

Vaccines and Related Biological Products Advisory Committee Meeting

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.



BNT162b2

[COMIRNATY (COVID-19 Vaccine, mRNA)]

Evaluation of a Booster Dose (Third Dose)

**VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY
COMMITTEE BRIEFING DOCUMENT**

MEETING DATE: 17 September 2021

TABLE OF CONTENTS

LIST OF TABLES	3
LIST OF FIGURES	3
EXECUTIVE SUMMARY	6
1. BACKGROUND INFORMATION AND UNMET MEDICAL NEED	8
1.1. Real-World Effectiveness and Unmet Need Due to Breakthrough Infection	8
1.2. Study C4591001 – Post Hoc Analysis of Cases by Time Since Vaccination	13
2. OVERVIEW OF CLINICAL PHASE 1/2/3 STUDY C4591001.....	15
2.1. Overview of Methods for Evaluation of a Booster (Third) Dose – Study C4591001	15
2.2. Immunogenicity Analysis Methods and Results	16
2.2.1. Phase 1	16
2.2.1.1. Statistical Methods	16
2.2.1.2. Immunogenicity Results – Phase 1 Booster Substudy	16
2.2.1.3. Phase 1 Booster Immunogenicity - Discussion and Conclusions	21
2.2.2. Phase 3	22
2.2.2.1. Immunogenicity Endpoints and Analysis Methods – Phase 3 Booster Substudy	22
2.2.2.2. Immunogenicity Results – Phase 3 Booster Substudy	23
2.3. Safety and Tolerability Results	32
2.3.1. Phase 1	32
2.3.2. Phase 3	36
2.3.2.1. Reactogenicity	36
2.3.2.2. Adverse Events.....	40
2.3.3. Safety Conclusions	42
2.4. A Third Dose of BNT162b2 Administered in a Clinical Study To Describe Coadministration With Prevnar 20 (PCV20)	43
3. REAL-WORLD DATA ON THE PUBLIC HEALTH IMPACT OF BOOSTER DOSES OF MRNA VACCINES	44
4. PHARMACOVIGILANCE	45
5. BENEFIT/RISK ASSESSMENT	46
6. REFERENCES	50

LIST OF TABLES

Table 1.	Incidence of First COVID-19 Occurrence From 01JUL2021 to 31AUG2021 by Time Since Dose 2 of BNT162b2 – Phase 2/3 Subjects \geq 16 Years of Age and Older Who Received Two Doses of BNT162b2	14
Table 2.	SARS-CoV-2 Neutralization Assays Supporting Pfizer & BioNTech COVID-19 Vaccine Program.....	16
Table 3.	Vaccine Administration Timing – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 μ g).....	24
Table 4.	Demographic Characteristics – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 μ g) – Booster Safety Population	25
Table 5.	Immunogenicity Populations – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 μ g)	26
Table 6.	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 μ g) – Dose 3 Booster Evaluable Immunogenicity Population.....	28
Table 7.	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 μ g) – Dose 3 Booster Evaluable Immunogenicity Population.....	29
Table 8.	Frequency of Systemic Events Reported By E-Diary in Phase 3 of Study C4591001: Among Participants \geq 18-55 Years Of Age After Booster (Dose 3) and After Dose 2 Among Participants 16-55 Years Of Age	38
Table 9.	Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 μ g).....	40
Table 10.	Studies Contributing to Pharmacovigilance	45

LIST OF FIGURES

Figure 1.	Adjusted VE Against SARS-CoV-2 Infections: KPSC Members \geq 12 Years of Age.....	12
-----------	---	----

Figure 2. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralizing Titers (NT50) for Wild-Type (Reference Strain) and B.1.351 (Beta) Variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18-55 Years of Age and 65 to 85 Years of Age)19

Figure 3. Geometric Mean Titers and 95% CIs for SARS-CoV-2 Plaque Reduction Neutralization Assay (NT50) for Wild-Type (Reference Strain) and B.1.617.2 (Delta) Variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18-55 Years of Age and 65 to 85 Years of Age).....20

Figure 4. Geometric Mean Titers and 95% Confidence Intervals, Reference Strain SARS-CoV-2 Neutralization Assay – NT50 – 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 Population31

Figure 5. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population34

Figure 6. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population35

Figure 7. 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.....37

Figure 8. 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 Population39

ABBREVIATIONS

Abbreviations	Definition
ADR	adverse drug reaction
AE	adverse event
CDC	(US) Centers for Disease Control
CI	confidence interval
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
GMFR	geometric mean-fold rise
GMR	geometric mean ratio
GMT	geometric mean titers
HIV	human immunodeficiency virus
IM	intramuscular
KPSC	Kaiser Permanente Southern California
LLOQ	lower limit of quantitation
LNP	lipid nanoparticles
MI	myocardial infarction
MoH	Ministry of Health
mRNA	messenger ribonucleic acid
NATT	nucleic acid amplification test
PRNT	plaque-reduction neutralization tests
PVP	pharmacovigilance plan
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
sBLA	Supplemental Biologics License Application
SOC	system organ class
US	United States
VAED	vaccine associated enhanced disease
VE	vaccine effectiveness
VOC	variant of concern
WHO	World Health Organization

EXECUTIVE SUMMARY

The prophylactic, RNA-based SARS-CoV-2 vaccine BNT162b2 [COMIRNATY (COVID-19 Vaccine, mRNA)], developed by BioNTech SE and Pfizer Inc, received US FDA approval on 23 August 2021 for prevention of COVID-19 disease in individuals ≥ 16 years of age. BNT162b2 is currently administered intramuscularly (IM) as a series of two 30- μ g doses (0.3 mL each) three weeks apart. Pfizer-BioNTech COVID-19 Vaccine has been available for prevention of COVID-19 disease in individuals ≥ 16 years of age since December 2020 under an Emergency Use Authorization (EUA 27034; 11 December 2020). On 27 August 2021, Pfizer and BioNTech Manufacturing GmbH submitted a supplemental Biologics License Application (sBLA) to seek approval of a booster dose (third dose) of BNT162b2 in individuals ≥ 16 years of age administered intramuscularly approximately 6 months after Dose 2.

COVID-19 is a serious and potentially fatal or life-threatening human infection. The data from the pivotal Phase 3 clinical study (C4591001) showed that 2 doses of BNT162b2 vaccine administered 3 weeks apart confers protection against both symptomatic and severe COVID-19.¹ The duration of such protection is currently unknown; however, an analysis of efficacy up to six months after Dose 2 shows that the initial vaccine efficacy (96.2% from 7 days after Dose 2 to <2 months after Dose 2) slightly wanes over time, to 90.1% from >2 months to <4 months after Dose 2; and to 83.7 % for >4 months after Dose 2.

Recent data from Israel and the United States (as described in [Section 1.1](#) below) in the context of the delta Variant of Concern (VOC) predominant circulation suggest that vaccine protection against COVID-19 infection wanes approximately 6 to 8 months following the second dose. A retrospective cohort study conducted at Kaiser Permanente Southern California suggests that the observed erosion in vaccine effectiveness is likely primarily due to waning effectiveness rather than due to Delta escaping vaccine protection, given that (i) effectiveness against Delta infections was >90% early on; (ii) vaccine effectiveness decreases with increasing time since being fully vaccinated, irrespective of variant; and (iii) effectiveness against Delta variant hospitalizations remained high over the entire study period (see [Section 1.1](#)).

That vaccine effectiveness is waning over time is further supported by a recent FDA requested post-hoc analysis of breakthrough cases in the C4591001 pivotal Phase 3 clinical study. The analysis was performed for COVID-19 cases accrued during the current Delta variant surge (ie, during a defined time period beginning 01 July 2021 and through 31 August 2021). The analysis compared participants ≥ 16 years of age who were randomized to receive BNT162b2 and thus received the vaccine at the beginning of the study (original group) versus participants who were randomized to placebo and later crossed over to BNT162b2 (crossover group). The mean time from Dose 2 of BNT162b2 to 01 July 2021 was approximately 5 months for the crossover group and 10 months for the original group. Results showed that the incidence of breakthrough cases was higher among individuals who received Dose 2 at least 8 months before 01 July compared to those who received Dose 2 less than 4 months before 01 July 2021, confirming the waning of vaccine effectiveness over time.

The totality of the available data supports the public health need for a booster (third) dose of BNT162b2 at approximately 6 months after the second dose of BNT162b2 for individuals 16 years of age and older.

To address the need for a booster (third) dose against COVID-19, Pfizer/BioNTech designed a substudy of the C4591001 pivotal study that complies with the 25 May 2021 FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 and supports the use of a booster dose in individuals 16 years of age and older.² The FDA guidance specifies that the booster study must be adequately powered to demonstrate that the immune responses induced by the booster dose (serum neutralizing titers against SARS-CoV-2, as measured by seroresponse rates and GMTs), are statistically non-inferior compared to those elicited by the vaccine in the primary series. The FDA-specified success criteria include demonstration of a non-inferiority margin of -10% for seroresponse rates and a 1.5-fold margin for GMTs. Based on consultations with CBER, these criteria are also considered sufficient to support licensure of a booster following full approval of the primary series.

Phase 1 of this substudy, conducted in 23 participants 24 to 75 years of age, demonstrated that a booster (third) dose of 30 µg BNT162b2 administered approximately 6 months after the second vaccination of BNT162b2 had an acceptable safety profile and elicited robust immune responses against the wild-type (reference strain), as well as against the Beta and Delta variants of concern. Phase 3 of the substudy, conducted in 306 participants ≥18 to 55 years of age, showed that the vaccine was as well tolerated as the second primary dose and elicited immune responses (SARS-CoV-2 50% neutralizing titers) against the wild-type 1 month after the third dose that were non-inferior to the immune responses observed 1 month after the second primary dose, meeting the protocol pre-specified success criteria for GMTs and seroresponse rates. Furthermore, in accordance with FDA guidance, the safety and effectiveness of the booster dose demonstrated in individuals ≥18 to 55 years of age has been extrapolated to individuals 16 and 17 years of age and to individuals older than 55 years of age.

Finally, data from a recently initiated booster (third dose) vaccination program in the entire eligible population of Israel indicate that, in the face of waning immunity and in the period when the delta is the dominant variant, a booster dose of BNT162b2 has a reactogenicity profile similar to that seen after receipt of the second primary series dose and restores high levels of protection against COVID-19 outcomes (ie, back to approximately 95% protection).

Based on the above and consultation with CBER, Pfizer/BioNTech is requesting licensure of a booster dose (third dose) of BNT162b2 administered intramuscularly approximately 6 months after Dose 2 in individuals ≥16 years of age.

1. BACKGROUND INFORMATION AND UNMET MEDICAL NEED

BNT162b2 has been shown to be effective in preventing COVID-19 and to elicit an immune response that confers this protection. However, the duration of that protection is currently unknown. Data from clinical trials show that SARS-CoV-2 50% neutralizing titers to the reference strain decline from 1 month after vaccination to 6 months after vaccination; however, the significance of that decline is not clear, as no agreed correlate of protection against breakthrough infection has been identified.³ In the pivotal clinical trial, an analysis of efficacy up to six months after Dose 2 showed that the initial vaccine efficacy (96.2% from 7 days after Dose 2 to <2 months after Dose 2) slightly wanes over time, to 90.1% from >2 months to <4 months after Dose 2; and to 83.7% for >4 months after Dose 2.

Among vaccinated healthcare workers, decreased neutralizing antibody titers have been associated with vaccinees' breakthrough infections, along with increased viral load.⁴ As described below, emerging data suggest that vaccine protection may wane approximately 6 to 8 months following the second dose, and evidence is building to suggest that administration of booster doses of COVID-19 mRNA vaccines is potentially an urgent emerging public health issue.

Note that in the context of the pivotal clinical study (C4591001), in which healthy, immunocompetent adult participants received a third dose of BNT162b2 (30 µg), the terms "booster" and "Dose 3" are used interchangeably, as these participants had an observed robust immune response to the two-dose regimen, and hence the third dose is effectively a boost. In the broader context of the general population, Dose 3 may not necessarily be a booster dose if an individual is immunosuppressed or did not mount an effective immune response following their second dose.

1.1. Real-World Effectiveness and Unmet Need Due to Breakthrough Infection

As the Delta variant has become widely disseminated, rates of COVID-19 are again on the rise in the United States and across the world. Although unvaccinated individuals continue to account for most SARS-CoV-2 infections and severe cases of COVID-19, real-world data suggest that rates of breakthrough infections may be on the rise and that vaccine effectiveness (VE) may be waning over time.

A recent real-world, retrospective cohort study conducted in Israel showed a correlation between time since vaccination and the incidence of breakthrough infections among fully-vaccinated individuals ≥ 16 years of age.⁵ The analysis utilized healthcare records from an Israeli health maintenance organization that provides health coverage for 25% of the Israeli population and provides a representative sample. The study evaluated breakthrough infections between 01 June 2021 and 27 July 2021, a time when B.1.617.2 (Delta) was the predominant SARS-CoV-2 strain in circulation in Israel, using two logistic regression models that adjusted for demographic and clinical characteristics. The first model found the risk of breakthrough infection was 53% (95% CI: 40%, 68%) higher in early versus late vaccinees ($p < 0.001$), with similar results across age strata. Correspondingly, the second model demonstrated higher risk for breakthrough infection in individuals who were vaccinated in early months. For example, individuals vaccinated in January 2021 had a 2.26-fold increased risk (95% CI: 1.80, 3.01) for breakthrough infection versus those vaccinated in April 2021.

