 2.2)

Note: MedDRA (v25.1) coding dictionary applied.
Note: Human immunodeficiency virus (HIV)-positive participants are not included in this summary. Analyses of HIV-positive participants and their infants will be summarized separately.
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 adverse event. For "any 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.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (10:10) Source Data: adae Table Generation: 03MAY2023

Participants Randomised to Placebo and Who Received BNT162b2 After Unblinding

In maternal participants originally randomised to placebo, who received BNT162b2 after unblinding at 1-month postdelivery, from the first dose of BNT162b2 to 1 month after the second dose of BNT162b2 there were no SAEs reported.

Infant Participants

From birth to 1 month of age, SAEs were reported in 12.2% and 13.8% of infant participants in the BNT162b2 and placebo groups, respectively; none were assessed by the investigator as related.

From birth to 6 months of age, SAEs were reported in 13.5% and 15.1% of infant participants in the BNT162b2 and placebo groups, respectively; none was assessed by the investigator as related. In the BNT162b2 group, SAEs were most frequently reported in the SOCs of pregnancy, puerperium and perinatal conditions (5.8%) and congenital, familial and genetic disorders (5.8%), which were reported at similar frequencies n the placebo group (3.1% and 3.1%, respectively). By PT, all SAEs in the BNT162b2 group were reported in ≤3 participants each, except for jaundice neonatal (7 participants). In the placebo group, an SAE of neonatal pneumonia, assessed by the investigator as not related, was fatal.

Infants Born to HIV-Positive Participants

From birth to 6 months of age, SAEs were reported in 9.1% and 22.2% of infants born to HIV-positive participants in the BNT162b2 and placebo groups, respectively, none were assessed by the investigator as related. One infant born to an HIV-positive participant in the BNT162b2 group had a fatal SAE of pneumonia that was assessed by the investigator as not related to study vaccine.

Discontinuations from Study Due to Adverse Events

Maternal Participants

There were no maternal participants who were withdrawn due to AEs.

Infant Participants

In the placebo group, 1 infant was withdrawn due to a fatal SAE of neonatal pneumonia that was assessed by the investigator as not related. Additionally, 1 infant born to an HIV-positive participant maternal participant in the BNT162b2 group was withdrawn due to a fatal SAE of pneumonia that was assessed by the investigator as not related.

Adverse Events of Special Interest

Maternal Participants

No protocol-defined AESIs were reported in maternal participants during the study (before or after unblinding).

Infant Participants

Numerical differences between infant participants with reported congenital anomalies were observed between groups, with anomalies reported in 8 participants in the BNT162b2 group and 2 in the placebo group. None of the events were assessed by the investigator as related. All participants with reported AESIs were breastfed.

Table 30: Number (%) and Comparison of Participants Reporting at Least 1 Adverse Events of Special Interest From Birth to 6 Months of Age, by System Organ Class and Preferred Term – Safety Population (Infant)

	Maternal Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a]= 156)		Placebo (N[a]= 159)		Difference	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	%[d]	(95% CI[e])
Congenital, familial and genetic disorders	8 (5.1)	(2.2, 9.9)	2 (1.3)	(0.2, 4.5)	3.9	(-0.0, 8.7)
Atrial septal defect	3 (1.9)	(0.4, 5.5)	1 (0.6)	(0.0, 3.5)	1.3	(-1.7, 5.0)
DiGeorge's syndrome	1 (0.6)	(0.0, 3.5)	0	(0.0, 2.3)	0.6	(-1.7, 3.5)
Microcephaly	1 (0.6)	(0.0, 3.5)	0	(0.0, 2.3)	0.6	(-1.7, 3.5)
Mucopolysaccharidosis	1 (0.6)	(0.0, 3.5)	0	(0.0, 2.3)	0.6	(-1.7, 3.5)
Patent ductus arteriosus	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.5)	-0.6	(-3.5, 1.8)
Syndactyly	1 (0.6)	(0.0, 3.5)	0	(0.0, 2.3)	0.6	(-1.7, 3.5)
Trisomy 21	1 (0.6)	(0.0, 3.5)	0	(0.0, 2.3)	0.6	(-1.7, 3.5)
Ventricular septal defect	0	(0.0, 2.3)	1 (0.6)	(0.0, 3.5)	-0.6	(-3.5, 1.8)
Renal and urinary disorders	1 (0.6)	(0.0, 3.5)	0	(0.0, 2.3)	0.6	(-1.7, 3.5)
Vesicoureteric reflux	1 (0.6)	(0.0, 3.5)	0	(0.0, 2.3)	0.6	(-1.7, 3.5)

Note: MedDRA (v25.1) coding dictionary applied.
Note: Adverse event of special interest terms are from the COVID-19 program targeted medical event (TME) list dated 16Nov2022.
Note: Human immunodeficiency virus (HIV)-positive participants are not included in this summary. Analyses of HIV-positive participants and their infants will be listed separately.
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 adverse event. For "Any 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.
d. Difference in proportions, expressed as a percentage (BNT162b2 [30 µg] - placebo).
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (10:10) Source Data: adae Table Generation: 13MAR2024 (15:55)
(Database snapshot date: Safety [29Mar2023], Immunogenicity [09Jan2024]) Output File:

Other Significant Adverse Events

Maternal Participants

- Anaphylaxis/hypersensitivity: In the BNT162b2 group, there was 1 participant with hypersensitivity (allergy) of moderate severity that was reported 12 days after Dose 2, which was assessed by the investigator as not related to study intervention, and resolved within 3 days.
- Bell's palsy: There were no reported AEs of Bell's palsy in either vaccine group.
- Appendicitis: There were no reported AEs of appendicitis in either vaccine group.
- Lymphadenopathy: In the placebo group, there was 1 participant with lymphadenopathy (left axillary) of mild severity that was reported 2 days after Dose 1, which was assessed by the investigator as related, and resolved within 2 days. There were no reported AEs of axillary pain, lymph node pain, or lymphadenitis.

Other Safety Evaluations

Pregnancy Outcomes – Maternal Participants

Most maternal participants delivered via the vaginal route (69.0% in BNT162b2 and 66.1% in placebo), and fewer had an emergency Cesarean delivery (7.7% in BNT162b2 and 10.7%). For 1 HIV-positive participant in the BNT162b2 group, the outcome was a stillbirth.

Birth Outcomes – Infant Participants

Most infants were born at term and had favourable newborn assessment outcomes. Infant outcome is presented in the table below.

Table 31: Birth Outcomes – Safety Population (Infant)

	Maternal Vaccine Group (as Administered)			
	BNT162b2 (30 µg) (N[a]=167)		Placebo (N[a]=168)	
	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
<37 weeks 0 days	2 (1.2)	(0.1, 4.3)	8 (4.8)	(2.1, 9.2)
≥37 weeks - 41 weeks 6 days	162 (97.0)	(93.2, 99.0)	157 (93.5)	(88.6, 96.7)
≥42 weeks	2 (1.2)	(0.1, 4.3)	2 (1.2)	(0.1, 4.2)
Missing	1 (0.6)	(0.0, 3.3)	1 (0.6)	(0.0, 3.3)
Apgar score – 1 minute after delivery				
0-3	4 (2.4)	(0.7, 6.0)	4 (2.4)	(0.7, 6.0)
4-6	4 (2.4)	(0.7, 6.0)	9 (5.4)	(2.5, 9.9)
7-10	157 (94.0)	(89.3, 97.1)	152 (90.5)	(85.0, 94.5)
Missing	2 (1.2)	(0.1, 4.3)	3 (1.8)	(0.4, 5.1)
Apgar score – 5 minutes after delivery				
0-3	0	(0.0, 2.2)	1 (0.6)	(0.0, 3.3)
4-6	1 (0.6)	(0.0, 3.3)	4 (2.4)	(0.7, 6.0)
7-10	164 (98.2)	(94.8, 99.6)	160 (95.2)	(90.8, 97.9)
Missing	2 (1.2)	(0.1, 4.3)	3 (1.8)	(0.4, 5.1)
Apgar score – 10 minutes after delivery				
7-10	62 (37.1)	(29.8, 44.9)	63 (37.5)	(30.2, 45.3)
Missing	105 (62.9)	(55.1, 70.2)	105 (62.5)	(54.7, 69.8)
Infant cry immediately after delivery				
Yes	152 (91.0)	(85.6, 94.9)	147 (87.5)	(81.5, 92.1)
No	12 (7.2)	(3.8, 12.2)	14 (8.3)	(4.6, 13.6)
Missing	3 (1.8)	(0.4, 5.2)	7 (4.2)	(1.7, 8.4)
Infant suckle shortly after delivery				
Yes	154 (92.2)	(87.1, 95.8)	150 (89.3)	(83.6, 93.5)
No	8 (4.8)	(2.1, 9.2)	11 (6.5)	(3.3, 11.4)
Missing	5 (3.0)	(1.0, 6.8)	7 (4.2)	(1.7, 8.4)
Infant outcome				
Normal	153 (91.6)	(86.3, 95.3)	150 (89.3)	(83.6, 93.5)
Congenital malformation/anomaly	10 (6.0)	(2.9, 10.7)	6 (3.6)	(1.3, 7.6)
Other neonatal problem	3 (1.8)	(0.4, 5.2)	11 (6.5)	(3.3, 11.4)
Missing	1 (0.6)	(0.0, 3.3)	1 (0.6)	(0.0, 3.3)

a. N = number of infant participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 03APR2023 (10:02) Source Data: adscio Table Generation: 03MAY2023 (12:27) Output File: ./nda3/C4591015_BR/adfaio_s001

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Disposition

The disposition is described by age group below. None of the participants were excluded from the safety population.

