EMA/497785/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

COMIRNATY

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/II/0067

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

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

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Status of this report and steps taken for the assessment	
Description	**Date**
Start of procedure	03 Sep 2021
CHMP Rapporteur Assessment Report	23 Sep 2021
CHMP members comments	29 Sep 2021
Updated CHMP Rapporteur Assessment Report	01 Oct 2021
Opinion	04 Oct 2021

Procedure resources	
Rapporteur	Filip Josephson

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 2 September 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

To update sections 4.2, 4.8 and 5.1 of the SmPC based on interim safety and immunogenicity data of a third booster dose of Comirnaty (COVID-19 mRNA Vaccine BioNTech) from study C4591001, a "Phase 1/2/3, placebo-controlled, observer-blind, interventional, dose-finding, study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals". Further substantiating data is provided based on published real-world effectiveness data from Israel and the US. The package leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Introduction

BNT162b2 (Comirnaty), is to be administered intramuscularly (IM) as a series of two doses (0.3 mL each) three weeks apart. The MAH proposed to revise the currently approved dosing regimen to include a booster dose (third dose), which may be administered at approximately 6 months after Dose 2.

This AR summarises the data on immunogenicity and safety for a group of Phase 3 participants in Study C4591001 who received a booster (Dose 3) of BNT162b2 (30 µg).

Unblinding Considerations

Starting 14 December 2020, individuals ≥16 years of age have been progressively unblinded in the study to receive BNT162b2 vaccination when eligible per protocol. Since 10 May 2021, adolescents 12 to 15 years of age have been unblinded in the study to receive BNT162b2 as they became eligible. Unblinded participants continue in study follow-up in an open-label manner.

Participants randomised into Phase 3 booster and variant strain vaccine groups remain blinded to their randomisation assignment at this time. Sponsor and site personnel responsible for the ongoing conduct of the study remain blinded to individual participants' randomisation information for any who have not been unblinded. Safety evaluation for such participants by the study team remains blinded until a decision is made to unblind the entire study. A separate (from study conduct) unblinded submissions team is responsible for regulatory submissions.

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

3. Clinical Efficacy aspects

Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 registration study. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enrol enough participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. Booster groups were subsequently added to evaluate boostability and protection against variant virus strains.

3.1. Methods – analysis of data submitted

Booster and Variant Strain Evaluation

Phase 1

Phase 1 participants who were randomized to either BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg were offered booster vaccination (Dose 3) with BNT162b2 at 30 µg, approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This provided an early assessment of the safety and immunogenicity associated with a third vaccine dose.

Preliminary data from Phase 1 booster study participants who previously received BNT162b2 30 µg and then received a third dose of BNT162b2 30 µg, including neutralization of the B.1.351 (Beta) variant of SARS-CoV-2 and B.1.617.2 (Delta) variant of SARS-CoV-2 are presented in current AR as supporting information. Altogether 23 participants received a booster dose, whereas 11 of them were at age 18-55 and 12 at age 65-85.

Phase 2/3

Phase 2/3 of Study C4591001 commenced with the selected vaccine candidate and dose level (BNT162b2 at 30 µg) administered to participants randomized 1:1 to vaccine or placebo.

Phase 2 was conducted in the US. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants 18 to 85 years of age enrolled into the study when the Phase 2/3 part commenced, balancing younger (≤55 years of age) and older (>55 years of age) strata within each group. Phase 2 participants in this blinded part of the study also contribute to the overall efficacy and safety assessments in the Phase 3 portion of the study.

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

For further evaluation of booster effects and/or protection against emerging SARS-CoV-2 variants of concern, approximately 600 existing Phase 3 participants 18 to 55 years of age were randomized 1:1 to receive a booster (Dose 3) of either 30 µg BNT162b2 or a prototype vaccine based upon the B.1.351 (Beta) variant that originated in South Africa, BNT162b2$_{SA}$, approximately 6 months after their second dose of BNT162b2. Only data for those receiving BNT162b2 are included in this application.

Immunogenicity evaluation

Immunogenicity Endpoints in Study C4591001

BNT162b2 booster (Dose 3) effectiveness is based on immunobridging to the immune response after Dose 2 in participants. SARS-CoV-2 50% neutralizing titers were compared at 1-month post-Dose 3 to those observed at 1-month post-Dose 2, for the same participants for the SARS-CoV-2 reference strain.

Immunogenicity endpoints were:

i) geometric mean titers (GMT) and geometric mean ratio (GMR) of SARS-CoV-2 neutralizing titer at 1 month after Dose 3 to 1 month after Dose 2

ii) percentages and difference in percentages of participants with seroresponse at 1 month after Dose 3 and 1 month after Dose 2, where seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1); for baseline measurement <LLOQ, postvaccination measure ≥4 × LLOQ is considered seroresponse.

iii) geometric mean-fold rise (GMFR) from before Dose 3 to 1 month after Dose 3.

Immunogenicity Analysis Methods

Assay validation reports were provided in Module 2.7.1. Only a validated SARS-CoV-2 neutralization assay was used for Phase 3 immunogenicity data. Immunogenicity endpoints are summarized in Section 0 and immunogenicity analysis methods are summarized below.

CHMP's comment: The MAH states that only validated neutralization assay was used. According to the description in Module 2.7.1 mNeonGreen SARS-CoV-2 Microneutralization Assay is qualified and not validated. It was accepted that the neutralization assay is not yet validated in previous procedures (e.g. CMA and extension of indication) as vaccine efficacy data were presented and immunogenicity data were considered supportive only. However, the current application the validity of the neutralisation assay is crucial as no vaccine efficacy data of 3rd dose are presented. Therefore, the MAH is asked to submit validation reports for the immunogenicity assays used. Also, it is noted, that there is no information about neutralization assay with Beta and Delta strains.

In response to the preliminary list of questions, the MAH submitted the validation report for Wuhan strain dated at 09.02.2021. This document demonstrated the reliability of the assay. The validation report did not contain information about Delta and Beta strain validation. As the information in the application about these strains was supportive, we hereby do not pursue further this issue.

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

Population	**Description**
Enrolled	All participants who had a signed ICD.
Randomized	All participants who were assigned a randomization number in the IWR system.
Dose 3 booster evaluable immunogenicity	All eligible randomized participants who received 2 doses of BNT162b2 as initially randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1), received a third dose of BNT162b2 or BNT162b2SA as rerandomized, had at least 1 valid and determinate immunogenicity result after Dose 3 from a blood collection within an appropriate window (within 28-42 days after Dose 3), and had no

Population	Description
	other important protocol deviations as determined by the clinician.
Dose 3 booster all-available immunogenicity	All randomized participants who received 2 doses of BNT162b2 at initial randomization, received a third dose of BNT162b2 or BNT162b2$_{SA}$ at rerandomization, and had at least 1 valid and determinate immunogenicity result after Dose 3.
Booster safety	All participants who received at least 1 booster dose of the study intervention.

Noninferiority was assessed based on the GMR of SARS-CoV-2 neutralizing titers at 1 month after Dose 3 to 1 month after Dose 2 using a 1.5-fold margin and comparison of the point estimate of the GMR to 0.8. The GMR was calculated as the mean of the difference of logarithmically transformed titers for each participant (e.g., later time point minus earlier time point) and exponentiating the mean. The associated 2-sided 97.5% CIs were obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Noninferiority was declared if the lower bound of the 2-sided 97.5% CI for the GMR was >0.67 and the point estimate of the GMR was ≥0.8.

Noninferiority was also assessed based on the difference in percentages of participants with a seroresponse defined as a ≥4-fold rise from baseline (before Dose 1) at 1 month after Dose 3 and 1 month after Dose 2 using a 10% margin. If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. The difference in percentages (1 month after Dose 3 – 1 month after Dose 2) and the associated 2-sided 97.5% CI calculated using the adjusted Wald interval as described by Agresti and Min were provided. Noninferiority was declared if the lower limit of the 97.5% CI for the difference in percentages of participants with seroresponse was greater than -10%.

Noninferiority analyses were conducted for participants without prior serological or virological evidence, by N-binding antibody or nucleic acid amplification test (NAAT), respectively, of SARS-CoV-2 infection up to 1 month after Dose 3.

GMTs and GMFRs were provided with associated 2-sided 95% CIs calculated with reference to Student's t-distribution. Titers/concentrations below the LLOQ or denoted as BLQ were set to 0.5 × LLOQ for all analyses except for seroresponse.

Assuming a 20% non-evaluable rate, approximately 240 evaluable participants in the BNT162b2 booster group were planned to contribute to immunogenicity evaluation, to provide sufficient power for noninferiority evaluation with appropriate multiplicity adjustment for type I error control. The study had >99.9% power to demonstrate noninferiority based on GMR for the objectives in vaccine-experienced individuals using a 1.5-fold margin, and 99% power or 89% power to show noninferiority based on seroresponse rate under the assumption of moderate or high discordance in response status at 2 comparative timepoints for the objectives in vaccine-experienced individuals using a 10% margin.

Note that blood samples collected at Visit 1 (before Dose 1), Visit 3 (1 month post Dose 2), Visit 301 (before booster dose), Visit 302 (1 week after booster dose), and Visit 303 (1 month post booster dose) were planned to be tested for the immunogenicity assessment. During clinical testing, due to higher repeating rate, the viral reagent for the assay was not sufficient to complete testing of all samples. Testing was reprioritized for samples from critical time points for hypothesis testing, which resulted smaller number of sample size for the 1 week after booster dose visit.

CHMP´s comment: The immunogenicity endpoints chosen, as well as the non-inferiority margins are acceptable. Considering that there is no serological correlate of protection, the non-inferiority margins are considered arbitrary, but are commonly used for comparing immune responses in vaccine studies.

3.2. Results

Immunogenicity Populations

Among the 312 participants who were rerandomized to receive a booster (Dose 3) of BNT162b2 30 µg, the Dose 3 booster evaluable immunogenicity population included 268 participants, and those without evidence of infection up to 1 month after Dose 3 include 234 participants (Table 1). The most common reason for exclusion (30 [9.6%] participants) from the evaluable immunogenicity population was that they had important protocol deviation(s) as determined by the clinician. The majority of these protocol deviations included 16 (53.3%) participants with Visit 301 (booster [Dose 3] vaccination) conducted outside the protocol-specified window.

Table 1. Immunogenicity Populations – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Randomized)
	BNT162b2 (30 µg) n[a] (%)
Rerandomized[b]	312 (100.0)
Dose 3 booster all-available immunogenicity population	306 (98.1)
Subjects excluded from Dose 3 booster all-available immunogenicity population	6 (1.9)
Reason for exclusion	
Did not have at least 1 valid and determinate immunogenicity result after booster vaccination	6 (1.9)
Dose 3 booster evaluable immunogenicity population	268 (85.9)
Without evidence of infection up to 1 month after booster dose[c]	234 (75.0)
Subjects excluded from Dose 3 booster evaluable immunogenicity population	44 (14.1)
Reason for exclusion[d]	
Did not receive Dose 2 within 19-42 days after Dose 1	1 (0.3)
Did not receive a booster vaccination of BNT162b2 or BNT162b2$_{SA}$ as rerandomized	6 (1.9)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after booster vaccination	15 (4.8)
Had important protocol deviation(s) before 1 month post Dose 3 evaluation as determined by the clinician	30 (9.6)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. n = Number of subjects with the specified characteristic.
b. This value is the denominator for the percentage calculations.
c. Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1, 3, 301,

and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination.
d. Subjects may have been excluded for more than 1 reason.

The median duration between Dose 2 and Dose 3 was 6.8 months (range: 4.8 to 8.0 months). 49.7% of participants who received booster (Dose 3) administration between 6 and <7 months after receiving Dose 2. Fewer than 10% of participants received Dose 3 at <6 months following Dose 2. Dose 3 was administered ≥7 months after Dose 2 for41.0% of participants; this included 16 participants who received Dose 3 outside of the protocol defined window (ie, <150 days or >210 days after Dose 2).

CHMP's comment: The interval between dose 2 and dose 3 was approximately 6 months. No justification for this interval is given.

Demographics

The demographic characteristics of the study population are summarised in Table 2. Demographics in the Dose 3 booster evaluable immunogenicity population were generallysimilar to those without evidence of infection up to 1 month after the booster dose in the same population, similar to those in the Dose 3 booster all-available immunogenicity population, and similar to the booster safety population.

Table 2. Demographic Characteristics – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)
	BNT162b2 (30 µg)(N[a]=268) n[b] (%)
Sex	
Male	124 (46.3)
Female	144 (53.7)
Race	
White	218 (81.3)
Black or African American	28 (10.4)
American Indian or Alaska Native	2 (0.7)
Asian	11 (4.1)
Native Hawaiian or other Pacific Islander	1 (0.4)
Multiracial	4 (1.5)
Not reported	4 (1.5)
Ethnicity	
Hispanic/Latino	81 (30.2)
Non-Hispanic/non-Latino	185 (69.0)
Not reported	2 (0.7)
Country	
USA	268 (100.0)
Age at booster vaccination (years)	
Mean (SD)	41.1 (9.39)

Median	42.0
Min, max	(19, 55)
Body mass index (BMI)	
Underweight (<18.5 kg/m^2)	1 (0.4)
Normal weight (≥18.5-24.9 kg/m^2)	72 (26.9)
Overweight (≥25.0-29.9 kg/m^2)	86 (32.1)
Obese (≥30.0 kg/m^2)	109 (40.7)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.

CHMP's comment: It is noted that the study population was mainly obese or overweighed, which might influence the antibody titers negatively.

Noninferiority of Booster Response to Initial Regimen Response

Geometric Mean Ratio (GMR) of Neutralization Titers to Reference Strain

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), the immune response to BNT162b2 30 µg at 1 month after the booster (Dose 3) was noninferior to that observed at 1 month after Dose 2 in the same participants, based on SARS-CoV-2 50% neutralizing titers (Table 3).

The SARS-CoV-2 neutralizing GMT ratio of 1 month after Dose 3 to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which meets the 1.5-fold noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR ≥0.8.