Thus, the risk for breakthrough infection was significantly higher for individuals who were vaccinated early compared to those vaccinated later, suggesting waning of vaccine effectiveness.

The State of Israel Ministry of Health (Israel MoH) conducted an observational study to assess the effectiveness of BNT162b2 against various SARS-CoV-2 outcomes from 20 June 2021 through 17 July 2021. The study population consisted of residents of Israel (ie, the Census population) ≥ 16 years of age. Using previously-published methodology,⁶ VE estimates were assessed against hierarchical laboratory-confirmed SARS-CoV-2 outcomes: all SARS-CoV-2 infections (symptomatic and asymptomatic), symptomatic COVID-19 cases, COVID-19-related hospitalizations, COVID-19-related severe or critical hospitalizations, and death. Individuals were defined as unvaccinated if they had never received a COVID-19 vaccine, and were defined as fully vaccinated if at least 7 days had passed since receiving the second dose of BNT162b2. Incidence rates were calculated for unvaccinated and fully vaccinated individuals for each SARS-CoV-2 outcome after excluding people with previous laboratory-confirmed SARS-CoV-2 infection. A negative binomial regression model was used to derive incidence rate ratios with 95% CIs for each outcome adjusted for age group, sex, and calendar week.

In this evaluation, among individuals ≥ 16 years of age, BNT162b2 effectiveness against SARS-CoV-2 infection was only 39.0% (95% CI: 9.0%, 59.0%) and against symptomatic COVID-19 was 40.5% (95% CI: 8.7%, 61.2%) between 20 June 2021 and 17 July 2021. This was considerably lower than published effectiveness estimates from an earlier time period. Specifically, between 24 January 2021 to 03 April 2021 VE against these same endpoints was $\geq 95\%$ for all age groups.⁶ Further, effectiveness estimates from 20 June 2021 to 17 July 2021 showed that VE against SARS-CoV-2 infections and against symptomatic COVID-19 progressively declined as time-from-vaccine increased, with individuals ≥ 16 years of age vaccinated in January having only 16% effectiveness against symptomatic COVID-19, which was not statistically significantly different from zero. By contrast, those who were fully vaccinated in April 2021 had 79% (60, 88) effectiveness against symptomatic COVID-19. These data were interpreted by MoH officials to suggest that waning of the vaccine, and not the introduction of the B.1.617.2 (Delta) variant (which became the predominant strain in July), was primarily driving declining VE estimates.⁷ In addition, a subsequent Israel MoH evaluation showed that between 20 June 2021 and 07 August 2021 effectiveness among adults ≥ 65 years of age against severe COVID-19 dropped to approximately $< 60\%$ for persons vaccinated early in the Israeli MoH vaccine campaign (ie, January or February) compared to those vaccinated in March, when effectiveness was $> 80\%$.⁸

Another, independent analysis of the Israel MoH data confirmed that individuals vaccinated earlier experienced higher rates of SARS-CoV-2 infections and severe COVID-19.⁹ The study used data on all PCR (polymerase-chain reaction) positive test results among Israeli residents who were fully vaccinated before June 2021 and compared rates of SARS-CoV-2 infection and severe COVID-19 between individuals who were vaccinated in different time periods using a Poisson regression analysis to adjust for age group and other possible confounding factors. The rates of both documented SARS-CoV-2 infections and severe COVID-19 increased as more time after the second vaccine dose elapsed. Individuals

≥60 years of age who received their second dose in March 2021 were 1.6 (95% CI: 1.3, 2.0) times more protected against infection and 1.7 (1.0, 2.7) times more protected against severe COVID-19 compared to those who received their second dose in January 2021. Similar results were found for all age groups. The authors concluded that the study confirmed a strong effect of waning immunity in all age groups after six months.

On 18 August 2021, the CDC published two studies^{10,11} showing similar reductions in effectiveness against SARS-CoV-2 infections. The first study¹⁰ estimated the effectiveness of two doses of BNT162b2 between 01 March 2021 and 01 August 2021 among nursing home residents using data from the National Healthcare Safety Network, which included >3800 nursing homes in the United States. A generalized linear mixed effects model with a zero-inflated Poisson distribution was used to estimate the ratio of infection rates among fully vaccinated and unvaccinated residents after adjusting for calendar week, facility-level cumulative SARS-CoV-2 infection rates, weekly local county incidence of SARS-CoV-2 infections, and the CDC Social Vulnerability Index score for each facility's county. BNT162b2 effectiveness against SARS-CoV-2 infection (measured ≥14 days after the second dose) fell from 74.7% (95% CI: 70.0%, 78.8%) between 01 March 2021 and 09 May 2021 to 53.1% (95% CI: 49.1%, 56.7%) between 21 June 2021 and 01 August 2021. The latter period corresponded to a time point at which many nursing home residents had been fully vaccinated roughly six months ago, and the B.1.617.2 (Delta) variant accounted for the vast majority of infections in the United States. A similar trend was observed for the Moderna COVID-19 mRNA-1273 vaccine. The authors determined that the effects of waning and the introduction of the B.1.617.2 (Delta) variant could not be fully teased apart, but that “an additional dose of COVID-19 vaccine might be considered for nursing home and long-term care facility residents to optimize a protective immune response.”

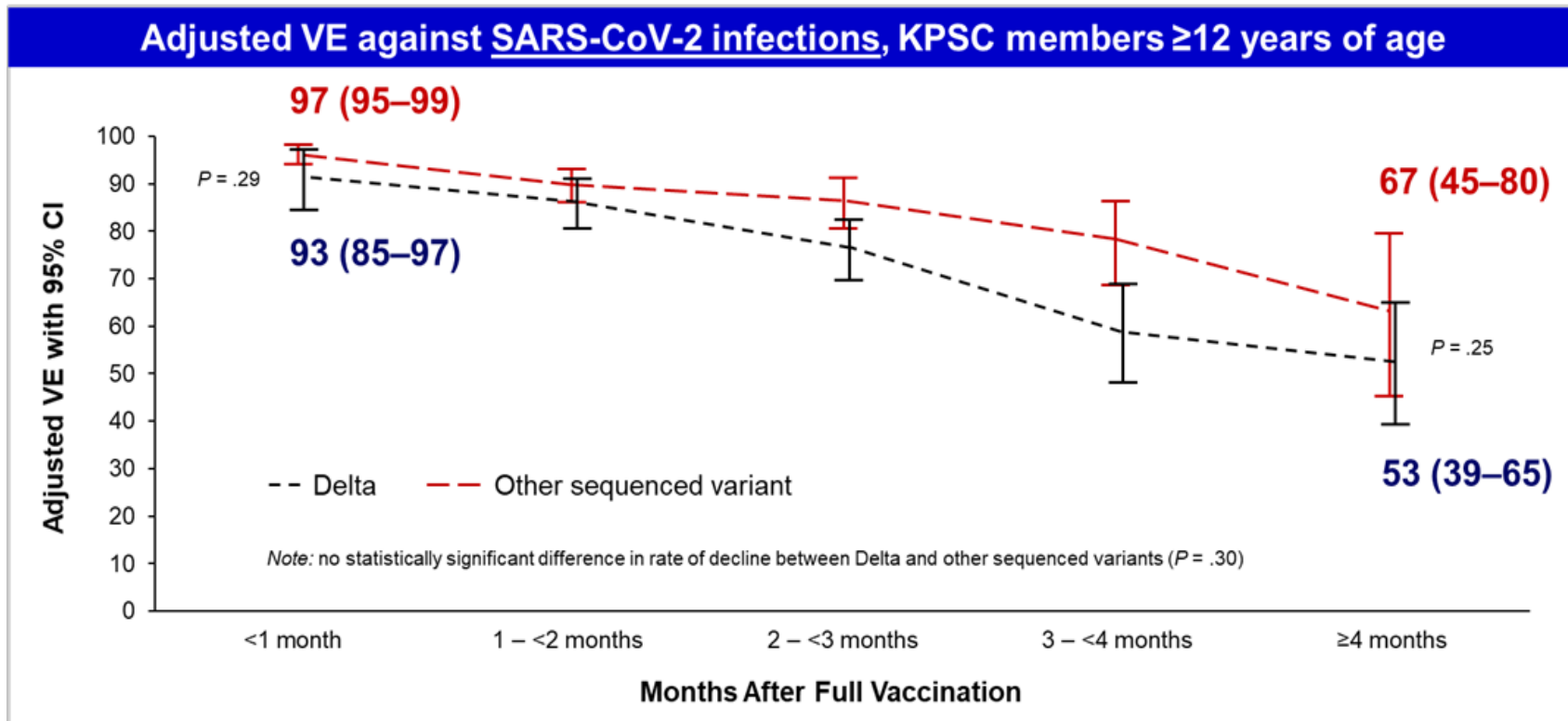
The second CDC study,¹¹ which was based on a retrospective analysis of four linked databases that included information about rates of reported SARS-CoV-2 infections and vaccination coverage for residents of the state of New York ≥18 years of age, showed similar findings. Among New York adult residents, VE against infection for fully vaccinated individuals declined from approximately 91% during May 2021 to <80% after 12 July 2021. The findings were not vaccine-specific; however, 91% of individuals in the study had received an mRNA vaccine. Again, the authors determined that the effects of waning and the introduction of the B.1.617.2 (Delta) variant could not be fully teased apart.

To better differentiate the impact of Delta from potential waning immunity on observed reductions in effectiveness against SARS-CoV-2 infections, another recent study conducted at the Kaiser Permanente Southern California (KPSC) integrated health system in the United States evaluated overall and variant-specific real-world effectiveness of BNT162b2 against SARS-CoV-2 infections and COVID-19-related hospitalizations by time since vaccination.¹² In the retrospective cohort study, electronic health records from KPSC between Dec 14, 2020 and Aug 8, 2021 were analyzed to assess BNT162b2 VE against SARS-CoV-2 infections and COVID-19-related hospitalization. Effectiveness calculations were based on hazard ratios from adjusted Cox models. In the KPSC study, effectiveness against infections declined from 88% (95% CI: 86, -89) during the first month after full vaccination to 47% (43–51) after ≥5 months. Among sequenced infections, VE estimates against both Delta and other (non-Delta) sequenced variants were high at <1 month after full vaccination (VE against Delta:

93% [85–97] vs other variants: 97% [95–99], $p=.289$). At ≥ 4 months after full vaccination, VE against Delta infections declined to 53% (39–65) and VE against other variants to 67% (45–80), $p=.254$. The difference in rate of decline in VE between Delta and other variants was not statistically significant ($p=.303$) (Figure 1). VE against hospitalization for Delta for all ages was high overall (93% [85–97]). Thus, the variant-specific analysis suggested that reductions in BNT162b2 effectiveness over time are likely primarily due to waning effectiveness rather than Delta escaping vaccine protection given that (i) effectiveness against Delta infections was $>90\%$ early on, (ii) reductions in effectiveness in infections by time since being fully vaccinated were observed irrespective of variant, and (iii) effectiveness against Delta hospitalizations remained high over the entire study period.

While the KPSC study and recent CDC studies have shown VE against hospitalization has remained high (mostly $>90\%$) despite introduction of the B.1.617.2 (Delta) variant and potential for waning,¹³ this should be carefully monitored, as data from Israel (as described above) suggest reduced effectiveness against severe disease could eventually follow observed reductions in effectiveness against SARS-CoV-2 infections.¹³ Moreover, reductions in effectiveness against infections could lead to increased transmission, especially in the face of the highly transmissible B.1.617.2 (Delta) variant. Policymakers will need to continue to monitor VE over time and may need to consider recommendations for booster doses to restore initial high levels of protection observed early in the vaccination program, and to help control heightened transmission of B.1.617.2 (Delta) as we enter the upcoming fall/winter viral respiratory season.

Figure 1. Adjusted VE Against SARS-CoV-2 Infections: KPSC Members ≥ 12 Years of Age



*Whole genome sequencing was performed on all PCR+ samples collected Mar 4, 2021 – Jul 21, 2021.

1.2. Study C4591001 – Post Hoc Analysis of Cases by Time Since Vaccination

Using data from the pivotal clinical efficacy study (C4591001), a post-hoc analysis was performed for COVID-19 cases accrued during the current delta variant surge (ie, during a defined time period beginning 01 July 2021 and through 31 August 2021). The analysis included data for participants ≥ 16 years of age and compared incidence rates for confirmed COVID-19 cases among “early” versus “late” vaccinees: ie, incidence was compared between participants who were randomized to receive BNT162b2 and thus received the vaccine at the beginning of the study (original group) versus participants who were randomized to placebo and later crossed over to BNT162b2 (crossover group). The mean time from Dose 2 of BNT162b2 to 01 July 2021 was approximately 5 months for the crossover group and 10 months for the original group.

Overall, the post-hoc analysis of COVID-19 cases accrued during the current delta variant surge showed a 26.3% (95% CI: 7.4%, 41.4%) relative vaccine efficacy for the group vaccinated later (crossover group) compared to the group vaccinated earlier (original group), with a difference in incidence rates of -18.6 per 1000 person-years of follow-up. The magnitude of risk reduction, 26% higher for the more recently vaccinated compared to individuals vaccinated earlier, highlights the public health importance of time since immunization.

The impact of elapsed time since completion of Dose 2 on vaccine efficacy in those vaccinated more distant to the Delta variant wave cannot be determined from this analysis due to the lack of a placebo control, but longer-term vaccine efficacy for the original group relative to placebo can be derived based on an assumption of vaccine efficacy for the more recently vaccinated crossover group and the observed relative vaccine efficacy. If protection against COVID-19 falls below 70% at a mean exposure of 5 months, efficacy would be expected to be below 60% at a mean exposure of 10 months.