Participants 2 to <5 Years of Age

Table 32: Disposition of Participants by Age Group – All Assigned Participants Age Group: 2–<5 Years

	Vaccine Group (as Assigned) BNT162b2 (3 µg)			
	Immunomodulatory Therapy (N[a]=9)	Solid Organ Transplant (N[a]=15)	Stem Cell Transplant (N[a]=13)	Total (N[a]=37)
	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Assigned	9 (100.0)	15 (100.0)	13 (100.0)	37 (100.0)
Vaccinated[c]				
Dose 1	9 (100.0)	15 (100.0)	13 (100.0)	37 (100.0)
Dose 2	9 (100.0)	15 (100.0)	12 (92.3)	36 (97.3)
Dose 3	9 (100.0)	15 (100.0)	11 (84.6)	35 (94.6)
Dose 4	7 (77.8)	13 (86.7)	6 (46.2)	26 (70.3)
3 µg	7 (77.8)	6 (40.0)	6 (46.2)	19 (51.4)
10 µg	0	7 (46.7)	0	7 (18.9)
Completed 1-month post-Dose 2 visit	9 (100.0)	15 (100.0)	12 (92.3)	36 (97.3)
Completed 1-month post-Dose 3 visit	8 (88.9)	15 (100.0)	10 (76.9)	33 (89.2)
Completed 1-month post-Dose 4 visit	7 (77.8)	13 (86.7)	6 (46.2)	26 (70.3)
Completed the study[d]	7 (77.8)	12 (80.0)	6 (46.2)	25 (67.6)
Withdrawn from study	2 (22.2)	3 (20.0)	7 (53.8)	12 (32.4)
Withdrawn after Dose 1 and before Dose 2	0	0	1 (7.7)	1 (2.7)
Reason for withdrawal				
Other	0	0	1 (7.7)	1 (2.7)
Withdrawn after Dose 2 and before Dose 3	0	0	1 (7.7)	1 (2.7)
Reason for withdrawal				
Withdrawal by parent/guardian	0	0	1 (7.7)	1 (2.7)
Withdrawn after Dose 3 and before Dose 4	2 (22.2)	2 (13.3)	5 (38.5)	9 (24.3)
Reason for withdrawal				
Lost to follow-up	0	0	1 (7.7)	1 (2.7)
Protocol deviation	0	0	1 (7.7)	1 (2.7)
Withdrawal by parent/guardian	2 (22.2)	2 (13.3)	2 (15.4)	6 (16.2)
Refused further study procedures	0	0	1 (7.7)	1 (2.7)
Withdrawn after Dose 4	0	1 (6.7)	0	1 (2.7)
Reason for withdrawal				
Withdrawal by parent/guardian	0	1 (6.7)	0	1 (2.7)

Note: There is one participant in 12–<18 age group at enrollment with medication error of 10 mg instead of 30 mg at dose 4 is included in the table.
a. N = number of participants in the specified group or total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Protocol amendment 4 allows for age-appropriate dosing at each vaccination visit. Participants who turned 5 years of age or turned 12 years of age during the study received an age-appropriate higher dose at a subsequent vaccination visit.
d. Includes participants who completed the study 6 months after Dose 3 (per protocol amendment 3) and participants who completed the study 6 months after Dose 4 (per protocol amendment 4).
PFIZER CONFIDENTIAL SDTM Creation: 13AUG2023 (20:14) Source Data: adds Table Generation: 30NOV2023 (21:15)
(Database snapshot date : 10AUG2023) Output File: ./nda3/C4591024_CSR_SAFETY/adds_s002

Participants 5 to <12 Years of Age

Table 33: Disposition of Participants by Age Group – All Assigned Participants Age Group: 5–<12 Years

	Vaccine Group (as Assigned) BNT162b2 (10 µg)			
	Immunomodulatory Therapy (N[a]=19) n[b] (%)	Solid Organ Transplant (N[a]=24) n[b] (%)	Stem Cell Transplant (N[a]=22) n[b] (%)	Total (N[a]=65) n[b] (%)
Assigned	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
Vaccinated[c]				
Dose 1	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
Dose 2	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
Dose 3	17 (89.5)	24 (100.0)	22 (100.0)	63 (96.9)
10 µg	17 (89.5)	23 (95.8)	22 (100.0)	62 (95.4)
30 µg	0	1 (4.2)	0	1 (1.5)
Dose 4	14 (73.7)	20 (83.3)	17 (77.3)	51 (78.5)
10 µg	12 (63.2)	19 (79.2)	15 (68.2)	46 (70.8)
30 µg	2 (10.5)	1 (4.2)	2 (9.1)	5 (7.7)
Completed 1-month post-Dose 2 visit	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
Completed 1-month post-Dose 3 visit	17 (89.5)	24 (100.0)	22 (100.0)	63 (96.9)
Completed 1-month post-Dose 4 visit	14 (73.7)	20 (83.3)	17 (77.3)	51 (78.5)
Completed the study[d]	16 (84.2)	20 (83.3)	18 (81.8)	54 (83.1)
Withdrawn from study	3 (15.8)	4 (16.7)	4 (18.2)	11 (16.9)
Withdrawn after Dose 1 and before Dose 2	0	0	0	0
Withdrawn after Dose 2 and before Dose 3	2 (10.5)	0	0	2 (3.1)
Reason for withdrawal				
Other	1 (5.3)	0	0	1 (1.5)
Withdrawal by parent/guardian	1 (5.3)	0	0	1 (1.5)
Withdrawn after Dose 3 and before Dose 4	0	4 (16.7)	3 (13.6)	7 (10.8)
Reason for withdrawal				
Protocol deviation	0	1 (4.2)	0	1 (1.5)
Withdrawal by participant	0	0	1 (4.5)	1 (1.5)
Withdrawal by parent/guardian	0	3 (12.5)	2 (9.1)	5 (7.7)
Withdrawn after Dose 4	1 (5.3)	0	1 (4.5)	2 (3.1)
Reason for withdrawal				
Lost to follow-up	0	0	1 (4.5)	1 (1.5)
Protocol deviation	1 (5.3)	0	0	1 (1.5)

Note: There is one participant in 12–<18 age group at enrollment with medication error of 10 mg instead of 30 mg at dose 4 is included in the table.
a. N = number of participants in the specified group or total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Protocol amendment 4 allows for age-appropriate dosing at each vaccination visit. Participants who turned 5 years of age or turned 12 years of age during the study received an age-appropriate higher dose at a subsequent vaccination visit.
d. Includes participants who completed the study 6 months after Dose 3 (per protocol amendment 3) and participants who completed the study 6 months after Dose 4 (per protocol amendment 4).
PFIZER CONFIDENTIAL SDTM Creation: 13AUG2023 (20:14) Source Data: adds Table Generation: 30NOV2023 (21:15)
(Database snapshot date : 10AUG2023) Output File: ./nda3/C4591024_CSR_SAFETY/adds_t002

Participants 12 to <18 Years of Age

Table 34: Disposition of Participants by Age Group – All Assigned Participants Age Group: 12–<18 Years

	Vaccine Group (as Assigned) BNT162b2 (30 µg)			
	Immunomodulatory Therapy (N[a]=7) n[b] (%)	Solid Organ Transplant (N[a]=1) n[b] (%)	Stem Cell Transplant (N[a]=7) n[b] (%)	Total (N[a]=15) n[b] (%)
Assigned	7 (100.0)	1 (100.0)	7 (100.0)	15 (100.0)
Vaccinated[c]				
Dose 1	7 (100.0)	1 (100.0)	7 (100.0)	15 (100.0)
Dose 2	7 (100.0)	1 (100.0)	7 (100.0)	15 (100.0)
Dose 3	7 (100.0)	1 (100.0)	6 (85.7)	14 (93.3)
Dose 4	5 (71.4)	1 (100.0)	3 (42.9)	9 (60.0)
Completed 1-month post-Dose 2 visit	7 (100.0)	1 (100.0)	6 (85.7)	14 (93.3)
Completed 1-month post-Dose 3 visit	7 (100.0)	1 (100.0)	6 (85.7)	14 (93.3)
Completed 1-month post-Dose 4 visit	5 (71.4)	1 (100.0)	3 (42.9)	9 (60.0)
Completed the study[d]	5 (71.4)	0	3 (42.9)	8 (53.3)
Withdrawn from study	2 (28.6)	1 (100.0)	4 (57.1)	7 (46.7)
Withdrawn after Dose 1 and before Dose 2	0	0	0	0
Withdrawn after Dose 2 and before Dose 3	0	0	1 (14.3)	1 (6.7)
Reason for withdrawal				
Withdrawal by parent/guardian	0	0	1 (14.3)	1 (6.7)
Withdrawn after Dose 3 and before Dose 4	2 (28.6)	0	3 (42.9)	5 (33.3)
Reason for withdrawal				
Lost to follow-up	0	0	1 (14.3)	1 (6.7)
Withdrawal by participant	1 (14.3)	0	0	1 (6.7)
Withdrawal by parent/guardian	1 (14.3)	0	2 (28.6)	3 (20.0)
Withdrawn after Dose 4	0	1 (100.0)	0	1 (6.7)
Reason for withdrawal				
Protocol deviation	0	1 (100.0)	0	1 (6.7)

Note: There is one participant in 12–<18 age group at enrollment with medication error of 10 mg instead of 30 mg at dose 4 is included in the table.
a. N = number of participants in the specified group or total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Protocol amendment 4 allows for age-appropriate dosing at each vaccination visit. Participants who turned 5 years of age or turned 12 years of age during the study received an age-appropriate higher dose at a subsequent vaccination visit.
d. Includes participants who completed the study 6 months after Dose 3 (per protocol amendment 3) and participants who completed the study 6 months after Dose 4 (per protocol amendment 4).
PFIZER CONFIDENTIAL SDTM Creation: 13AUG2023 (20:14) Source Data: adds Table Generation: 30NOV2023 (21:15)
(Database snapshot date : 10AUG2023) Output File: ./nda3/C4591024_CSR_SAFETY/adds_s002

Participants ≥18 Years of Age

Table 35: Disposition of Participants by Age Group – All Assigned Participants Age Group: ⩾18 Years

	Vaccine Group (as Assigned) BNT162b2 (30 µg)			
	Immunomodulatory Therapy (N^a=5)	Non-Small Cell Lung Cancer (N^a=1)	Haemodialysis (N^a=1)	Total (N^a=7)
	n^b (%)	n^b (%)	n^b (%)	n^b (%)
Assigned	5 (100.0)	1 (100.0)	1 (100.0)	7 (100.0)
Vaccinated[c]				
Dose 1	5 (100.0)	1 (100.0)	1 (100.0)	7 (100.0)
Dose 2	5 (100.0)	1 (100.0)	1 (100.0)	7 (100.0)
Dose 3	5 (100.0)	1 (100.0)	1 (100.0)	7 (100.0)
Dose 4	3 (60.0)	1 (100.0)	0	4 (57.1)
Completed 1-month post-Dose 2 visit	5 (100.0)	1 (100.0)	1 (100.0)	7 (100.0)
Completed 1-month post-Dose 3 visit	4 (80.0)	1 (100.0)	1 (100.0)	6 (85.7)
Completed 1-month post-Dose 4 visit	3 (60.0)	1 (100.0)	0	4 (57.1)
Completed the study[d]	3 (60.0)	1 (100.0)	0	4 (57.1)
Withdrawn from study	2 (40.0)	0	1 (100.0)	3 (42.9)
Withdrawn after Dose 1 and before Dose 2	0	0	0	0
Withdrawn after Dose 2 and before Dose 3	0	0	0	0
Withdrawn after Dose 3 and before Dose 4	2 (40.0)	0	1 (100.0)	3 (42.9)
Reason for withdrawal				
Other	1 (20.0)	0	0	1 (14.3)
Withdrawal by participant	1 (20.0)	0	1 (100.0)	2 (28.6)
Withdrawn after Dose 4	0	0	0	0