The lower bound of the 2-sided 97.5% CI for the GMR is >1, which indicates a statisticallygreater response following booster (Dose 3) administration than that observed following Dose 2.

The GMR result for the Dose 3 booster all-available immunogenicity population was similar to those observed for the Dose 3 booster evaluable immunogenicity population.

CHMP's comment: The GMTs were clearly superior after dose 3 compared to after dose 2, and the non-inferiority margins were clearly met. The seroresponse rates were very high after the second dose (98%, and as can be expected were high also after the third dose (99.5%).

Efficacy has been demonstrated after two doses, although the duration of protection is unknown. The role of persisting high antibody titres and the role of immunological memory are currently not characterised for protection against covid-19.

Table 3. Geometric Mean Ratio – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

					Sampling Time Point		
					1 Month After Booster Dose	1 Month After Dose 2 (BNT162b2)	1 Month After Booster Dose/1 Month After Dose 2
Objective[a]	Assay at 1 Month After Booster Dose	Assay at 1 Month After Dose 2	Vaccine Group (as Randomized)	n[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (97.5% CI[e])
E1a	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	BNT162b2 (30 µg)	210	2476.4 (2210.1, 2774.9)	753.7 (658.2, 863.1)	3.29 (2.76, 3.91)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT =nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody[serum] negative at Visit 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.

a. The first primary objective to be evaluated in Phase 3 booster portion of the study, where 'E' represents BNT162b2-experienced subjects and 'a' represents GMR estimands.
b. n = Number of subjects with valid and determinate assay results for both the specified assays at the given dose/sampling time point within specified window.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student tdistribution).
e. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.

Table 4. Percentage Difference of Subjects Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

					Sampling Time Point		Difference	
					1 Month After Booster Dose	1 Month After Dose 2 (BNT162b2)	(1 Month After Booster Dose – 1 Month After Dose 2)	
Objective [a]	Assay at 1 Month After Booster Dose	Assay at 1 Month After Dose 2	Vaccine Group (as Randomized)	N[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	%[e]	(97.5% CI[f])[g]
E1b	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	BNT162b2 (30 µg)	198	197 (99.5) (97.2, 100.0)	194 (98.0) (94.9, 99.4)	1.5	(-0.7, 3.7)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 ×LLOQ is considered a seroresponse.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody[serum] negative at Visit 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
a. The first primary objective to be evaluated in Phase 3 booster portion of the study, where 'E' represents BNT162b2-experienced subjects and 'b' represents seroresponserate estimands.
b. N = number of subjects with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specifiedwindow. These values are the denominators for the percentage calculations.
c. n = Number of subjects with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
f. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
g. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is greater than -10.

Difference in Seroresponse Rate to Reference Strain

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after thebooster (Dose 3), a high proportion of participants (99.5%) had seroresponse (defined as ≥4-fold rise from baseline before Dose 1) at 1 month after Dose 3 compared with 98.0% at 1 month after Dose 2 (Table 4).

The difference in proportions of participants with a seroresponse 1 month after the booster (Dose 3) and 1 month after Dose 2 (Dose 3 – Dose 2) was 1.5% (2-sided 97.5% CI: -0.7, 3.7%), which meets the 10% noninferiority margin (i.e., lower bound of the 2-sided 97.5% CIwas greater than -10%).

The seroresponse result for the Dose 3 booster all-available immunogenicity population was similar to those observed for the Dose 3 booster evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection.

SARS-CoV-2 Neutralizing Titers

Geometric Mean Titers (GMTs) to Reference Strain

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), at 1 month after the booster (Dose 3) of BNT162b2 30 µg, SARS-CoV-2 50% neutralizing GMTs increased substantially relative to GMTs observed prior to receipt of Dose 3 (Table 5).

The median duration between receipt of Dose 2 and the booster with Dose 3 was 6.8 months. GMTs had declined by the time the booster (Dose 3) was administered. From Dose 2 up to the day of Dose 3 administration (before booster vaccination), GMTs were 136.2 (2-sided 95% CI: 121.5, 152.6), which represents a 5.59-fold reduction compared to that observed at 1 month after Dose 2.

Following booster (Dose 3) vaccination, GMTs were increased by 7 days post-Dose 3 to 1418.7 (95% CI: 1263.3, 1593.3). By 1 month after Dose 3, GMTs were further elevated to 2374.2 (95% CI: 2134.1, 2641.3), a level 17.4-fold that observed on the day of booster vaccination (prior to receipt of Dose 3).

Overall, among participants in the Dose 3 booster evaluable immunogenicity population, the neutralizing GMTs at 1 month after Dose 3 were substantially greater than that observed at 1 month after Dose 2 (ie, 3-fold), showing a strong boost to the neutralizing antibody response.

The SARS-CoV-2 50% neutralizing GMTs for all participants in the Dose 3 booster evaluable immunogenicity population regardless of prior infection status and the Dose 3 booster all-available immunogenicity population were similar to those observed for the Dose 3 booster evaluable immunogenicity population without evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3).

Table 5. Geometric Mean Titers – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized) BNT162b2 (30 µg) n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer) 1/Prevax		217	10.4 (10.0, 10.9)
	2/1 Month	214	762.0 (663.3, 875.5)
	3/Prevax	213	136.2 (121.5, 152.6)
	3/Day 7	108	1418.7 (1263.3, 1593.3)
	3/1 Month	232	2374.2 (2134.1, 2641.3)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; Prevax = pre-vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Seroresponse Rate to Reference Strain

Seroresponse rates (defined as ≥4-fold rise from baseline before Dose 1) are summarised in Table 6.

Table 6. Number (%) of Subjects Achieving Seroresponse – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	N[b]	Vaccine Group (as Randomized) BNT162b2 (30 µg) n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	2/1 Month	202	198 (98.0) (95.0, 99.5)
	3/Prevax	197	152 (77.2) (70.7, 82.8)
	3/Day 7	98	96 (98.0) (92.8, 99.8)
	3/1 Month	215	214 (99.5) (97.4, 100.0)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; Prevax = pre-vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of pastSARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement isbelow the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of subjects with valid and determinate assay results for the specified assay both before vaccination and atthe given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of subjects with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.

CHMP's comment: The GMT and seroresponse rate results support the increased immune responses after a third dose compared to 1 month after dose 2, and before dose 3. It is noted that about 20% of study population had become seronegative at the day for receiving 3rd dose. It is unclear if these subjects had longest time period from the last dose or it is related to the demographic characteristics such as age and BMI.

Phase 1 Booster (Dose 3) Immunogenicity at 1 Month Post-Dose 3 in Study C4591001: SARS-CoV-2 Wild-Type and Beta and Delta Variant Neutralization Data

This MAH has submitted preliminary results from a subset of younger (18 to 55 years of age) and older (65 to 85 years of age) participants in the Phase 1 part of Study C4591001 who completed the initial two-dose series of BNT162b2 30 µg, given approximately 3 weeksapart, and then received a

third dose (booster) of BNT162b2 30 µg approximately 7 to 9 months after the second dose. Data were collected through the cut-off date of 13 May 2021.

Immunogenicity Endpoints and Analysis Methods

SARS-CoV-2 50% neutralization titers were assessed in sera drawn before BNT162b2 Dose 1 (on Day 1); 7 days and 1 month after BNT162b2 Dose 2; before Dose 3; and 7 daysand 1 month after Dose 3. Neutralization titers were determined as described previously against the designated wild-type (recombinant USA-WA1/2020) and against the B.1.351 (recombinant USA-WA1/2020 bearing the full spike gene from Beta variant) and against B.1.617.2(recombinant USA-WA1/2020 with the full spike gene from the Delta variant) lineage targetstrains. All samples from each of the time points were analysed for this evaluation (i.e., previously tested samples were reanalysed).

Study population

The study was conducted at 2 sites in the US. As of the data cut-off date (13 May 2021), 23/24 original Phase 1 participants who received 2 doses of BNT162b2 30 µg received a third dose (booster) of BNT162b2 30 µg. One original participant declined to receive Dose 3.

Table 7. Demographic Characteristics – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

	Initial Age Group	
	18-55 Years of Age	**65-85 Years of Age**
	(N[a]=11) n[b] (%)	**(N[a]=12) n[b] (%)**
Sex		
Male	2 (18.2)	6 (50.0)
Female	9 (81.8)	6 (50.0)
Race		
White	8 (72.7)	12 (100.0)
Black or African American	1 (9.1)	0
Asian	2 (18.2)	0
Ethnicity		
Non-Hispanic/non-Latino	11 (100.0)	12 (100.0)
Age at booster dose (years)		
Mean (SD)	38.8 (10.00)	69.3 (2.96)
Median	39.0	69.0
Min, max	(24, 55)	(65, 75)

a. N = number of subjects in the specified group. This value is the denominator for the percentagecalculations.
b. n = Number of subjects with the specified characteristic.

Immunogenicity results for booster group in Phase I study

Reference strain and beta strain comparison

The Dose 3 all-available immunogenicity population included all randomized participantswho received 2 doses of BNT162b2 as initially randomized, received a third BNT162b2 dose, and had at least 1 valid and determinate immunogenicity result after Dose 3. Valid neutralization titers were obtained from all 23 participants.

Geometric Mean Titers (GMTs)

SARS-CoV-2 neutralization GMTs against the wild-type USA-WA1/2020 strain (a clinicalstrain isolated in January 2020) substantially increased after Dose 3. GMTs at 1 month afterDose 3 were 2119 (95% CI: 1229.1, 3653.4) for younger participants 18 to 55 years of age, and 2032 (95% CI: 1232.6, 3349.3) for older participants 65 to 85 years of age, which were >5-fold and >7-fold, respectively, those of the GMTs observed at 1 month after Dose 2(Figure 3).

Geometric mean Fold Rise (GMFRs)

GMFRs against the wild-type strain from before Dose 3 to 1 month after Dose 3 were 25.7(95% CI: 12.4, 53.3) for younger adults, and 49.4 (95% CI: 29.2, 83.3) for older adults (see Table 8).

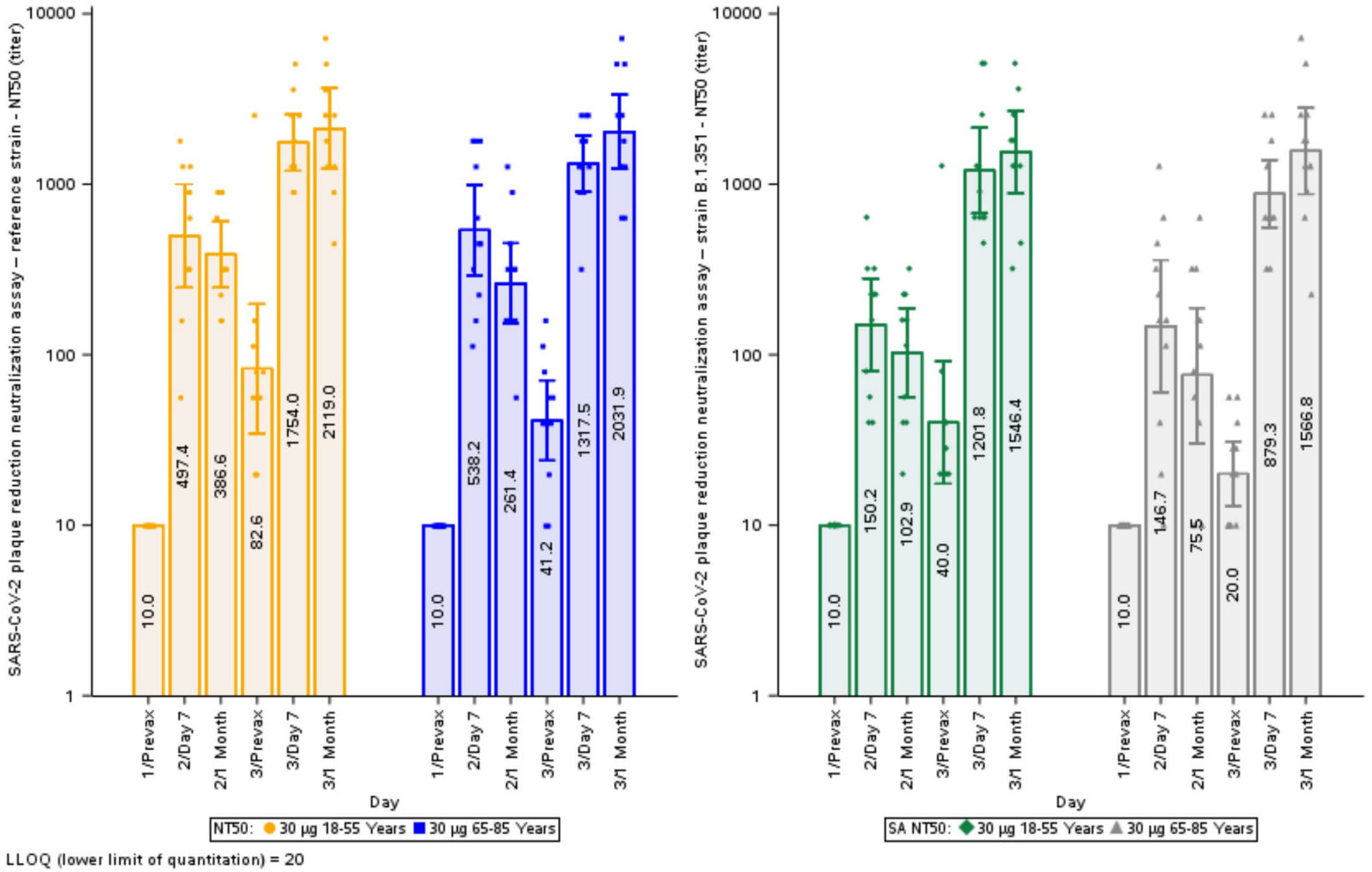
A third dose of BNT162b2 administered 7 to 9 months after the original two-dose series also increased the neutralizing titers against the B.1.351 SARS-CoV-2 recombinant virus (recombinant virus was based on the USA-WA1/2020 clinical strain and incorporated the complete spike gene from the B.1.351 variant[2]). At 1 month after Dose 3, GMTs were 1546 (95% CI: 888.1, 2692.4) for younger participants, and 1567 (95% CI: 875.2, 2804.7) for older participants, which were >15-fold and >20-fold, respectively, those of the GMTs observed at 1 month after Dose 2 (Figure 1).