In addition, an increase in incidence rates was observed with increasing time since Dose 2 (Table 1), and these rates were substantially higher than those observed in prior analyses before the Delta variant was circulating (15.6 per 1000 person-years, which includes the period between Dose 1 and Dose 2 for which the vaccine effect was not fully established vs. 43.5 cases per 1000 person-years from 01 July 2021 to 31 August 2021 for those with less than 4 months between Dose 2 and 01 July 2021). This seems likely due to the Delta variant surge.

These results suggest that a booster (third) dose of BNT162b2 given approximately 6 months after the second dose of BNT162b2 should be considered to restore high levels of protection against SARS-CoV-2 infection.

Table 1. Incidence of First COVID-19 Occurrence From 01JUL2021 to 31AUG2021 by Time Since Dose 2 of BNT162b2 – Phase 2/3 Subjects ≥16 Years of Age and Older Who Received Two Doses of BNT162b2

Efficacy Endpoint	Vaccine Group								
	Placebo Crossover to BNT162b2 (30 µg)			Original BNT162b2 (30 µg)			Total		
	n1 ^a	Surveillance Time ^b (n2 ^c)	IR (/1000 PY) ^d	n1 ^a	Surveillance Time ^b (n2 ^c)	IR (/1000 PY) ^d	n1 ^a	Surveillance Time ^b (n2 ^c)	IR (/1000 PY) ^d
First COVID-19 occurrence from 01JUL2021 to 31AUG2021	149	2.866 (17729)	51.989	163	2.310 (18713)	70.548	312	5.176 (36442)	60.273
Time from Dose 2 of BNT162b2 to 01JUL2021									
<4 Months	26	0.597 (3555)	43.522	0	0.000 (1)	0.000	26	0.598 (3556)	43.510
≥4-<6 Months	108	2.018 (12345)	53.515	0	0.001 (3)	0.000	108	2.019 (12348)	53.502
≥6-<8 Months	15	0.250 (1829)	59.883	4	0.076 (530)	52.330	19	0.327 (2359)	58.117
≥8-<10 Months	-	- (0)	-	73	0.951 (7690)	76.733	73	0.951 (7690)	76.733
≥10 Months	-	- (0)	-	86	1.282 (10489)	67.082	86	1.282 (10489)	67.082

Note: Subjects who received 2 planned doses of BNT162b2 and remained at risk till at least 01JUL2021 were included in the analysis. Subjects who were enrolled in Phase 3 boostability and VOC assessment of the study were excluded.

a. n1 = Number of subjects meeting the endpoint definition.

b. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 01JUL2021 to the earliest of confirmed case, death, withdrawn from the study, or 31AUG2021.

c. n2 = Number of subjects at risk for the endpoint.

d. Incidence rate (IR) is calculated as number of subjects meeting the endpoint definition/total surveillance time across all subjects at risk for the endpoint within the specific group.

PFIZER CONFIDENTIAL SDTM Creation: 09SEP2021 (07:36) Source Data: adc19efu Table Generation: 09SEP2021 (14:08)

(Data Cutoff Date: 31AUG2021, Database Snapshot Date: 08SEP2021) Output File: ./nda2_unblinded/C4591001_B_VRB/adc19ef_ve_covfup_bnt2d_vrb

2. OVERVIEW OF CLINICAL PHASE 1/2/3 STUDY C4591001

This section describes the evaluation of a third (booster) dose of BNT162b2 (30 µg) in clinical study C4591001. This is the ongoing, randomized, placebo-controlled study that demonstrated the efficacy, immunogenicity, and safety of a 2-dose series of 30 µg BNT162b2 for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. After the final efficacy analysis was completed, the protocol was amended to provide for evaluation of the safety and immunogenicity of a booster (third) dose of 30 µg BNT162b2 in both Phase 1 and Phase 2/3 participants.

2.1. Overview of Methods for Evaluation of a Booster (Third) Dose – Study C4591001

Phase 1 and Phase 3 participants who initially received BNT162b2 30 µg as a 2-dose series separated by 21 days were administered a booster (third) dose of BNT162b2 approximately 6 months after their second dose.

Information on reactogenicity events (local reactions and systemic events) and antipyretic/pain medication use was recorded by the study participants each evening for 7 days after Dose 3 using prompts from an electronic diary (e diary). Adverse events (AEs) were reported for 1 month after Dose 3 and serious adverse events (SAEs) are collected through 6 months after Dose 3.

Blood samples for determination of SARS-CoV-2 neutralizing titers had been collected from these participants before their first dose of BNT162b2 and at designated time points after Dose 1 and/or Dose 2; for the booster sub-study, blood samples were collected immediately before Dose 3 and at 7 days and 1 month after the booster dose.

Neutralizing titers were determined against wild-type (reference strain) in sera from both Phase 1 and Phase 3 participants; titers against the Beta and Delta variants were determined in sera from Phase 1 participants only.

The SARS-CoV-2 neutralization assays used for the analyses reported here are listed in Table 2. The plaque-reduction neutralization tests (PRNTs) used for Phase 1 data are exploratory assays and have been described previously^{14,15} The reference strain SARS-CoV-2 neutralization assay (mNeonGreen microneutralization assay, SARS-CoV-2 mNG NT) is a validated assay used for the Phase 3 data to assess non-inferiority of the immune response after Dose 3 compared to after Dose 2.

PRNT titers were determined against:

- **Wild-type** – The designated wild-type (recombinant USA-WA1/2020; clinical strain isolated in January 2020);
- **Beta variant** – B.1.351 (recombinant USA-WA1/2020 bearing the full spike gene from Beta variant);^{14,16}
- **Delta variant** – B.1.617.2 (recombinant USA-WA1/2020 with the full spike gene from the Delta variant).^{14,16}

All samples from each time point were analyzed for this evaluation (ie, previously tested samples¹⁶ were reanalyzed to ensure comparability of neutralization titers between the wild-type and Beta variant and between the wild-type and Delta variant) to ensure the most accurate assessments of persistence of neutralizing antibodies and response to Dose 3 (booster) of BNT162b2 30 µg.

Table 2. SARS-CoV-2 Neutralization Assays Supporting Pfizer & BioNTech COVID-19 Vaccine Program				
Assay Name	Assay Platform	Strain/Variant	Status	Study Phase
SARS-CoV-2 mNG NT (WT)	mNeonGreen Microneutralization	Wildtype (USA-WA1/2020)	Qualified	C4591001 Phase 1
SARS-CoV-2 mNG NT (WT)	mNeonGreen Microneutralization	Wildtype (USA-WA1/2020)	Validated	C4591001 Phase 2/3 C4591001 WT booster
SARS-CoV-2 PRNT (WT)	Plaque reduction assay	Wildtype (USA-WA1/2020)	Exploratory	C4591001 Phase 1
SARS-CoV-2 PRNT (Beta)	Plaque reduction assay	Beta (B.1.351)	Exploratory	C4591001 Phase 1
SARS-CoV-2 PRNT (Delta)	Plaque reduction assay	Delta (B.1.617.2)	Exploratory	C4591001 Phase 1

NT= neutralization test; PRNT = plaque reduction neutralization test; WT = wild-type.

2.2. Immunogenicity Analysis Methods and Results

2.2.1. Phase 1

2.2.1.1. Statistical Methods

In Phase 1, PRNT geometric mean titers (GMTs) were determined at each time point for wild-type and Beta strains and at a subset of the time points for Delta strains. PRNT GMTs were calculated by exponentiating the mean of logarithmically transformed assay results; the associated 2-sided 95% CIs were obtained from the natural log scale of the results using the Student's *t* distribution and exponentiating the confidence limits. Geometric mean ratios (GMRs) for comparing strains and/or timepoints were calculated as the mean of the difference of logarithmically transformed neutralizing titers for each participant (ie, variant strain minus wild-type strain, 1 month after Dose 3 minus 1 month after Dose 2) and exponentiating the mean. Associated 2-sided CIs for GMRs were obtained using the Student's *t* distribution for the mean difference on the logarithm scale and exponentiating the confidence limits

2.2.1.2. Immunogenicity Results – Phase 1 Booster Substudy

Study Population – Phase 1

A total of 23 Phase 1 participants who had received 2 doses of BNT162b2 (30 µg) received a booster dose of 30 µg BNT162b2 (N=11 in the younger 18 to 55 years of age group and

N=12 in the older 65 to 85 years of age group). Most participants received the booster (third) dose approximately 8 months after their second vaccination (mean = 8.3 months).

Approximately 87% of participants were white, and all were non-Hispanic/non-Latino; approximately 65% were female; and the median age was 39.0 years (range: 24 to 55 years) in the younger age group and was 69.0 years (range: 65 to 75 years) in the older age group.

Data presented here for Phase 1 booster dose participants are for the Dose 3 all-available immunogenicity population, which included all randomized participants who 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.

Neutralization Titers Against Wild-Type

SARS-CoV-2 neutralization GMTs against the wild-type USA-WA1/2020 strain substantially increased after Dose 3. GMTs at 1 month after Dose 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, the GMTs observed at 1 month after Dose 2 (Figure 2, left side). 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. From 7 days to 1 month after the second dose, neutralizing GMTs decreased – in younger adults (from 497.4 to 386.6) and in older adults (from 538.2 to 261.4). In contrast, from 7 days to 1 month after the third dose, neutralizing GMTs increased – in younger adults (from 1754.0 to 2119.0) and in older adults (from 1317.5 to 2031.9).

Neutralization Titers Against the Beta Variant

A third dose also increased the neutralizing titers against recombinant SARS-CoV-2 with the Beta variant spike. 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, the GMTs observed at 1 month after Dose 2 (Figure 2, right side). GMFRs 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. From 7 days to 1 month after the second dose, neutralizing GMTs decreased – in younger adults (from 150.2 to 102.9) and in older adults (from 146.7 to 75.5). In contrast, from 7 days to 1 month after the third dose, neutralizing GMTs increased – in younger adults (from 1201.8 to 1546.4) and in older adults (from 879.3 to 1566.8).

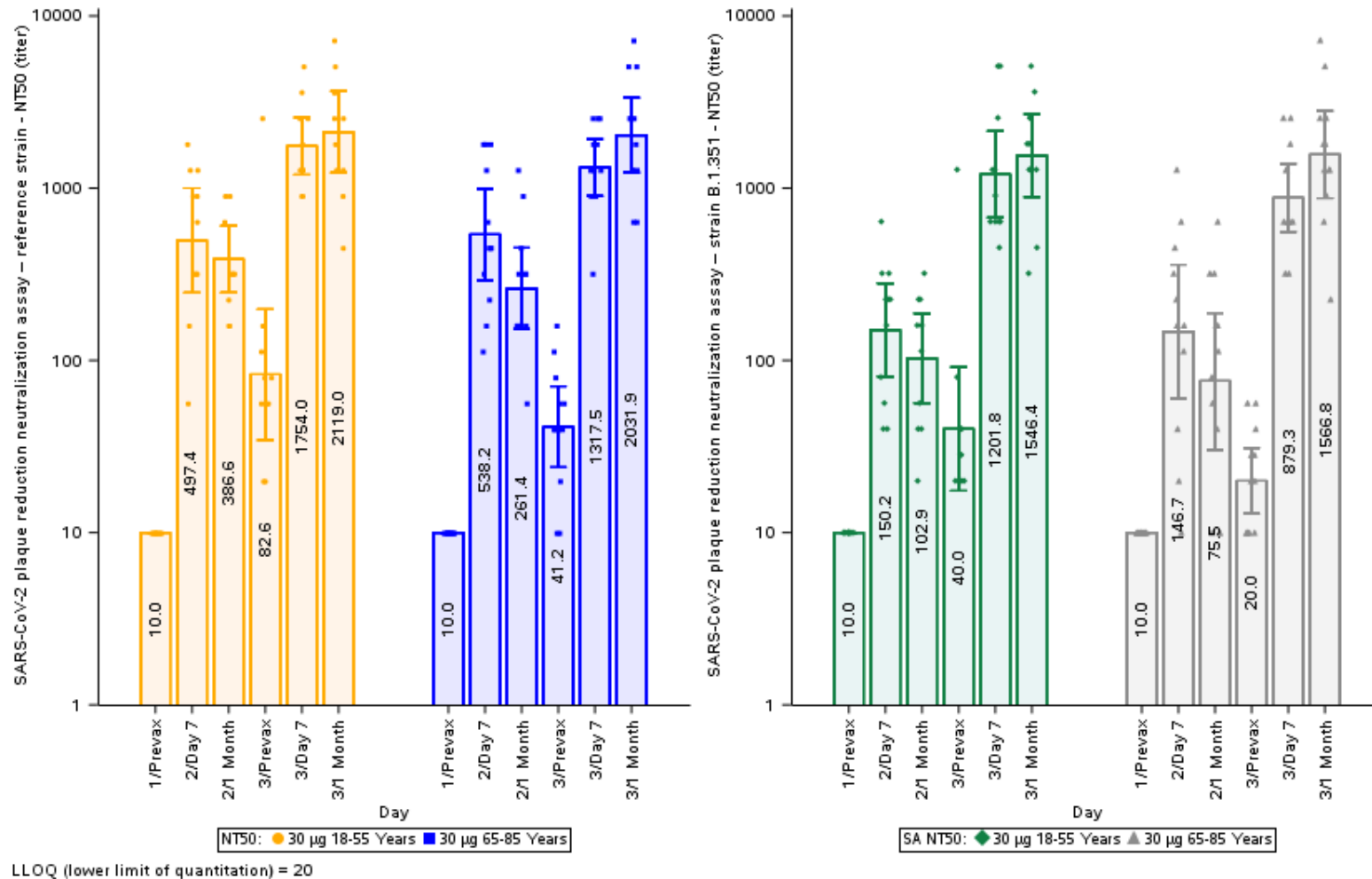
The difference between neutralizing titers against the wild-type virus and the Beta variant observed after Dose 2 narrowed after BNT162b2 Dose 3 (Figure 2). Specifically, at 1 month after Dose 2, the geometric mean ratios (GMRs) of neutralizing titers against the Beta variant to neutralizing titers against 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).