Note: There is one participant in 12–<18 age group at enrollment with medication error of 10 mg instead of 30 mg at dose 4 is included in the table.
a. N = number of participants in the specified group or total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Protocol amendment 4 allows for age-appropriate dosing at each vaccination visit. Participants who turned 5 years of age or turned 12 years of age during the study received an age-appropriate higher dose at a subsequent vaccination visit.
d. Includes participants who completed the study 6 months after Dose 3 (per protocol amendment 3) and participants who completed the study 6 months after Dose 4 (per protocol amendment 4).
PFIZER CONFIDENTIAL SDTM Creation: 13AUG2023 (20:14) Source Data: adds Table Generation: 30NOV2023 (21:15)
(Database snapshot date : 10AUG2023) Output File: ./nda3/C4591024_CSR_SAFETY/adds_s002

Demographics

Participants 2 to <5 Years of Age

Table 36: Demographic Characteristics of Participants by Age Group – Safety Population Age Group: 2–<5 Years

	Vaccine Group (as Administered) BNT162b2 (3 µg)			
	Immunomodulatory Therapy (N[a]=9) n[b] (%)	Solid Organ Transplant (N[a]=15) n[b] (%)	Stem Cell Transplant (N[a]=13) n[b] (%)	Total (N[a]=37) n[b] (%)
Sex				
Male	5 (55.6)	7 (46.7)	10 (76.9)	22 (59.5)
Female	4 (44.4)	8 (53.3)	3 (23.1)	15 (40.5)
Race				
White	9 (100.0)	11 (73.3)	12 (92.3)	32 (86.5)
Black or African American	0	2 (13.3)	0	2 (5.4)
Asian	0	1 (6.7)	0	1 (2.7)
Multiracial	0	0	1 (7.7)	1 (2.7)
Not reported	0	1 (6.7)	0	1 (2.7)
Ethnicity				
Hispanic/Latino	1 (11.1)	1 (6.7)	4 (30.8)	6 (16.2)
Non-Hispanic/non-Latino	8 (88.9)	14 (93.3)	9 (69.2)	31 (83.8)
Country				
Brazil	1 (11.1)	5 (33.3)	4 (30.8)	10 (27.0)
Germany	1 (11.1)	2 (13.3)	7 (53.8)	10 (27.0)
United States	7 (77.8)	8 (53.3)	2 (15.4)	17 (45.9)
Age at vaccination (years)				
Mean (SD)	3.1 (0.60)	3.6 (0.83)	3.1 (0.76)	3.3 (0.78)
Median	3.0	4.0	3.0	3.0
Min, max	(2, 4)	(2, 5)	(2, 4)	(2, 5)
Baseline SARS-CoV-2 status				
Positive[c]	1 (11.1)	3 (20.0)	0	4 (10.8)
Negative[d]	8 (88.9)	12 (80.0)	9 (69.2)	29 (78.4)
Missing	0	0	4 (30.8)	4 (10.8)

Abbreviations: 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. 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.

PFIZER CONFIDENTIAL SDTM Creation: 27FEB2024 (16:15) Source Data: adsl Table Generation: 29MAR2024 (02:48)
(Database snapshot date : 10AUG2023, 23FEB2024) Output File: ./nda3/C4591024_CSR_SERO/adsl_t005

Participants 5 to <12 Years of Age

Table 37: Demographic Characteristics of Participants by Age Group – Safety Population Age Group: 5–<12 Years

	Vaccine Group (as Administered) BNT162b2 (10 µg)			
	Immunomodulatory Therapy (N[a]=19) n[b] (%)	Solid Organ Transplant (N[a]=24) n[b] (%)	Stem Cell Transplant (N[a]=22) n[b] (%)	Total (N[a]=65) n[b] (%)
Sex				
Male	7 (36.8)	15 (62.5)	17 (77.3)	39 (60.0)
Female	12 (63.2)	9 (37.5)	5 (22.7)	26 (40.0)
Race				
White	17 (89.5)	21 (87.5)	19 (86.4)	57 (87.7)
Black or African American	1 (5.3)	0	3 (13.6)	4 (6.2)
Asian	0	1 (4.2)	0	1 (1.5)
Multiracial	0	1 (4.2)	0	1 (1.5)
Not reported	1 (5.3)	1 (4.2)	0	2 (3.1)
Ethnicity				
Hispanic/Latino	6 (31.6)	2 (8.3)	2 (9.1)	10 (15.4)
Non-Hispanic/non-Latino	13 (68.4)	22 (91.7)	19 (86.4)	54 (83.1)
Not reported	0	0	1 (4.5)	1 (1.5)
Country				
Brazil	5 (26.3)	2 (8.3)	3 (13.6)	10 (15.4)
Germany	3 (15.8)	7 (29.2)	15 (68.2)	25 (38.5)
United States	11 (57.9)	15 (62.5)	4 (18.2)	30 (46.2)
Age at vaccination (years)				
Mean (SD)	8.7 (2.16)	8.1 (2.01)	8.5 (1.71)	8.4 (1.94)
Median	10.0	8.0	8.5	9.0
Min, max	(5, 11)	(5, 11)	(6, 11)	(5, 11)
Baseline SARS-CoV-2 status				
Positive[c]	1 (5.3)	0	0	1 (1.5)
Negative[d]	15 (78.9)	17 (70.8)	17 (77.3)	49 (75.4)
Missing	3 (15.8)	7 (29.2)	5 (22.7)	15 (23.1)

Abbreviations: 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. 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.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2024 (16:15) Source Data: adsl Table Generation: 29MAR2024 (02:48)
(Database snapshot date : 10AUG2023, 23FEB2024) Output File: ./nda3/C4591024_CSR_SERO/adsl_s005

Participants 12 to <18 Years of Age

Table 38: Demographic Characteristics of Participants by Age Group – Safety Population Age Group: 12–<18 Years

	Vaccine Group (as Administered) BNT162b2 (30 µg)			
	Immunomodulatory Therapy (N[a]=7) n[b] (%)	Solid Organ Transplant (N[a]=1) n[b] (%)	Stem Cell Transplant (N[a]=7) n[b] (%)	Total (N[a]=15) n[b] (%)
Sex				
Male	5 (71.4)	1 (100.0)	2 (28.6)	8 (53.3)
Female	2 (28.6)	0	5 (71.4)	7 (46.7)
Race				
White	6 (85.7)	1 (100.0)	7 (100.0)	14 (93.3)
Asian	1 (14.3)	0	0	1 (6.7)
Ethnicity				
Hispanic/Latino	3 (42.9)	0	1 (14.3)	4 (26.7)
Non-Hispanic/non-Latino	4 (57.1)	1 (100.0)	6 (85.7)	11 (73.3)
Country				
Brazil	3 (42.9)	0	1 (14.3)	4 (26.7)
Germany	4 (57.1)	0	6 (85.7)	10 (66.7)
United States	0	1 (100.0)	0	1 (6.7)
Age at vaccination (years)				
Mean (SD)	13.4 (1.62)	14.0 (-)	12.6 (1.13)	13.1 (1.39)
Median	13.0	14.0	12.0	12.0
Min, max	(12, 16)	(14, 14)	(12, 15)	(12, 16)
Baseline SARS-CoV-2 status				
Positive[c]	3 (42.9)	0	1 (14.3)	4 (26.7)
Negative[d]	1 (14.3)	1 (100.0)	6 (85.7)	8 (53.3)
Missing	3 (42.9)	0	0	3 (20.0)

Abbreviations: 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. 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.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2024 (16:15) Source Data: adsl Table Generation: 29MAR2024 (02:48)
(Database snapshot date : 10AUG2023, 23FEB2024) Output File: ./nda3/C4591024_CSR_SERO/adsl_s005

Participants ≥18 Years of Age

Table 39: Demographic Characteristics of Participants by Age Group – Safety Population Age Group: ⩾18 Years

	Vaccine Group (as Administered) BNT162b2 (30 µg)			
	Immunomodulatory Therapy (N[a]=5)	Non-Small Cell Lung Cancer (N[a]=1)	Haemodialysis (N[a]=1)	Total (N[a]=7)
	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Sex				
Male	2 (40.0)	1 (100.0)	1 (100.0)	4 (57.1)
Female	3 (60.0)	0	0	3 (42.9)
Race				
White	1 (20.0)	0	0	1 (14.3)
Black or African American	2 (40.0)	0	0	2 (28.6)
American Indian or Alaska Native	0	1 (100.0)	0	1 (14.3)
Multiracial	1 (20.0)	0	0	1 (14.3)
Not reported	1 (20.0)	0	1 (100.0)	2 (28.6)
Ethnicity				
Hispanic/Latino	2 (40.0)	1 (100.0)	1 (100.0)	4 (57.1)
Non-Hispanic/non-Latino	3 (60.0)	0	0	3 (42.9)
Country				
Brazil	1 (20.0)	0	0	1 (14.3)
Germany	1 (20.0)	0	0	1 (14.3)
United States	2 (40.0)	0	0	2 (28.6)
Mexico	1 (20.0)	1 (100.0)	1 (100.0)	3 (42.9)
Age at vaccination (years)				
Mean (SD)	49.0 (20.35)	40.0 (-)	62.0 (-)	49.6 (17.81)
Median	39.0	40.0	62.0	40.0
Min, max	(31, 73)	(40, 40)	(62, 62)	(31, 73)
Baseline SARS-CoV-2 status				
Positive[c]	1 (20.0)	1 (100.0)	0	2 (28.6)
Negative[d]	4 (80.0)	0	1 (100.0)	5 (71.4)

Abbreviations: 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. 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.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2024 (16:15) Source Data: adsl Table Generation: 29MAR2024 (02:48)
(Database snapshot date : 10AUG2023, 23FEB2024) Output File: ./nda3/C4591024_CSR_SERO/adsl_s005

Vaccine as Administered and Vaccine Administration Timing

Participants 2 to <5 Years of Age

All assigned participants received Dose 1 of BNT162b2 3 µg. For Dose 2 and Dose 3, all participants who received immunomodulatory therapy and solid organ transplant, received BNT162b2 3 µg. In participants who received a stem cell transplant, 12 participants (92.3%) and 11 participants (84.6%), respectively, received BNT162b2 3 µg at Dose 2 and Dose 3. For Dose 4, 51.4% of all participants received BNT162b2 3 µg and 18.9% received BNT162b2 10 µg. Participants who aged up received the age-appropriate dose at the next dose. All participants who received BNT162b2 10 µg at Dose 4 were in the solid organ transplant group. In total, 81.1%, 54.1%, and 70.3% of participants received Dose 2, Dose 3, and Dose 4 of BNT162b2, respectively, within the protocol-specific time frame.