GMFRs against B.1.351 from before Dose 3 to 1 month after Dose 3 were 38.7 (95% CI: 19.8, 75.5) for younger adults, and 78.3 (95% CI: 40.7, 150.6) for older adults (see Table 6).

The difference between neutralizing titers against the wild-type virus and the B.1.351 SARS-CoV-2 lineage observed after Dose 2 narrowed after BNT162b2 Dose 3 (Figure 3). Specifically, at 1 month after Dose 2, the GMRs of neutralizing titers against the B.1.351 virus to neutralizing titers against the wild-type virus were 0.27 (95% CI: 0.18, 0.39) for younger adults and 0.29 (95% CI: 0.17, 0.49) for older adults; at 1 month after Dose 3, the corresponding GMRs increased to 0.73 (95% CI: 0.52, 1.02) and 0.77 (95% CI: 0.51, 1.16).

CHMP's comment: The phase 1 data support the overall conclusion from the phase 3 data, i.e. that neutralising antibody titres are increased to high levels after the third dose, at least as high as after the second dose, possibly higher. The sample size is small, and therefore the confidence intervals are large. The results of neutralising antibody responses against the beta variant are also of interest and the results indicate a broader immune response after a third dose compared to the second dose, but as already stated the sample size is small and confidence intervals wide. This data needs verification in a larger sample.

Figure 1. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralizing Titers (NT50) – Phase 1 Booster – InitialBNT162b2 (30 µg) –



LLOQ (lower limit of quantitation) = 20

Dose 3 Booster All-Available Immunogenicity Population

Table 8. Summary of Geometric Mean Fold Rises From Before Vaccination to Each Subsequent Time Point – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population

		Initial Age Group			
		18-55 Years of Age		65-85 Years of Age	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	2/Day 7	11	49.7 (24.7, 100.1)	12	53.8 (29.2, 99.3)
	2/1 Month	11	38.7 (24.7, 60.4)	12	26.1 (15.2, 45.0)
	3/Day 7	11	21.2 (11.2, 40.3)	12	32.0 (19.5, 52.6)
	3/1 Month	11	25.7 (12.4, 53.3)	12	49.4 (29.2, 83.3)
SARS-CoV-2 plaque reduction neutralization assay – strain B.1.351 - NT50 (titer)	2/Day 7	11	15.0 (8.1, 28.0)	12	14.7 (6.0, 36.0)
	2/1 Month	11	10.3 (5.7, 18.7)	12	7.6 (3.0, 18.8)
	3/Day 7	11	30.0 (17.3, 52.0)	12	44.0 (24.6, 78.7)
	3/1 Month	11	38.7 (19.8, 75.5)	12	78.3 (40.7, 150.6)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NT50 = 50%neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: GMFR for after booster dose is based on pre-booster dose visit. For all other visits GMFR is based on pre-dose 1 visit.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for the specified assay both beforevaccination and at the given dose/sampling time point.

c. GMFRs and the corresponding 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.

Reference strain and delta strain comparison

Geometric Mean Titers (GMTs)

Neutralizing GMTs against recombinant virus with the Delta variant spike on a wild-typegenetic background showed a similar pattern of higher, broader neutralizing titers after Dose 3 as compared to after Dose 2 (Figure 2, Table 9).

GMTs against the wild-type (reference) USA-WA1/2020 strain substantially increased afterDose 3 compared to GMTs obtained after Dose 2. GMTs at 1 month after Dose 3 were 1748.5 (95% CI: 1030.7, 2966.2) for younger participants, and 1595.9 (95% CI: 810.9, 3140.6) for older participants, which were approximately 5-fold and 8-fold, respectively, those of the GMTs observed at 1 month after Dose 2 (Figure 2, Table 9).

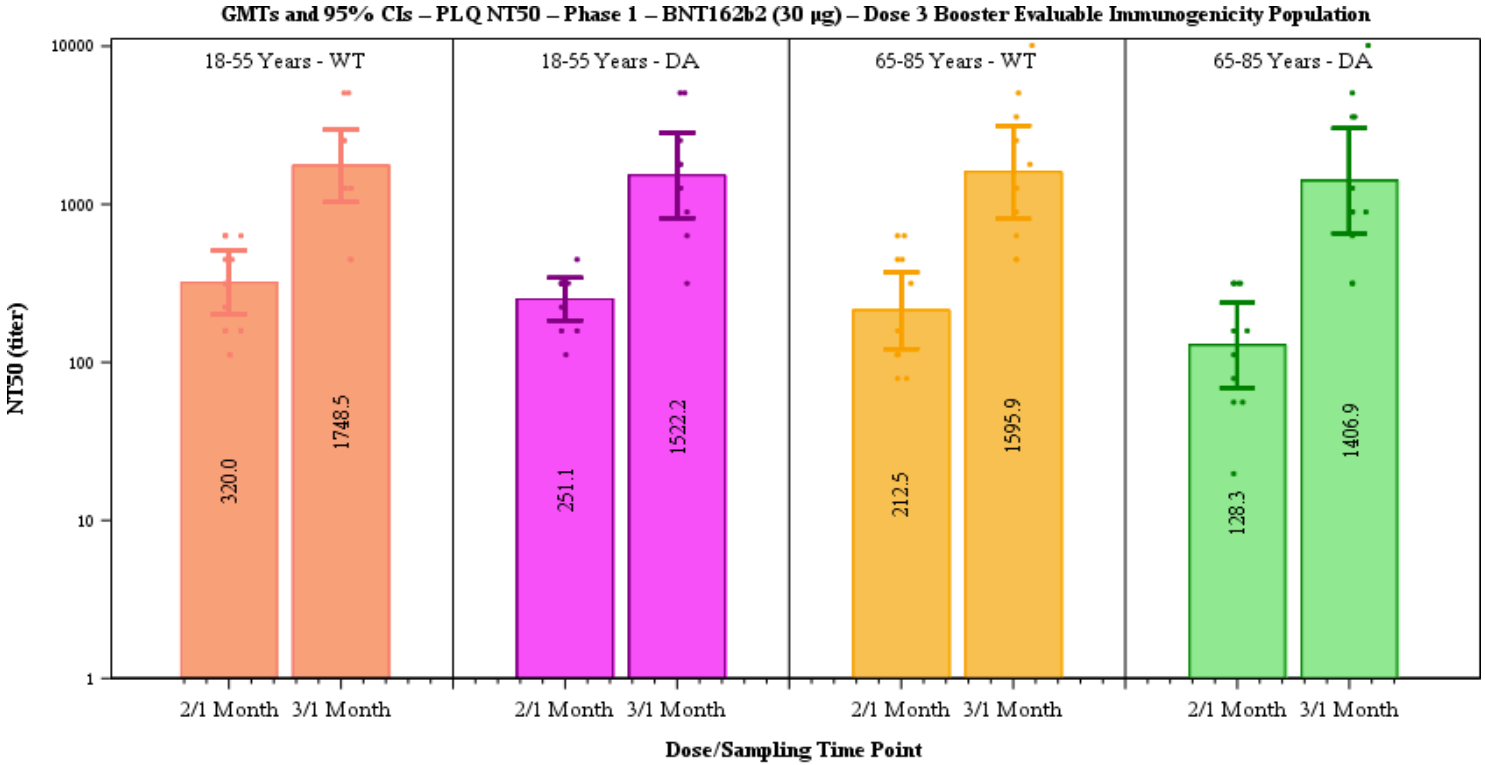
A third dose of BNT162b2 administered 7 to 9 months after the original two-dose series alsoincreased the neutralizing titers against the B.1.617.2 (Delta) variant strain. (Figure 2, Table 9).

Geometric Mean Ratios (GMRs)

At 1 month after Dose 2, the GMR of neutralizing titers for younger adults against theB.1.617.2 (Delta) variant strain to neutralizing titers against the wild-type strain were 0.78 (95% CI: 0.62, 0.99); at 1 month after Dose 3, the GMR increased to 0.87 (95% CI: 0.71, 1.07). Similarly, in older adults at 1 month after Dose 2, the GMR of neutralizing titers againstthe B.1.617.2 (Delta) variant strain to neutralizing titers against the wild-type strain were 0.60 (95% CI: 0.43, 0.84); at 1 month after Dose 3 increased to 0.88 (95% CI: 0.68, 1.14) (Table 10).

GMRs for neutralizing titers against the wild-type (reference) strain and against the B.1.617.2 (Delta) variant strain at 1 month after Dose 3 compared to neutralizing titers against the wild-type strain at 1 month after Dose 2 ranged from 4.76 to 7.51, showing substantial increases after the booster (Dose 3) of BNT162b2 compared to Dose 2 (Table 11)

CHMP's comment: The results for the delta variant are overall in agreement with the results for the beta variant and the reference strain. In Table 11, GMR, note that neutralising antibodies against the delta variant after dose 3 are compared to the neutralising antibody titres to the reference strain after dose 2 and 3. It is not clear if it is appropriate to directly compare titres against different virus strains. As above, the sample size is small and confidence intervals wide, precluding conclusions. The presented results are considered supportive of a booster response, but further analyses are required, i.e. a larger sample size and comparisons relating to the same variant at different time points.



Abbreviations: DA = delta; GMT = geometric mean titer; NT50 = 50% neutralizing titer;
PLQ NT50 = SARS-CoV-2 plaque reduction neutralization assay – NT50 (titer); WT = wild type.
Note: Dots represent individual antibody levels.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (22:39)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster_Delta/adva_f002_sars_50_b2_eval_da_p1

Figure 2 - Geometric Mean Titers and 95% CIs for SARS-CoV-2 Plaque Reduction Neutralization Assay – NT50 – Phase 1Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

Table 9. Summary of Geometric Mean Titers – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Initial Age Group: 18-55 Years of Age n[b]	18-55 Years of Age GMT[c] (95% CI[c])	Initial Age Group: 65-85 Years of n[b]	65-85 Years of GMT[c] (95% CI[c])
SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	2/1 Month	10	320.0 (200.5, 510.7)	11	212.5 (121.5, 371.6)
	3/1 Month	10	1748.5 (1030.7, 2966.2)	11	1595.9 (810.9, 3140.6)
SARS-CoV-2 plaque reduction neutralization assay – strain B.1.617.2 (delta) - NT50 (titer)	2/1 Month	10	251.1 (184.1, 342.4)	11	128.3 (69.1, 238.2)
	3/1 Month	10	1522.2 (817.9, 2833.0)	11	1406.9 (654.1, 3025.8)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for the specified assays at the given dose/sampling time point.

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Table 10. Summary of Geometric Mean Ratios – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

Assay	Dose/Sampling Time Point[a]	Initial Age Group			
		18-55 Years of Age		65-85 Years of	
		n[b]	GMR[c] (95% CI[c]) CI[c])	n[b]	GMR[c] (95%
SARS-CoV-2 plaque reduction neutralization assay – strain B.1.617.2 (delta) - NT50 (titer) to reference strain - NT50 (titer)	2/1 Month	10	0.78 (0.62, 0.99)	11	0.60 (0.43, 0.84)
	3/1 Month	10	0.87 (0.71, 1.07)	11	0.88 (0.68, 1.14)

Abbreviations: GMR = geometric mean ratio; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus2.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for both the specified assays at the given dose/sampling time point.

c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean differences in the logarithms of the assays and the corresponding CIs(based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Table 11. Summary of Geometric Mean Ratios – Comparison of 1 Month After Dose 3 to 1 Month After Dose 2 – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population

Assay		Initial Age Group						
		18-55 Years of Age			65-85 Years of Age			
		1 Month After Dose 2 (BNT162b2)	1 Month After Dose 3	1 Month After Dose 3/1 Month After Dose 2	1 Month After Dose 2 (BNT162b2)	1 Month After Dose 3	1 Month After Dose 3/1 Month After Dose 2	
Assay at 1 Month After Dose 2	Assay at 1 Month After Dose 3	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (95% CI[c])	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (95% CI[c])
SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	10	320.0 (200.5, 510.7)	1748.5 (1030.7, 2966.2)	5.46 (3.00, 9.97)	11	212.5 (121.5, 371.6)	1595.9 (810.9, 3140.6)	7.51 (4.62, 12.22)
SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	SARS-CoV-2 plaque reduction neutralization assay – strain B.1.617.2 (delta) - NT50 (titer)	10	320.0 (200.5, 510.7)	1522.2 (817.9, 2833.0)	4.76 (2.53, 8.95)	11	212.5 (121.5, 371.6)	1406.9 (654.1, 3025.8)	6.62 (3.57, 12.30)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. n = Number of subjects with valid and determinate assay results for the specified assays at both time points under given age group.

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean differences in the logarithms of the assays and the corresponding CIs (based on the Student t distribution).

3.3. Discussion

Immune Response to Booster (Dose 3) of BNT162b2 30 µg

The presented interim results for a third dose of BNT162b2 given at approximately 6 months after dose 2, show that higher neutralising titres are obtained after the third dose compared to the second dose. No justification on why the timepoint was chosen to give 3rd dose, was provided with the initial submission package, but was clarified in the responses to the LoQ. The neutralising titres had declined before the third dose was given compared to 1 month after dose 2, as can be expected, but were still clearly elevated compared to baseline levels. As there is no serological correlate of protection, the relevance of the waning titres is currently unknown. It is clear that immunological memory is elicited by the initial doses, and that a booster response can be obtained. The role of a third dose for long-term protection is not known at this stage.