Neutralization Titers Against the Delta Variant

A third dose of BNT162b2 also increased the neutralizing titers against recombinant SARS-CoV-2 with the Delta variant spike. At 1 month after Dose 3, GMTs were 1321 (95% CI: 698.5, 2498.3) for younger adults, and 1479 (95% CI: 734.9, 2975.8) for older adults, which were approximately 5-fold and 12-fold, respectively, the GMTs observed at 1 month after Dose 2 (Figure 3).

The difference between neutralizing titers against the wild-type virus and the Delta variant observed after Dose 2 narrowed after BNT162b2 Dose 3 (Figure 3). Specifically, at 1 month after Dose 2, the geometric mean ratios (GMRs) of neutralizing titers against the Delta variant to neutralizing titers against the wild-type virus were 0.78 (95% CI: 0.63, 0.96) for younger adults and 0.63 (95% CI: 0.46, 0.86) for older adults; at 1 month after Dose 3, the corresponding GMRs increased to 0.85 (95% CI: 0.71, 1.03) and 0.92 (95% CI: 0.71, 1.18), respectively.

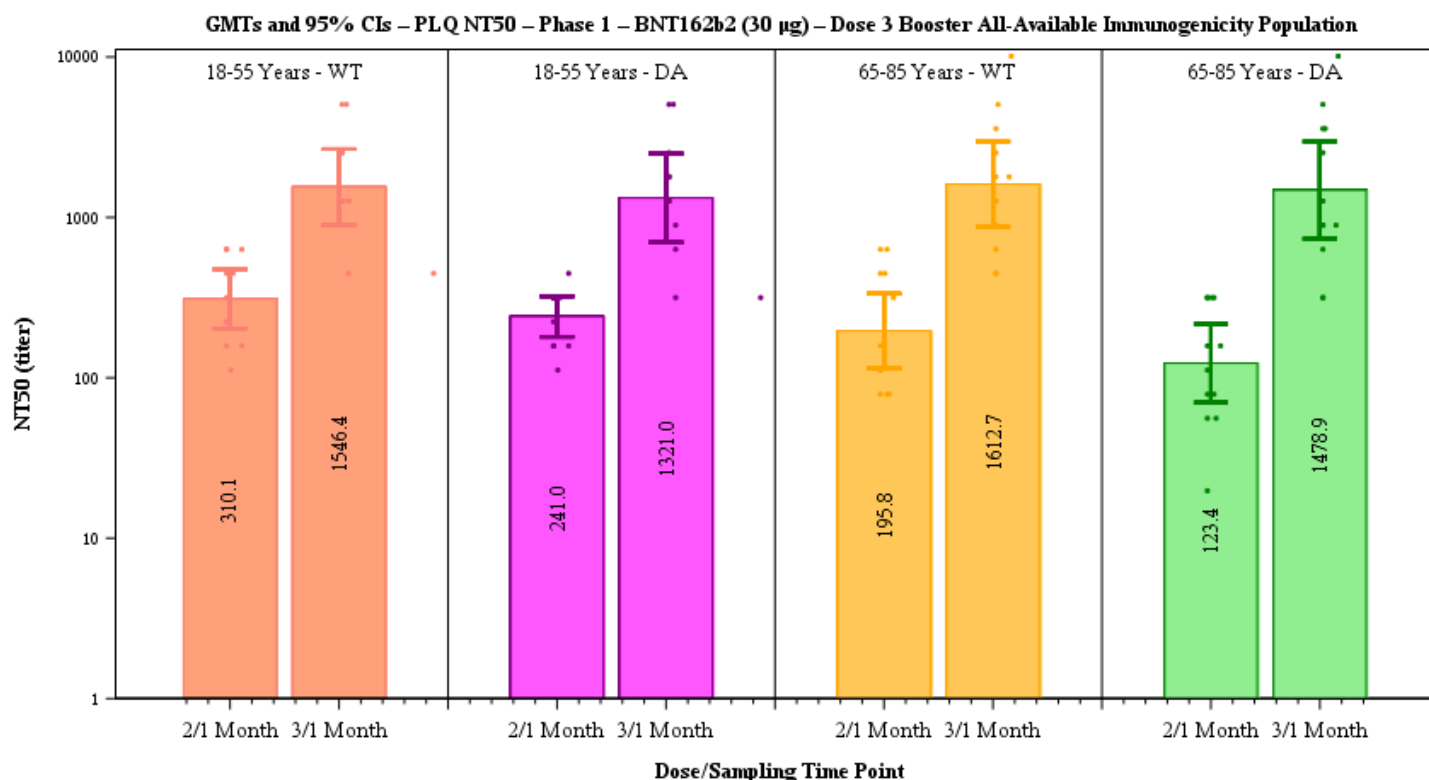
Figure 2. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralizing Titers (NT50) for Wild-Type (Reference Strain) and B.1.351 (Beta) Variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18-55 Years of Age and 65 to 85 Years of Age)



Wild-type (Reference Strain)

Beta variant (B.1.351)

Figure 3. Geometric Mean Titers and 95% CIs for SARS-CoV-2 Plaque Reduction Neutralization Assay (NT50) for Wild-Type (Reference Strain) and B.1.617.2 (Delta) Variant – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population (18-55 Years of Age and 65 to 85 Years of Age)



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 (22:34)

(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: /nda3/C4591001_P1_Booster_Delta/adva_f002_sars_50_b2_aai_da_pl

2.2.1.3. Phase 1 Booster Immunogenicity - Discussion and Conclusions

A third dose of BNT162b2 30 µg administered 7 to 9 months after the initial two-dose series in adults 18 to 55 and 65 to 85 years of age boosted serum neutralizing titers against the original SARS-CoV-2 wild-type strain, the Beta variant, and the Delta variant, resulting in an increase of neutralizing titers that were >5-fold, >15-fold, and >5-fold, respectively, those observed after Dose 2.

Furthermore, the difference in neutralizing titers between the wild-type and the variant viruses narrowed after the third dose compared with those after the second dose, showing that a booster dose increases the breadth of neutralizing response against SARS-CoV-2 variants. The kinetics of neutralizing titers changed from falling neutralizing titers during the month after the second dose to rising neutralizing titers during the month after the third dose. This phenomenon of increased magnitude and breadth and improved kinetics of the humoral response has also been observed when booster doses of pre-pandemic influenza vaccines were administered after a primary immunization series.¹⁷

Some SARS-CoV-2 variants have been associated with more rapid transmission, and potentially, greater pathogenicity,¹⁸ leading to concerns about the potential for reduced vaccine-mediated protection. Studies of in vitro neutralization of a number of SARS-CoV-2 variants have found that the tested BNT162b2-immune sera neutralize all SARS-CoV-2 variants assayed to date, including the Beta and Delta variants.^{14,19,20,21,22,23,24} Although the neutralization activity of BNT162b2-immune sera against recombinant SARS-CoV-2 with the B.1.351 lineage spike was lower, the efficacy and effectiveness of BNT162b2 against the Beta variant has remained very high, particularly for severe outcomes.^{14,25,26} In the Phase 2/3 study, there was 100% observed vaccine efficacy of BNT162b2 against COVID-19 in the subgroup of participants from South Africa, with all 9 cases of COVID-19 in South Africa occurring in the placebo group. In 8 of these cases viral sequence could be obtained, and all 8 were confirmed as caused by the B.1.351 (Beta) variant.²⁵ Real-world data also indicate that two doses of BNT162b2 are 75%, 88%, and 90% effective against B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.7 (Alpha) variants, respectively.^{26,27}

The high neutralizing titers against the Beta and Delta variants after a third dose, exceeding those after two doses, and the more comparable titers for the wild-type and variant strains after Dose 3 are encouraging. These data suggest that a third dose could re-establish the efficacy levels shown 1 month after two doses, prolong duration of protection, and further increase the breadth of protection.

2.2.2. Phase 3

Sera from Phase 3 booster substudy participants were analyzed using the reference strain SARS-CoV-2 neutralization assay (mNeonGreen microneutralization assay, SARS-CoV-2 mNG NT). Titers against the Beta and Delta variants were not determined for Phase 3 participants.

2.2.2.1. Immunogenicity Endpoints and Analysis Methods – Phase 3 Booster Substudy

Immunogenicity endpoints in Phase 3 were:

- GMT - geometric mean titer of SARS-CoV-2 neutralizing activity
- GMR - geometric mean ratio of SARS-CoV-2 neutralizing titer at 1 month after Dose 3 to the neutralizing titer at 1 month after Dose 2
- GMFR - geometric mean-fold rise in neutralizing titer from before Dose 3 to 1 month after Dose 3.
- Percentages of participants with seroresponse - Seroresponse was defined as a ≥ 4 -fold rise in neutralizing titer from baseline (before Dose 1). For participants with a baseline titer less than the lower limit of quantitation ($< \text{LLOQ}$), seroresponse is defined as a postvaccination titer of $\geq 4 \times \text{LLOQ}$.

In the Phase 3 substudy of C4591001, the basis for demonstrating BNT162b2 booster (Dose 3) effectiveness is immunobridging: demonstration that the immune response to BNT162b2 30 μg at 1 month after Dose 3 is noninferior to that observed at 1 month after Dose 2 (when 95% efficacy was established in the primary analysis for this study), based on SARS-CoV-2 50% neutralizing titers to the reference strain in participants without prior evidence of SARS-CoV-2 infection up to 1 month following Dose 3.^a

The immunobridging success criteria included prespecified margins for the geometric mean ratio (GMR) and seroresponse. 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. 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 seroresponse at 1 month after Dose 3 and 1 month after Dose 2 using a 10% margin. 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%.

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

^a Prior serological or virological evidence of SARS-CoV-2 infection was determined by N-binding antibody or nucleic acid amplification test (NAAT), respectively.

Results from all-available population were similar to those for the evaluable immunogenicity population and are not included in this briefing document.

2.2.2.2. Immunogenicity Results – Phase 3 Booster Substudy

2.2.2.2.1. Study Population and Vaccine Administration Timing

In the Phase 3 booster substudy, a total of 312 participants who previously received the BNT162b2 30 µg two-dose regimen in Phase 3 of the study were rerandomized to receive a booster (Dose 3) of BNT162b2 30 µg. All received a third vaccination, and 309 completed the booster vaccination period from Dose 3 to the 1-month follow-up visit after Dose 3. Four participants withdrew from the study after receiving Dose 3, including 2 (0.6%) lost to follow-up and 2 (0.6%) who withdrew from the study.

Among these 312 participants, 6 received a prototype vaccine based upon the B.1.351 (Beta) variant that originated in South Africa (BNT162b2_{SA}) in error (this vaccine was being administered to a second randomized group). Safety and immunogenicity data are presented in this briefing document only for the 306 participants who received BNT162b2 30 µg.

Among the 312 randomized participants, most received Dose 3 between 6 and 8 months after Dose 2; the median duration between Dose 2 and Dose 3 was 6.8 months (range: 4.8 to 8.0 months) (Table 3).

Table 3. 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

The demographic characteristics of the 306 participants who received BNT162b2 are shown in Table 4. This population was generally similar to the safety population and the efficacy populations analyzed for Phase 2/3 participants who had a median follow-up time of 2 months post-Dose 2 at the time of the prespecified final analysis of efficacy. Booster group participants had a diverse medical history profile consistent with that of individuals in the general population, as also noted in prior analyses of Phase 2/3 C4591001 participants. There were no participants with confirmed HIV in this Phase 3 booster population.

Table 4. 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

Evaluable Immunogenicity Population

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 included

234 participants (Table 5). 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 (16 participants, 53.3% of those with deviations leading to exclusion) had the Dose 3 vaccination visit outside the protocol-specified window.

Table 5. 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.	
PFIZER CONFIDENTIAL SDTM Creation: 29JUL2021 (23:01) Source Data: adsl Table Generation: 18AUG2021 (23:57)	
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: .nda2_unblinded/C4591001_G1/adva_s008_imm_pop_p3_g1	

2.2.2.2.2. Noninferiority of the Booster Response (Dose 3 Relative to Dose 2)

Geometric Mean Ratio (GMR) of Neutralization Titers (Dose 3 Relative to Dose 2)

Among participants in the evaluable immunogenicity population 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 6).

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 (ie, lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR \geq 0.8.

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

Difference in Seroresponse Rate (Dose 3 Relative to Dose 2)

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), a high proportion of participants (99.5%) had a seroresponse at 1 month after Dose 3, compared with 98.0% at 1 month after Dose 2 (Table 6).

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 (ie, lower bound of the 2-sided 97.5% CI was greater than -10%).

In addition, the US FDA requested that a post hoc analysis be performed using the prebooster (Dose 3) titer (rather than the pre-Dose 1 titer) as the baseline for determining booster dose seroresponse. Using this alternative definition, for the evaluable immunogenicity population, the seroresponse rate was 93.9% 1 month after the booster (Dose 3), compared with 97.8% 1 month after Dose 2. The difference in seroresponse rates was -3.9% (2-sided 95% CI: -8.2, 0.4%).