Participants 5 to <12 Years of Age

All assigned participants received Dose 1 and Dose 2 of BNT162b2 10 µg. For Dose 3, a total of 62 participants (95.4%) received BNT162b2 10 µg and 1 participant (1.5%) in the solid organ transplant group received BNT162b2 30 µg. For Dose 4, a total of 46 participants (70.8%) received BNT162b2 10 µg and 5 participants (7.7%) received BNT162b2 30 µg. Participants who aged up received the age-

appropriate dose at the next dose. In total, 92.3%, 49.2%, and 66.2% of participants received Dose 2, Dose 3, and Dose 4 of BNT162b2, respectively, within the protocol-specific time frame.

Participants 12 to <18 Years of Age

All assigned participants received Dose 1 and Dose 2 of BNT162b2 30 µg. For Dose 3, a total of 14 participants (93.3%) received BNT162b2 30 µg. For Dose 4, a total of 8 participants (53.3%) received BNT162b2 30 µg. One participant (14.3%) in the immunomodulatory group received BNT162b2 10 µg at Dose 4 due to a dosing error. In total, 100.0%, 46.7%, and 46.7% of participants received Dose 2, Dose 3, and Dose 4 of BNT162b2, respectively, within the protocol-specific time frame.

Participants ≥18 Years of Age

All assigned participants received Dose 1, Dose 2, and Dose 3 of BNT162b2 30 µg. For Dose 4, a total of 4 participants (57.1%) received BNT162b2 30 µg. In total, 85.7%, 57.1%, and 57.1% of participants received Dose 2, Dose 3, and Dose 4 of BNT162b2, respectively, within the protocol-specific time frame.

E-Diary Transmission

Reactogenicity and antipyretic/pain medication use was recorded for 7 days after study vaccination. The e-diary entries from the participant were the primary data source for these events.

Participants 2 to <5 Years of Age

Across all participants 2 to <5 years of age, transmission rates during the 7 days after vaccination were 78.4% to 100.0% after Dose 1, 75.0% to 91.7% after Dose 2, 71.4% to 94.3% after Dose 3, and 73.7% to 100.0% after Dose 4.

Participants 5 to <12 Years of Age

Across all participants 5 to <12 years of age, transmission rates during the 7 days after vaccination were 87.7% to 96.9% after Dose 1, 84.6% to 92.3% after Dose 2, 66.1% to 90.3% after Dose 3, and 60.9% to 87.0% after Dose 4.

Participants 12 to <18 Years of Age

Across all participants 12 to <18 years of age, transmission rates during the 7 days after vaccination were 60.0% to 93.3% after Dose 1, 53.3% to 86.7% after Dose 2, 71.4% to 100.0% after Dose 3, and 50.0% to 87.5% after Dose 4.

Participants ≥18 Years of Age

Across all participants ≥18 years of age, transmission rates during the 7 days after vaccination were 71.4% to 100.0% after Dose 1, 71.4% to 100.0% after Dose 2, 57.1% to 71.4 % after Dose 3, and 25.0% to 100.0% after Dose 4.

Reactogenicity

Local Reactions

Across all age groups, the majority of local reactions were mild or moderate in severity. No severe or Grade 4 local reactions were reported.

Participants 2 to <5 Years of Age

Frequencies of any local reaction (redness, swelling, pain at the injection site) within 7 days after each dose of BNT162b2 3 µg were similar (Dose 1: 18.9%, Dose 2: 14.3%, Dose 3: 14.3%, Dose 4: 21.1%).

Pain at the injection site was the most frequently reported local reaction, and the frequency was similar after each Dose (Dose 1: 16.2%, Dose 2: 14.3%, Dose 3: 14.3%, Dose 4: 15.8%).

Across all groups, the median onset for any local reaction after receiving BNT162b2 3 µg was Day 1 for Dose 1, Dose 2, and Dose 3, and was Day 2 for Dose 4. Local reactions resolved within a median duration of 1 days, 1 days, 1-6 days, and 1-2 days after onset for Dose 1, 2, 3, and 4, respectively. After Dose 3, one participant in the solid organ transplant group reported swelling with a median duration of 6 days.

Participants 5 to <12 Years of Age

Frequencies of any local reaction (redness, swelling, pain at the injection site) within 7 days after each dose of BNT162b2 10 µg were similar (Dose 1: 66.2%, Dose 2: 63.1%, Dose 3: 52.5%, Dose 4: 54.3%). Pain at the injection site was the most frequently reported local reaction, and the frequency was similar after each Dose (Dose 1: 61.5%, Dose 2: 60.0%, Dose 3: 49.2%, Dose 4: 54.3%.

Across all groups, the median onset for any local reaction after receiving BNT162b2 10 µg was Day 1.0 for Dose 1, Dose 2, Dose 3, and Dose 4. Local reactions resolved within a median duration of 1-2.5 days, 1-2 days, 1-4 days, and 2-3 days after onset for Dose 1, 2, 3, and 4, respectively.

Participants 12 to <18 Years of Age

Frequencies of any local reaction (redness, swelling, pain at the injection site) within 7 days after each dose of BNT162b2 30 µg were similar (Dose 1: 80.0%, Dose 2: 80.0%, Dose 3: 71.4%, Dose 4: 75.0%). Pain at the injection site was the most frequently reported local reaction, and the frequency was similar after each Dose (Dose 1: 73.3%, Dose 2: 73.3%, Dose 3: 71.4%, Dose 4: 62.5%).

Across all groups, the median onset for any local reaction after receiving BNT162b2 30 µg was Day 2, Day 1, Day 1, and Day 2, for Dose 1, Dose 2, Dose 3, and Dose 4, respectively. Local reactions resolved within a median duration of 2-3.5 days, 2-3 days, 4.5-7 days, and 1-5 days after onset for Dose 1, 2, 3, and 4, respectively. Duration of local reactions was observed to be marginally higher in the immunomodulatory group, however, considering the small number of subjects, this cannot be considered clinically significant.

Participants ≥18 Years of Age

Frequencies of any local reaction (redness, swelling, pain at the injection site) within 7 days after each dose of BNT162b2 30 µg were similar (Dose 1: 85.7%, Dose 2: 71.4%, Dose 3: 60.0%, Dose 4: 75.0%). Pain at the injection site was the most frequently reported local reaction and the frequency was similar after each Dose of BNT162b2 30 µg (Dose 1: 85.7%, Dose 2: 71.4%, Dose 3: 60.0%, Dose 4: 75.0%).

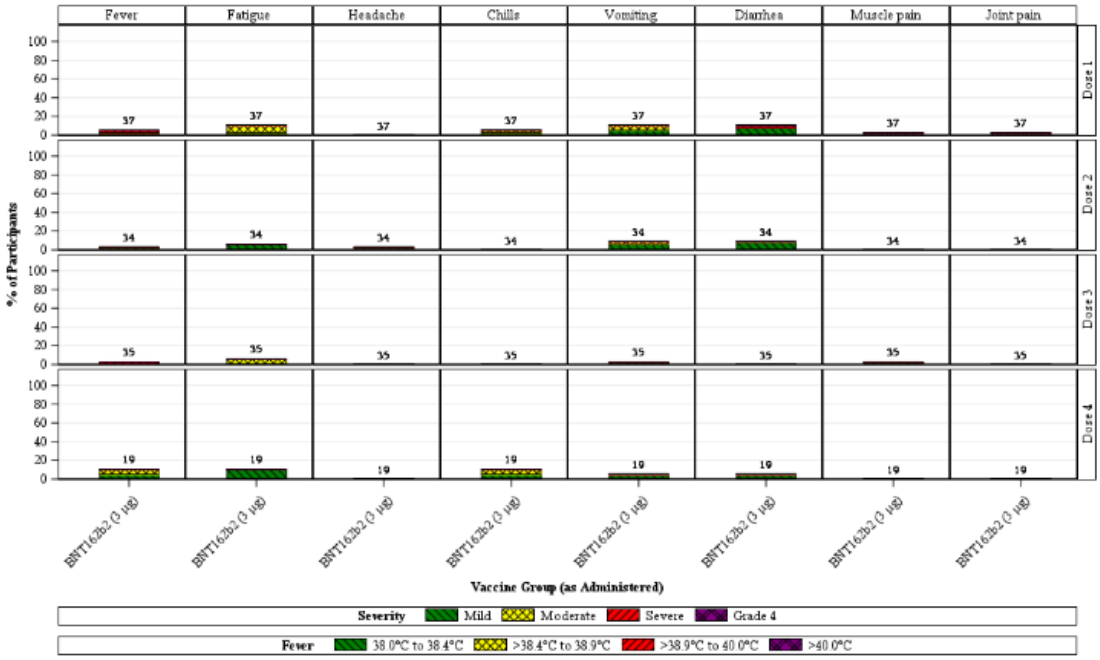
Across all groups, the median onset for any local reaction after receiving BNT162b2 30 µg was Day 1.0, Day 2.0, Day 2.0, and Day 2.0, for Dose 1, Dose 2, Dose 3, and Dose 4, respectively. Local reactions resolved within a median duration of 2 days, 3 days, 1 to 2 days, and 2 to 4 days after onset for Dose 1, 2, 3, and 4, respectively.

Systemic Events

Across all age groups, the majority of systemic events were mild or moderate in severity and incidence of severe systemic events was low. No Grade 4 systemic events were reported.