The presented data were obtained in younger adults, 18-55 years of age, and only very limited data from the phase 1 part of study C4591001 (n=12) in subjects 65-85 years of age. It can be anticipated that elderly subjects would need of a booster dose within a shorter interval compared to younger adults, due to immune senescence with increasing age. It is noted that subjects over 65 years had elevated neutralising titres before the third dose compared to baseline. The MAH was asked to present any plans to further study the effect of a third dose in elderly subjects and clarified that study C4591031 will provide safety and efficacy data for a third dose in elderly (over 55 years) individuals.

There are no data on a third dose in subjects younger than 18 years of age, and therefore the posology section mentioning the use of a third dose should be limited to subjects 18 years of age and older. The MAH was asked present any plans to further study the effect of a third dose in adolescents and clarified that study C4591031 will provide safety and efficacy data for a third dose in younger (i.e. below 18 years of age) individuals. Also, further studies are being planned to evaluate the safety and immunogenicity of a booster dose in participants 12-15 years of age and participants <12 years.

Preliminary results on neutralising antibody titres to the beta and delta variants were presented from a small group of subjects from the phase 1 part of the study. The small sample size limits the conclusions that can be drawn and are considered supportive of increased titers following a third dose compared to a second dose, and possibly also a broader antibody repertoire, although this would need to be confirmed in a larger sample.

As the efficacy evaluation is based entirely on immunogenicity data, it is crucial that the neutralization assay, which was used to measure vaccine induced antibodies, is fully validated. In the initial submission package, only the brief qualification report from December 2020 was available, and no validation reports were found in the dossier although the MAH stated in the Clinical Overview that the method is fully validated. Therefore, the MAH was requested to submit the assay validation report and the neutralisation assays for the variant strains. The issue is solved as the MAH submitted neutralization assay validation report dated at 09.02.2021 in their responses to the RSI.

It seems difficult to conclude on an optimal vaccination schedule to ensure long-term protection against several variants of SARS-CoV2. There are no data on duration of protection available, and there is no comparison of two doses given at least 3 weeks apart compared to three doses with the third dose given around 6 months after the second dose. In addition, there are no data on other time points for the third dose. Thus, the benefit of a third dose is a potential added duration of immunity together with a potential broadening of the antibody repertoire to cover new variants.

The current data are of course obtained in a clinical trial setting, while the dose interval between dose 1 and 2 can be considerably longer in a practical use. In fact, several countries have recommended

longer dose intervals during at least in initial phases of vaccination campaigns. The effect of a longer dose interval between dose 1 and 2 and the effect on a third dose is currently unknown. It is possible that a longer interval between dose 1 and 2 result in increased responses to dose 2, and thereby also opening for an even longer interval to dose 3.

The MAH stated that further studies of BNT162b2 booster and boosting with vaccine candidates that usethe same mRNA technology but encode spike glycoproteins from variants of concern, such as B.1.351 and B.1.617.2, are ongoing or planned, respectively, including a study with a larger number of participants and randomization of participants to booster or placebo. The results of these studies are awaited when available. In addition, data on giving an additional dose of Comirnaty to subjects who have received one or two doses of other covid-19 vaccines previously would also be of value.

In conclusion, the benefit of a third dose given at approximately 6 months after the second dose can be summarised as potentially resulting in a longer lasting protection and broadened antibody repertoire.

4. Clinical Safety aspects

The primary safety objective regarding the third dose was:

- To describe the safety and tolerability profile of BNT162b2 given as a third dose to BNT162b2 experienced participants by using interim data for BNT162b2 given as a third dose to BNT162b2 experienced participants only are reported in this CSR.

The assessment of boostability was conducted in a subset of Phase 3 participants aged 18-55 years of age at selected sites in the US who received a third dose of BNT162b2 at 30 µg at least 6 months after their second dose.

4.1. Methods – analysis of data submitted

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff are blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

Inclusion criteria for the boostability and protection-against-VOCs subset:

- Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.
- Newly enrolled participants enrolled to receive 2 doses of BNT162b2$_{SA}$; male or female participants between the ages of 18 and 55 years, inclusive, at enrolment.
- Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

Eligible individuals were those who continued to meet C4591001 inclusion and exclusion criteria and met criteria specific to boostability assessments, had completed both Dose 1 and Dose 2 of BNT162b2 30µg, and consented to be rerandomized to receive 30 µg of either BNT162b2 orBNT162b2SAas a third dose.

Table 12. Investigation Product Lot Numbers – Interim – Booster (Dose 3)

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number[a] (Pfizer)
BNT162b2 (30 µg)	BioNTech	EE8493Y	PA2087473/P220395-0073L
		EJ0553Z	PA2085061/P220395-0070L
		ER9449Z	PA2096794/P220395-0079L
Diluent: 0.9% sodium chloride solution for injection	Pfizer	DK1589	N/A
		DK2074	N/A

Abbreviation: N/A = not applicable.
Note: C4591001 End of Study Information and Quality Control (QC) Record for Study Drug Appendix (Section D) dated 11 Aug 2021 was used to create this table.
a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
Protocol C4591001 Investigational Product Lot Numbers Table – Interim – Booster (Dose 3), Final, Version 1.1, 19 Aug 2021.

E-diary

Participants in the subset of BNT162b2-experienced participants evaluated for BNT162b2 30 µg boostability were asked to monitor and record **local reactions, systemic events**, and **antipyretic medication** use in the reactogenicity e-diary for 7 days following each administration of the study intervention.

AEs and SAEs

Participants in the BNT162b2-experienced subset evaluated for BNT162b2 30 µg boostability, AEs were collected from the time the participant provided informed consent (for participation in the subset) through and including Visit 303 (1-month follow-up visit after Dose 3) for those receiving 1 additional dose and Visit 305 (1 month follow-up visit after Dose 4) for those who received 2 additional doses. For both schedules, this equated to collection for up to 1 month after the last dose. SAEs were collected from the time the participant provided informed consent (for participation in the subset) through and including Visit 306 (5 or 6 months after the last dose, depending upon group). Acute reactions (immediate AEs) were collected within the first 30 minutes after administration of the study intervention.

AESI

While AESIs were not prespecified in the protocol, Pfizer utilizes a safety review as part of the signal detection processes that highlights specified TMEs of clinical interest. TMEs are specific AE terms reviewed on an ongoing basis by routine safety data review procedures throughout the clinical study. Although not prespecified in the protocol, TMEs are maintained in a separate list as part of the Safety Surveillance Review Plan for the vaccine program. By definition, TMEs are considered to be AESIs specific for a product or program's protocol(s). They are based on review of known pharmacology, toxicology findings, possible class effects, published literature, and potential signals arising from safety data assessments. The list of TMEs is customized for each development program and is dynamic. For this study, the list of TMEs includes events of interest because of their association with COVID-19 and terms of interest for vaccines in general. Terms are chosen from the MedDRA dictionary and may include PTs, high level term, high level group terms, or standardized MedDRA queries (SMQs; all evaluated as broad and narrow).

CHMP´s Comment:

In total 312 subjects aged 18-55 years from the part of the Phase 3 study executed in US have been included in a subset that received a third dose of BNT162b2 at 30 µg ≥5 months after their second dose. The participants used an E-diary to record all local reactions, systemic events and antipyretic

medications for 7 days after the third dose was administered. Adverse events were recorded up to one month after the third dose and SAEs were collected up to 5-6 months after the last dose.

It is endorsed that subjects already included in the phase 3 study were used to evaluate the safety and efficacy of a third dose, however, number of subjects followed up for AEs and SAEs is very small, which clearly limits the possibility to detect any seldom occurring events.

4.2. Results

Disposition

Table 13. Disposition of All Randomized Subjects – Phase 3 – BNT162b2 – Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Randomized)
	BNT162b2 (30 µg) (N[a]=312) n[b] (%)
Rerandomized	312 (100.0)
Did not receive booster vaccination	0
Vaccinated	312 (100.0)
Booster vaccination	312 (100.0)
Completed booster vaccination period[c]	309 (99.0)
Discontinued from booster vaccination period but continued in the study	0
Discontinued after booster vaccination	0
Withdrawn from the study	4 (1.3)
Withdrawn after booster vaccination	4 (1.3)
Reason for withdrawal	
Lost to follow-up	2 (0.6)
Withdrawal by subject	2 (0.6)

a. N = number of randomized subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Booster vaccination period: from booster vaccination to the 1-month follow-up visit after the booster vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adds Table Generation: 16AUG2021 (23:05)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adds_s002_p3_g1_rand

Table 14. Vaccine as Administered – Phase 3 – BNT162b2 – Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

Vaccine (as Administered)	Vaccine Group (as Randomized)
	BNT162b2 (30 µg) (N[a]=312) n[b] (%)
Received booster vaccination	312 (100.0)
Did not receive booster vaccination	0
Booster vaccination	
BNT162b2 (30 µg)	306 (98.1)
$BNT162b2_{SA}$ (30 µg)	6 (1.9)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 16AUG2021 (23:05)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/advx_s002_adm_p3_g1_rand

Of the 312 participants who received a third dose, 6 participants who were rerandomized to receive a third dose of BNT162b2 30 µg were instead administered $BNT162b2_{SA}$ by error. These participants are not included in the Dose 3 booster evaluable immunogenicity population analyses or safety analyses of the BNT162b2 booster group, to avoid confounding the BNT162b2 booster results interpretation

Table 15. Vaccine Administration Timing – Phase 3 – BNT162b2 – Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Randomized)
	BNT162b2 (30 µg) (N[a]=312) n[b] (%)
Rerandomized	312 (100.0)
Did not receive booster vaccination	0
Booster vaccination[c]	312 (100.0)
<5 Months	1 (0.3)
≥5-<6 Months	28 (9.0)
≥6-<7 Months	155 (49.7)
≥7 Months	128 (41.0)
Mean (SD)	6.8 (0.56)
Median	6.8
Min, max	(4.8, 8.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Months calculated since Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 16AUG2021 (23:05)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/advx_s002_time_p3_g1_rand

Table 16. Follow-up Time After Booster Dose – Phase 3 – BNT162b2 – Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=306) n[b] (%)
Total exposure from booster vaccination to cutoff date	
<2 Months	1 (0.3)
≥2-<4 Months	305 (99.7)
Mean (SD)	2.7 (0.15)
Median	2.6
Min, max	(1.1, 2.8)
Total exposure from Dose 2 to cutoff date	
≥6-<8 Months	4 (1.3)
≥8-<10 Months	248 (81.0)
≥10 Months	54 (17.6)
Mean (SD)	9.4 (0.57)
Median	9.5
Min, max	(7.5, 10.8)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 16AUG2021 (23:05)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adsl_fu_d2_p3_g1

Demographics and Baseline Characteristics Phase 3 Booster (Dose 3)

Table 17. Demographic Characteristics– Phase 3 – BNT162b2 – Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) (N[a]=306) n[b] (%)
Sex	
Male	140 (45.8)
Female	166 (54.2)
Race	
White	249 (81.4)
Black or African American	28 (9.2)
American Indian or Alaska Native	2 (0.7)
Asian	16 (5.2)
Native Hawaiian or other Pacific Islander	1 (0.3)
Multiracial	4 (1.3)
Not reported	6 (2.0)
Ethnicity	
Hispanic/Latino	85 (27.8)
Non-Hispanic/non-Latino	219 (71.6)
Not reported	2 (0.7)
Country	
USA	306 (100.0)
Age at booster vaccination (years)	
Mean (SD)	41.3 (9.44)
Median	42.0
Min, max	(19, 55)
Body mass index (BMI)	
Underweight (<18.5 kg/m^2)	1 (0.3)
Normal weight (≥18.5-24.9 kg/m^2)	82 (26.8)
Overweight (≥25.0-29.9 kg/m^2)	101 (33.0)
Obese (≥30.0 kg/m^2)	122 (39.9)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 16AUG2021 (23:05)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adsl_s005_demo_p3_g1_1d30_saf

CHMP´s comment:

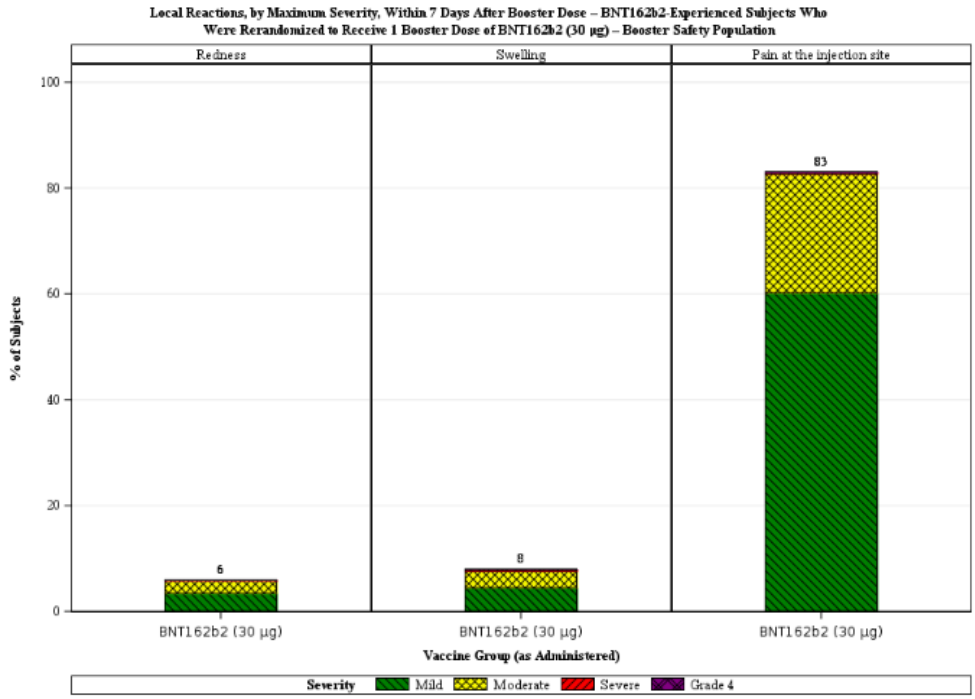
Among the 312 initially included subjects that received a third dose, six of them received a dose of BNT162b2$_{SA}$ by error instead of BNT162b2 30 µg, therefore the safety population constitutes of 306 subjects. Most of the subjects (91%) received their third dose ≥6 months after Dose 2. Almost all subjects (n=305) had a follow up of 2-4 months after the third dose. Subjects were roughly similarly distributed between gender. The majority of the subjects were white (81%), and it is noted that many of them (72%) had a BMI suggesting overweight or obesity.