Table 6. 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

Objective ^a	Assay at 1 Month After Booster Dose	Assay at 1 Month After Dose 2	Vaccine Group (as Randomized)	n ^b	Sampling Time Point		
					1 Month After Booster Dose	1 Month After Dose 2 (BNT162b2)	1 Month After Booster Dose/1 Month After Dose 2
					GMT ^c (95% CI ^e)	GMT ^c (95% CI ^e)	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.

- 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.
- 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.
- 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.
- 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 t distribution).
- 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.

PFIZER CONFIDENTIAL SDTM Creation: 16AUG2021 (09:19) Source Data: adva Table Generation: 17AUG2021 (09:14)

(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adva_s004_gmr1_p3_g1_evl

Table 7. Percentage Difference of Subjects Achieving Seroreponse – 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

Objective ^a	Assay at 1 Month After Booster Dose	Assay at 1 Month After Dose 2	Vaccine Group (as Randomized)	N ^b	Sampling Time Point		Difference (1 Month After Booster Dose – 1 Month After Dose 2)
					1 Month After Booster Dose	1 Month After Dose 2 (BNT162b2)	
					n ^c (%) (95% CI ^d)	n ^c (%) (95% CI ^d)	% ^e (97.5% CI) ^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: Seroreponse 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 seroreponse.

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 seroreponse rate 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 specified window. These values are the denominators for the percentage calculations.
- c. n = Number of subjects with seroreponse 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.

PFIZER CONFIDENTIAL SDTM Creation: 16AUG2021 (09:19) Source Data: adva Table Generation: 18AUG2021 (11:35)

(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adva_s005_diff1_p3_g1_ev1

2.2.2.2.3. SARS-CoV-2 Neutralizing Titers and Fold Rises

Geometric Mean Titers (GMTs)

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (third) dose, the SARS-CoV-2 50% neutralizing GMT increased substantially after the booster vaccination, from 136.2 before Dose 3 to 2374.2 1 month after Dose 3 (Figure 4). The GMT after the booster dose was 3 times those observed 1 month after Dose 2, showing a strong boost of the neutralizing antibody response.

From baseline (prior to receipt of Dose 1) to 1 month after Dose 2, the GMT substantially increased to 73-times the prevaccination GMT, from 10.4 (2-sided 95% CI: 10.0, 10.9) to 762.0 (2-sided 95% CI: 663.3, 875.5). The median duration between receipt of Dose 2 and the booster with Dose 3 was 6.8 months (Table 3). The GMT had declined by the time the booster (Dose 3) was administered: from 762.0 (2-sided 95% CI: 663.3, 875.5) 1 month after Dose 2 to 136.2 (2-sided 95% CI: 121.5, 152.6) at the time of booster administration. Following the booster (third) dose, the GMT increased to 1418.7 (95% CI: 1263.3, 1593.3) at 7 days post-Dose 3. By 1 month after Dose 3, the GMT increased further to 2374.2 (95% CI: 2134.1, 2641.3).

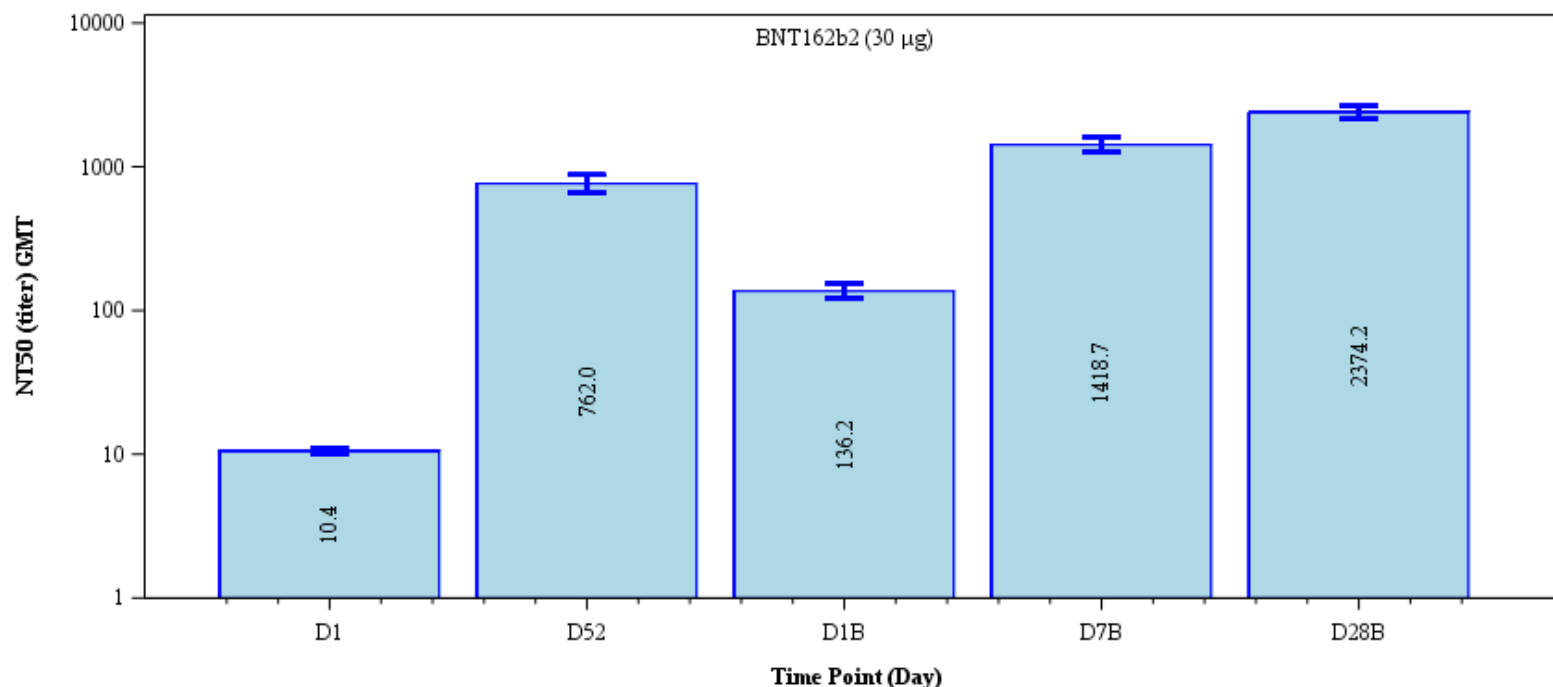
Geometric Mean Fold-Rise (GMFR) in Titers

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after the booster (Dose 3), the GMFR of SARS-CoV-2 50% serum neutralizing titers from before Dose 3 to 7 days after Dose 3 was 13.5 (2-sided 95% CI: 11.3, 16.3). At 1 month after Dose 3, the GMFR from before Dose 3 was 17.4 (2-sided 95% CI: 15.2, 20.0).

Seroresponse Rate

In the Dose 3 booster evaluable population, among participants without prior evidence of SARS-CoV-2 infection up to 1 month after the booster dose (Dose 3), the proportion of participants with seroresponse at 1 month after Dose 2 had been 98.0% (2-sided 95% CI: 95.0, 99.5). By the time of booster (Dose 3) administration (before booster vaccination), the proportion of participants with seroresponse had declined to 77.2% (2-sided 95% CI: 70.7, 82.8). At 7 days after Dose 3, the proportion of participants with seroresponse was 98.0% (2-sided 95% CI: 92.8, 99.8), and by 1 month after the booster (Dose 3) the seroresponse rate increased further to 99.5% (2-sided 95% CI: 97.4%, 100.0%).

Figure 4. Geometric Mean Titers and 95% Confidence Intervals, Reference Strain SARS-CoV-2 Neutralization Assay – NT50 – 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



Abbreviations: B = booster vaccination; D = day; GMT = geometric mean titer; 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.

Note: Number within each bar denotes geometric mean titer.

PFIZER CONFIDENTIAL SDTM Creation: 16AUG2021 (09:19) Source Data: adva Table Generation: 18AUG2021 (22:21)

(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: ./nda2_unblinded/C4591001_G1/adva_f002_nt50_p3_g1

2.2.2.2.4. Immunogenicity Conclusions – Phase 3

SARS-CoV-2 reference strain 50% neutralizing titers following Dose 3 of BNT162b2 (30 µg) were noninferior to titers observed after Dose 2, and met the prespecified 1.5-fold noninferiority criterion for the GMR (ie, lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR ≥0.8. The prespecified 10% noninferiority margin for the difference in seroresponse rates was also met (ie, lower bound of the 2-sided 97.5% CI was greater than -10%). Substantial increases over pre-boost levels for neutralizing GMTs and high seroresponse rates were observed at 1 month after Dose 3, demonstrating a robust effect of the third dose of BNT162b2 30 µg.

Phase 3 booster data showed that a third dose of BNT162b2 30 µg, administered between 4.8 and 8.0 months after completing the two-dose regimen, elicited neutralizing titers much higher than the neutralizing titers after Dose 2.

2.3. Safety and Tolerability Results

Safety data are presented in this briefing document for Phase 1 booster study participants from Dose 3 to 1 month after Dose 3; for Phase 3 participants, safety data include information collected from the booster (Dose 3) to 1 month after Dose 3, and from Dose 3 to the data cutoff date (17 June 2021), which accounts for at least 2 months post-Dose 3.

2.3.1. Phase 1

All 23 participants who received a booster (third) dose of BNT162b2 were included in the safety analysis. Overall, a third dose was well tolerated.

Local Reactions

Younger participants 18 to 55 years of age reported mild to moderate local reactions, which were primarily pain at the injection site after Dose 3 (Figure 5). In this age group, a higher percentage of participants reported local reactions after the first dose (91%) than after either the second (82%) or third dose (82%).

In older participants 65 to 85 years of age, mild to moderate pain at the injection site was the only local reaction reported (Figure 5). Again, a higher percentage of participants reported local reactions after the first BNT162b2 dose (75%) than after either the second (67%) or third dose (67%). A higher percentage of younger than older participants reported local reactions after each dose.

Systemic Events

A lower percentage of younger adults reported systemic events after the first BNT162b2 dose (73%) than after either the second (100%) or third dose (91%). In this age group, fatigue, headache, chills, and muscle pain were reported by more participants after both Doses 2 and 3 than after Dose 1 (Figure 6). Systemic events were predominantly mild to moderate in severity. Fever was more common after Dose 3 than after Doses 1 or 2.

As in the younger adult group, a lower percentage of participants in the older adult group reported systemic events after the first BNT162b2 dose (25%) than after the second (58%) or third dose (67%). In this older age group, fatigue, headache, chills, muscle pain, and joint pain were reported by more participants after Doses 2 and 3 than after Dose 1 (Figure 6). No participant in this age group reported a severe systemic event. No fever was reported after the first or third dose. A lower percentage of older than younger participants reported systemic events after each dose.

Adverse Events

There were no adverse events reported in the 1 month after Dose 3 of BNT162b2 30 µg.