Participants 2 to <5 Years of Age

Figure 3: Systemic Events by Maximum Severity, Within 7 Days After Each Dose –– Safety Population Age Group: 2-<5 Years



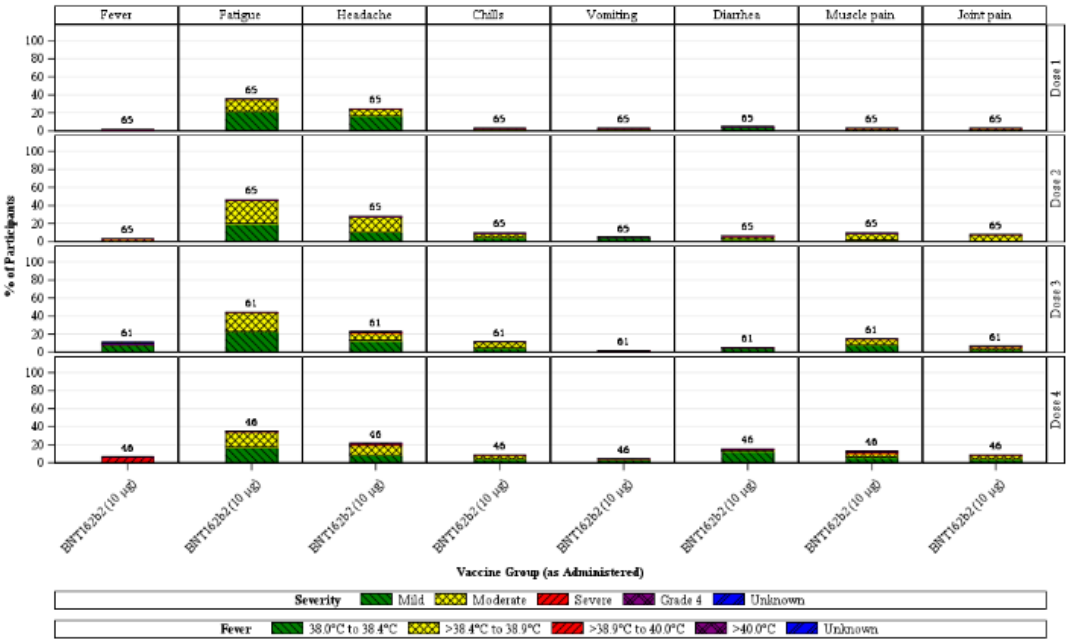
Note: Participants who aged into the next age group received the age-appropriate dose. For participants with a dose level change due to increasing age, all events that occurred after the dose level change were not included in the analysis.
Note: For participants with medication error, all events that occurred after the medication error were not included in the analysis.
Note: Events were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: The number above each bar denotes the number of participants (N) in each vaccine group who provided at least 1 yes or no response for the specified reaction within 7 days of the specified dose. This is the denominator used to calculate the percentages shown.
PFIZER CONFIDENTIAL SDTM Creation: 13AUG2023 (21:14) Source Data: adfacevd Table Generation: 27SEP2023 (02:06)

After any dose, fevers ≥38.0°C were reported by 5 participants (13.5%), with 2 participants (5.4%) reporting a fever ≥38.0°C to 38.4°C, 1 participant (2.7%) reporting a fever ≥38.4°C to 38.9°C, and 2 participants (5.4%) reporting a fever ≥38.9°C to 40.0°C. No participants reported fever ≥40.0°C. Antipyretic or pain medication use was reported by 7 participants (18.9%) after any Dose.

The median onset for systemic events was Day 5, Day 3.5, Day 3, Day 3 for Dose 1, 2, 3, and 4, respectively. Systemic events resolved within a median duration of 1-5 days, 1-3 days, 1-2 days, and 1-4 days after onset for Dose 1, 2, 3, and 4, respectively.

Participants 5 to <12 Years of Age

Figure 4: Systemic Events by Maximum Severity, Within 7 Days After Each Dose –– Safety Population Age Group: 5-<12 Years



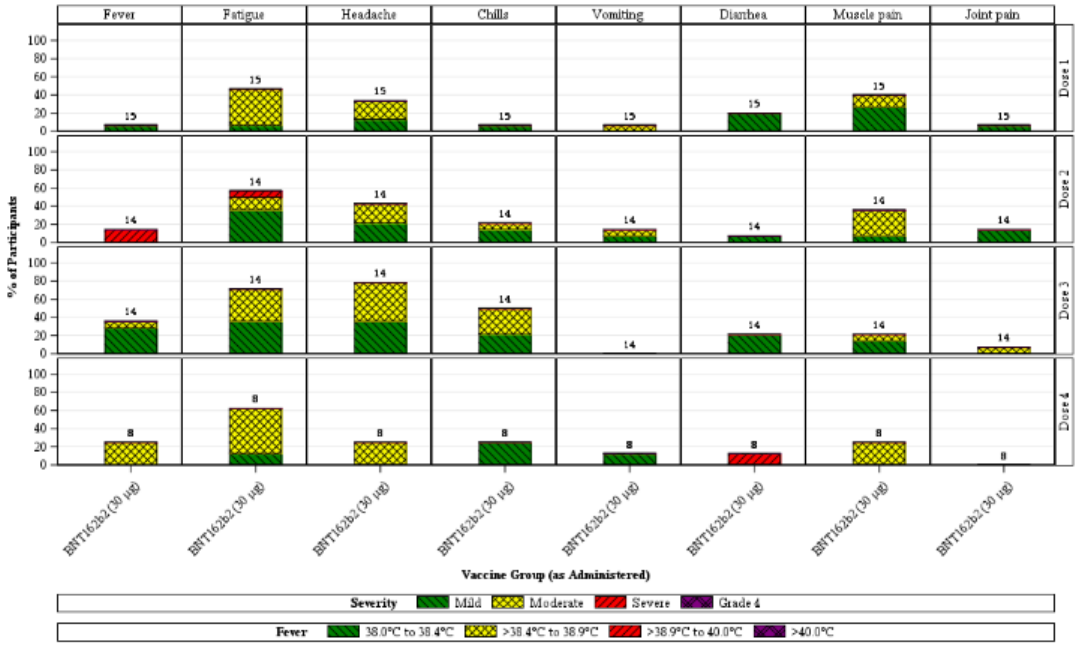
Note: Participants who aged into the next age group received the age-appropriate dose. For participants with a dose level change due to increasing age, all events that occurred after the dose level change were not included in the analysis.
Note: For participants with medication error, all events that occurred after the medication error were not included in the analysis.
Note: Events were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: The number above each bar denotes the number of participants (N) in each vaccine group who provided at least 1 yes or no response for the specified reaction within 7 days of the specified dose. This is the denominator used to calculate the percentages shown.
PFIZER CONFIDENTIAL SDTM Creation: 13AUG2023 (21:14) Source Data: adfacevd Table Generation: 27SEP2023 (02:06)

After any dose, fevers ≥38.0°C were reported by participants 10 participants (15.4%), with 3 participants (4.6%) each reporting fevers ≥38.0°C to 38.4°C, ≥38.4°C to 38.9°C, and ≥38.9°C to 40.0°C. The 3 participants who reported fevers ≥38.9°C to 40.0°C were all reported after Dose 4. One participant (1.5%) reported a fever of unknown temperature. No participants reported fever ≥40.0°C. Antipyretic or pain medication use was reported by 23 participants (35.4%).

The median onset for systemic events was Day 2 for Dose 1, 2, 3, and 4. Systemic events resolved within a median duration of 1-7 days, 1-3 days, 1-3 days, and 1-1.5 days after onset for Dose 1, 2, 3, and 4, respectively. Two participants in the immunomodulatory therapy group reported new or worsened joint pain with duration of 4 and 10 days.

Participants 12 to <18 Years of Age

Figure 5: Systemic Events by Maximum Severity, Within 7 Days After Each Dose –– Safety Population Age Group: 12-<18 Years



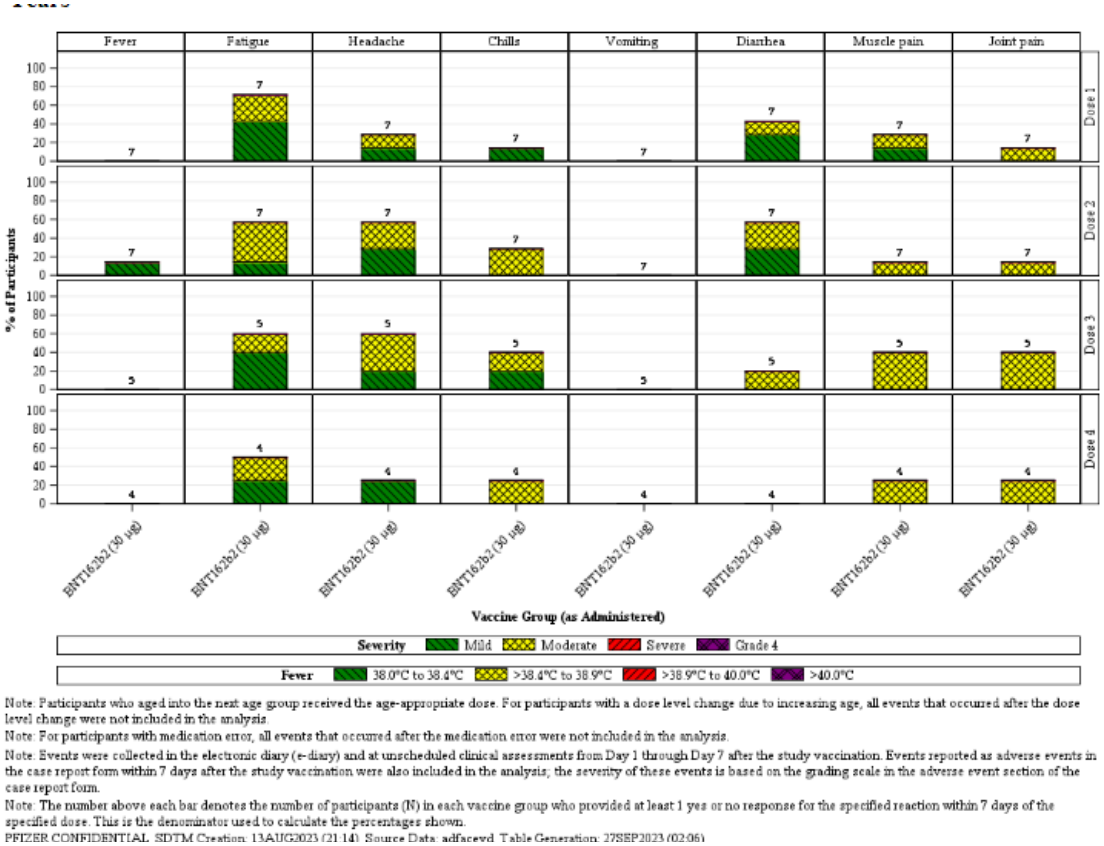
Note: Participants who aged into the next age group received the age-appropriate dose. For participants with a dose level change due to increasing age, all events that occurred after the dose level change were not included in the analysis.
Note: For participants with medication error, all events that occurred after the medication error were not included in the analysis.
Note: Events were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: The number above each bar denotes the number of participants (N) in each vaccine group who provided at least 1 yes or no response for the specified reaction within 7 days of the specified dose. This is the denominator used to calculate the percentages shown.
PFIZER CONFIDENTIAL SDTM Creation: 13AUG2023 (21:14) Source Data: adfacevd Table Generation: 27SEP2023 (02:06)

After any dose, fevers ≥38.0°C were reported by 6 participants (40.0%). Three participants (20.0%) reported a fever ≥38.0°C to 38.4°C, 1 participant (6.7%) reported a fever ≥38.4°C to 38.9°C, and 2 participants (13.3%) reported a fever ≥38.9°C to 40.0°C. No participants reported fever ≥40.0°C. Antipyretic or pain medication use was reported by 9 participants (60.0%) after any Dose. Two severe events were reported (diarrhoea and fatigue).