4.2.1. Safety evaluations

4.2.1.1. Local Reactions

Pain at the injection site was most frequently reported local reaction after booster (Dose3) administration, reported by 83.0% of participants out of N=289 with e-diary data, as illustrated in the figure below:

Figure 3. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2 Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 ug) – Booster Safety Population



Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adfacevd Table Generation: 18AUG2021 (22:21)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: /nda2_unblinded/C4591001_G1/adce_f001_lr_max_p3_g1

C

14.21. Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)		
		BNT162b2 (30 µg)	
Local Reaction	N[a]	n[b] (%)	(95% CI[c])
Redness[d]			
Any	289	17 (5.9)	(3.5, 9.3)
Mild	289	10 (3.5)	(1.7, 6.3)
Moderate	289	7 (2.4)	(1.0, 4.9)
Severe	289	0	(0.0, 1.3)
Grade 4	289	0	(0.0, 1.3)
Swelling[d]			
Any	289	23 (8.0)	(5.1, 11.7)
Mild	289	13 (4.5)	(2.4, 7.6)
Moderate	289	9 (3.1)	(1.4, 5.8)
Severe	289	1 (0.3)	(0.0, 1.9)
Grade 4	289	0	(0.0, 1.3)
Pain at the injection site[e]			
Any	289	240 (83.0)	(78.2, 87.2)
Mild	289	174 (60.2)	(54.3, 65.9)
Moderate	289	65 (22.5)	(17.8, 27.7)
Severe	289	1 (0.3)	(0.0, 1.9)
Grade 4	289	0	(0.0, 1.3)
Any local reaction[f]	289	240 (83.0)	(78.2, 87.2)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the booster dose.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
a. N = number of subjects reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Mild: >2.0 to 5.0 cm; moderate: >5.0 to 10.0 cm; severe: >10.0 cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
e. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.
f. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adfacevd Table Generation: 16AUG2021 (21:12)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adce_s010_lr_p3_g1_saf

The median onset for all local reactions after Dose 3 was Day 1 to Day 2 (Day 1 was the day of vaccination) and were resolved within a median duration of 1 to 2 days. Overall, the pattern of local reactions reported in this Phase 3 booster group after Dose 3 was generally similar to that observed in prior analyses of Phase 2/3 participants after Dose 2 (refer to C4591001 6-Month Update Interim CSR, dated 29 April 2021).

CHMP´s comment:

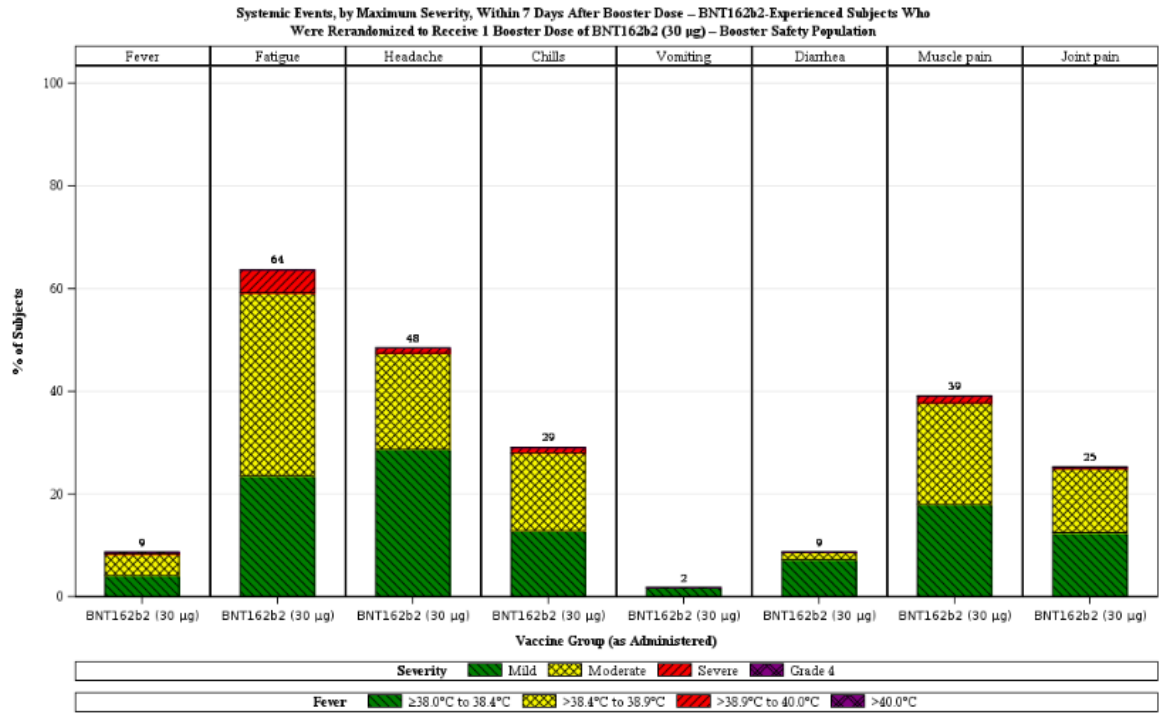
Information regarding reactogenicity was based on data from the E-diary as reported back of 289 subjects.

Overall, the local reactogenicity profile shown after the third dose appears to be in line with the reactogenicity profile observed after the second dose of the vaccine, with pain at the injection site as the most commonly reported reaction. Severe reactions occurred very rarely.

4.2.1.2. Systemic Events

Systemic events reported after booster (Dose 3) administration out of N=289 participants with e-diary data, of any severity and in decreasing order of frequency, were as illustrated in the figure below:

Figure 4. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 ug) – Booster Safety Population



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adfacevd Table Generation: 18AUG2021 (22:21)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adce_f001_se_max_p3_g1

14.24. Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)		
		BNT162b2 (30 µg)	
Systemic Event	N[a]	n[b] (%)	(95% CI[c])
Fever			
≥38.0°C	289	25 (8.7)	(5.7, 12.5)
≥38.0°C to 38.4°C	289	12 (4.2)	(2.2, 7.1)
>38.4°C to 38.9°C	289	12 (4.2)	(2.2, 7.1)
>38.9°C to 40.0°C	289	1 (0.3)	(0.0, 1.9)
>40.0°C	289	0	(0.0, 1.3)
Fatigue[d]			
Any	289	184 (63.7)	(57.8, 69.2)
Mild	289	68 (23.5)	(18.8, 28.9)
Moderate	289	103 (35.6)	(30.1, 41.5)
Severe	289	13 (4.5)	(2.4, 7.6)
Grade 4	289	0	(0.0, 1.3)
Headache[d]			
Any	289	140 (48.4)	(42.5, 54.4)
Mild	289	83 (28.7)	(23.6, 34.3)
Moderate	289	54 (18.7)	(14.4, 23.7)
Severe	289	3 (1.0)	(0.2, 3.0)
Grade 4	289	0	(0.0, 1.3)
Chills[d]			
Any	289	84 (29.1)	(23.9, 34.7)
Mild	289	37 (12.8)	(9.2, 17.2)
Moderate	289	44 (15.2)	(11.3, 19.9)
Severe	289	3 (1.0)	(0.2, 3.0)
Grade 4	289	0	(0.0, 1.3)
Vomiting[e]			
Any	289	5 (1.7)	(0.6, 4.0)
Mild	289	5 (1.7)	(0.6, 4.0)
Moderate	289	0	(0.0, 1.3)
Severe	289	0	(0.0, 1.3)
Grade 4	289	0	(0.0, 1.3)
Diarrhea[f]			
Any	289	25 (8.7)	(5.7, 12.5)
Mild	289	21 (7.3)	(4.6, 10.9)
Moderate	289	4 (1.4)	(0.4, 3.5)
Severe	289	0	(0.0, 1.3)
Grade 4	289	0	(0.0, 1.3)

New or worsened muscle pain[d]			
Any	289	113 (39.1)	(33.4, 45.0)
Mild	289	52 (18.0)	(13.7, 22.9)
Moderate	289	57 (19.7)	(15.3, 24.8)
Severe	289	4 (1.4)	(0.4, 3.5)
Grade 4	289	0	(0.0, 1.3)
New or worsened joint pain[d]			
Any	289	73 (25.3)	(20.4, 30.7)
Mild	289	36 (12.5)	(8.9, 16.8)
Moderate	289	36 (12.5)	(8.9, 16.8)
Severe	289	1 (0.3)	(0.0, 1.9)
Grade 4	289	0	(0.0, 1.3)
Any systemic event[g]	289	223 (77.2)	(71.9, 81.9)
Use of antipyretic or pain medication[h]	289	135 (46.7)	(40.8, 52.6)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the booster dose.
Note: Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of subjects reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
g. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
h. Severity was not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adfacevd Table Generation: 16AUG2021 (21:12)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adce_s020_se_p3_g1_saf

After Dose 3, most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently, in <2 % of participants for all systemic events except for severe fatigue (4.5%). Severe muscle pain was reported in 4 participants (1.4%), and severe headache or severe chills were reported in 3 participants each (1.0%). Severe joint pain was reported in 1 participant (0.3%). A fever of >38.9 °C to 40 °C was reported in 1 participant (0.3%); this individual had oral temperatures of 39.1 °Con Day 2 and 38.6 °Con Day 3, that returned to normal on Days 4 through 7. No Grade 4 systemic events were reported after Dose 3.

The median onset for all systemic events after Dose 3 was Day 2 to Day 4 (Day 1 was the day of vaccination), and systemic events resolved within a median duration of 1 to 2 days. Overall, the pattern of systemic events reported in this Phase 3 booster group after Dose 3 was generally similar to that observed in prior analyses of Phase 2/3 participants after Dose2 (refer to C4591001 6-Month Update Interim CSR, dated 29 April 2021).

CHMP´s comment:

The most common systemic event was fatigue (64%) of which 40% were moderate or severe. Almost half of the study population (n=135) used antipyretic or pain medication after the third dose. One subject reported an increased temperature >39ºC.

The limited number of subjects showed a similar pattern of systemic events and use of antipyretic or pain medication as what was observed after the second dose in the Phase 2/3 analysis of study C4591001.

4.2.1.3. Adverse Events

Safety evaluation of AEs is from Dose 3 to 1 month after Dose 3, and from Dose 3 to the data cut-off date (17 June 2021) which accounts for at least 2 months post-Dose 3 has been provided by the MAH.

Table 18. Number (%) of Subjects Reporting at Least 1 Adverse Event from Booster Dose to 1 Month After Booster Dose – Phase 3 – BNT162b2 – Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)
Adverse Event	BNT162b2 (30 µg) (N[a]=306) n[b] (%)
Any adverse event	44 (14.4)
Related[c]	24 (7.8)
Severe	1 (0.3)
Life-threatening	0
Any serious adverse event	0
Related[c]	0
Severe	0
Life-threatening	0
Any nonserious adverse event	44 (14.4)
Related[c]	24 (7.8)
Severe	1 (0.3)
Life-threatening	0
Any adverse event leading to withdrawal	0
Related[c]	0
Severe	0
Life-threatening	0
Death	0

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any adverse event," n = number of subjects reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adae Table Generation: 16AUG2021 (23:11)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adae_s091_all_pd2_p3_g1_1d30

From Dose 3 to the data cut-off date (17 June2021), in addition to the participants who reported AEs up to 1month after Dose 3 one additional participant reported AE, for a cumulative number of participants with any AE of 45/306 (14.7%). As of the cut-off date, events considered by the investigator as related to study intervention remained the same as at 1 month after Dose 3, reported by 24/306 participants (7.8%). In addition to the participant with a severe AE of lymphadenopathy that was reported up to 1 month after Dose 3, as of the data cut-off date there was one additional participant who reported a severe AE; this event was considered an unrelated SAE (acute myocardial infarction). As of the data cut-off date, no events leading to withdrawal were reported and no study participants in this Phase 3 booster group died.

Adverse Events from Dose 3 to 1 Month after Dose 3

The most commonly reported AE was lymphadenopathy, in 16/306 participants (5.2%). AE frequencies in SOCs for such reactogenicity terms were:

- general disorders and administration site conditions: 2.6%
- musculoskeletal and connective tissue disorders: 2.3%
- nervous system disorders: 1.6%
- gastrointestinal disorders: 1.3%.