Figure 5. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

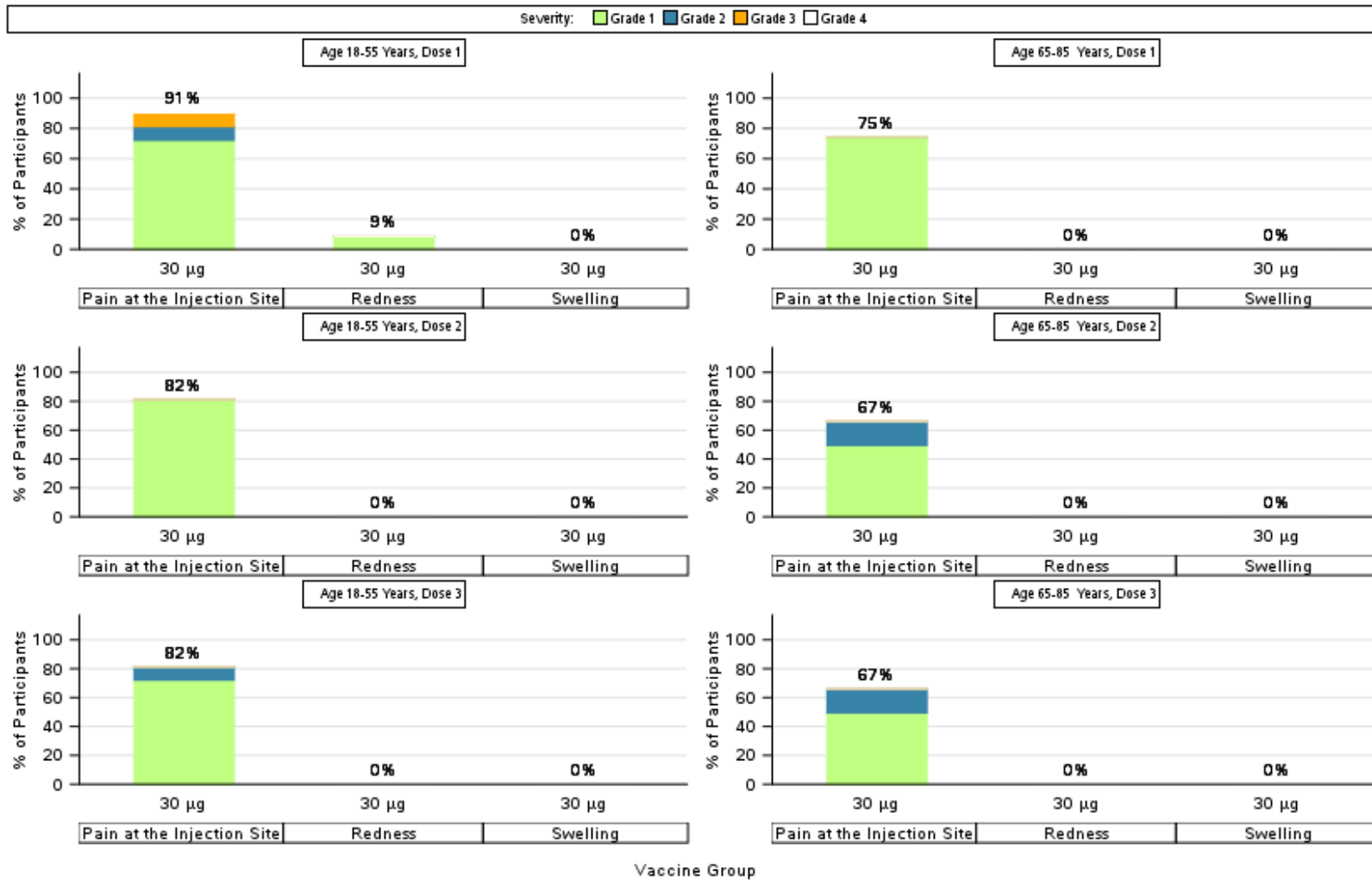
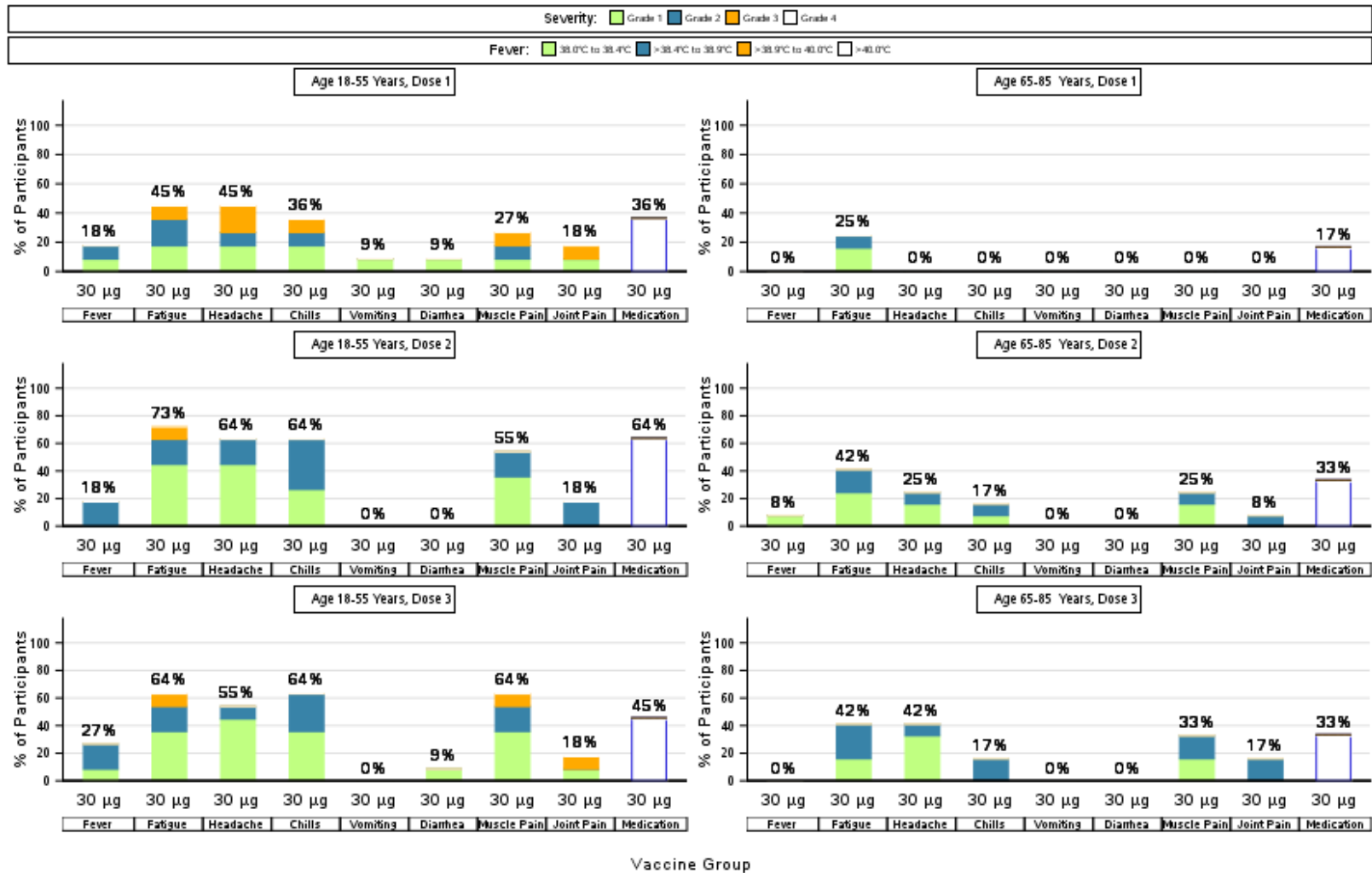


Figure 6. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population



2.3.2. Phase 3

2.3.2.1. Reactogenicity

A total of 289 participants had e-diary data reported after booster (Dose 3) administration.

Among these adults ≥ 18 to 55 years of age, the frequency and severity of local reactions and systemic events were generally similar to those previously reported in this study for the 16 to 55 years of age group after the second dose of BNT162b2.

Local Reactions

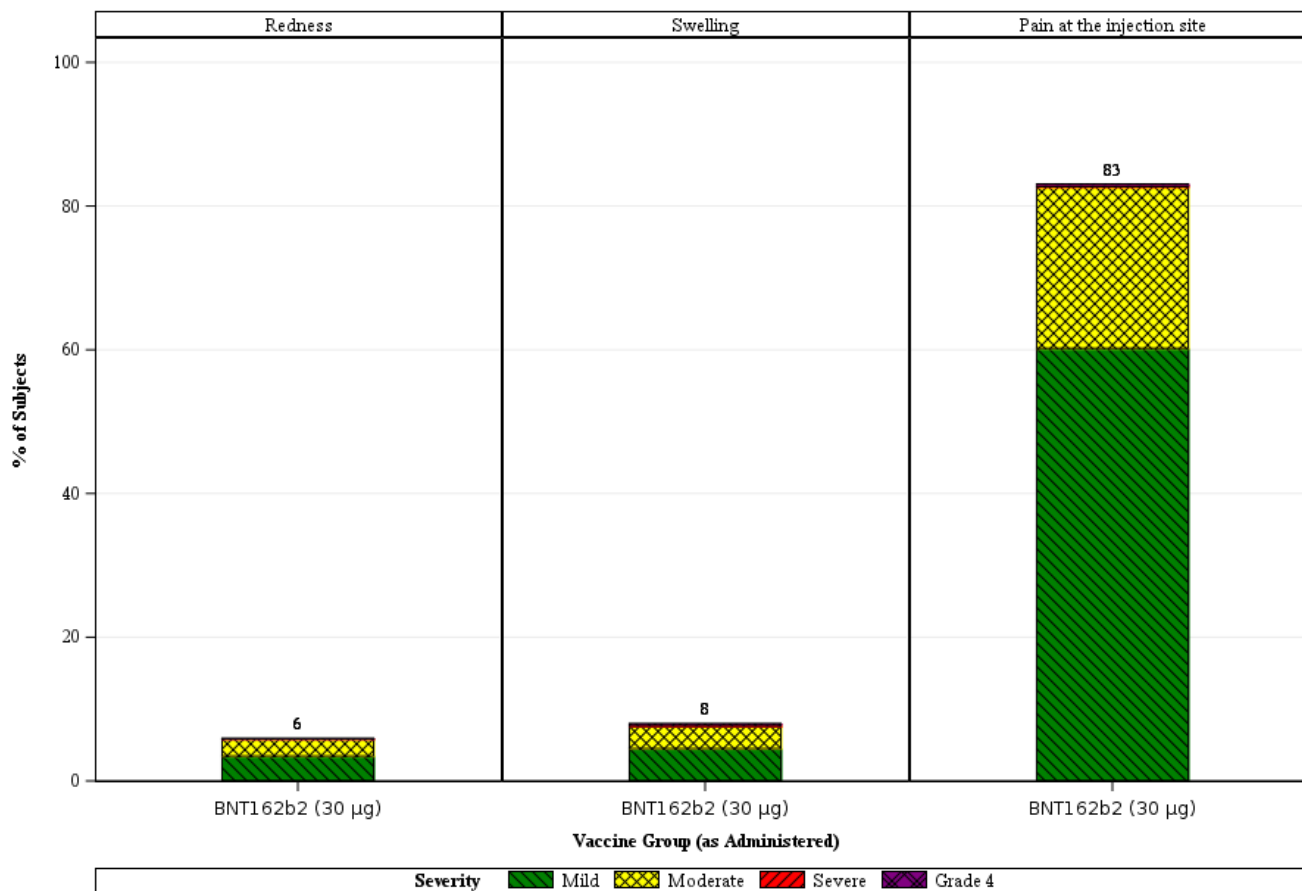
Local Reactions After the Booster (Third) Dose

Pain at the injection site was the most frequently reported local reaction after booster (Dose 3) administration, reported by 83.0% of participants; redness was reported by 5.9%, and swelling by 8.0% of participants (Figure 7). These frequencies are similar to the frequencies previously observed in this study after Dose 2 of BNT162b2 in the 16 to 55 years of age group (N=2682): pain at the injection site, 78.3%; redness, 5.6%; swelling, 6.8%.

After Dose 3, most local reactions were mild or moderate in severity. Severe local reactions were reported in 2 participants, including 1 (0.3%) with severe pain at the injection site and 1 (0.3%) with severe swelling at the injection site. No Grade 4 local reactions were reported after Dose 3.

The median onset for all local reactions after Dose 3 was Day 1 to Day 2 (Day 1 was the day of vaccination), and local reactions resolved within a median duration of 1 to 2 days.

Figure 7. 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

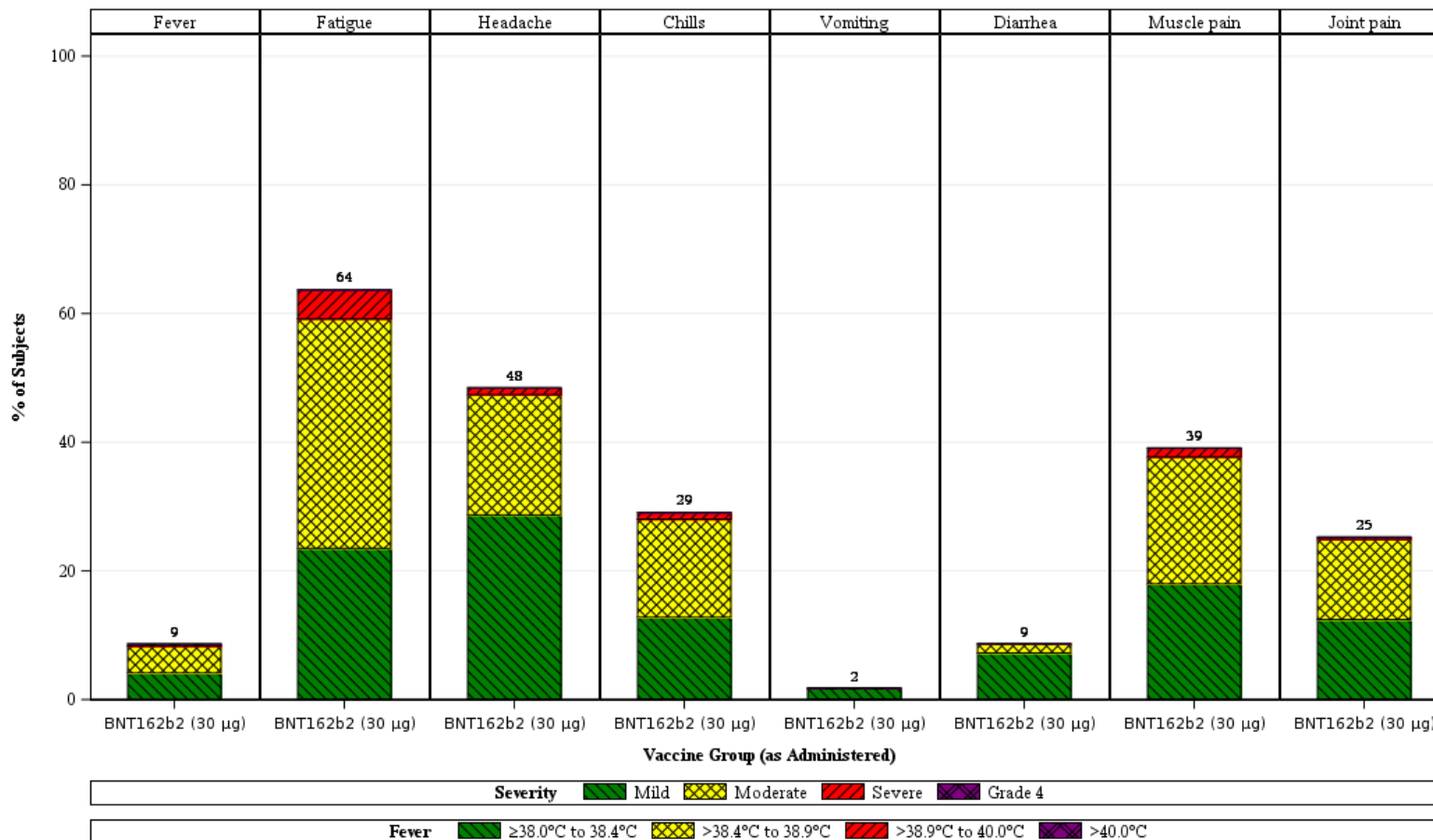
Systemic Events

The frequency of systemic events and use of antipyretic or pain medications reported by e-diary after booster (Dose 3) administration was generally similar to the frequency of systemic events previously reported in this study for the 16 to 55 years of age group after the second dose of BNT162b2 (Table 8). After Dose 3, most systemic events were mild or moderate in severity (Figure 8). Severe systemic events were reported infrequently (Table 8). A fever of >38.9 °C was reported in 1 participant; this individual had oral temperatures of 39.1 °C on Day 2 and 38.6 °C on 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.