The median onset for systemic events was Day 2 for Dose 1, 2, 3, and 4. Systemic events resolved within a median duration of 1.5 -10 days, 1-4 days, 1-5 days, and 1-5.5 days after onset for Dose 1, 2, 3, and 4, respectively. One participant in the immunomodulatory therapy group reported vomiting that resolved in 10 days.

Participants ≥18 Years of Age

Figure 6: Systemic Events by Maximum Severity, Within 7 Days After Each Dose –– Safety Population Age Group: ≥18 Years



Note: Participants who aged into the next age group received the age-appropriate dose. For participants with a dose level change due to increasing age, all events that occurred after the dose level change were not included in the analysis.
Note: For participants with medication error, all events that occurred after the medication error were not included in the analysis.
Note: Events were collected in the electronic diary (e-diary) and at unscheduled clinical assessments from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: The number above each bar denotes the number of participants (N) in each vaccine group who provided at least 1 yes or no response for the specified reaction within 7 days of the specified dose. This is the denominator used to calculate the percentages shown.
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One participant (20.0%) in the immunomodulatory therapy group reported a fever of ≥38.0°C to 38.4°C after Dose 2. No participants reported fever ≥40.0°C. Antipyretic or pain medication use was reported by 4 participants (57.1%) after any Dose.

The median onset for systemic events was Day 1, Day 2, Day 1, Day 2 for Dose 1, 2, 3, and 4, respectively. Systemic events resolved within a median duration of 1-5 days, 1-3.5 days, 1-8 days, and 1-5 days after onset for Dose 1, 2, 3, and 4, respectively.

Adverse Events

Summary of Adverse Events

The AE profile after vaccination of children 2 to <18 years of age mostly reflected reactogenicity events or unrelated infections typically observed in a paediatric population with immunocompromising conditions, with a low incidence of severe AEs. The AE profile after vaccination of adults ≥18 years of age mostly reflected reactogenicity events or unrelated infections typically observed in an adult population with immunocompromising conditions, with a low incidence of severe AEs. Across all age groups, the majority of local and systemic reactions were mild or moderate in severity. No Grade 4 systemic reactions were reported. The majority of AEs were in the infections and infestations SOC, and all AESIs were likely related to participant's underlying condition. There were no deaths, no SAEs assessed as related by the investigator, no life-threatening AEs, and no AEs leading to withdrawal.

Summary of Adverse Events from Dose 1 to 1 Month After Dose 2

AEs were reported by 14 participants (37.8%) who were 2 to <5 years, 15 participants (23.1%) who were 5 to <12 years of age, 2 participants (13.3%) who were 12 to <18 years of age, and 1 participant (14.3%) who was ≥18 years of age.

- 4 participants (10.8%) who were 2 to <5 years of age reported nonserious AEs that were assessed as related, and they were all severe.
- 5 participants (7.7%) who were 5 to <12 years of age reported nonserious AEs that were assessed as related.
- 1 participant (14.3%) who was 12 to <18 years of age in the stem cell transplant group who reported nonserious AEs that were assessed as related.
- 1 participant (14.3%) ≥18 years of age reported a severe, nonserious AE that was not assessed as related.

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

AEs were reported by 9 participants (25.7%) who were 2 to <5 years of age, 8 participants (12.9%) who were 5 to <12 years of age, and 2 participants (14.3%) who were 12 to <18 years of age. No participants ≥18 years of age reported an AE.

2 participants (5.7%) who were 2 to <5 years of age reported nonserious AEs that were assessed as related. SAEs were reported by 4 participants (11.4%) in the safety population all 4 participants (26.7%) were in the solid organ transplant group. Two of the SAEs were classified as severe.

3 participants (4.8%) who were 5 to <12 years of age reported nonserious AEs that were assessed as related. There was 1 participant (5.9%) in the immunomodulatory group who reported a severe SAE.

The participant who was 12 to <18 years of age in the stem cell transplant group reported nonserious AEs that were assessed as related.

Summary of Adverse Events from Dose 4 to 1 Month After Dose 4

AEs were reported by 2 participants (10.5%) who were 2 to <5 years of age and 7 participants (15.2%) who were 5 to <12 years of age. No AEs were reported by participants who were >12 years of age.

1 participant (5.3%) who was 2 to <5 years of age in the immunomodulatory therapy group reported nonserious AEs that were assessed as related to study intervention by the investigator.

All participants who were 5 to <12 years of age who reported AEs were in the solid organ transplant group. There was 1 participant (5.3%) who reported a nonserious AE that was assessed as related.

Table 40: Number (%) of Participants Reporting at Least 1 Adverse Event from Dose 1 to 1 month after Dose 4, by System Organ Class and Preferred Term by Age Group – Safety Population

	Vaccine Group (as Administered) Age Group							
	BNT162b2 (3 µg) 2–<5 Years (N[a]=37)		BNT162b2 (10 µg) 5–<12 Years (N[a]=65)		BNT162b2 (30 µg) 12–<18 Years (N[a]=15)		BNT162b2 (30 µg) ≥18 Years (N[a]=7)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any Event	24 (64.9)	(47.5, 79.8)	35 (53.8)	(41.0, 66.3)	4 (26.7)	(7.8, 55.1)	5 (71.4)	(29.0, 96.3)
Blood and lymphatic system disorders	1 (2.7)	(0.1, 14.2)	3 (4.6)	(1.0, 12.9)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Anaemia	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Leukopenia	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Lymphadenitis	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Lymphadenopathy	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Neutropenia	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Cardiac disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Palpitations	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Congenital, familial and genetic disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Tumour necrosis factor receptor-associated periodic syndrome	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Ear and labyrinth disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Ear pain	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Eye disorders	3 (8.1)	(1.7, 21.9)	3 (4.6)	(1.0, 12.9)	0	(0.0, 21.8)	0	(0.0, 41.0)
Amblyopia	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Eye discharge	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Eye inflammation	1 (2.7)	(0.1, 14.2)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Eye irritation	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Eye pain	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Ocular discomfort	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Photophobia	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Uveitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Gastrointestinal disorders	5 (13.5)	(4.5, 28.8)	11 (16.9)	(8.8, 28.3)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Abdominal pain	0	(0.0, 9.5)	2 (3.1)	(0.4, 10.7)	0	(0.0, 21.8)	0	(0.0, 41.0)
Abdominal pain upper	0	(0.0, 9.5)	2 (3.1)	(0.4, 10.7)	0	(0.0, 21.8)	0	(0.0, 41.0)
Crohn's disease	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Dental caries	1 (2.7)	(0.1, 14.2)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Diarrhoea	1 (2.7)	(0.1, 14.2)	2 (3.1)	(0.4, 10.7)	0	(0.0, 21.8)	0	(0.0, 41.0)
Gastritis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Intestinal obstruction	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Melaena	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Vomiting	2 (5.4)	(0.7, 18.2)	4 (6.2)	(1.7, 15.0)	0	(0.0, 21.8)	0	(0.0, 41.0)
General disorders and administration site conditions	6 (16.2)	(6.2, 32.0)	6 (9.2)	(3.5, 19.0)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Chest pain	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Chills	0	(0.0, 9.5)	0	(0.0, 5.5)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Dystrophic calcification	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Injection site bruising	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Injection site erythema	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)

	Vaccine Group (as Administered) Age Group							
	BNT162b2 (3 µg) 2–<5 Years (N[a]=37)		BNT162b2 (10 µg) 5–<12 Years (N[a]=65)		BNT162b2 (30 µg) 12–<18 Years (N[a]=15)		BNT162b2 (30 µg) ≥18 Years (N[a]=7)	
System Organ Class Preferred Term	n[a] (%)	(95% CI[c])	n[a] (%)	(95% CI[c])	n[a] (%)	(95% CI[c])	n[a] (%)	(95% CI[c])
Injection site pain	2 (5.4)	(0.7, 18.2)	2 (3.1)	(0.4, 10.7)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Medical device site inflammation	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Pyrexia	4 (10.8)	(3.0, 25.4)	1 (1.5)	(0.0, 8.3)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Hepatobiliary disorders	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Cholelithiasis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Immune system disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Kidney transplant rejection	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Infections and infestations	14 (37.8)	(22.5, 55.2)	18 (27.7)	(17.3, 40.2)	3 (20.0)	(4.3, 48.1)	2 (28.6)	(3.7, 71.0)
Adenovirus infection	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Bronchiolitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Clostridium difficile colitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Conjunctivitis	1 (2.7)	(0.1, 14.2)	3 (4.6)	(1.0, 12.9)	0	(0.0, 21.8)	0	(0.0, 41.0)
Cytomegalovirus viraemia	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Dengue fever	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Device related infection	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Epstein-Barr viraemia	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Epstein-Barr virus infection	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Gangrene	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Gastroenteritis	3 (8.1)	(1.7, 21.9)	2 (3.1)	(0.4, 10.7)	0	(0.0, 21.8)	0	(0.0, 41.0)
Gastrointestinal infection	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Herpes zoster	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Impetigo	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Influenza	2 (5.4)	(0.7, 18.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Nasopharyngitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Oral candidiasis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Otitis externa	0	(0.0, 9.5)	3 (4.6)	(1.0, 12.9)	0	(0.0, 21.8)	0	(0.0, 41.0)
Otitis media	2 (5.4)	(0.7, 18.2)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Otitis media chronic	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Pharyngitis streptococcal	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Rhinovirus infection	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Sinusitis	0	(0.0, 9.5)	2 (3.1)	(0.4, 10.7)	0	(0.0, 21.8)	0	(0.0, 41.0)
Staphylococcal impetigo	0	(0.0, 9.5)	0	(0.0, 5.5)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Stoma site cellulitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Tonsillitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Tooth infection	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Tracheitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Upper respiratory tract infection	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Urinary tract infection	4 (10.8)	(3.0, 25.4)	4 (6.2)	(1.7, 15.0)	2 (13.3)	(1.7, 40.5)	1 (14.3)	(0.4, 57.9)
Viral rash	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Viral rhinitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Viral sinusitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Vulvovaginitis	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)