Table 19. Number (%) of Subjects Reporting at Least 1 Adverse Event from Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2 – Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=306)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])
Any event	44 (14.4)	(10.6, 18.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	16 (5.2)	(3.0, 8.4)
Lymphadenopathy	16 (5.2)	(3.0, 8.4)
EAR AND LABYRINTH DISORDERS	1 (0.3)	(0.0, 1.8)
Cerumen impaction	1 (0.3)	(0.0, 1.8)
Ear pain	1 (0.3)	(0.0, 1.8)
GASTROINTESTINAL DISORDERS	4 (1.3)	(0.4, 3.3)
Nausea	2 (0.7)	(0.1, 2.3)
Eructation	1 (0.3)	(0.0, 1.8)
Irritable bowel syndrome	1 (0.3)	(0.0, 1.8)
Salivary duct obstruction	1 (0.3)	(0.0, 1.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (2.6)	(1.1, 5.1)
Injection site pain	2 (0.7)	(0.1, 2.3)
Pain	2 (0.7)	(0.1, 2.3)
Chills	1 (0.3)	(0.0, 1.8)
Facial pain	1 (0.3)	(0.0, 1.8)
Fatigue	1 (0.3)	(0.0, 1.8)
Swelling	1 (0.3)	(0.0, 1.8)
Swelling face	1 (0.3)	(0.0, 1.8)
INFECTIONS AND INFESTATIONS	1 (0.3)	(0.0, 1.8)
Diverticulitis	1 (0.3)	(0.0, 1.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (1.3)	(0.4, 3.3)
Arthropod bite	1 (0.3)	(0.0, 1.8)
Contusion	1 (0.3)	(0.0, 1.8)
Procedural pain	1 (0.3)	(0.0, 1.8)
Skin laceration	1 (0.3)	(0.0, 1.8)
INVESTIGATIONS	3 (1.0)	(0.2, 2.8)
Vitamin D decreased	1 (0.3)	(0.0, 1.8)
Weight decreased	1 (0.3)	(0.0, 1.8)
White blood cell count decreased	1 (0.3)	(0.0, 1.8)
METABOLISM AND NUTRITION DISORDERS	2 (0.7)	(0.1, 2.3)
Decreased appetite	1 (0.3)	(0.0, 1.8)
Dyslipidaemia	1 (0.3)	(0.0, 1.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (2.3)	(0.9, 4.7)
Back pain	2 (0.7)	(0.1, 2.3)
Neck pain	2 (0.7)	(0.1, 2.3)
Exostosis	1 (0.3)	(0.0, 1.8)
Pain in extremity	1 (0.3)	(0.0, 1.8)
Plantar fasciitis	1 (0.3)	(0.0, 1.8)

NERVOUS SYSTEM DISORDERS	5 (1.6)	(0.5, 3.8)
Headache	2 (0.7)	(0.1, 2.3)
Dizziness	1 (0.3)	(0.0, 1.8)
Dysgeusia	1 (0.3)	(0.0, 1.8)
Migraine	1 (0.3)	(0.0, 1.8)
Syncope	1 (0.3)	(0.0, 1.8)
PSYCHIATRIC DISORDERS	2 (0.7)	(0.1, 2.3)
Anxiety	2 (0.7)	(0.1, 2.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1.0)	(0.2, 2.8)
Dermatitis contact	2 (0.7)	(0.1, 2.3)
Rash	1 (0.3)	(0.0, 1.8)

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adae Table Generation: 16AUG2021 (23:11)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adae_s130_1md1_p3_g1

CHMP's comment:

AEs presented belonged specifically to the SOCs blood and lymphatic system disorders (PT lymphadenopathy), general disorders and administration site conditions (local and systemic reactogenicity) and musculoskeletal disorders.

Related Adverse Events

From Dose 3 to 1 month after Dose 3, 24/306 participants (7.8%) had AEs assessed by the investigator as related to study intervention. The most common related events were lymphadenopathy cases, in 16/306 participants (5.2%). Most of the other related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 7/306 participants (2.3%).

All cases of ***lymphadenopathy*** had an onset within 1 to 4 days after BNT162b2 booster (Dose3) administration, and most were reported as recovered/resolved as of the data cut-off date, most within ≤5 days after onset. These cases predominantly occurred in female participants and located in axillary nodes. One participant who had lymphadenopathy after receiving Dose 3 had also previously experienced lymphadenopathy (with onset on the fourth day after Dose 2) during the blinded placebo-controlled period, as reported in the C4591001 6-Month Update Interim CSR. No participants in the booster safety population reported a past medical history of lymphadenopathy. All lymphadenopathy cases occurring after Dose 3 were Grade 1, with one exception: One case of lymphadenopathy was graded as severe and judged by the investigator as related to study intervention: left axillary lymphadenopathy was reported in a study participant 40-49 years of age with onset at 2 days post-Dose 3, lasting for 5 days, and reported as recovered/resolved. The investigator-judged severity was based on the participant reporting that the lymphadenopathy prevented use of the affected arm.

Overall, the incidence of lymphadenopathy in this Phase 3 booster group was higher than previously observed in Phase 2/3 AE analyses. Lymphadenopathy has been identified as a vaccine-related event and is more common after a booster (Dose 3) is administered reflecting a potent immune response.

One event of ***dysgeusia*** "with coffee" (verbatim reporting) was reported in a study participant 20-29 years of age with onset at 2 days after Dose 3, that was reported as recovered/resolved 72 days from onset. The event was Grade 1 in severity and considered by the investigator to be related to study intervention. This participant also reported nausea "caused by coffee" (verbatim reporting) at 2 days

after Dose 3 that was recovered/resolved by 7 days after onset. At 3 days after Dose 3, the study participant again reported nausea along with headache and injection site pain that were all reported as recovered/resolved 6 days after onset. All of these events were considered by the investigator as related to study intervention. This participant also had severe fatigue recorded as a systemic event in the e-diary on Day 3 after Dose 3.

CHMP's comment:

Cases evaluated as related comprised especially events lymphadenopathy (5.2%), which resolved mostly within 5 days after the third dose. One case was graded as severe.

One case of mild dysgeusia was evaluated as related to study drug and reversible (72 days after dose 3).

Immediate Adverse Events

No immediate events were reported within 30 minutes after booster (Dose 3) vaccination.

Severe or Life-Threatening Adverse Events

From Dose 3 to 1 month after Dose 3, one severe event (lymphadenopathy) was reported by 1 participant with an onset at 2 days post-Dose 3 and recovered/resolved 5 days from onset. No life-threatening (Grade 4) events were reported.

Adverse Events from Dose 3 to the Data Cut-off Date

From Dose 3 to the data cut-off date (17 June2021), which represents at least 2 months of post-Dose 3 follow-up, the cumulative number of participants with any AE included one additional AE beyond the 1-month post-Dose 3 period of follow-up.

The additional event was acute myocardial infarction, reported as an unrelated SAE of Grade 3 severity that was recovered/resolved with sequelae. The study participant 40-49 years of age with a BMI of 27.9 kg/m^3 received BNT162b2 30 µg Dose 1 on Day 0, Dose 2 on Day 21, and Dose 3 on Day 24. Sixty two (62) days after receiving Dose 3 the study participant presented to the emergency department with excruciating pain radiating from chest to the left jaw area; an electrocardiogram was unremarkable with no significant changes, troponin was elevated at 1.4 ng/mL (normal range not reported), a chest x-ray was normal except for mild hyperinflation, and a computerized tomography angiogram showed minimal atherosclerotic calcification and a calcified granuloma in the caudate lobe of the liver. The study participant was diagnosed as having acute myocardial infarction (non-ST elevated) and was hospitalized upon cardiac consultation. The event was reported as Grade 3 SAE considered by the investigator as not related to study intervention and was reported as recovered/resolved with sequelae within 1 day of onset. The study participant had visited the emergency department 3 to 4 months prior due the current hospitalisation. The study participant was discharged from the hospital for this episode 64 days after receiving Dose 3. The study participant was readmitted to the hospital one day later with dizziness, blurred vision, diaphoresis, chest pain, fatigue, and heartburn. The study participant reported that the "heart was racing," and the heart rate was noted to be 51 beats per minute. The troponin levels were elevated but declining (values not provided).

CHMP´s comment:

Overall, among the 306 subjects that received a third dose, 44 (14%) reported any adverse events up to one month after administration of the third dose. No events of death were reported. Twenty-four of the adverse events were considered related by the investigator, of which lymphadenopathy (n=16)

was most commonly reported. One of the events of left axillary lymphadenopathy was graded as severe and lasted for 5 days. It is noted that in this limited study population, the incidence of lymphadenopathy was higher after the third dose compared to what was observed after the second dose in the Phase 2/3 analysis of study C4591001 (5.2% vs 0.4%). The information regarding different frequencies of lymphadenopathy has been included in the SmPC by the MAH.

Dysgeusia "with coffee" was reported in one study participant, the event was considered related to the vaccine by the investigator and resolved 72 days after the third dose.

One overweight 40-49 year-old study participant, with a confounding medical history reported an acute myocardial infarction 3 months after the third dose. The event was not considered related to the study treatment by the investigator, which can be agreed.

It can be concluded that a low number of adverse events have been reported after the third dose. However, the sample size is very limited, and it is therefore not possible to draw conclusions regarding uncommon or rare adverse events.

4.2.2. Deaths, Serious Adverse Events, Safety-Related Participant Withdrawals, and Other Significant Adverse Events

Deaths

No deaths were reported in the Phase 3 BNT162b2 booster safety population as of the data cut-off date (17 June2021).

Serious Adverse Events

No SAEs were reported in the Phase 3 BNT162b2 booster safety population up to 1 month after Dose 3 and one SAE was reported from Dose 3 to the Data cut-off date. This event was reported in a 40-49-year-old study participant diagnosed with myocardial infarction, is described above in the section for Adverse Events.

Safety-Related Participant Withdrawals

No participants in the Phase 3 BNT162b2 booster safety population were withdrawn due to AEs from Dose 3 to the data cut-off date (17 June 2021).

Other Significant Adverse Events

AEs of specific clinical interest, such as those in the FDA and CDC list of AESIs for COVID-19, were reviewed up to the data cut-off date (17 June 2021) and are summarized below. No cases of anaphylaxis, hypersensitivity, Bell's palsy, appendicitis, or myocarditis/pericarditis were reported in the Phase 3 BNT162b2 booster group from Dose3 to the data cut-off date.

CHMP´s Comment:

No events of death were reported. One event of SAE (myocardial infarction), described in the section above, has been reported.

No cases of anaphylaxis, hypersensitivity, Bell's palsy, appendicitis, or myocarditis/pericarditis were reported. However, due to the very small number of included subjects, the possibility to draw firm conclusion regarding the risk of less common occurring AEs/SAE is limited.

4.2.3. Other Safety Assessments

Severe COVID-19 Illness

No AEs were reported that suggested any potential cases of severe COVID-19 among participants in the Phase 3 BNT162b2 booster group, from Dose 3 to the data cut-off date (17 June 2021).

Pregnancy

No pregnancies were reported in the Phase 3 BNT162b2 booster group from Dose 3 to the data cut-off date (17 June2021).

CHMP´s Comment:

No events of severe Covid-19 illness or pregnancies were reported among the subjects included in this third dose subset of the phase 3 study (C4591001).

4.3. Discussion

In total 312 subjects aged 18-55 years from the part of the Phase 3 study (C4591001) executed in US have been included in a subset that received a third dose of BNT162b2 at 30 µg ≥5 months after their second dose. Six individuals received a dose of BNT162b2SA by error instead of BNT162b2 30 µg, limiting the finally evaluated safety population to 306 subjects. Local reactions, systemic events and antipyretic medications were recorded in an E-diary for 7 days after administration of the third dose. Adverse events were recorded up to one month after the third dose and SAEs are collected up to 5-6 months after the last dose. 305 of the subjects had a follow up of 2-4 months after the third dose.

The distribution between gender was within similar range. A majority were overweighed or obese (72%).

The most reported local reaction was pain at the injection site (83%), of which the majority were mild to moderate. No subjects reported Grade 4 local reaction. The most commonly systemic event was fatigue (64%) of which 40% were moderate or severe. Almost half of the study population (n=135) used antipyretic or pain medication after the third dose. These results are in line with the reported data after the second dose in the Phase 2/3 analysis of study C4591001.

The MAH has further clarified, why a difference is observed between the number of included individuals (306) and the number of individuals that reported local reactions and systemic events (289).

Among the 306 subjects, 44 (14%) reported any adverse events up to one month after administration of the third dose. AEs presented belonged specifically to the SOCs blood and lymphatic system disorders (PT lymphadenopathy), general disorders and administration site conditions (local and systemic reactogenicity) and musculoskeletal disorders. No events of death were reported. The incidence of lymphadenopathy was higher after the third dose compared to what was observed after the second dose in the Phase 2/3 analysis of study C4591001 (5.2% vs 0.4%). The MAH has proposed an update of the SmPC regarding increased frequency of lymphadenopathy after the third dose, which is endorsed.

One event of dysgeusia "with coffee" was considered related by the physician and of mild and reversible (resolved after 72 days). One event of SAE (myocardial infarction) was considered not related to vaccination due to confounding risk factors in the medical history.

It is noted that many individuals have received a third dose in the frame of the vaccination campaign in Israel. The MAH has submitted the number and type of post-marketing events that it detected in its

safety database. Overall, no specific AE pattern is observed in the presented data that may raise a new safety concern.

It can be concluded that the reactogenicity profile of the third dose is in line with the data reported after administration of the second dose. However, the submitted data is limited in terms of the numbers of vaccinees included in the study and the duration of follow up does therefore not allow any firm conclusions regarding the pattern and incidence of uncommon or rare AEs/SAEs.

5. Changes to the Product Information

As a result of this variation, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated to introduce a booster dose (third dose) of Comirnaty for individuals 18 years of age and older. The Package Leaflet (PL) is updated accordingly (see Attachment 1).

6. Request for supplementary information

6.1. Other concerns

Clinical aspects

1. The MAH is asked to provide any available post-marketing safety information where subjects have received a 3rd booster dose.
2. Please provide information on plans for further clinical studies of a third dose in elderly (over 55 years) and younger (i.e. below 18 years of age).
3. Validation reports for the neutralization assay for both WT and variant virus strains are requested.
4. The lower age limit for a third dose should be changed to 18 years in the SmPC.
5. A justification for the required interval of 6 months between dose 2 and 3 should be provided. In case the timing of the third dose could be considered more flexible the SmPC needs to be updated accordingly.
6. The MAH is asked to clarify why not all 306 subjects were included in the reactogenicity evaluation (n=289).

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

7.1. Other concerns

Clinical aspects

Question 1

The MAH is asked to provide any available post-marketing safety information wheresubjects have received a 3rd booster dose.

Summary of the MAH's response

Pfizer is responsible for the management of post-authorization safety data on behalf of the MAH, BioNTech, according to the Pharmacovigilance Agreement. Data from BioNTech are included in the report when applicable.

Pfizer's safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, noninterventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

The limitations of post-marketing adverse drug event reporting should be considered wheninterpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.
- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of AE reports does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

A summary of post-authorization or post-approval AE reports received by the Company, from 19 December 2020 (earliest conditional approval date) through the DLP of 18 June 2021,1 following a third dose of Comirnaty, is presented below.