Table 8. Frequency of Systemic Events Reported By E-Diary in Phase 3 of Study C4591001: Among Participants ≥18-55 Years Of Age After Booster (Dose 3) and After Dose 2 Among Participants 16-55 Years Of Age

Systemic Event	% of Participants Reporting the Event	
	≥18 to 55 Years of Age	(16 to 55 Years of Age)
	After Booster (Dose 3) N = 289	After Dose 2 N = 2682
Any Systemic Event		
Fatigue	63.7%	61.5%
Headache	48.4%	54.0%
Muscle Pain	39.1%	39.3%
Chills	29.1%	37.8%
Joint Pain	25.3%	23.8%
Fever (>38.0°C)	8.7%	16.4%
Diarrhea	8.7%	10.0%
Vomiting	1.7%	2.2%
Use of antipyretic or pain medication	46.7%	45.2%
Severe Systemic Events		
Fatigue	4.5%	5.3%
Headache	1.0%	3.4%
Muscle Pain	1.4%	2.3%
Chills	1.0%	2.6%
Joint Pain	0.3%	1.0%
Fever (>38.9°C)	0.3%	1.5%
Diarrhea	0.0%	0.2%
Vomiting	0.0%	0.1%

Figure 8. 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

2.3.2.2. Adverse Events

2.3.2.2.1. Overview of Adverse Events

The Phase 3 booster safety population included 306 participants, who had a median duration of 6.8 months between receiving the second and third doses (Table 3). The median follow-up time after receiving Dose 3 was 2.6 months (range: 1.1 to 2.8 months) (Table 9).

	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	

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

From Dose 3 to 1 month after Dose 3, among the 306 participants in the booster safety population, 44 (14.4%) reported at least one AE and 24 (7.8%) reported at least one AE considered by the investigator to be related to study intervention. One participant (0.3%) reported a severe AE (lymphadenopathy; onset at 2 days post-Dose 3 and recovered/resolved 5 days from onset). No immediate events were reported within 30 minutes after booster (Dose 3) administration. No deaths, SAEs or life-threatening (Grade 4) AEs were reported. No AEs leading to withdrawal were reported.

Most AEs reported during this period reflect reactogenicity events reported by the investigator as AEs. 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%.

The most commonly reported AE was lymphadenopathy, in 16/306 participants (5.2%). Lymphadenopathy is discussed below in [Section 2.3.2.2.2](#), Adverse Events of Clinical Interest.

Lymphadenopathy was also the most frequently reported AE assessed by the investigator as related to study intervention (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%).

Summary of Adverse Events from Dose 3 to Data Cutoff Date

From Dose 3 to the data cutoff date (17 June 2021), which represents at least 2 months of post-Dose 3 follow-up (median of 2.6 months), only 1 additional AE was reported beyond the 1-month post-Dose 3 period of follow-up.

The event was a severe SAE (acute myocardial infarction) reported 62 days after Dose 3 by an individual in their forties, and the event was considered unrelated to study intervention by the investigator. This participant had a medical history pertinent to the etiology of the MI. The MI was reported as recovered/resolved with sequelae within 1 day of onset following treatment.

As of the data cutoff date, no participants in the Phase 3 safety population had withdrawn from the study due to AEs, and none had died.

No AEs were reported that suggested any potential cases of severe COVID-19 among participants in the Phase 3 BNT162b2 booster group.

No pregnancies were reported in the Phase 3 BNT162b2 booster group from Dose 3 to the data cutoff date (17 June 2021).

2.3.2.2.2. Adverse Events of Clinical Interest

No cases of anaphylaxis, hypersensitivity, Bell's palsy, appendicitis, or myocarditis/pericarditis were reported in the Phase 3 BNT162b2 booster group from Dose 3 to the data cutoff date.

Overall, other than the unrelated SAE of acute myocardial infarction secondary to stimulant abuse, there were no AESIs reflecting the conditions targeted by the CDC list in this booster group as of the data cutoff date.

Adverse Drug Reactions

Adverse reactions (ADRs), defined as AEs for which there is reason to conclude that the vaccine caused the event, have been identified from clinical study safety data and are specified in the current product labeling. No new ADRs were identified from safety data associated with booster (Dose 3) administration of BNT162b2 30 µg in the Phase 3 BNT162b2 booster group.

One notable difference for this Phase 3 booster adult population was the higher frequency of lymphadenopathy after Dose 3 (5.2%) compared to the frequency of lymphadenopathy associated with the first two doses: 0.4% in individuals ≥ 16 years of age and 0.8% in adolescents 12 to 15 years of age.

Lymphadenopathy

In the Phase 3 booster safety population, 16/306 participants (5.2%) had cases of lymphadenopathy reported from Dose 3 to 1 month after Dose 3, of which all were considered by the investigator as related to study intervention. All cases of lymphadenopathy had an onset within 1 to 4 days after BNT162b2 booster (Dose 3) administration, and most were reported as recovered/resolved as of the data cutoff date, most within ≤ 5 days after onset. These cases predominantly occurred in female participants and were located in axillary nodes. Only 1 participant who had lymphadenopathy after receiving Dose 3 had also previously experienced lymphadenopathy during the blinded placebo-controlled period (with onset on the fourth day after Dose 2). No participants in the booster safety population reported a past medical history of lymphadenopathy at baseline (before Dose 1).

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 participant in their early 40s, 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.

Lymphadenopathy has been identified as an adverse reaction causally associated with the vaccine and is thought to be related to the development of the immune response to the vaccine. As Dose 3 is a booster, it is not surprising that stimulation of a lymph node reaction by vaccination would be present in the setting of a significant increase in neutralizing antibodies observed after Dose 3. While related to vaccination, this ADR is generally mild and self-limited and is unlikely to impede a booster vaccination program.

2.3.3. Safety Conclusions

Phase 1

Phase 1 data from 23 participants 24 to 75 years of age (11 in the younger 18 to 55 years of age group and 12 in the older 65 to 85 years of age group) who received a booster (Dose 3) of BNT162b2 30 µg showed that the third dose was safe and well-tolerated, based on the reactogenicity profile for 7 days after Dose 3 and the AE profile up to 1 month after Dose 3.

Phase 3

Phase 3 data from 306 participants ≥ 18 to 55 years of age who received a booster (Dose 3) of BNT162b2 30 μg showed that the third dose was safe and well-tolerated, based on the reactogenicity profile for 7 days after Dose 3 and the AE profile up to 1 month after Dose 3 and up to the data cutoff date of 17 June 2021 (which represents at least 2 months post-Dose 3).

Reactogenicity after Dose 3 was mostly mild to moderate and short-lived (ie, median onset of 1 to 4 days post-dose and resolved 1 to 2 days after onset). Local reactions after Dose 3 presented predominantly as injection site pain. Frequently reported systemic events were fatigue, headache, muscle/joint pain, and chills.

The AE profile after Dose 3 reflected mostly reactogenicity or lymphadenopathy events and did not suggest any serious short-term safety concerns for BNT162b2 booster (Dose 3) vaccination. Lymphadenopathy has been identified previously as a BNT162b2 adverse reaction and is also noted in the booster safety population but at a higher frequency with Dose 3.

After Dose 3, with the exception of the unrelated SAE of Grade 3 acute myocardial infarction, there were no AESIs reflecting the conditions targeted by the CDC list in this booster group as of the data cutoff date.

No related SAEs, withdrawals due to AEs, or deaths were reported following Dose 3 administration.

2.4. A Third Dose of BNT162b2 Administered in a Clinical Study To Describe Coadministration With Prevnar 20 (PCV20)

An additional study (NCT04887948) was conducted to describe the co-administration of Prevnar 20[®] (20-valent pneumococcal conjugate vaccine, PCV20) and a booster (third) dose of BNT162b2. Individuals ≥ 65 years of age who had received Dose 2 of BNT162b2 in Study C4591001 at least 6 months previously were randomized to receive (i) PCV20 and a third (booster) dose of BNT162b2; (ii) PCV20 and saline; or (iii) the third (booster) dose of BNT162b2 and saline (BNT162b2 control group), with approximately 190 participants randomized per group.

Safety data are available through approximately 1 month after vaccination in this ongoing study. Among the 372 participants who received the booster dose of BNT162b2, either with PCV20 (N=187) or with saline (N=185), the vaccine was generally well tolerated; reactogenicity events were mostly mild to moderate and were similar to what has been observed previously in clinical studies of the 2-dose regimen in older adults. These results provide additional data supporting a good tolerability profile for a third dose of BNT162b2 administered at least 6 months after the second dose in individuals ≥ 65 years of age.

These data are presented here for information only, as supportive safety data in individuals 65 years of age and older. These data are intended to complement the data submitted to support the booster dose but have not been submitted to CBER as part of the sBLA.

3. REAL-WORLD DATA ON THE PUBLIC HEALTH IMPACT OF BOOSTER DOSES OF mRNA VACCINES

As a result of emerging evidence of waning immunity and increasing rates of transmission and infection following the introduction of the Delta variant, the Israel MoH initiated a BNT162b2 booster (third dose) program for older adults and immunocompromised individuals who were previously fully immunized, a program that has since been expanded to the entire vaccine-eligible population. Early unpublished data from an Israeli health maintenance organization suggest that a third booster dose is highly effective in a setting where B.1.617.2 (Delta) accounts for nearly all cases. These initial booster data show that giving of a third dose of BNT162b2 to individuals >60 years of age was associated with 86% effectiveness against testing positive for SARS-CoV-2 infection from at least 7 days after Dose 3.

A recent Israel MoH study also confirmed that a third (booster) dose of BNT162b2 restored very high levels of protection against COVID-19 even in a period when Delta was the dominant strain.²⁸ The study included 1,144,690 individuals age 60 years and older who were eligible for a booster dose between July 30, 2021 and August 22, 2021. Vaccine status was defined using dynamic cohorts in which individuals initially belonged to the ‘non-booster’ cohort and entered the ‘booster’ cohort 12 days after receiving a third dose of BNT162b2. Rates of infection and severe COVID-19 outcomes per person-days at risk were compared between individuals who did and did not receive a third dose, using Poisson regression and adjusting for possible confounding factors, including age, sex, sector, and calendar day. Individuals who received the booster dose were 11.4-fold (95% CI: 10.0, 12.9) less likely to develop a confirmed infection and 15.5-fold (95% CI: 10.5, 22.8) less likely to develop severe illness compared to those who were previously fully vaccinated but did not receive a booster dose. The authors highlight that this additional protection after receiving a booster translated to roughly 95% effectiveness against COVID-19 endpoints in the Delta era—which is comparable to levels of BNT162b2 effectiveness seen early in the vaccine rollout, when the Alpha variant was predominant.

Since the rollout of the booster (third) dose program in Israel, 2.7 million Israelis ≥ 12 years of age have received a third dose of BNT162b2, the great majority over 60 years of age. No new safety signals or adverse events have been identified; the reactogenicity profile has appeared similar to the profile seen after the receipt of the second dose; and rates of adverse events reported after the third dose are lower than those observed after Dose 1 or Dose 2.

Thus, Israel has clearly demonstrated that, in the face of waning immunity, a booster (third dose) program can be implemented safely at a national level and that a booster dose of BNT162b2 is an effective strategy to restore high levels of protection against COVID-19 outcomes (ie, back to roughly 95%) in a period when Delta is the dominant strain.

4. PHARMACOVIGILANCE

Upon approval, Pfizer/BioNTech will include the booster dose into the ongoing pharmacovigilance activities previously agreed with the FDA for the primary two-dose schedule. These activities are succinctly summarized in Table 10.

Table 10. Studies Contributing to Pharmacovigilance	
Study Title	Summary of Objectives
Ongoing Studies	
C4591001: 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.	To evaluate the safety, tolerability, immunogenicity, and efficacy of BNT162b2. An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of VAED/VAERD. Surveillance is planned for 2 years following Dose 2.
C4591007 substudy: A Phase 3 substudy of 750 participants 5 to <12 years of age (randomized 2:1 to receive BNT162b2 10 µg or placebo) and 500 participants 12-15 years of age (open label receipt of BNT162b2 30 µg).	To obtain serum samples within the first ~4 days after vaccination for potential Troponin I testing, in order to evaluate the frequency of subclinical myocarditis amongst individuals 5 to 15 years of age.
C4591008: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine in US healthcare workers, their families, and their communities.	To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the BNT162b2 since EUA
C4591012: Post-emergency use authorization active safety surveillance study among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech COVID-19 Vaccine.	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including anaphylaxis, myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine
C4591021: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine	To assess the potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID 19 mRNA vaccine.
C4591031 substudy: A Phase 3 substudy of 1000 participants with documented receipt of 2 prior 30 µg doses of BNT162b2 (the second dose received at least 6 months ago), 16 to 30 years of age (randomized 1:1 in a crossover design to receive 30 µg BNT162b2 or placebo at baseline and the alternative 4 weeks later).	To obtain serum samples within the first ~4 days after vaccination for potential Troponin I testing, in order to evaluate the frequency of subclinical myocarditis amongst individuals 16 to 30 years of age.