	Vaccine Group (as Administered) Age Group							
	BNT162b2 (3 µg) 2–<5 Years (N=37)		BNT162b2 (10 µg) 5–<12 Years (N=65)		BNT162b2 (30 µg) 12–<18 Years (N=15)		BNT162b2 (30 µg) ≥18 Years (N=7)	
System Organ Class Preferred Term	n[a] (%)	(95% CI[c])	n[a] (%)	(95% CI[c])	n[a] (%)	(95% CI[c])	n[a] (%)	(95% CI[c])
Injury, poisoning and procedural complications	3 (8.1)	(1.7, 21.9)	2 (3.1)	(0.4, 10.7)	0	(0.0, 21.8)	0	(0.0, 41.0)
Fall	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Foreign body in eye	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Postoperative ileus	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Radius fracture	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Skin abrasion	1 (2.7)	(0.1, 14.2)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Investigations	0	(0.0, 9.5)	3 (4.6)	(1.0, 12.9)	0	(0.0, 21.8)	0	(0.0, 41.0)
Blood iron decreased	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Body temperature increased	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Donor specific antibody present	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Metabolism and nutrition disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Hyponatraemia	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Musculoskeletal and connective tissue disorders	2 (5.4)	(0.7, 18.2)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Arthritis	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Muscular weakness	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Myositis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Synovitis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Metastases to bone	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Nervous system disorders	0	(0.0, 9.5)	2 (3.1)	(0.4, 10.7)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Dizziness	0	(0.0, 9.5)	0	(0.0, 5.5)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Headache	0	(0.0, 9.5)	2 (3.1)	(0.4, 10.7)	1 (6.7)	(0.2, 31.9)	0	(0.0, 41.0)
Psychiatric disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Attention deficit hyperactivity disorder	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Renal and urinary disorders	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	2 (28.6)	(3.7, 71.0)
Azotaemia	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Renal colic	0	(0.0, 9.5)	0	(0.0, 5.5)	0	(0.0, 21.8)	1 (14.3)	(0.4, 57.9)
Reproductive system and breast disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Breast enlargement	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Breast pain	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Respiratory, thoracic and mediastinal disorders	2 (5.4)	(0.7, 18.2)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Cough	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Dyspnoea	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Pulmonary vein stenosis	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Skin and subcutaneous tissue disorders	3 (8.1)	(1.7, 21.9)	4 (6.2)	(1.7, 15.0)	0	(0.0, 21.8)	0	(0.0, 41.0)
Acne	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Dermatitis	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Dermatomyositis	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Eczema	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Purpura	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Rash	1 (2.7)	(0.1, 14.2)	2 (3.1)	(0.4, 10.7)	0	(0.0, 21.8)	0	(0.0, 41.0)
Rash erythematous	1 (2.7)	(0.1, 14.2)	0	(0.0, 5.5)	0	(0.0, 21.8)	0	(0.0, 41.0)
Surgical and medical procedures	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Catheter removal	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Vascular disorders	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)
Hypertension	0	(0.0, 9.5)	1 (1.5)	(0.0, 8.3)	0	(0.0, 21.8)	0	(0.0, 41.0)

Note: MedDRA (v26.0) coding dictionary applied.
Note: Participants who aged into the next age group received the age-appropriate dose. For participants with a dose level change due to increasing age, all events that occurred after the dose level change were not included in the analysis.
Note: For participants with medication error, all events that occurred after the medication error were not included in the analysis.
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 adverse event. For "any 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.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2024 (16:15) Source Data: adaexa Table Generation: 28JUN2024 (02:07)
(Database snapshot date : 10AUG2023, 23FEB2024) Output File: ./nda3/C4591024_CSR_ADHOC/adae_s150_dl_1mpd4_soc

Analysis of Adverse Events

Analysis of Adverse Events from Dose 1 to 1 Month After Dose 2

AEs were reported by 14 participants (37.8%) who were 2 to <5 years, 15 participants (23.1%) who were 5 to <12 years of age, 2 participants (13.3%) who were 12 to <18 years of age, and 1 participant (14.3%) who was ≥18 years of age:

- In participants 2 to <5 years of age, the SOCs containing the most frequently reported AEs in all disease subsets were infections and infestations and general disorders and administration site conditions (18.9% and 10.8%, respectively).
- In participants 5 to <12 the SOCs containing the most frequently reported AEs in all disease subsets were general disorders and administration site conditions, gastrointestinal disorders, and infections and infestations (6.2%, 6.2%, and 4.6% respectively). Many of the AEs were reflective of reactogenicity events that were reported as AEs (e.g., injection site pain, vomiting, injection site erythema), or are commonly reported for this age group.
- In participants 12 to <18 years of age, 1 participant (14.3%) in the immunomodulatory therapy group reported an AE of urinary traction infection. The participant (14.3%) in the stem cell transplant group reported AEs of chills, injection site pain, pyrexia, dizziness, and headache, many of which were reflective of reactogenicity events that were reported as AEs.
- The 1 participant (20.0%) who was ≥18 years of age was in the immunomodulatory therapy group and reported AEs of urinary tract infection and vulvovaginitis.

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

AEs were reported by 9 participants (25.7%) who were 2 to <5 years of age, 8 participants (12.9%) who were 5 to <12 years of age, and 2 participants (14.3%) who were 12 to <18 years of age. No participants ≥18 years of age reported an AE.

- In participants who were 2 to <5 years of age, the SOC containing the most frequently reported AEs in all disease subsets was infections and infestations (17.1%).
- In participants who were 5 to <12 years of age, the SOC containing the most frequently reported AEs in all disease subsets was general disorders and administration site conditions (3.2%). All other SOCs containing reported AEs were reported by 1 participant each. In the blood and lymphatic system disorders SOC, 1 participant (5.9%) in the immunomodulatory therapy group reported lymphadenopathy. The general disorders and administration AEs were reflective of reactogenicity events that were reported as AEs (e.g., injection site bruising, injection site pain).
- In participants who were 12 to <18 years of age, the participant in the immunomodulatory therapy group reported an AE in the infections and infestations SOC (PT: urinary tract infection) and the participant in the stem cell transplant group reported an AE in the nervous system disorders SOC (PT: headache).

Analysis of Adverse Events from Dose 4 to 1 Month After Dose 4

AEs were reported by 2 participants (10.5%) who were 2 to <5 years of age and 7 participants (15.2%) who were 5 to <12 years of age, and 1 participant (25.0%) who was ≥18 years of age. No AEs were reported by participants who were 12 to <18 years of age:

- In participants who were 2 to <5 years of age, the participant in the immunomodulatory therapy group reported a related AE in the musculoskeletal and connective tissue disorders SOC (PT:

synovitis). The participant in the solid organ transplant group reported AEs in the infections and infestations SOC (PTs: conjunctivitis and urinary tract infection).

- In participants who were 5 to <12 years of age, the SOCs containing the most frequently reported AEs were infections and infestations (8.7%) and gastrointestinal disorders (4.3%). The most frequently reported AE in this age group was otitis externa, which was reported in 3 participants in the solid organ transplant group.
- In participants who were ≥18 years of age, the only participant in the NSCLC group reported an AE in the neoplasms, benign, malignant, and unspecified (including cysts and polyps) SOC (PT: metastases to bone).

Related Adverse Events

Related Adverse Events from Dose 1 to 1 Month After Dose 2

Related AEs were reported by 4 participants (10.8%) who were 2 to <5 years, 5 participants (7.7%) who were 5 to <12 years of age, and 1 participant (6.7%) who was 12 to <18 years of age. No participants ≥18 years of age reported a related AE.

- In participants 2 to <5 years of age, the participant in the immunomodulatory therapy group reported a related AE of purpura and the participant in the solid organ transplant group reported a related AE of injection site pain. In the stem cell transplant group, 1 participant reported a related AE of eye inflammation, and 1 participant reported a related AE of injection site pain.
- In participants 5 to <12, the SOC containing the most frequently reported related AEs was general disorders and administration site conditions (4.6%), which were reflective of reactogenicity events that were reported as AEs (e.g., injection site pain, injection site erythema).
- In participants 12 to <18 years of age, 1 participant (14.3%) in the stem cell transplant group reported related events of injection site pain, dizziness, and headache, which were all nonserious.

Related Adverse Events from Dose 3 to 1 Month After Dose 3

Related AEs were reported by 2 participants (5.7%) who were 2 to <5 years of age, 3 participants (4.8%) who were 5 to <12 years of age, and 1 participant (7.1%) who was 12 to <18 years of age. No participants ≥18 years of age reported an AE.

- In participants who were 2 to <5 years of age, 1 participant (11.1%) in the immunomodulatory therapy group and 1 participant (6.7%) in the solid organ transplant group reported related AEs (skin abrasion and gastritis, respectively); both were nonserious.
- In participants who were 5 to <12 years of age, 2 participants (11.8%) in the immunomodulatory therapy group and 1 participant (4.3%) in the solid organ transplant group reported related AEs (lymphadenopathy, body temperature increased, and injection site bruising, respectively); all were nonserious.
- In participants who were 12 to <18 years of age, 1 participant (16.7%) was in the stem cell transplant group and reported a related AE of headache that was nonserious.

Related Adverse Events from Dose 4 to 1 Month After Dose 4

AEs were reported by 1 participant (5.3%) who was 2 to <5 years of age and 1 participant (2.2%) who was 5 to <12 years of age. No AEs were reported by participants who were >12 years of age:

- In participants who were 2 to <5 years of age, the 1 participant (14.3%) was in the immunomodulatory therapy group and reported a related, nonserious AE of synovitis.

- In participants who were 5 to <12 years of age, the 1 participant (5.3%) was in the solid organ transplant group and reported a related, nonserious AE of diarrhoea.

Severe and Life-Threatening Adverse Events

Severe and Life-Threatening Adverse Events from Dose 1 to 1 Month After Dose 2

No life-threatening AEs were reported. Severe AEs were reported by 4 participants (10.8%) who were 2 to <5 years of age and 1 participant (14.3%) who was ≥18 years of age.

- In participants 2 to <5 years of age, the participants in the solid organ transplant group reported severe AEs of gastroenteritis and urinary tract infection. The participants in the stem cell transplant group reported severe AEs of dental caries and pyrexia.
- 1 participant (20.0%) who was ≥ 18 years of age in the immunomodulatory therapy group reported a severe AE (urinary tract infection).

Severe and Life-Threatening Adverse Events from Dose 3 to 1 Month After Dose 3

No life-threatening AEs were reported. Severe AEs were reported by 2 participants (5.7%) who were 2 to <5 years of age (solid organ transplant group: gastroenteritis, postoperative ileus) and 1 participant (1.6%) who was 5 to <12 years of age (immunomodulatory therapy group: intestinal obstruction). No participants >12 years of age reported a severe or life-threatening AE.

Severe and Life-Threatening Adverse Events from Dose 4 to 1 Month After Dose 4

No severe or life-threatening AEs were reported by participants in any age group.

Deaths

No deaths were reported from study vaccination through end of study.

Serious Adverse Events from Dose 1 to End of Study

From Dose 1 to end of the study, 11 participants (29.7%) who were 2 to <5 years of age, 11 participants (16.9%) who were 5 to <12 years of age, and 2 participants (28.6%) who were ≥18 years of age reported at least 1 SAE. No participants 12 to <18 years of age reported an SAE and no SAEs were assessed as related.