There was a total of 71 case reports involving patients who received 3 doses of Comirnaty (53 medically confirmed and 18 nonmedically confirmed), containing 174 events. Out of these 71, there were 12 seriouscases of which 1 reported a fatal outcome. All but one of these cases reported that the thirddose was administered in a context of medication error/off-label use/overdose.

Table 20 below represents the main characteristics of the 71 cases.

Table 20 – General overview of 71 cases

		Number of Cases	Percentage (%)
Sex			
	FEMALE	32	45.1%
	MALE	28	39.4%
	NO DATA	11	15.5%
Age Range			
Min = 17.0 Years	Less than or equal to 17 years	1	1.4%
Max = 96.0 Years	18 - 30 years	4	5.6%
	31 - 50 years	7	9.9%
Mean = 62.1	51 - 64 years	8	11.3%
Median = 67.0	65 - 74 years	12	16.9%
Standard Deviation = 21.41	Greater than or equal to 75 years	13	18.3%
n = 45	Unknown	26	36.6%
Case Outcome			
	FATAL	1	1.4%
	NOT RECOVERED/NOT RESOLVED	3	4.2%
	RECOVERED/RESOLVED	8	11.3%
	RECOVERING/RESOLVING	3	4.2%
	UNKNOWN	56	78.9%
Country Where Event Occured Top 10 Case Count			
	UNITED STATES	52	73.2%
	FRANCE	8	11.3%
	SPAIN	4	5.6%
	ITALY	2	2.8%
	BELGIUM	1	1.4%
	CANADA	1	1.4%
	ISRAEL	1	1.4%
	SLOVAKIA	1	1.4%
	UNITED KINGDOM	1	1.4%
Source			
	Spontaneous	71	100.0%
Case Seriousness			
	SERIOUS	12	16.9%
	NONSERIOUS	59	83.1%

The reported PTs by seriousness in the 71 cases are presented in Table 21. There are 50 cases coding to at-risk events without associated AEs; in the remaining 21 cases the most frequently co-reported AEs (>2 occurrences), regardless seriousness, were Pyrexia (8), Fatigue (4), Atrial fibrillation and Pain in extremity (3 each).

Table 21. Preferred Terms by Seriousness

Preferred Term(s)	Serious	Nonserious	Total
Off label use		20	20
Extra dose administered	1	18	19
Incorrect dose administered	3	16	19
Overdose		18	18
Pyrexia	5	3	8
Inappropriate schedule of product administration		7	7
Wrong product administered		6	6
Product use issue		5	5
Fatigue	2	2	4
Accidental overdose		3	3
Atrial fibrillation	3		3
Pain in extremity		3	3
Arthralgia	1	1	2
Dizziness	2		2
Malaise		2	2
Speech disorder		2	2
Tinnitus	2		2
Vertigo	2		2
Abdominal pain upper		1	1
Accidental exposure to product		1	1
Ageusia		1	1
Asthenia	1		1
Balance disorder		1	1
Blood blister		1	1
Blood urine present		1	1
Cardiac fibrillation	1		1
Crying		1	1
Death	1		1
Diarrhoea		1	1
Drooling		1	1
Expired product administered		1	1
Eye pain	1		1
Fall	1		1
Gait disturbance		1	1
Haematoma		1	1
Headache	1		1
Incorrect route of product administration		1	1
Influenza		1	1
Intentional overdose		1	1
Movement disorder		1	1
Muscular weakness	1		1
Myalgia	1		1
Nervousness		1	1
Neutropenia	1		1
Oral discomfort		1	1
Oral disorder		1	1
Oral mucosal blistering		1	1

Preferred Term(s)	Serious	Nonserious	Total
Pain		1	1
Peripheral swelling		1	1
Poor quality product administered		1	1
Product administered at inappropriate site		1	1
Product quality issue		1	1
Product temperature excursion issue		1	1
Pulmonary embolism	1		1
Somnolence	1		1
Splenic rupture	1		1
Thrombosis	1		1
Tongue blistering		1	1
Transplant rejection	1		1
Underdose		1	1
Urinary bladder haemorrhage	1		1
Urinary incontinence		1	1
Vaccination site pain		1	1
Weight decreased		1	1
Wrong technique in product usage process		1	1
All PTs	**36**	**138**	**174**

Italics terms refer to at-risk events.

In the 21 cases reporting AEs following the third dose administration, the interval betweenthe second and the third dose was not provided in 7 cases; in the remaining 14 cases, it was reported as:

- ≥ 0 ≤10 days: 3 cases
- ≥ 11 ≤ 25 days: 5 cases
- ≥ 26 days ≤ 112 days: 6 cases

Out of 71 cases reporting that the patients received the third dose, 8 referred to immunocompromised patients2; 3 of these cases coded to at-risk events, without associated AEs; of the remaining 5 cases, all from France reporting clinical AEs, 2 were nonserious and 3 were serious.

- A case with fatal outcome (PTs: Death, Transplant rejection, Speech disorder, Malaise, Overdose) was reported. The available information is provided below.

  A 50-57-year-old patient received 3 doses of BNT162b2 on Day 0, Day 32 and Day 65. Medical history included, chronic obstructive pulmonary disease, nonalcoholic liver cirrhosis and organ transplant in 2019. Concomitant medications were not reported but the patient had been hospitalized a few days prior for suspected acute organ rejection. The patient unexpectedly died 2 days after the third dose (cause of death was unknown). The report noted that there was no cardiovascular antecedent, no hypertension, no kidney damage and normal coronary angiography, and ultrasound (dates and details were not specified). The patient had no specific complaints immediately after the third dose; per the reporter the patient speech was a little inconsistent the day after the third dose and was not feeling well. The patient died 2 days after the third dose. It is unknown if an autopsy was done. Follow-up attempts were completed, and no further information is expected.

MAHs comment: There is not a clear cause of death in this patient, however the recent hospitalisation for treatment of suspected acute rejection suggests the possibility of underlying pathology with respect to his transplanted organs.

- The second serious case (PTs: Pulmonary embolism, Off label use, Overdose) referred to a 60-69-year-old patient with a medical history of dialysis since 2015, kidney transplant in 2016 for toxic tubulointerstitial nephropathy, arteriovenous fistula thrombosis in 2018, permanent closure of the paroxysmal atrial fibrillation in 2019, dysmorphic liver, splenic nodule; small intestine angiodysplasia, obesity and renal failure with baseline creatinine 130-150 at µM. The patient tolerated very well the first 2 doses of BNT162b2 (interval between the 2 doses unknown). Due to the fact that the patient was under immunosuppressive treatment (belatacept), the patient received a third dose (interval from the second dose unknown) of the vaccine. Four days later, the patient complained of dyspnoea (saturation =93%), and bilateral proximal pulmonary embolism was detected.

- The third serious case (PTs: Neutropenia, Incorrect dose administered) involved a 40-49-year-old patient with a medical history of lymphoma and chemotherapy, who received the third dose 85 days after the second dose. The patient experienced neutropenia with an unknown outcome, 6 days after the third dose. The patient had experienced neutropenia also after the first dose (latency and outcome unknown).

- In a nonserious case, a 60-69-year-old patient (PTs: Off label use, Inappropriate schedule of product administration, Vaccination site pain, Extra dose administered) with a medical history of ankylosing spondylitis, psoriasis, inflammatory bowel disease, autoimmune disease, received a third dose of BNT162b2. After the third dose the patient experienced a mild pain at injection site. The outcome of the event was unknown.

- In a nonserious case, a 40-49-year-old immunocompromised patient (PTs: Haematoma, Peripheral swelling, Pain in extremity, Extra dose administered) with a medical history of orphan disease and organ transplant, experienced haematoma of foot and of closed fistula, swelling of foot with severe pain, 2 days after the administration of the third dose of BNT162b2. The patient did not recover.

MAH's evaluation: The review of the cases included in the safety database did not reveal any safety issue.

Among the publications on the safety information about the administration of the third dose of COVID-19 vaccine, a couple of papers reported information about occurrence of COVID disease and local/ systemic reactions after the third dose.

Bar-On et al. published 1-month data (30 July 2021 through 31 August 2021) from the Israeli Ministry of Health database regarding 1,137,804 persons 60 years of age and older who had received the third dose at least 5 months after the first 2 doses. These data were also presented at the VRBPAC meeting on 17 September 2021. The rates of confirmed COVID-19 and severe illness were substantially lower among those who received a booster (third) dose of the Comirnaty vaccine.

Hause et al. reported data on third dose collected between 12 August and 19 September 2021, through v-safe (a voluntary, smartphone-based surveillance system) on more than 11,000 recipients receiving Comirnaty and more than 10,000 receiving Spikevax. For both mRNA vaccines, local reactions were reported more frequently after third than second dose and systemic reactions were reported less frequently after third than second dose, but no new safety issues were observed. The interpretations of the results of this paper are limited by the voluntary enrolment, the lack of information about the immunocompromised status of the recipients, the

fact that a causal relationship between a vaccine and clinically serious adverse events reported after vaccination cannot be established and insufficient data were available to determine patterns of adverse reactions after receipt of an additional dose from a manufacturer different from the primary series.

Assessment of the MAH's response

The MAH has given a summary of post-marketing AE reports, as collected in the MAH's safety database from 19 December 2020 (earliest conditional approval date) through the DLP of 18 June 2021, following a third dose of Comirnaty.

A total of 71 case reports involving patients who received 3 doses of Comirnaty containing 174 events have been received. 12 cases were serious with 1 reported fatal outcome. Almost all cases were labelled as medication error.

There are 50 cases coding to at-risk events without associated AEs; in the remaining 21 cases the most frequently co-reported AEs (>2 occurrences), regardless seriousness, were Pyrexia (8), Fatigue (4), Atrial fibrillation and Pain in extremity (3 each).

The MAH provided descriptions for 5 cases with AEs (3 serious (covering the fatal outcome), 2 non serious) observed in immunocompromised individuals.

Overall, no specific AE pattern is observed in the presented data that may raise a new safety concern.

Issue solved.

Question 2

Please provide information on plans for further clinical studies of a third dose in elderly (over 55 years) and younger (i.e. below 18 years of age).

Summary of the MAH's response

Pfizer/BioNTech are currently conducting study C4591031, a Phase 3 randomized, placebo-controlled, observer-blind study to evaluate the safety, tolerability, and efficacy of a booster dose of BNT162b2 30 µg. Participants ≥16 years of age who completed a 2-dose primary series of BNT162b2 30 µg at least 6 months prior to randomization were enrolled and randomized at a ratio of 1:1 to receive either BNT162b2 30 µg or placebo. Randomization was stratified by age, such that approximately 60% of participants enrolled were to be ≥16 to 55 years of age and approximately 40% of participants >55 years of age. Approximately 10,000 participants were randomized in the study.

The statistical framework employed for this study is periodic statistical summaries (planned to be every 2 months over the scheduled 6-month follow-up period) using statistical guidelines, rather than the traditional hypothesis testing framework with strong control of overall type 1 error across analysis time points. A descriptive statistical approach will be used with point estimates of VE (boosted relative to unboosted) and unadjusted (for multiplicity) 95% CIs at each time point (2, 4, and 6 months). In addition, to help put these results into perspective, an inferred VE for the unboosted group (relative to an unvaccinated population) will be calculated. Specifically, assuming that the newly boosted group has the same VE (relative to an unvaccinated population) over time that was observed in the parent C4591001 trial, an inferred unvaccinated (placebo) disease rate can be obtained at various time points and used to calculate the inferred VE (relative to

unvaccinated) for the unboosted group. The results of the first analysis at 2 months are due to be available in Q4 2021. Due toauthorizations and recommendations for receipt of a booster dose, from 24 September 2021 study participants may be unblinded and receive a booster dose if they had been randomized to placebo. Each participant will be included in the 2-month analysis until they are unblinded(if applicable).

Study C4591031 will therefore provide safety and efficacy data for a third dose in elderly(over 55 years) and younger (i.e. below 18 years of age) individuals.

Further studies are being planned to evaluate the safety and immunogenicity of a boosterdose in participants 12-15 years of age and participants <12 years. The first of these is currently planned to start in early 2022.

Assessment of the MAH's response

The MAHs answer is accepted.

Issue solved.

Question 3

Validation reports for the neutralization assay for both WT and variant virus strains are requested.

Summary of the MAH's response
For the C4591001 booster study analyses, only the WT mNeonGreen microneutralization assay is validated. The plaque reduction assays (PRNT) are exploratoryand do not have validation reports.

MAH submitted validation report dated 9.02.2021.

SYNOPSIS

This report describes the validation of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (SARS-CoV-2 mNG NT) used for the detection of serum antibodies capable of neutralizing SARS-CoV-2. The assay readout of 50% virus neutralization titer was validated per protocol VR-MVP-10074.

The SARS-CoV-2 mNG NT is a biofunctional assay that measures neutralizing antibodies against SARS-CoV-2. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to contain a mNeonGreen (mNG) reporter gene in open reading frame 7 of the viral genome that produces green fluorescence upon productive infection of cells. This reporter virus generates similar plaque morphologies and indistinguishable growth curves from wild-type virus.

This assay is described in the test method VR-TM-10298.

Briefly, serially diluted test serum samples are mixed with SARS-CoV-2 mNG virus in a 96-well plate to allow virus-specific antibodies to bind to the virus. This serum-virus mixture is then transferred onto a Vero cell monolayer and incubated overnight to allow for infection by non-neutralised virus. Productive viral infection is detected by enumerating green-fluorescent viral foci using a cell-imaging reader. The total number of cells per well is calculated by enumerating Vero cell nuclei stained blue with Hoechst 33342. An infection ratio is then calculated for each well, whereby the total number of virus infected (green) cells is divided by the total number of cells present (blue nuclei). A sample titer is defined as

the reciprocal serum dilution at which a specific percentage of the virus is neutralised, e.g., 50%, 80% or 90%

(termed "Titer Determining Value", TDV).

- Based on dilutional linearity and assay precision, the lower limit of quantitation (LLOQ) was determined to be a titer equal to 41 and the upper limit of quantitation (ULOQ) was determined to be a titer equal to 3,187. Samples with titers greater than the ULOQ may be pre-diluted before testing to yield titers within the validated assay range.
- Intermediate precision assessment demonstrated overall assay variability of 26.5% RSD.
- Serum samples are run in replicate in the SARS-CoV-2 mNG NT. Based on the assay performance, it was determined that the replicate titer ratio for a sample must be less than or equal to 2.55 (sample extravariability rule).

Assessment of the MAH's response
The MAH submitted the validation report, which evaluates the test performance using modified Wuhan strain of SARS-CoV-2 mNG virus. No validation report using Delta and Beta strains has been received. As the current application focuses on the Wuhan strain and only supportive information about Beta and Delta strains, the validation report is acceptable.

The results documented in this validation report for the SARS-CoV-2 mNG NT provide evidence that the assay is validated and suitable for its intended use in testing clinical, epidemiological, and non-clinical study samples. The assay demonstrated dilutional linearity and precision that met predefined acceptance criteria.

The MAH's answer is accepted.

Issue solved.

Question 4

The lower age limit for a third dose should be changed to 18 years in the SmPC.

Summary of the MAH's response
The MAH acknowledges and has accepted the relevant changes in the hereby submitted version of the Product Information.

Assessment of the MAH's response

The MAHs answer is accepted.

Issue solved.

Question 5

A justification for the required interval of 6 months between dose 2 and 3 should be provided. In case the timing of the third dose could be considered more flexible the SPC needs to be updated accordingly.

Summary of the MAH's response

In the study C4591001, a booster dose of 30 µg BNT162b2 was administered in the Phase 1 participants approximately 7 to 9 months after the primary series. The participants in the Phase 2/3 part of the study received a booster dose with a median interval of 6.8 months postDose 2, ranging from 4.8 to 8.0 months post Dose 2.

Per protocol prespecified criteria, the immunogenicity evaluable population received the booster dose within a defined window of <150 days (5 months) and >210 days (7 months) after Dose 2. The SARS-CoV-2 neutralising GMT ratio of 1 month after Dose 3 to 1 monthafter Dose 2 met the noninferiority criteria (3.29; 2-sided 97.5% CI: 2.76, 3.91).

The immunogenicity all-evaluable population included subjects who received the booster dose within a broader interval of 4.8 to 8 months post Dose 2 and resulted in a comparable GMR ratio that similarly met the noninferiority criteria (3.11; 2-sided 97.5% CI: 2.63, 3.68)(Supplemental Table 14.10 in Interim Report – BNT162b2 Booster).

Further, Phase 3 data from the C4591001 study showed that a booster (Dose 3) of BNT162b230 µg was safe and well-tolerated.

Based on the wider than 6 months (4.8 to 8 months post Dose 2) range of the interval between primary vaccination series and a third booster dose in the population studied in thePhase 1 and Phase 2/3 part of the study C4591001 and the safety and effectiveness data obtained in this study, a booster (third) dose of Comirnaty may be administered intramuscularly approximately 6 months after the second dose.

Assessment of the MAH's response

The MAHs answer is accepted.

Issue solved.

Question 6

The MAH is asked to clarify why not all 306 subjects were included in the reactogenicity evaluation (n=289).

Summary of the MAH's response

In the Phase 3 booster population, all participants were given an e-diary to record promptedlocal reactions and systemic events on Days 1 to 7 post-Dose 3, and the reactogenicity analysis is based on all participants who completed the e-diary. The CSR e-diary transmission table (Table 22) shows 17 participants (5.6%) did not have any transmitted e-diary data post-Dose 3. Hence the reactogenicity evaluation was only done on 289 subjects.

Table 22. E-Diary Transmission – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg)

	Vaccine Group (as Administered)
	BNT162b2 (30 µg) n[a] (%)

Received booster vaccination[b]	306
E-diary	
Not transmitted[c]	17 (5.6)
Transmitted[d]	
Day 1	243 (79.4)
Day 2	266 (86.9)
Day 3	264 (86.3)
Day 4	264 (86.3)
Day 5	258 (84.3)
Day 6	252 (82.4)
Day 7	258 (84.3)
All 7 days[e]	164 (53.6)

a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. If no data for temperature, local reactions, fever/pain medication, or systemic events are reported for the entire electronic diary (e-diary) collection period (Day 1 through Day 7), the e-diary is considered not transmitted.
d. If any data for temperature, local reactions, fever/pain medication, or systemic events are reported for the specified day or set of days (i.e., "all 7 days"), the e-diary is considered transmitted.
e. "All 7 days" includes Day 1 through Day 7 after vaccination. Day 1 is the day of vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (13:45) Source Data: adfacevd Table Generation: 16AUG2021(21:12)
(Data Cut-off Date: 17JUN2021, Database Snapshot Date: 27JUL2021) OutputFile: ./nda2_unblinded/C4591001_G1/adce_s200_trns_p3_g1_saf

Assessment of the MAH's response

The MAHs answer is accepted.

Issue solved.

Conclusion:

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

8. Overall conclusion and impact on the benefit-risk balance

The present submission is intended to support addition of safety and immunogenicity data after of a third dose of BNT162b2 into the SmPC (sections 4.2, 4.8 and 5.1).

The MAH has submitted immunogenicity and safety data of a third dose of BNT162b2 (30 µg) given to a subset of US participants in Phase 3 Study C4591001 who previously received two doses of BNT162b2 (30 µg). This group is comprised of approximately 300 adults 18 to 55 years of age who received a third dose of BNT162b2 (30 µg) approximately 6 (4.8 to 8.0) months after receipt of Dose

2, with safety and immune response evaluations at 1 month after Dose 3. Immune responses at 1 month after Dose 3 were compared to immune responses 1 month after Dose 2.

Supportive data were also provided from Phase 1 participants in study C4591001 (N=23) in the younger (18 to 55 years of age, N=11) and older (65 to 85 years of age, N=12) age groups who received three doses of BNT162b2 (30 µg), including neutralising serum titres against wild-type (reference) and VOC strains Beta and Delta of SARS-CoV-2.

Immunogenicity

The presented data on a third dose of BNT162b2 given at approximately 6 months after dose 2, show that higher neutralising titres are obtained after the third dose compared to the second dose. The neutralising titres had declined before the third dose was given compared to 1 month after dose 2, as can be expected, but were still quantifiable. It may be hypothesised that the third dose gives rise to a more lasting protection, and possibly also a broader coverage against viral variants with decreased vaccine susceptibility.

Available data mainly pertain to adults aged 18-55 years of age. Very limited data from the phase 1 part of study C4591001 (n=12) are available in subjects 65-85 years of age. It may be anticipated that elderly subjects would be in need of a booster dose within a shorter interval compared to younger adults, due to immune senescence with increasing age. There are no data on a third dose in subjects younger than 18 years of age.

Preliminary results on neutralising antibody titres to the beta and delta variants were presented from a small group of subjects from the phase 1 part of the study. These showed increased titres, compared to one month after two doses only.

As the efficacy evaluation is based entirely on immunogenicity data, it is crucial that the neutralisation assay, which was used to measure vaccine induced antibodies, is fully validated. In the initial submission data package, only the brief qualification report from December 2020 was available, and no validation reports were found in the dossier although the MAH stated in the Clinical Overview that the method is fully validated. In addition, the neutralisation assays for the variant strains also need validation. Therefore, the assay validation reports were requested. As a response, the MAH submitted the neutralisation assay validation report dated at 09.02.2021, which was found to be a relevant document, that provided sufficient evidence of the validity of the method using modified Wuhan strain of SARS-Cov-2. This validation report does not contain validation of Beta and Delta variants, however as information about VOCs in phase 1 study was submitted as supportive data, the issue is hereby not pursued further.

Presently, it does not seem possible to conclude on an optimal vaccination schedule to ensure long-term protection against several variants of SARS-CoV2; e.g., there is no RCT comparing protection with two doses given at least 3 weeks apart and that with three doses, when the third dose given around 6 months after the second dose.

The current data are obtained in a clinical trial setting where the interval between doses is relatively fixed. In real life, the interval between dose 1 and 2 can be considerably longer than the three weeks used in the pivotal trial for Comirnaty. In fact, several nations have recommended longer dose intervals, at least during the initial phases of the vaccination campaigns. The effect of a longer dose interval between dose 1 and 2 and the effect on a third dose is currently unknown. It is possible that a longer interval between dose 1 and 2 result in increased responses to dose 2, and thereby prolonging the time to waning of immunity.

In conclusion, the benefit of a third dose given at approximately 6 months after the second dose, and measured one month thereafter, is restoring neutralising titers to a higher level that what was seen one month after dose two, when this was given three weeks after dose one.

Safety

The safety data set constitutes of 306 subjects aged 18-55 years who received a third dose of BNT162b2 30 µg. Half of the subjects received their third dose 6-7 months after Dose 2 and almost all subjects (n=305) had a follow up of 2-4 months after the third dose. It was noted that a majority (72%) were overweight or obese.

Information regarding reactogenicity was based on data reported in the E-diary of 289 subjects. The most commonly reported local reaction pain at the injection site (83%), of which 60% were mild and 23% moderate. None of the subjects reported a grade 4 local reaction. The most commonly reported systemic event was fatigue (64%) of which 40% were moderate or severe. Almost half of the study population (n=135) used antipyretic or pain medication after the third dose. These results are in line with what was presented for the subjects aged 18-55 years that received Dose 2 in the phase 2/3 study (C4591001).

Among the 306 subjects, 44 (14%) reported any adverse events up to one month after administration of the third dose. AEs presented belonged specifically to the SOCs blood and lymphatic system disorders (PT lymphadenopathy), general disorders and administration site conditions (local and systemic reactogenicity) and musculoskeletal disorders. No deaths were reported. Lymphadenopathy (n=16) was the most commonly reported PT deemed related by the investigator. The incidence of lymphadenopathy was notably higher after the third dose compared to what was observed after the second dose in the Phase 2/3 study (5.2% vs 0.4%). The MAH has proposed an update of the SmPC regarding the increased frequency of lymphadenopathy after the third dose, which is supported.

While reasonably similar reactogenicity profile compared to after the second dose, has been shown in subjects 18-55 years, no data are available in younger or older subjects. The safety results from dose 1 and 2 in the large phase 3 study showed that reactogenicity and adverse events were of similar or lower frequency and severity in elderly subjects compared to younger adults. Based on previous experience and the safety results in younger adults, the safety conclusions can thus be extrapolated to older subjects. For subjects under 18 years of age higher reactogenicity is expected, also based on experience with two doses.

The safety dataset is sufficiently large to characterise the reactogenicity of the third dose. However, its size does not suffice to characterise the nature and frequency of less common adverse events. Particularly, it is not known whether the risk for vaccine induced myo/pericarditis, which has been observed to be higher after the second dose compared to the first, increases further after a third dose.

Available post marketing data have indicated that the risk of myo/pericarditis is higher in younger adults than older, and highest in young men. For adolescents, estimates of the size of this risk remain even more uncertain. The MAH proposed that a third dose be indicated for individuals down to the age of 16. However, the lack of characterisation of reactogenicity as well as considerable uncertainty regarding the myo/pericarditis risk in adolescents, presently preclude any indication for the third dose in non-adults.

Benefit-risk discussion

It has been shown that a third dose given approximately 6 months after the primary vaccination series more than restores neutralising titres in adults, compared to what was seen one month after

dose two. However, as there is no serological correlate of protection, the relevance of restoring the waning titres is currently unknown. Notably, epidemiological data on vaccine efficacy, and the potential waning of the protective effect of Comirnaty against symptomatic covid-19 over time have not been evaluated within this procedure. Therefore, while the immunogenicity and reactogenicity of a third dose have been sufficiently characterised, the proper timing and impact of a third dose across different populations has not been established. Furthermore, the risk of more rare and serious side effects such as myocarditis remains uncharacterised. Consequently, the decision whether, when and for whom to implement a third dose of Comirnaty needs to be taken based on emerging epidemiological vaccine efficacy or effectiveness data in different age groups and given differing comorbidities, including immunosuppression.

Based on the immunological data, it is considered that a third dose could translate into an increased duration of protection, and possibly increased protection against variants of concern, which provide a substantial potential benefit in some epidemiological situations. However, it should be noted that the available data does not allow to draw a definite conclusion.

In summary, the benefit-risk of a third dose of Comirnaty in adults, given at least six months after the second dose, has been shown to be positive, provided that its implementation is appropriately guided by vaccine efficacy data supporting its utility, taking into account remaining uncertainties about the safety profile. The benefit-risk balance of a third dose for adolescents has not been demonstrated to be positive, due to lack of data.

More information on the safety and immunogenicity of a third dose of Comirnaty will be collected in the remit of the ongoing C4591001 study and the MAH will submit an update to the RMP to reflect a third booster dose in the first half of November.

9. Recommendations

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

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to introduce a booster dose (third dose) of Comirnaty for individuals 18 years of age and older, based on interim safety and immunogenicity data from the interventional study C4591001, " A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals". The package leaflet is updated accordingly.

☒is recommended for approval.

Amendments to the marketing authorisation

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

10. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

SmPC new text

A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available vaccine effectiveness data, taking into account limited safety data. The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

The interchangeability of Comirnaty with other COVID-19 vaccines to complete the primary vaccination course or the booster dose (third dose) has not been established. Individuals who have received 1 dose of Comirnaty should receive a second dose of Comirnaty to complete the primary vaccination course and for any additional doses.

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age, who completed the original Comirnaty 2-dose course, received a booster dose (third dose) of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%). %). A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses. The risk of myocarditis after a third dose of Comirnaty has not yet been characterised.

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a $\geqslant$ 4-fold rise in NT50 from baseline (before primary series).

For more information, please refer to the Summary of Product Characteristics.