Table 10. Studies Contributing to Pharmacovigilance	
Study Title	Summary of Objectives
Planned Studies	
C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA vaccine in the United States.	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population of all ages, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System
C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the US Department of Defense population following Emergency Use Authorization	To assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine.
C4591021 substudy: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. Substudy to investigate natural history of post-vaccination myocarditis and pericarditis.	To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.
C4591036: Pediatric Heart Network Study: Working title: <i>Myocarditis/pericarditis follow-up study within the Pediatric Heart Network.</i>	To characterize the clinical course, risk factors, resolution, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis/pericarditis.

5. BENEFIT/RISK ASSESSMENT

Booster Vaccination – An Unmet Public Health Need

As the Delta variant has spread widely, rates of COVID-19 are again on the rise in the United States and in many other countries around the world. Although unvaccinated individuals continue to account for most SARS-CoV-2 infections and severe cases of COVID-19, real-world data from Israel and the United States suggest that rates of breakthrough infections are rising faster in individuals who were vaccinated earlier in the vaccination campaigns compared to those who have been vaccinated more recently. Evidence gathered in studies conducted both in Israel and in the United States by Kaiser Permanente Southern California and the CDC indicate that the observed decrease of vaccine effectiveness against COVID-19 infections is primarily due to waning of vaccine immune responses over time rather than a result of the Delta variant escaping vaccine protection. While the waning is slightly more pronounced against the Delta variant, it does occur irrespective of the VOC. In addition, the short-term vaccine effectiveness (VE) against the delta VOC is very high in all age groups and is comparable to that induced by the vaccine against the wild type strain in the pivotal Phase 3 study.

Although VE against hospitalizations and other severe COVID-19 outcomes remain high in all age groups in the United States, reports from Israel have shown that sustained VE reductions against infections may be followed by VE decreases against hospitalizations and other severe outcomes, especially among those most vulnerable (eg, over 65 years of age) who were vaccinated earlier in the vaccination campaign (eg, January-February 2021). Based on these epidemiological trends, the Government of Israel launched a third dose (booster) roll out campaign that started with the population >60 years of age and health care workers and immediately expanded to the entire eligible population of 12 years of age and older in an attempt to prevent a potential exponential upsurge of infections and hospitalizations.

Given that an epidemiological pattern similar to the one observed in Israel may be occurring in the United States and elsewhere, consideration of the approval of a booster dose of BNT162b2 approximately 6 months after of the second primary dose is warranted.

Immunogenicity of a Booster (Third) Dose of BNT162b2 in Study C4591001

The immunogenicity of a booster dose of BNT162b2 was measured in a substudy of the C4591001 pivotal study that is in compliance with the 25 May 2021 FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19.

Phase 1 data were evaluated for younger (18 to 55 years of age) and older (65 to 85 years of age) participants who were given Dose 3 of 30 µg BNT162b2 7 to 9 months after completing the two-dose series of BNT162b2 30 µg. The results demonstrate that serum neutralizing titers at 1 month after Dose 3 were higher than the responses observed 1 month after Dose 2. Specifically, titers against the original SARS-CoV-2 wild-type strain, the B.1.351 (Beta) variant, and the B.1.617.2 (Delta) variant at 1 month after Dose 3 were 5-times, 15-times, and from 4.76- to 7.51-times those attained at 1 month after Dose 2.

While titers against the wild-type were higher than those against the Beta and Delta variants, importantly, the difference in neutralizing titers between wild-type and variant strains narrowed after the third dose compared to after the second dose, showing that a booster dose reduces the gap between wild-type and variant strain neutralization and results in increased magnitude and breadth of the humoral response. These results suggest that, by eliciting strong booster responses against major VOCs, BNT162b2 may reasonably be expected to provide the breadth of protection needed during a period where the Delta variant is highly prevalent.

Additionally, the Phase 3 booster substudy data show that, in adults ≥ 18 to 55 years of age who were without evidence of SARS-CoV-2 infection through 1 month after Dose 3, administration of a third dose of BNT162b2 30 µg approximately 6 months after completion of the 2-dose regimen met the protocol prespecified 1.5-fold noninferiority success criterion for the GMR (ie, lower bound of the 2-sided 97.5% CI >0.67 and point estimate ≥ 0.8), and the immune response after Dose 3 was statistically higher than the response after Dose 2 (the lower bound of the 2-sided 97.5% CI for the GMR is >1). Furthermore, the prespecified 10% noninferiority margin for the difference in seroresponse rates was also met (ie, lower bound of the 2-sided 97.5% CI was greater than -10%). Finally, in accordance with US FDA's May 2021 Guidance for Industry,² the use of a booster dose in individuals 16 and 17 years of age

and in individuals older than 55 years of age is based on extrapolation of the safety and effectiveness demonstrated in adults at least 18 to 55 years of age in the Phase 2 booster study.

Overall, the present Phase 1 and Phase 3 booster data show that a third dose of BNT162b2 administered approximately 6 months after completing the two-dose regimen induces a strong and broad immune response that is expected to confer extended protection against COVID-19, including variants of concern.

Safety and Tolerability of a Booster (Third) Dose of BNT162b2 in Study C4591001

The safety and tolerability of a booster (third) dose of 30 µg BNT162b2 (administered approximately 6 months after completion of the two-dose regimen) have been evaluated in:

- 306 Phase 3 participants ≥ 18 to 55 years of age who had a median duration of 6.8 months between receiving the second and third doses, and a median follow-up time of 2.6 months after the booster (Dose 3); and in
- 23 Phase 1 participants (11 in the younger 18 to 55 years of age group and 12 in the older 65 to 85 years of age group) who had a mean of 8.3 months between receiving the second and third doses and were followed for safety through 1 month after Dose 3.

The reactogenicity and adverse event profile observed after the booster (Dose 3) was generally similar to that observed following Dose 2 of the initial two-dose regimen, which suggests no potentiation of reactogenicity or any new safety concern arising from administration of a third dose.

The reactogenicity events during the 7-day period after booster (Dose 3) were typically mild to moderate, arose within the first 1 to 2 days after dosing, and were short-lived. Reactogenicity after Dose 3 administration was generally similar to that observed following Dose 2 in the 16 to 55 years of age group participants who received the initial two-dose regimen.

As of the data cutoff date of 17 June 2021, the AE profile up to at least 2 months after Dose 3 mostly reflects reactogenicity events, with low incidences of related and/or severe events and no serious events within 1 month after Dose 3. Review of AEs, SAEs, and events of clinical interest suggested no short-term safety concerns after Dose 3 administration. One exception was the increase in frequency of lymphadenopathy after Dose 3 (5.2%) in adults compared with the first two doses: (0.4%) in individuals ≥ 16 years of age and 0.8% in adolescents. Lymphadenopathy has been observed after vaccination and is thought to be related to the development of the immune response to the vaccine.

Overall, the safety profile associated with a third dose of BNT162b2 at 30 µg administered approximately 6 months after completing the two-dose regimen is highly similar to the safety profile of the initial regimen itself, with no new safety concerns identified in the booster population and no increased reactogenicity or unusual AEs or other safety findings. The consistency of the safety profile for BNT162b2 through at least 6 months of follow-up after Dose 2, and the similarities of safety profiles across adolescent and adult age groups,

reasonably suggest that the booster (Dose 3) safety profile for Phase 3 adults at least 18 to 55 years of age may be extrapolated to individuals 16 and 17 years of age and >55 years of age.

Initial Confirmatory Safety and Effectiveness Evidence of BNT162b2 Booster (Third Dose) in the Israel National Immunization Program

As a result of emerging evidence of waning immunity and increasing rates of infection and hospitalization following the introduction of the Delta variant, the Israel Ministry of Health launched a BNT162b2 booster (third dose) program covering the entire vaccine-eligible population from 12 years of age and older. Data reported publicly by the Ministry of Health (but not yet peer reviewed) clearly demonstrated that, in the face of waning immunity, a booster (third dose) program can be implemented safely at a national level and that a booster dose of BNT162b2 is an effective strategy to restore high levels of protection against COVID-19 outcomes in a period when Delta is the dominant strain.

Overall Benefit/Risk Conclusions

The potential risks and benefits as assessed by the safety profile and by the efficacy and immunogenicity of BNT162b2 demonstrated in the pivotal clinical study are balanced in favor of the potential benefits of adding a booster dose (third dose) to the vaccination schedule.

Based on the data summarized in this briefing document and in consultation with CBER, Pfizer/BNT is requesting licensure of a booster dose (third dose) of BNT162b2 administered intramuscularly approximately 6 months after Dose 2 in individuals ≥ 16 years of age.

6. REFERENCES

- ¹ Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603-15.
- ² Food and Drug Administration (FDA). Emergency Use Authorization for Vaccines to Prevent COVID-19. Guidance for Industry. May 2021. Available at: <https://www.fda.gov/media/142749/download>.
- ³ Krammer F. Correlates of protection from SARS-CoV-2 infection. *Lancet* 2021;397:1421-3.
- ⁴ Bergwerk M, Gonen, T, Lustig Y, et al. Covid-19 Breakthrough infections in vaccinated health care workers. *NEJM*. 2021;[ePub]10.1056/NEJMoa2109072.
- ⁵ Mizrahi B, Lotan R, Kalkstein N, et al. Correlation of SARS-CoV-2 breakthrough infections to time-from-vaccine; preliminary study. medRxiv 2021. Preprint. [ePub];doi:10.1101/2021.07.29.21261317.
- ⁶ Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet* 2021;397(10287):1819-29. doi:10.1016/S0140-6736(21)00947-8. Available at: [https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(21\)00947-8.pdf](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(21)00947-8.pdf).
- ⁷ Israel Ministry of Health, Epidemiology Division: COVID-19 Weekly Data Update, 20 July 2021. Available at: https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf.
- ⁸ Israel Ministry of Health, Epidemiology Division: COVID-19 Weekly Data Update, 11 August 2021. Available at: https://www.gov.il/BlobFolder/reports/vpb-12082021/he/files_publications_corona_vpb-12082021-01.pdf.
- ⁹ Goldberg Y. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. medRxiv 2021. DOI: 10.1101/2021.08.24.21262423
- ¹⁰ Nanduri SA, Pilishvili T, Derado G, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. 2021;70 Early Release. Available at: <https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e3.htm>

- 11 Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. *MMWR Morb Mortal Wkly Rep* Aug 18, 2021;70; Early Release. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e1.htm?s_cid=mm7034e1_w
- 12 Tartof, SY. Six-Month Effectiveness of BNT162B2 mRNA COVID-19 Vaccine in a Large US Integrated Health System: A Retrospective Cohort Study. Available at SSRN: <https://ssrn.com/abstract=3909743> or <http://dx.doi.org/10.2139/ssrn.3909743>
- 13 Tenforde MW, Self WH, Naioti EA, Ginde AA, Douin DJ, Olson SM. Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults *MMWR Morb Mortal Wkly Rep* 2021;70 Early Release. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm?s_cid=mm7034e2_w
- 14 Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum. *N Engl J Med* 2021;384:1466-8.
- 15 Muruato AE, Fontes-Garfias CR, Ren P, et al. A high-throughput neutralizing antibody assay for COVID-19 diagnosis and vaccine evaluation. *Nat Commun* 2020;11:4059.
- 16 Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-Based COVID-19 vaccine candidates. *N Engl J Med* 2020;383(25):2439-50.
- 17 Galli G, Hancock K, Hoschler K, et al. Fast rise of broadly cross-reactive antibodies after boosting long-lived human memory B cells primed by an MF59 adjuvanted prepandemic vaccine. *Proc Natl Acad Sci U S A* 2009;106:7962-7.
- 18 US Centers for Disease Control and Prevention (CDC). SARS-CoV-2 Variant Classifications and Definitions. 2021. Accessed 04 May 2021. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html#print>
- 19 World Health Organization (WHO). Tracking SARS-CoV-2 variants. 2021. Accessed 22 June 2021. Available at: <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>
- 20 Xie X, Liu Y, Liu J, et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. *Nat Med* 2021;27:620-1.
- 21 Zou J, Xie X, Fontes-Garfias CR, et al. The effect of SARS-CoV-2 D614G mutation on BNT162b2 vaccine-elicited neutralization. *NPJ Vaccines* 2021;6:44.

- ²² Muik A, Wallisch AK, Sanger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. *Science* 2021;371:1152-3.
- ²³ Liu J, Liu Y, Xia H, et al. BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. *Nature* 2021 [Epub];doi: 10.1038/s41586-021-03693-y
- ²⁴ Liu Y, Liu J, Xia H, et al. BNT162b2-Elicited Neutralization against new SARS-CoV-2 spike variants. *N Engl J Med* 2021 [Epub];doi:10.1056/NEJMc2106083
- ²⁵ Thomas SJ, Moreira ED, Kitchin N, et al. Six month safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2021 [Submitted].
- ²⁶ Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. *N Engl J Med* 2021 [Epub];doi:10.1056/NEJMc2104974
- ²⁷ Bernal JL, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. *medRxiv* 2021 [Epub];doi:0.1101/2021.05.22.21257658
- ²⁸ Bar-On YM et al. BNT162b2 vaccine booster dose protection: A nationwide study from Israel. *medRxiv* 2021 Pages 2021.08.27.21262679. DOI: 10.1101/2021.08.27.21262679.