- In participants <12 years of age, most of the SAEs were from the infections and infestations SOC (participants 2 to <5 years of age [18.9%] and participants 5 to <12 years of age [7.7%]).
- In participants ≥ 18 years of age, 1 participant (20.0%) in the immunomodulatory therapy group reported an SAE of renal colic and 1 participant (100.0%) in the haemodialysis group reported SAEs of melaena, gangrene, and azotaemia.

Safety-Related Participant Withdrawals

No participants were withdrawn because of adverse events from Dose 1 to end of study.

Other Significant Adverse Events

From study vaccination through end of study, no protocol-designated AESIs of myo/pericarditis or exacerbation of underlying immunocompromising conditions were reported. Other AEs of specific interest due to their autoimmune or neuroinflammatory nature, theoretical association with vaccines, or known occurrence in patients with COVID-19 are surveilled as AESIs. All reported AESIs in this study were due to worsening of participants underlying condition. No participants >12 years of age reported an AESI.

- In participants 2 to <5 years of age from Dose 1 to end of the study, 2 participants (5.4%) reported at least 1 AESI, and both participants (22.2%) were in the immunomodulatory group. One participant (11.1%) reported an AESI of uveitis and 1 participant (11.1%) reported an AESI of rash erythematous.
- In participants 5 to <12 years of age, 5 participants (7.7%) reported at least 1 AESI. Of these 5 participants, 3 participants (15.8%) were in the immunomodulatory therapy group (PTs of: tumour necrosis factor receptor-associated periodic syndrome, Crohn's disease, dermatomyositis, and dystrophic calcification) and 2 participants (8.3%) were in the solid organ transplant group (PTs of: kidney transplant rejection and donor specific antibody present).

Incidence Rate of Confirmed COVID-19 Cases After Dose 1

Overall, there was a small number of confirmed COVID-19 cases (n=45) reported by participants after Dose 1 to end of study.

Participants 2 to <5 Years of Age

In participants who received BNT162b2 3 µg, the IR of first COVID-19 occurrence after Dose 1, from 7 days after Dose 3, and from 7 days after Dose 4 in the immunomodulatory therapy group was 663.287, 633.565, and 751.543 per 1000 person-years of follow up, respectively. The IR of first COVID-19 occurrence after Dose 1 and from 7 days after Dose 3 in the solid organ transplant group was 492.251 and 181.266 per 1000 person-years of follow up, respectively, and no case occurred from 7 days after Dose 4. The IR of first COVID-19 occurrence after Dose 1 in the stem cell transplant group was 234.737 per 1000 person-years of follow up, and no case occurred after 7 days after Dose 3 onwards.

Participants 5 to <12 Years of Age

In participants who received BNT162b2 10 µg, the IR of first COVID-19 occurrence after Dose 1, from 7 days after Dose 3, and from 7 days after Dose 4 in the immunomodulatory therapy group was 952.660, 770.895, and 519.559 per 1000 person-years of follow up, respectively. The IR of first COVID-19 occurrence after Dose 1, from 7 days after Dose 3, from 7 days after Dose 4 in the solid organ transplant group was 621.808, 422.059, and 577.623, per 1000 person-years of follow up, respectively. The IR of first COVID-19 occurrence after Dose 1, from 7 days after Dose 3, from 7 days after Dose 4 in the stem cell transplant group was 428.509, 364.594, and 381.064 per 1000 person-years of follow up, respectively. There was a separation in the KM curves between the immunomodulatory therapy and the other two disease groups, which potentially corresponds to the lower GMTs observed in the immunomodulatory therapy disease group.

Participants 12 to <18 Years of Age

In participants who received BNT162b2 30 µg, the IR of first COVID-19 occurrence after Dose 1 and from 7 days after Dose 3, in the immunomodulatory therapy group was 861.947 and 602.226 per 1000 person-years of follow up, respectively. No case occurred in solid organ transplant group. The IR of first COVID-19 occurrence after Dose 1 and from 7 days after Dose 3, in the stem cell transplant group was 422.499 and 616.976 per 1000 person-years of follow up, respectively. No case occurred in solid organ transplant group.

Participants ≥18 Years of Age

In participants who received BNT162b2 30 µg, the IR of first COVID-19 occurrence after Dose 1, from 7 days after Dose 3, from 7 days after Dose 4, in the immunomodulatory therapy group was 697.708 and 1144.984, and 3397.674 per 1000 person-years of follow up, respectively. No case occurred in non-small cell lung cancer and haemodialysis groups.

Surveillance of COVID-19 Cases

Confirmed COVID-19 Cases, Severe COVID-19 Illness, and MIS-C

There were few episodes of confirmed COVID-19 cases (n=45) reported by participants across all age groups throughout the study and primarily represented mild to moderate illness.

One participant 5 to <12 years of age reported COVID-19 that met 1 or more severe illness criteria (protocol-defined) and no cases of MIS-C were reported.

7.3. Discussion

C4591015

This report presents the final safety data from the phase 3 study C4591015 where pregnant women were randomised to receive either 30 µg of BNT162b2 (n=174) or placebo (n=174) administered in 2 doses, 21 days apart at 24 to 34 weeks' gestation. HIV positive subjects could be included if they were on stable antiretroviral therapy and a viral load of <50 copies/mL. These subjects could therefore not be seen as immunocompromised. The study was limited in size due to the national recommended COVID-19 vaccination of pregnant women.

The reactogenicity profile was in line with previous results from non-pregnant adult subjects. The reactions were transient and most of them were mild to moderate at intensity. The most reported local reaction was pain at injection site (83% dose1; 75% dose2). The most frequently reported systemic events were fatigue (50%) and headache (34-41%). Fever was reported in 1-4% (dose 1 and 2 respectively). Most reported AEs were related to reactogenicity. The frequency of participants reporting any SAE was low and comparable to what was reported in the placebo group (5.6% and 5.5%, respectively). Two related AEs were reported among the maternal participants receiving BNT162b2 (tachypnoea and injection site pain). None of the infants experienced AEs related to maternal vaccination. No new safety concern was identified in this limited study population.

C4591024

This report presents the final safety data of the phase 2b study C4591024 that enrolled a total of 124 immunocompromised participants aged 2 to <5 years (n=37), 5-<12 years (n=65) 12-<18 years (n=15) and ≥18 years (n=7). The study evaluated a 4-dose schedule (the first 2 doses separated by 21 days), with a third dose occurring 28 days after the second dose. The fourth dose was administered 3-6 months after Dose 3, at the discretion of the investigator. The dose for each of the 4 vaccinations depended on the age of participants at time of vaccination (>12 years of age: 30-µg dose, 5 to <12 years of age: 10-µg dose, 2 to <5 years: 3-µg dose).

Most of the reactogenicity evens were transient and mild to moderate at intensity. Children aged 2-<5 years old were presented with a mild reactogenicity profile with a low frequency of both local and systemic events (<21%), similar as for non-immunocompromised subjects presented in other studies. Children aged 5 to <12 years that constituted the largest age group (n=65) in this limited study reported local reactions (most common pain at injection site: 53-63%) and systemic events where fatigue (46-61%). Fever was reported in 1,5-12%, none had fever >40°C. Among the subjects ≥12 years old (n=22), the reactogenicity profile are in line with the data that has been presented previously for non-immunocompromised subjects. The majority of AEs were in the infections and infestations SOC, and all AESIs were likely related to participant's underlying condition. There were no deaths, no SAEs assessed

as related by the investigator, no life-threatening AEs, and no AEs leading to withdrawal. No new safety concerns were identified in this limited study population of immunocompromised subjects.

8. Changes to the Product Information

As a result of this group of variations, sections 4.4, 4.6, 4.8 and 5.1 of the SmPC are being updated to reflect the outcome of this assessment. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9. Request for supplementary information

9.1. Other concerns

Clinical aspects

1. Please replace the table 8 in SmPC with a short text describing that antibody titre was lower in pregnant women compared to non-pregnant women from historical control group.
2. Please replace the table 9 in SmPC with a short text describing that antibody titre was higher after the 4th dose in all studied immunocompromised groups.
3. In study C4591024 there was about 20% of participants in age group 5-<18 with unknown baseline SARS-CoV-2 status. The reason is unknown and need a clarification.
4. See comment in the SmPC section 4.8 in separate document.

10. Assessment of the responses to the request for supplementary information

10.1. Other concerns

Clinical aspects

Question 1
Please replace the table 8 in SmPC with a short text describing that antibody titre was lower in pregnant women compared to non-pregnant women from historical control group.

Summary of the MAH's response

Please refer to Section 5.1 of the SmPC for response and proposed revision.

Assessment of the MAH's response

Conclusion: Issue solved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 2
Please replace the table 9 in SmPC with a short text describing that antibody titre was higher after the 4th dose in all studied immunocompromised groups.

Summary of the MAH's response

Please refer to Section 5.1 of the SmPC for response and proposed revision.

Assessment of the MAH's response

Conclusion: Issue solved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 3
In study C4591024 there was about 20% of participants in age group 5-<18 with unknown baseline SARS-CoV-2 status. The reason is unknown and need a clarification.

Summary of the MAH's response
There are 2 age groups within the 5-<18 years category which comprise of 5-<12-year-olds and 12–<18-year-olds. Considering the total evaluable immunogenicity population the following table demonstrates that the 5-<18 age bracket contains the majority of missing baseline SARS-CoV-2 results as the 5- <12 years age group was the highest enrolling group (n = 56), and therefore also had the highest number of missing results (n=14).

Age Group (years)	**Total Number of Participants – Dose 3 Evaluable Immunogenicity Population (N)**	**Number of Missing Baseline SARS-CoV-2 Status, n (%)**
2-<5	26	3 (11.5)
5-<12	56	14 (25.0)
12-<18	11	3 (27.3)
≥18	4	0
Total	97	20 (20.6)

As the total denominator of the study is small (N=124), and that of the evaluable immunogenicity population is further reduced (n=97), small fluctuations in the number of participants with a missing result would lead to large changes in the percentage.

The baseline COVID status was unknown for some participants due to the analyses not being able to be performed (e.g. blood sample/swab not taken, indeterminate result).

Assessment of the MAH's response:

The Applicant explained that absence of the baseline sample (blood or nasal swab) or unclear test result caused the "unknown baseline Covid-19 status" label for about 20 % of participants.

Conclusion: Issue solved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question: 4
See comment in the SmPC section 4.8 in separate document.

Summary of the MAH's response
Please refer to Section 4.8 of the SmPC for response and proposed revision.

Assessment of the MAH's response

Conclusion Issue solved

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance