FDA U.S. FOOD & DRUG ADMINISTRATION

August 26, 2022

Via Email: lburke@judicialwatch.org

Lauren M. Burke
Judicial Watch, Inc.
425 Third Street, SW, Suite 800
Washington, DC 20024

Re: FDA FOIA Request 2021-5541; *Judicial Watch, Inc. v. HHS,* 22-cv-00730-RC

Dear Ms. Burke,

Pursuant to the Joint Status Report filed on July 12, 2022 in the above-referenced matter, attached please find our response to the Freedom of Information Act (FOIA) request number **2021-5541**. This production represents our complete response to your request; no additional productions are anticipated.

Attached are 58 pages of records from the FDA's Center for Biologics Evaluation and Research (CBER) (Bates numbered FDA-CBER-2021-5541-00001 to -00058) some of which contain redactions. We have withheld portions of four pages, and we are releasing 54 pages in full.

We have withheld portions of pages under Exemption (b)(6), 5 U.S.C. § 552(b)(6). That exemption protects information from disclosure when its release would cause a clearly unwarranted invasion of personal privacy. FOIA Exemption 6 is available to protect information in personnel or medical files and similar files. This requires a balancing of the public's right to disclosure against the individual's right to privacy.

Please direct any questions regarding this response to Assistant United States Attorney Marcia Sowles of the Department of Justice, at (202) 514-4960 or Marcia.Sowles@usdoj.gov.

Sincerely,

Ricci J. Ward -S Digitally signed by Ricci J. Ward -S Date: 2022.08.26 08:10:54 -04'00'

Ricci Ward for Beth Brockner Ryan
Chief, Access Litigation and Freedom of Information Branch
Division of Disclosure and Oversight Management
Office of Communication Outreach and Development
Center for Biologics Evaluation and Research

Attachments
cc:
Marcia Sowles, Federal Programs Branch, USDOJ (By email)
Leah Edelman, Office of the Chief Counsel, FDA (By email)

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Next Page | Export Data | Import Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
BioNTech SE

2. Date of Submission *(mm/dd/yyyy)*
07/14/2021

3. Sponsor Address

Address 1 *(Street address, P.O. box, company name c/o)*
An der Goldgrube 12

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City: Mainz
State/Province/Region: N/A
Country: Germany
ZIP or Postal Code: 55131

4. Telephone Number *(Include country code if applicable and area code)*
215-280-5503

6A. IND Number *(If previously assigned)*
019736

6B. Select One: ☑ Commercial ☐ Research

5. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
COVID-19 Vaccine (BNT162, PF-07302048)

Continuation Page for #5

7A. (Proposed) Indication for Use
Active immunization to prevent COVID-19 caused by SARS-CoV-2

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☑ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☑ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #7

7B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*

8. Phase of Clinical Investigation to be conducted ☑ Phase 1 ☑ Phase 2 ☑ Phase 3 ☐ Other *(Specify)*:

9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
BB-IND 013812, BB-IND 013278, BLA 125549

10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..

Serial Number: 0 4 0 6

11. This submission contains the following *(Select all that apply)*

☐ Initial Investigational New Drug Application (IND)
☐ Response to Clinical Hold
☐ Response To FDA Request For Information
☐ Request For Reactivation Or Reinstatement
☐ Annual Report
☐ General Correspondence
☐ Development Safety Update Report (DSUR)
☐ Other *(Specify)*:

Protocol Amendment
☐ New Protocol
☐ PMR/PMC Protocol
☐ Change in Protocol
☐ New Investigator
☐ Human Factors Protocol

Information Amendment
☐ Chemistry/Microbiology
☐ Pharmacology/Toxicology
☑ Clinical/Safety
☐ Statistics
☐ Clinical Pharmacology

Request for
☐ Meeting
☐ Proprietary Name Review
☐ Special Protocol Assessment
☐ Formal Dispute Resolution

IND Safety Report
☐ Initial Written Report
☐ Follow-up to a Written Report

12. For Originals, is the product a combination product (21 CFR 3.2(e))? ☐ Yes ☐ No

Combination Product Type *(See instructions)*

Request for Designation (RFD) Number

13. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*

☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8

Expanded Access Use, 21 CFR 312.300

☐ Individual Patient, Non-Emergency 21 CFR 312.310
☐ Intermediate Size Patient Population, 21 CFR 312.315
☐ Individual Patient, Emergency 21 CFR 312.310(d)
☐ Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only

CBER/DCC Receipt Stamp	DDR Receipt Stamp	Division Assignment
		IND Number Assigned

14. Contents of Application – This application contains the following items *(Select all that apply)*

- [x] 1. Form FDA 1571 *(21 CFR 312.23(a)(1))*
- [ ] 2. Table of Contents *(21 CFR 312.23(a)(2))*
- [ ] 3. Introductory statement *(21 CFR 312.23(a)(3))*
- [ ] 4. General Investigational plan *(21 CFR 312.23(a)(3))*
- [ ] 5. Investigator's brochure *(21 CFR 312.23(a)(5))*
- [ ] 6. Protocol *(21 CFR 312.23(a)(6))*
  - [ ] a. Study protocol *(21 CFR 312.23(a)(6))*
  - [ ] b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
  - [ ] c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
- 6. Protocol *(Continued)*
  - [ ] d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572
- [ ] 7. Chemistry, manufacturing, and control data *(21 CFR 312.23(a)(7))*
  - [ ] Environmental assessment or claim for exclusion *(21 CFR 312.23(a)(7)(iv)(e))*
- [ ] 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
- [x] 9. Previous human experience *(21 CFR 312.23(a)(9))*
- [ ] 10. Additional information *(21 CFR 312.23(a)(10))*
- [ ] 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- [ ] 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

15. Is any part of the clinical study to be conducted by a contract research organization? [x] Yes [ ] No

If Yes, will any sponsor obligations be transferred to the contract research organization? [ ] Yes [x] No

If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred *(use continuation page)*. **Continuation Page for #15**

16. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations

Özlem Türeci, MD, Chief Medical Officer, BioNTech SE

17. Name and Title of the person responsible for review and evaluation of information relevant to the safety of the drug

Özlem Türeci, MD, Chief Medical Officer, BioNTech SE

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

18. Name of Sponsor or Sponsor's Authorized Representative

Neda Aghajani Memar, Pharm.D., Director, Pfizer Global Regulatory Affairs - Vaccines

19. Telephone Number *(Include country code if applicable and area code)*

(b) (6)

20. Facsimile (FAX) Number *(Include country code if applicable and area code)*

(845) 474-3500

21. Address

Address 1 *(Street address, P.O. box, company name c/o)*

235 East 42nd Street

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

219/9/69

City: New York

State/Province/Region: NY

Country: United States of America

ZIP or Postal Code: 10017

22. Email Address

(b) (6)

23. Date of Sponsor's Signature *(mm/dd/yyyy)*

07/13/2021

24. Name of Countersigner

25. Address of Countersigner

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City

State/Province/Region

Country: United States of America

ZIP or Postal Code

26. Email Address

WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

27. Signature of Sponsor or Sponsor's Authorized Representative

Neda Aghajani Memar

Digitally signed by Neda Aghajani Memar
DN: cn=Neda Aghajani Memar, o, ou, email (b) (6) c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2021.07.13 14:45:30 -04'00'

Sign

28. Signature of Countersigner

Sign

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

Please do NOT send your completed form to this PRA Staff email address.

Pfizer Global Regulatory Affairs
Pfizer Inc.
235 East 42nd Street/New York, NY 10017-5755

Global Product Development

14 July 2021

Marion Gruber, Ph.D.
Director
Office of Vaccines Research and Review
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

SN 0406

Re: Covid-19 Vaccine (BNT162/PF-07302048) BB-IND 19736

IND Amendment – Clinical Information Amendment

Dear Dr. Gruber,

Reference is made to BB-IND 19736 for the COVID-19 vaccine (BNT162; PF-07302048), which Pfizer and BioNTech are developing for the indication of active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The IND was effective on 29 April 2020.

Reference is also made to Study C4591001 protocol entitled, "*A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals*" and the current C4591001 Clinical Protocol incorporating Amendment 16 submitted to the IND on 02 June 2021 (SN 0353).

The purpose of this submission is to provide preliminary safety and immunogenicity data for C4591001 Phase 1 participants who completed the two-dose BNT162b2 30 µg series and then received a third (booster) dose of BNT162b2 30 µg, including SARS-CoV-2 serum neutralizing titers against wild-type (USA-WA1/2020) and B.1.351 lineage target strains determined before and after booster vaccination. The report, entitled Phase 1 Booster Safety and Immunogenicity Data up to 1 Month Post-Dose 3 of BNT162b2 30 µg in Study C4591001, is provided in Module 1.11.3.

This submission has been scanned for viruses using McAfee VirusScan Enterprise Version 8.8 and is virus free. The submission is being sent via the Gateway.

Should you have any questions regarding this submission, or require additional information, please contact me via phone at (b) (6); via facsimile at 845-474-3500; or via e-mail at (b) (6)

Sincerely,

Neda Aghajani Memar, Pharm.D.
Director
Pfizer Global Regulatory Affairs

CC: Ramachandra S. Naik, Ph.D.
CC: Laura Gottschalk, Ph.D.
CC: Captain Michael Smith, Ph.D.

COVID-19 Vaccine (BNT162, PF-07302048)

BB-IND 19736

Phase 1 Booster Safety and Immunogenicity Data up to 1 Month Post-Dose 3 of BNT162b2 30 µg in Study C4591001

July 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
BLA	Biologics License Application
CI	confidence interval
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Application
GMFR	geometric mean fold rise
GMT	geometric mean titer
IND	Investigational New Drug
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NT50	50% neutralizing titer
SAP	statistical analysis plan
SD	standard deviation
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19

1. BACKGROUND

Reference is made to BB-IND 19736 for the COVID-19 vaccine (BNT162; PF-07302048), which Pfizer and BioNTech are developing, and which is currently available in the United States (US) under Emergency Use Authorization (EUA) 27034 for the prevention of Coronavirus Disease 2019 (COVID-19) in individuals ≥12 years of age. The Investigational New Drug (IND) application was effective on 29 April 2020 and Pfizer initiated the pivotal clinical study (C4591001) in the United States on 04 May 2020.

C4591001 includes additional study groups to evaluate boostability. The purpose of this clinical information amendment is to provide preliminary safety and immunogenicity data for C4591001 Phase 1 participants who completed the two-dose BNT162b2 30 µg series and then received a third (booster) dose of BNT162b2 30 µg, including SARS-CoV-2 serum neutralizing titers against wild-type (USA-WA1/2020) and B.1.351 lineage target strains determined before and after booster vaccination.

2. STUDY C4591001 PHASE 1 BNT162B2 BOOSTER ANALYSIS

2.1. Study Design and Evaluations

C4591001 Phase 1 participants who were originally randomized to receive either BNT162b1 or BNT162b2 at dose levels of 10, 20, or 30 µg were offered booster vaccination with BNT162b2 at 30 µg, approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This Phase 1 booster group provided an early assessment of the safety and immunogenicity associated with a third vaccine dose against the SARS-CoV-2 reference strain and against a variant of interest.

Safety and immunogenicity associated with the two-dose regimen of BNT162b2 has been described previously.[1] These data were also included in the initial Biologics License Application (BLA) submitted to the US Food and Drug Administration (FDA) on 18 May 2021.

This submission includes preliminary findings from a subset of younger (18 to 55 years of age) and older (65 to 85 years of age) participants in the Phase 1 part of Study C4591001 who completed the initial two-dose series of BNT162b2 30 µg, given approximately 3 weeks apart, and then received a third dose (booster) of BNT162b2 30 µg approximately 7 to 9 months after the second dose. Data were collected through the cutoff date of 13 May 2021.

Details of booster group safety and immunogenicity analyses and methods are provided in Protocol C4591001 and in the Statistical Analysis Plan and summarized below.

2.2. Endpoints and Analysis Methods

2.2.1. Safety Endpoints and Analysis Methods

Safety evaluations after BNT162b2 Dose 3 (booster) included reports of local reactions (injection site pain, redness, swelling) and systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain, joint pain) and use of antipyretic medications in the 7 days after BNT162b2 booster administration as reported by participants in electronic

diaries. For comparison, reactogenicity data after the initial two-dose regimen of BNT162b2 (Dose 1 and Dose 2) are presented for these same participants who received the booster (Dose 3). The occurrence of adverse events (AEs) and serious AEs (SAEs) was assessed up to 1 month after BNT162b2 Dose 3.

Safety endpoints are presented as counts, percentages, and associated Clopper-Pearson 2-sided 95% CIs with AEs categorized by MedDRA term (version 23.1) for each group.

2.2.2. Immunogenicity Endpoints and Analysis Methods

A 50% plaque-reduction neutralization test (the highest serum dilution that prevented the formation of more than 50% of viral plaques) was used to determine geometric mean titers (GMTs) of serum-mediated virus suppression as described previously.[2,3]

SARS-CoV-2 50% neutralization titers were assessed in sera drawn before BNT162b2 Dose 1 (on Day 1); 7 days and 1 month after BNT162b2 Dose 2; before Dose 3; and 7 days and 1 month after Dose 3. Neutralization titers were determined as described previously against the designated wild-type (recombinant USA-WA1/2020) and against the B.1.351 (recombinant USA-WA1/2020 bearing the full spike gene from Beta variant) lineage target strains.[1,2] All samples from each of the time points were analyzed for this evaluation (ie, previously tested samples[1] were reanalyzed) to ensure the most accurate assessments of persistence of neutralizing antibodies and response to the third dose (booster) of BNT162b2.

SARS-CoV-2 serum neutralizing 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 fold rises (GMFRs) were calculated by exponentiating the mean of the difference of logarithmically transformed assay results. Geometric mean ratios (GMRs) between strains were calculated as the mean of the difference of logarithmically transformed neutralization titers for each participant (ie, B.1.351 strain minus wild-type strain) and exponentiating the mean. Associated 2-sided CIs for GMFRs and GMRs were obtained using the Student's *t* distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

2.3. Results

2.3.1. Safety Results

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

Study disposition and Dose 3 administration timing are summarized in Table 1 and Table 2. The mean time (SD) from the second to the third dose was similar in the younger (8.2 [0.27] months) and older (8.4 [0.12] months) age groups.

Demographic characteristics of Phase 1 participants have been reported previously[1] and are summarized for this booster analysis in Table 3.

Table 1. Disposition of All Randomized Subjects – Phase 1 Booster – Initial BNT162b2 (30 µg)

	Initial Age Group	
	18-55 Years of Age	65-85 Years of Age
	(N[a]=11) n[b] (%)	(N[a]=12) n[b] (%)
Received booster dose	11 (100.0)	12 (100.0)
Withdrawal from the study	0	0

a. N = number of randomized subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 08JUN2021 (16:52) Source Data: adds Table Generation: 09JUN2021 (05:51)
(Cutoff Date: 13MAY2021, Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster/adds_s002_disp_b2_p1

Table 2. Vaccine Administration Timing – Phase 1 Booster – Initial BNT162b2 (30 µg)

	Initial Age Group	
	18-55 Years of Age	65-85 Years of Age
	(N[a]=11) n[b] (%)	(N[a]=12) n[b] (%)
Dose 1	11 (100.0)	12 (100.0)
Dose 2[c]	11 (100.0)	12 (100.0)
<14 Days	0	0
14-20 Days	0	0
21-27 Days	11 (100.0)	12 (100.0)
28-34 Days	0	0
35-41 Days	0	0
42-48 Days	0	0
49-55 Days	0	0
>55 Days	0	0
Mean (SD)	21.3 (0.65)	21.0 (0.00)
Median	21.0	21.0
Min, Max	(21.0, 23.0)	(21.0, 21.0)

Table 2. Vaccine Administration Timing – Phase 1 Booster – Initial BNT162b2 (30 µg)

	Initial Age Group	
	18-55 Years of Age	65-85 Years of Age
	(N[a]=11) n[b] (%)	(N[a]=12) n[b] (%)
Received the booster vaccination[d]	11 (100.0)	12 (100.0)
<7 Months	0	0
7-<8 Months	3 (27.3)	0
8-<9 Months	8 (72.7)	12 (100.0)
≥9 Months	0	0
Mean (SD)	8.2 (0.27)	8.4 (0.12)
Median	8.2	8.4
Min, Max	(7.9, 8.8)	(8.2, 8.5)

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. Days calculated since Dose 1.
d. Months calculated since Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 08JUN2021 (16:52) Source Data: adsl Table Generation: 09JUN2021 (16:43)
(Cutoff Date: 13MAY2021, Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster/advx_s002_time_b2_p1

Table 3. Demographic Characteristics – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

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

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 08JUN2021 (16:52) Source Data: adsl Table Generation: 08JUN2021 (23:09)
(Cutoff Date: 13MAY2021, Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster/adsl_s005_demo_b2_p1

All 23 participants who received the third dose (booster) of BNT162b2 were included in the safety analysis. Overall, a third dose was well tolerated. 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 1; see also Table 4). 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 1; see also Table 4). 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.

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%) (Figure 2; see also Table 5). 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. 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%) (Figure 2; see also Table 5). 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. 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.

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

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

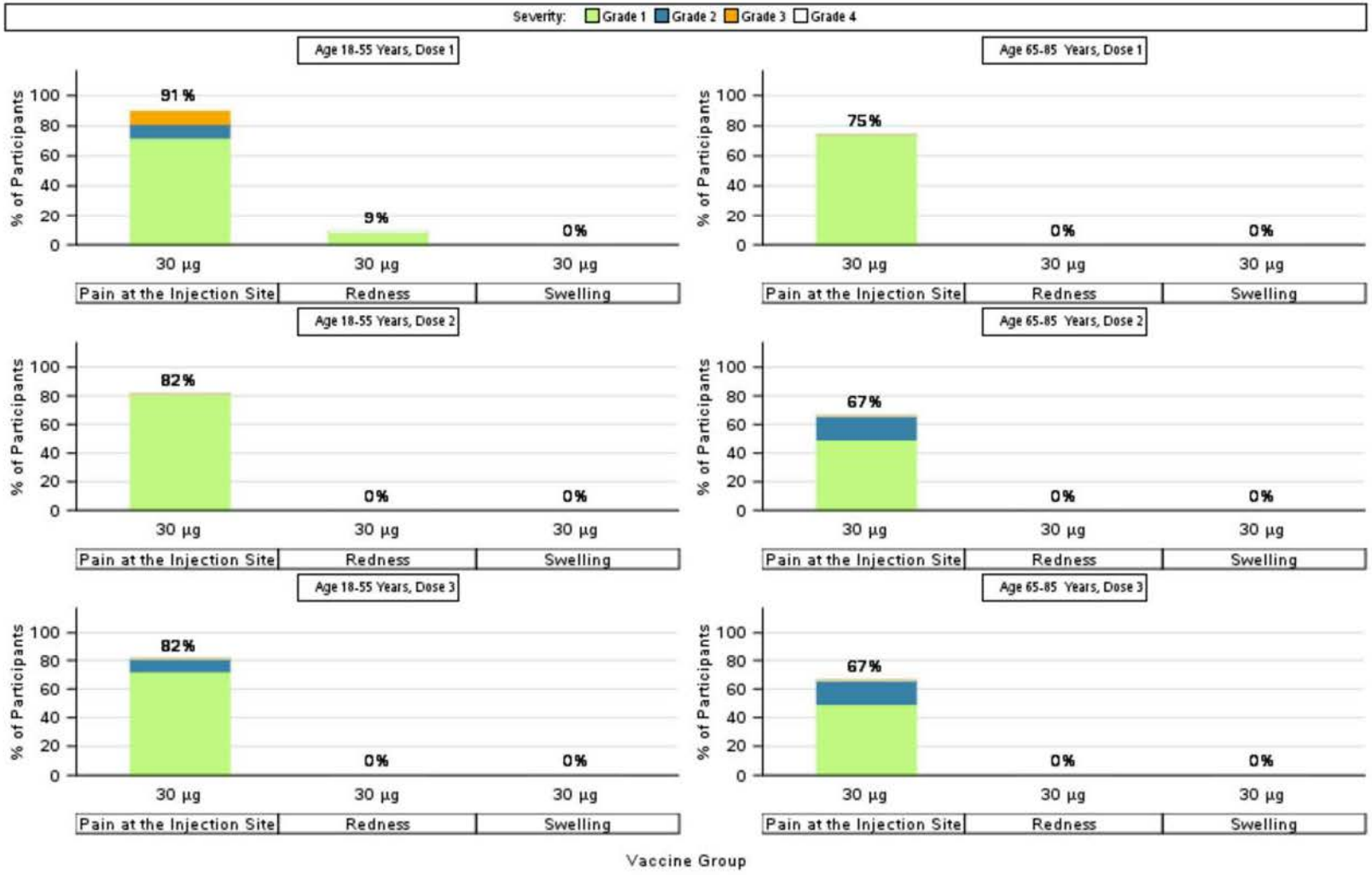
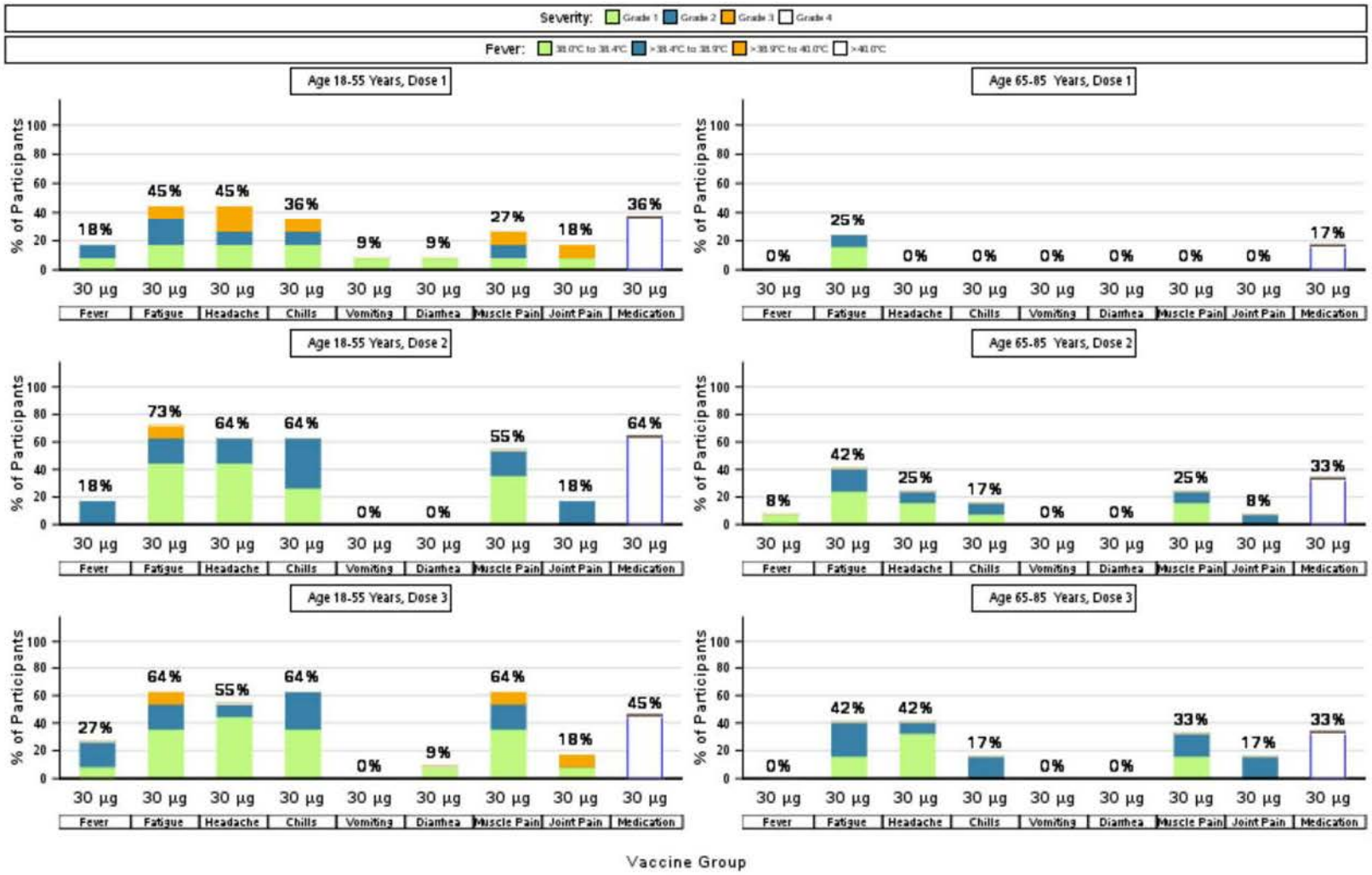


Figure 2. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population



2.3.2. Immunogenicity Results

The Dose 3 all-available immunogenicity population 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.

SARS-CoV-2 neutralization GMTs against the wild-type USA-WA1/2020 strain (a clinical strain isolated in January 2020) 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, those of the GMTs observed at 1 month after Dose 2 (Figure 3).

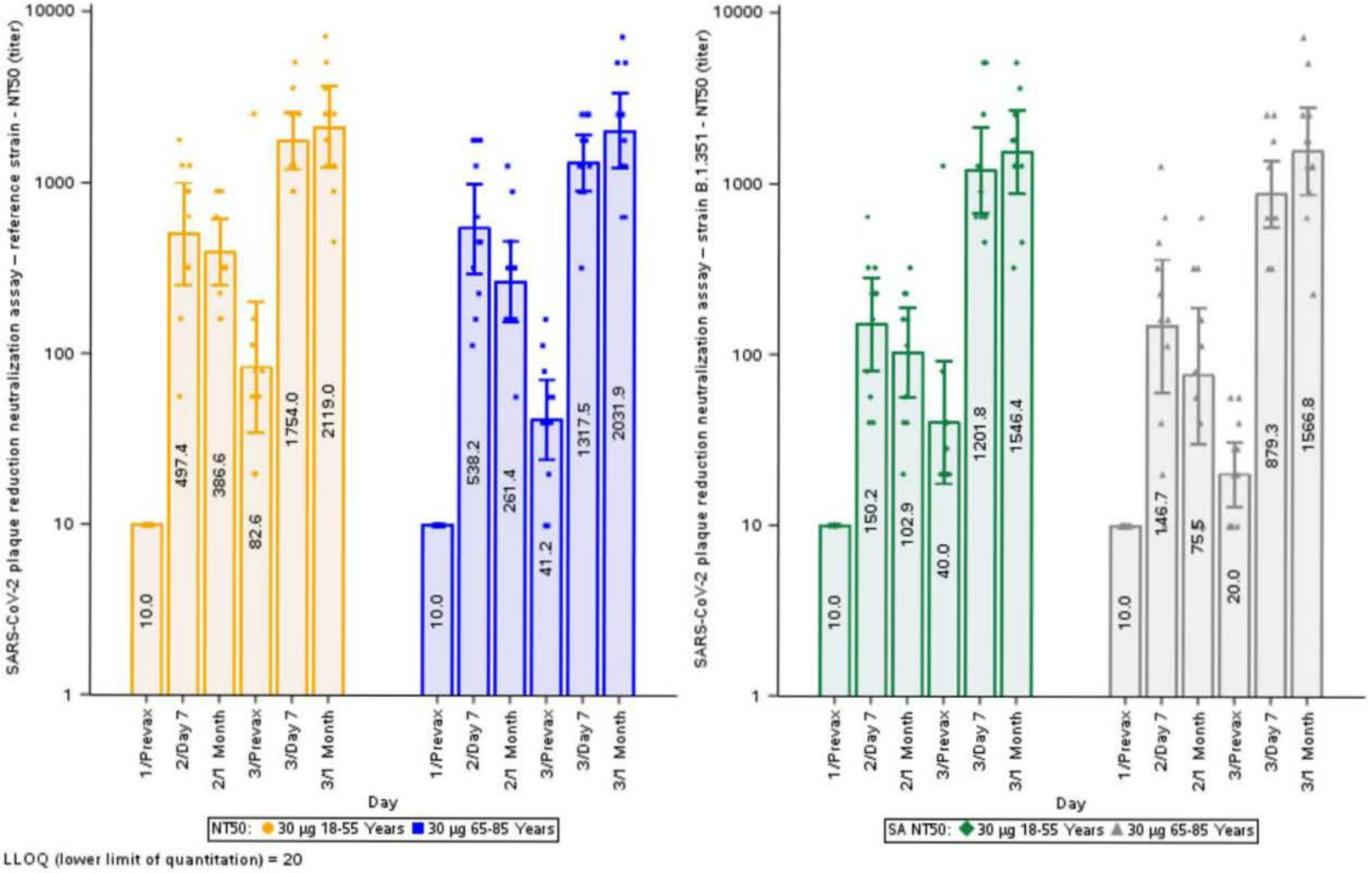
GMFRs against the wild-type strain from before Dose 3 to 1 month after Dose 3 were 25.7 (95% CI: 12.4, 53.3) for younger adults, and 49.4 (95% CI: 29.2, 83.3) for older adults (see Table 6).

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

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

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

Figure 3. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralizing Titers (NT50) – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population



LLOQ (lower limit of quantitation) = 20

2.4. 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 was safe, well tolerated, and highly immunogenic.

BNT162b2 Dose 3 boosted serum neutralizing responses against the original SARS-CoV-2 wild-type strain, resulting in an increase of neutralizing titers that were >5-fold those observed after Dose 2. A third dose also substantially boosted the serum neutralizing titers against recombinant SARS-CoV-2 with the B.1.351 (Beta) variant spike mutations to >15-fold those observed after the second dose. Furthermore, the difference in neutralizing titers against the wild-type and B.1.351 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. This phenomenon of increased magnitude and breadth of humoral response has also been observed when booster doses of pre-pandemic influenza vaccines were administered after a primary immunization series.[4]

Some SARS-CoV-2 variants have been associated with more rapid transmission, and potentially, greater pathogenicity,[5] 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 BNT162b2-immune sera neutralize all SARS-CoV-2 variants tested to date, including B.1.351 and B.1.617.2 (Delta variant).[2,6,7,8,9,10,11] 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 B.1.351 variant has remained very high, particularly for severe outcomes.[2,12,13] 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 8/9 cases after Dose 2 (all in placebo recipients) that had determinant sequences confirmed as caused by the B.1.351 variant.[12] 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.[13,14]

It is possible that protection against variants that show reduced neutralization by BNT162b2-immune sera could wane more quickly than protection against more readily neutralized strains. The high neutralizing titers against the B.1.351 strain after a third dose, exceeding those after two doses, and the more comparable titers between the wild-type and B.1.351 strains after Dose 3 is encouraging. These data suggest that a third dose could prolong protection and further increase the breadth of protection.

Correlates of protection have not been established for COVID-19; therefore, the durability of protection from vaccination and the required frequency of booster doses are unknown at this time. To date, results from the global Phase 1/2/3 study of BNT162b2 indicate robust protection lasting at least 6 months, despite modest waning of immunity over time.[12,15] Booster doses have the potential to keep protection high if immunity continues to decline over time.

Further studies of BNT162b2 booster dosing and boosting with vaccine candidates that use the same nucleoside-modified mRNA technology but encode spike glycoproteins from variants of concern, such as B.1.351, are ongoing or planned, including a study with a larger number of participants.

3. ADDITIONAL TABLES, LISTINGS, AND FIGURES

Table 4. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
1	Redness[d]						
	Any	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Swelling[d]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Unknown	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Pain at the injection site[e]						
	Any	11	10 (90.9)	(58.7, 99.8)	12	9 (75.0)	(42.8, 94.5)
	Mild	11	8 (72.7)	(39.0, 94.0)	12	9 (75.0)	(42.8, 94.5)
	Moderate	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any local reaction[f]	11	10 (90.9)	(58.7, 99.8)	12	9 (75.0)	(42.8, 94.5)
2	Redness[d]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Unknown	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Swelling[d]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Unknown	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)

Table 4. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Pain at the injection site[e]						
	Any	11	9 (81.8)	(48.2, 97.7)	12	8 (66.7)	(34.9, 90.1)
	Mild	11	9 (81.8)	(48.2, 97.7)	12	6 (50.0)	(21.1, 78.9)
	Moderate	11	0	(0.0, 28.5)	12	2 (16.7)	(2.1, 48.4)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any local reaction[f]	11	9 (81.8)	(48.2, 97.7)	12	8 (66.7)	(34.9, 90.1)
3	Redness[d]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Unknown	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Swelling[d]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Unknown	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Pain at the injection site[e]						
	Any	11	9 (81.8)	(48.2, 97.7)	12	8 (66.7)	(34.9, 90.1)
	Mild	11	8 (72.7)	(39.0, 94.0)	12	6 (50.0)	(21.1, 78.9)
	Moderate	11	1 (9.1)	(0.2, 41.3)	12	2 (16.7)	(2.1, 48.4)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any local reaction[f]	11	9 (81.8)	(48.2, 97.7)	12	8 (66.7)	(34.9, 90.1)
Any dose	Redness[d]						
	Any	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Swelling[d]						

Table 4. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Unknown	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Pain at the injection site[e]						
	Any	11	11 (100.0)	(71.5, 100.0)	12	11 (91.7)	(61.5, 99.8)
	Mild	11	8 (72.7)	(39.0, 94.0)	12	8 (66.7)	(34.9, 90.1)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	3 (25.0)	(5.5, 57.2)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any local reaction[f]	11	11 (100.0)	(71.5, 100.0)	12	11 (91.7)	(61.5, 99.8)

Note: Reactions were collected in the electronic diary (e-diary) from day of booster dose to Day 7 after vaccination.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
a. N = number of subjects reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Mild: >2.0 to 5.0 cm; moderate: >5.0 to 10.0 cm; severe: >10.0 cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
e. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.
f. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.
PFIZER CONFIDENTIAL SDTM Creation: 08JUN2021 (16:53) Source Data: adfacevd Table Generation: 09JUN2021 (17:13)
(Cutoff Date: 13MAY2021, Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster/adce_s010_lr_b2_p1

Table 5. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
1	Fever						
	≥38.0°C	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	≥38.0°C to 38.4°C	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	>38.4°C to 38.9°C	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	>38.9°C to 40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	>40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Fatigue[d]						
	Any	11	5 (45.5)	(16.7, 76.6)	12	3 (25.0)	(5.5, 57.2)
	Mild	11	2 (18.2)	(2.3, 51.8)	12	2 (16.7)	(2.1, 48.4)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	1 (8.3)	(0.2, 38.5)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Headache[d]						
	Any	11	5 (45.5)	(16.7, 76.6)	12	0	(0.0, 26.5)
	Mild	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Moderate	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Severe	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Chills[d]						
	Any	11	4 (36.4)	(10.9, 69.2)	12	0	(0.0, 26.5)
	Mild	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Moderate	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Vomiting[e]						
	Any	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Diarrhea[f]						
	Any	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)

Table 5. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened muscle pain[d]						
	Any	11	3 (27.3)	(6.0, 61.0)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened joint pain[d]						
	Any	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any systemic event[g]	11	8 (72.7)	(39.0, 94.0)	12	3 (25.0)	(5.5, 57.2)
	Use of antipyretic or pain medication[h]	11	4 (36.4)	(10.9, 69.2)	12	2 (16.7)	(2.1, 48.4)
2	Fever						
	≥38.0°C	11	2 (18.2)	(2.3, 51.8)	12	1 (8.3)	(0.2, 38.5)
	≥38.0°C to 38.4°C	11	0	(0.0, 28.5)	12	1 (8.3)	(0.2, 38.5)
	>38.4°C to 38.9°C	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	>38.9°C to 40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	>40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Fatigue[d]						
	Any	11	8 (72.7)	(39.0, 94.0)	12	5 (41.7)	(15.2, 72.3)
	Mild	11	5 (45.5)	(16.7, 76.6)	12	3 (25.0)	(5.5, 57.2)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	2 (16.7)	(2.1, 48.4)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Headache[d]						
	Any	11	7 (63.6)	(30.8, 89.1)	12	3 (25.0)	(5.5, 57.2)
	Mild	11	5 (45.5)	(16.7, 76.6)	12	2 (16.7)	(2.1, 48.4)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	1 (8.3)	(0.2, 38.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Chills[d]						

Table 5. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Any	11	7 (63.6)	(30.8, 89.1)	12	2 (16.7)	(2.1, 48.4)
	Mild	11	3 (27.3)	(6.0, 61.0)	12	1 (8.3)	(0.2, 38.5)
	Moderate	11	4 (36.4)	(10.9, 69.2)	12	1 (8.3)	(0.2, 38.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Vomiting[e]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Diarrhea[f]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened muscle pain[d]						
	Any	11	6 (54.5)	(23.4, 83.3)	12	3 (25.0)	(5.5, 57.2)
	Mild	11	4 (36.4)	(10.9, 69.2)	12	2 (16.7)	(2.1, 48.4)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	1 (8.3)	(0.2, 38.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened joint pain[d]						
	Any	11	2 (18.2)	(2.3, 51.8)	12	1 (8.3)	(0.2, 38.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	1 (8.3)	(0.2, 38.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any systemic event[g]	11	11 (100.0)	(71.5, 100.0)	12	7 (58.3)	(27.7, 84.8)
	Use of antipyretic or pain medication[h]	11	7 (63.6)	(30.8, 89.1)	12	4 (33.3)	(9.9, 65.1)
3	Fever						
	≥38.0°C	11	3 (27.3)	(6.0, 61.0)	12	0	(0.0, 26.5)
	≥38.0°C to 38.4°C	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	>38.4°C to 38.9°C	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)

Table 5. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	>38.9°C to 40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	>40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Fatigue[d]						
	Any	11	7 (63.6)	(30.8, 89.1)	12	5 (41.7)	(15.2, 72.3)
	Mild	11	4 (36.4)	(10.9, 69.2)	12	2 (16.7)	(2.1, 48.4)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	3 (25.0)	(5.5, 57.2)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Headache[d]						
	Any	11	6 (54.5)	(23.4, 83.3)	12	5 (41.7)	(15.2, 72.3)
	Mild	11	5 (45.5)	(16.7, 76.6)	12	4 (33.3)	(9.9, 65.1)
	Moderate	11	1 (9.1)	(0.2, 41.3)	12	1 (8.3)	(0.2, 38.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Chills[d]						
	Any	11	7 (63.6)	(30.8, 89.1)	12	2 (16.7)	(2.1, 48.4)
	Mild	11	4 (36.4)	(10.9, 69.2)	12	0	(0.0, 26.5)
	Moderate	11	3 (27.3)	(6.0, 61.0)	12	2 (16.7)	(2.1, 48.4)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Vomiting[e]						
	Any	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Mild	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Diarrhea[f]						
	Any	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened muscle pain[d]						
	Any	11	7 (63.6)	(30.8, 89.1)	12	4 (33.3)	(9.9, 65.1)
	Mild	11	4 (36.4)	(10.9, 69.2)	12	2 (16.7)	(2.1, 48.4)
	Moderate	11	2 (18.2)	(2.3, 51.8)	12	2 (16.7)	(2.1, 48.4)

Table 5. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened joint pain[d]						
	Any	11	2 (18.2)	(2.3, 51.8)	12	2 (16.7)	(2.1, 48.4)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	2 (16.7)	(2.1, 48.4)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any systemic event[g]	11	10 (90.9)	(58.7, 99.8)	12	8 (66.7)	(34.9, 90.1)
	Use of antipyretic or pain medication[h]	11	5 (45.5)	(16.7, 76.6)	12	4 (33.3)	(9.9, 65.1)
Any dose	Fever						
	≥38.0°C	11	5 (45.5)	(16.7, 76.6)	12	1 (8.3)	(0.2, 38.5)
	≥38.0°C to 38.4°C	11	1 (9.1)	(0.2, 41.3)	12	1 (8.3)	(0.2, 38.5)
	>38.4°C to 38.9°C	11	4 (36.4)	(10.9, 69.2)	12	0	(0.0, 26.5)
	>38.9°C to 40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	>40.0°C	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Fatigue[d]						
	Any	11	9 (81.8)	(48.2, 97.7)	12	7 (58.3)	(27.7, 84.8)
	Mild	11	3 (27.3)	(6.0, 61.0)	12	3 (25.0)	(5.5, 57.2)
	Moderate	11	3 (27.3)	(6.0, 61.0)	12	4 (33.3)	(9.9, 65.1)
	Severe	11	3 (27.3)	(6.0, 61.0)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Headache[d]						
	Any	11	10 (90.9)	(58.7, 99.8)	12	5 (41.7)	(15.2, 72.3)
	Mild	11	5 (45.5)	(16.7, 76.6)	12	4 (33.3)	(9.9, 65.1)
	Moderate	11	3 (27.3)	(6.0, 61.0)	12	1 (8.3)	(0.2, 38.5)
	Severe	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Chills[d]						
	Any	11	9 (81.8)	(48.2, 97.7)	12	4 (33.3)	(9.9, 65.1)
	Mild	11	3 (27.3)	(6.0, 61.0)	12	1 (8.3)	(0.2, 38.5)
	Moderate	11	5 (45.5)	(16.7, 76.6)	12	3 (25.0)	(5.5, 57.2)
	Severe	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)

Table 5. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Vomiting[e]						
	Any	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Diarrhea[f]						
	Any	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Mild	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Moderate	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Severe	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened muscle pain[d]						
	Any	11	9 (81.8)	(48.2, 97.7)	12	5 (41.7)	(15.2, 72.3)
	Mild	11	4 (36.4)	(10.9, 69.2)	12	3 (25.0)	(5.5, 57.2)
	Moderate	11	3 (27.3)	(6.0, 61.0)	12	2 (16.7)	(2.1, 48.4)
	Severe	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	New or worsened joint pain[d]						
	Any	11	4 (36.4)	(10.9, 69.2)	12	2 (16.7)	(2.1, 48.4)
	Mild	11	1 (9.1)	(0.2, 41.3)	12	0	(0.0, 26.5)
	Moderate	11	1 (9.1)	(0.2, 41.3)	12	2 (16.7)	(2.1, 48.4)
	Severe	11	2 (18.2)	(2.3, 51.8)	12	0	(0.0, 26.5)
	Grade 4	11	0	(0.0, 28.5)	12	0	(0.0, 26.5)
	Any systemic event[g]	11	11 (100.0)	(71.5, 100.0)	12	10 (83.3)	(51.6, 97.9)
	Use of antipyretic or pain medication[h]	11	9 (81.8)	(48.2, 97.7)	12	7 (58.3)	(27.7, 84.8)

Note: Events were collected in the electronic diary (e-diary) from day of booster dose to Day 7 after vaccination. Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of subjects reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration;

Table 5. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 Booster – Initial BNT162b2 (30 µg) – Safety Population

		Initial Age Group					
		18-55 Years of Age			65-85 Years of Age		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])

Grade 4: emergency room visit or hospitalization for severe vomiting.
f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
g. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
h. Severity was not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 08JUN2021 (16:53) Source Data: adfacevd Table Generation: 09JUN2021 (17:12)
(Cutoff Date: 13MAY2021, Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster/adce_s020_se_b2_p1

Table 6. Summary of Geometric Mean Fold Rises From Before Vaccination to Each Subsequent Time Point – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population

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

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: GMFR for after booster dose is based on pre-booster dose visit. For all other visits GMFR is based on pre-dose 1 visit.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point.
c. GMFRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 08JUN2021 (16:53) Source Data: adva Table Generation: 09JUN2021 (05:18)
(Cutoff Date: 13MAY2021, Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster/adva_s002_gmfr_b2_aai_p1

4. REFERENCES

1 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;383:2439-50.

2 Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum. N Engl J Med 2021;384:1466-8.

3 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.

4 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.

5 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

6 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/

7 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.

8 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.

9 Muik A, Wallisch AK, Sänger 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.

10 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

11 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

12 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].

13 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

14 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

15 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.

Document Approval Record

Document Name:	C4591001 Phase 1 Booster Dosing - July 2021 - Clinical Information Amendment
Document Title:	C4591001 Phase 1 Booster Dosing - July 2021 - Clinical Information Amendment

Signed By:	Date(GMT)	Signing Capacity
Lockhart, Stephen Paul	13-Jul-2021 17:04:33	Business Line Approver

COVID-19 Vaccine (BNT162, PF-07302048)

IND BB-19,736

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

August 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
BLA	Biologics License Application
CI	confidence interval
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
EMA	European Medicines Agency
EUA	Emergency Use Application
FDA	Food and Drug Administration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
IND	Investigational New Drug
LLOQ	lower limit of quantitation
MAA	Marketing Authorization Application
NT50	50% neutralizing titer
PRNT	plaque-reduction neutralization test
SAP	statistical analysis plan
SD	standard deviation
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19

1. BACKGROUND

Reference is made to the COVID-19 vaccine (BNT162b2; PF-07302048; COMIRNATY), which Pfizer and BioNTech are developing.

In the United States (US), the Investigational New Drug (IND 19,736) application was effective on 29 April 2020 and Pfizer initiated the pivotal clinical study (C4591001) in the United States on 04 May 2020. The vaccine is currently available in the US under Emergency Use Authorization (EUA 27034) for the prevention of COVID-19 in individuals ≥12 years of age. A Biologics License Application (BLA) was submitted to the US Food and Drug Administration (FDA) on 18 May 2021 for individuals ≥16 years of age and is under review at this time.

A Marketing Authorization Application (MAA) was submitted to the European Medicines Agency (EMA) via a rolling review procedure that completed on 07 December 2020. Conditional marketing authorization was granted by EMA on 21 December 2020 for individuals ≥16 years of age and was subsequently expanded based on a Type II Variation approved on 28 May 2021 to include individuals ≥12 years of age.

Prior authorizations/approvals were based on pivotal data from Phase 1/2/3 Study C4591001. Study C4591001 includes additional study groups to evaluate boostability. The purpose of this report is to provide preliminary immunogenicity data for C4591001 Phase 1 participants who completed the two-dose BNT162b2 30 µg series and then received a third (booster) dose of BNT162b2 30 µg approximately 6 to 12 months later, including SARS-CoV-2 serum neutralizing titers against wild-type (USA-WA1/2020) and B.1.617.2 (Delta) variant lineages.

2. STUDY C4591001 PHASE 1 BNT162B2 BOOSTER ANALYSIS

2.1. Immunogenicity Endpoints and Analysis Methods

Details of booster group immunogenicity analyses and methods are provided in Protocol C4591001 and in the Statistical Analysis Plan and summarized below.

2.1.1. Endpoints

A 50% plaque-reduction neutralization test (PRNT) was used to determine neutralizing titers of serum-mediated virus suppression as described previously.[1,2]

PRNT titers were assessed in sera 1 month after BNT162b2 Dose 2 and 1 month after Dose 3. PRNT titers were determined as described previously against the designated wild-type (recombinant USA-WA1/2020; clinical strain isolated in January 2020) and against B.1.617.2 (recombinant USA-WA1/2020 with the full spike gene from the Delta variant).[1,3] All samples from each of the time points were analyzed for this evaluation (ie, previously tested samples[3] were reanalyzed to ensure comparability of neutralization titers against 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.

2.1.2. Analysis Methods

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) between 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.

2.1.3. Analysis Sets

The Dose 3 booster evaluable immunogenicity population included all participants who received Doses 1 and 2 of BNT162b2 as initially randomized, received Dose 3 of BNT162b2, had at least 1 valid and determinate immunogenicity result after Dose 3, and did not have any important protocol deviations.

The Dose 3 booster all-available immunogenicity population included all participants who received Doses 1 and 2 of BNT162b2 as initially randomized, received Dose 3 of BNT162b2, and had at least 1 valid and determinate immunogenicity result after Dose 3.

2.2. Immunogenicity Results

Immunogenicity associated with the two-dose regimen of BNT162b2 has been described previously and was submitted previously.[3]

Preliminary data from Study C4591001 Phase 1 booster (Dose 3) immunogenicity results are presented below for the Dose 3 booster evaluable immunogenicity population. Similar results were obtained for the Dose 3 booster all-available population as provided in Section 3.

Assay data for Phase 1 participants analyzed are listed in 16.2.6.1.1 Listing of Assay Data – Phase 1 Booster – Initial BNT162b2 (30 µg).

2.2.1. Disposition and Datasets Analyzed

PRNT titers were obtained from 23 participants in the Dose 3 booster all-available immunogenicity population (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). The PRNT assay is described in Section 2.1.2.

The Dose 3 booster evaluable immunogenicity population included 21 participants (N=10 in the younger age group and N=11 in the older age group).

2.2.2. SARS-CoV-2 Neutralizing Titers

Geometric Mean Titers (GMTs)

Neutralizing GMTs against recombinant virus with the Delta variant spike on a wild-type genetic background showed a similar pattern of higher, broader neutralizing titers after Dose 3 as compared to after Dose 2 (Figure 1, Table 1).

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

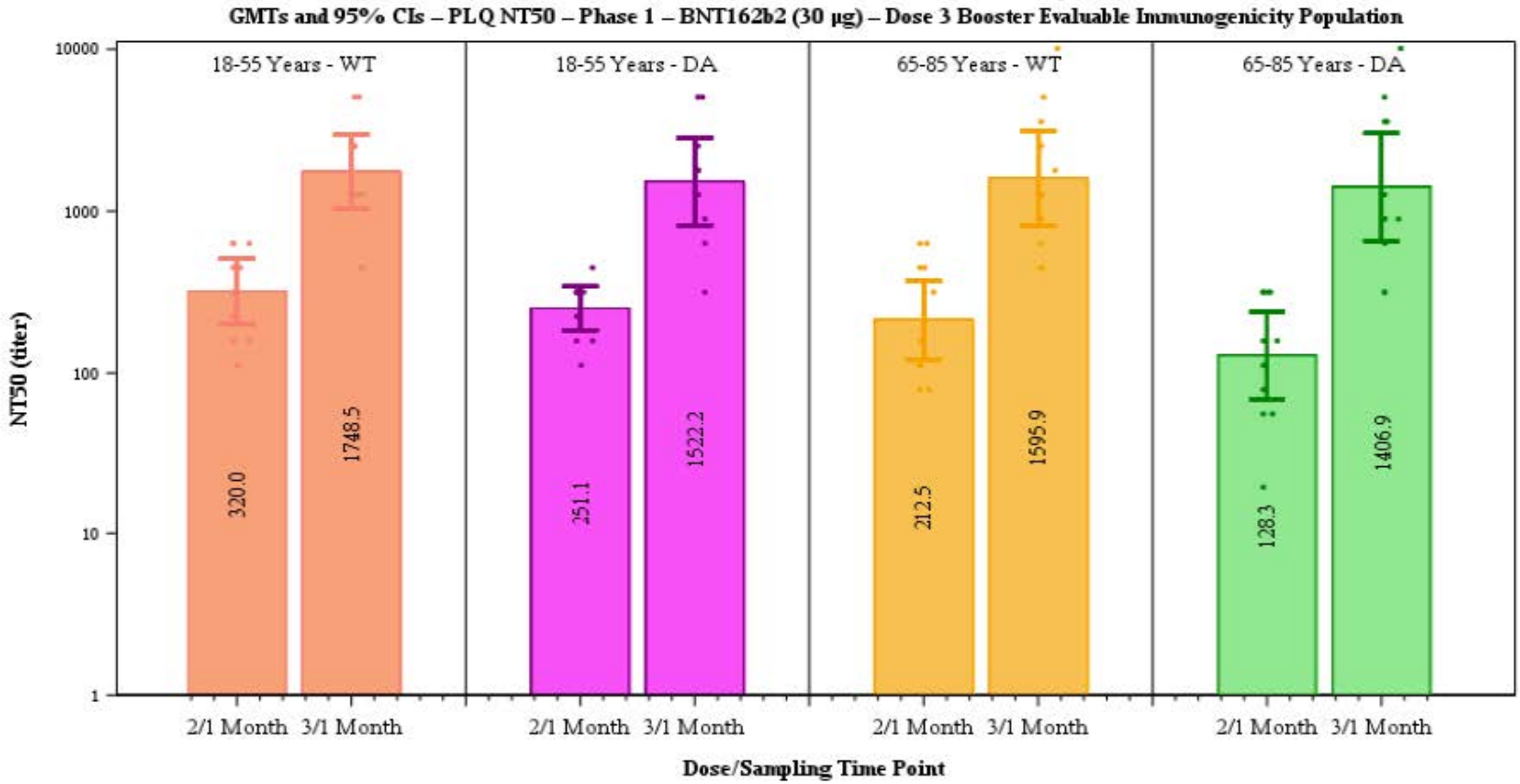
A third dose of BNT162b2 administered 7 to 9 months after the original two-dose series also increased the neutralizing titers against the B.1.617.2 (Delta) variant strain. At 1 month after Dose 3, GMTs were 1522.2 (95% CI: 817.9, 2833.0) for younger adults, and 1406.9 (95% CI: 654.1, 3025.8) for older adults, which were approximately 6-fold and 11-fold, respectively, those of the GMTs observed at 1 month after Dose 2 (Figure 1, Table 1).

Geometric Mean Ratios (GMRs)

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

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

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



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

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

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

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

a. Protocol-specified timing for blood sample collection.

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

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

PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (13:30)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster_Delta/adva_s001_gm_b2_eval_da_p1

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

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

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

a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for both the specified assays at the given dose/sampling time point.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean differences in the logarithms of the assays and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (20:34)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001 P1 Booster Delta/adva s004 gm b2 eval da p1 1

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

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

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

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

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

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

PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (19:49)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster_Delta/adva_s004_gm_b2_eval_da_p1

2.3. 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 increased neutralizing titers to the wild-type and B.1.617.2 (Delta) recombinant SARS-CoV-2 test strains to 4.76 to 7.51 times the titers seen after two vaccine doses. Furthermore, the observed difference in neutralizing titers against the wild-type and B.1.617.2 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. These data suggest that a third dose of BNT162b2 could prolong protection and further increase the breadth of protection against COVID-19.

This phenomenon of increased magnitude and breadth of humoral response has also been observed when booster doses of pre-pandemic influenza vaccines were administered after a primary immunization series.[4]

Some SARS-CoV-2 variants have been associated with more rapid transmission, and potentially, greater pathogenicity,[5] 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 BNT162b2-immune sera neutralize all SARS-CoV-2 variants tested to date, including B.1.351 and B.1.617.2 (Delta variant).[1,6,7,8,9,10,11] 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 B.1.351 variant has remained very high, particularly for severe outcomes.[1,12,13] 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 8/9 cases after Dose 2 (all in placebo recipients) for which the lineage of the infecting virus could be determined caused by the B.1.351 variant.[12] 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.[13,14]

Correlates of protection have not been established for COVID-19; therefore, the durability of protection from vaccination and the required frequency of booster doses are unknown at this time. To date, results from the global Phase 1/2/3 study of BNT162b2 indicate robust protection from COVID-19 lasting at least 6 months, despite modest waning of immunity over time.[12,15] Booster doses have the potential to keep protection high if immunity continues to decline over time.

Further studies of BNT162b2 booster dosing and boosting with vaccine candidates that use the same nucleoside-modified mRNA technology but encode spike glycoproteins from variants of concern, such as B.1.351 and B.1.617.2, are ongoing or planned, respectively, including a study with a larger number of participants and randomization of participants to booster or placebo.

3. ADDITIONAL TABLES, FIGURES, AND LISTINGS

Table 4. Summary of Geometric Mean Titers – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Initial Age Group: 18-55 Years of Age n[b]	18-55 Years of Age GMT[c] (95% CI[c])	Initial Age Group: 65-85 Years of Age n[b]	65-85 Years of Age GMT[c] (95% CI[c])
SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	2/1 Month	11	310.1 (203.3, 473.0)	12	195.8 (114.7, 334.4)
	3/1 Month	11	1546.4 (896.9, 2666.0)	12	1612.7 (875.5, 2970.8)
SARS-CoV-2 plaque reduction neutralization assay – strain B.1.617.2 (delta) - NT50 (titer)	2/1 Month	11	241.0 (180.1, 322.4)	12	123.4 (70.2, 216.9)
	3/1 Month	11	1321.0 (698.5, 2498.3)	12	1478.9 (734.9, 2975.8)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assays at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (13:30)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster_Delta/adva_s001_gm_b2_aai_da_p1

Table 5. Summary of Geometric Mean Ratios – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population

		Initial Age Group			
		18-55 Years of Age		65-85 Years of Age	
Assay	Dose/Sampling Time Point[a]	n[b]	GMR[c] (95% CI[c])	n[b]	GMR[c] (95% CI[c])
SARS-CoV-2 plaque reduction neutralization assay – strain B.1.617.2 (delta) - NT50 (titer) to reference strain - NT50 (titer)	2/1 Month	11	0.78 (0.63, 0.96)	12	0.63 (0.46, 0.86)
	3/1 Month	11	0.85 (0.71, 1.03)	12	0.92 (0.71, 1.18)

Abbreviations: GMR = geometric mean ratio; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for both the specified assays at the given dose/sampling time point.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean differences in the logarithms of the assays and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (20:33)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster_Delta/adva_s004_gm_b2_aai_da_p1_1

Table 6. Summary of Geometric Mean Ratios – Comparison of 1 Month After Dose 3 to 1 Month After Dose 2 – Phase 1 Booster – Initial BNT162b2 (30 µg) – Dose 3 Booster All-Available Immunogenicity Population

Assay		Initial Age Group							
		18-55 Years of Age			65-85 Years of Age				
		1 Month After Dose 2 (BNT162b2)	1 Month After Dose 3	1 Month After Dose 3/1 Month After Dose 2	1 Month After Dose 2 (BNT162b2)	1 Month After Dose 3	1 Month After Dose 3/1 Month After Dose 2		
Assay at 1 Month After Dose 2	Assay at 1 Month After Dose 3	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (95% CI[c])	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (95% CI[c])
SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	11	310.1 (203.3, 473.0)	1546.4 (896.9, 2666.0)	4.99 (2.81, 8.84)	12	195.9 (114.7, 334.4)	1612.7 (875.5, 2970.8)	8.23 (5.08, 13.35)
SARS-CoV-2 plaque reduction neutralization assay – reference strain - NT50 (titer)	SARS-CoV-2 plaque reduction neutralization assay – strain B.1.617.2 (delta) - NT50 (titer)	11	310.1 (203.3, 473.0)	1321.0 (698.5, 2498.3)	4.26 (2.30, 7.88)	12	195.9 (114.7, 334.4)	1478.9 (734.9, 2975.8)	7.55 (4.03, 14.16)

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

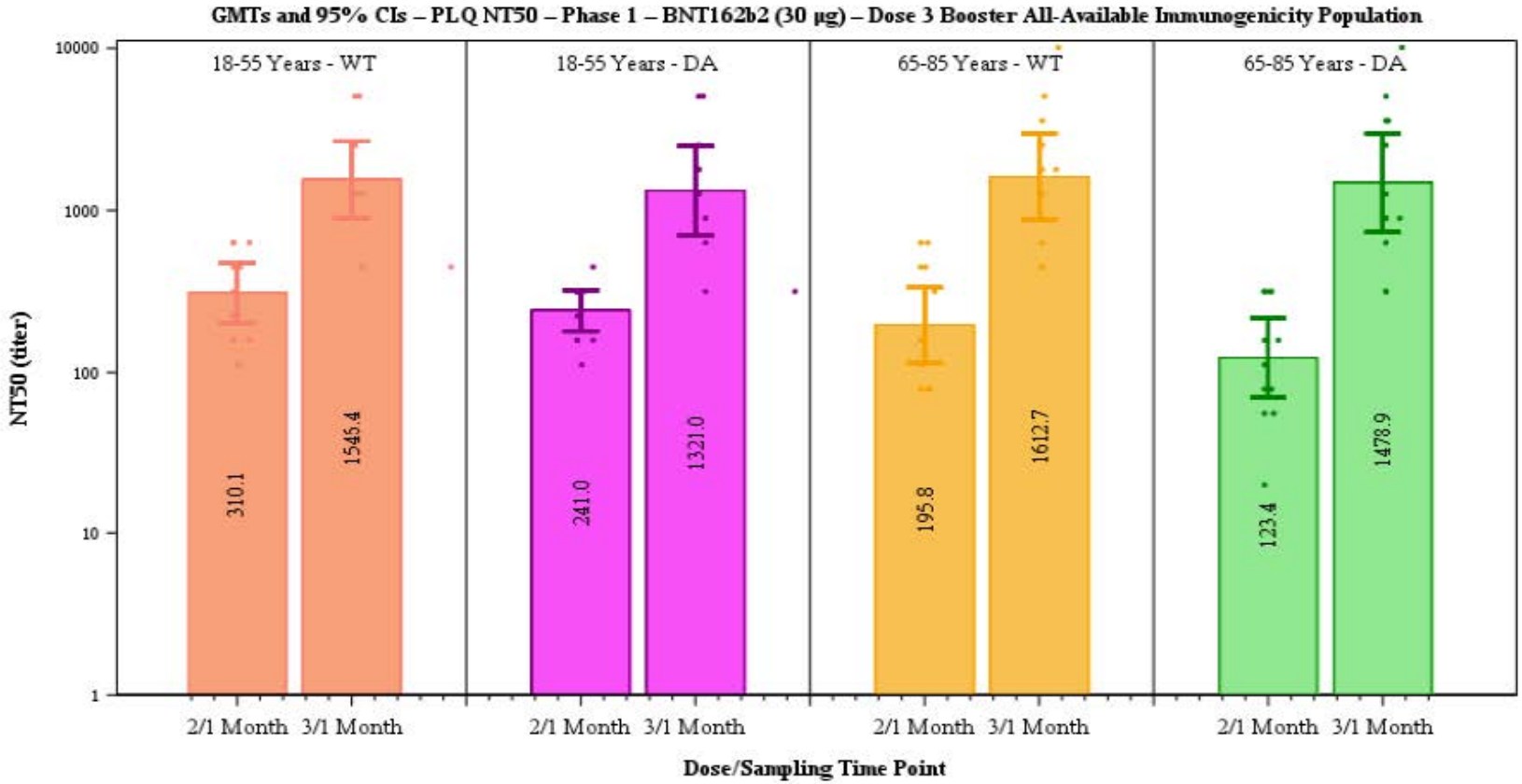
a. n = Number of subjects with valid and determinate assay results for the specified assays at both time points under given age group.

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

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

PFIZER CONFIDENTIAL SDTM Creation: 05AUG2021 (11:22) Source Data: adva Table Generation: 05AUG2021 (19:49)
(Data Cutoff Date: 13MAY2021, Database Snapshot Date: 08JUN2021) Output File: ./nda3/C4591001_P1_Booster_Delta/adva_s004_gm_b2_aai_da_p1

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



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_p1

4. REFERENCES

1 Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum. N Engl J Med 2021;384:1466-8.

2 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.

3 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;383:2439-50.

4 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.

5 US Centers for Disease Control and Prevention (CDC). SARS-CoV-2 Variant Classifications and Definitions. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html#print. Accessed 04 May 2021.

6 World Health Organization (WHO). Tracking SARS-CoV-2 variants. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed 22 June 2021.

7 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.

8 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.

9 Muik A, Wallisch AK, Sänger 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.

10 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

11 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

12 Thomas SJ, Moreira ED, Kitchin N, et al. Six month safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. medRxiv 2021. Preprint. [ePub];doi:10.1101/2021.07.28.21261159.

13 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

14 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

15 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.

Document Approval Record

Document Name:	C4591001 Phase 1 Sentinel Booster (Dose 3) Delta Data Clinical Information Amendment (Aug 2021)
Document Title:	C4591001 Phase 1 Sentinel Booster (Dose 3) Delta Data Clinical Information Amendment (Aug 2021)

Signed By:	Date(GMT)	Signing Capacity
Perez, John	13-Aug-2021 15:11:21	Final Approval

Pfizer Global Regulatory Affairs
Pfizer Inc.
235 East 42nd Street/New York, NY 10017-5755

Global Product Development

16 August 2021

Marion Gruber, Ph.D.
Director
Office of Vaccines Research and Review
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

SN 0453

Re: COVID-19 Vaccine (BNT162/PF-07302048) BB-IND 19736

IND Amendment – Clinical Information Amendment Phase 1 Booster (Dose 3) Immunogenicity at 1 Month Post-Dose 3 in Study C4591001: SARSCoV2 Wild-Type and Delta Variant Neutralization Data

Dear Dr. Gruber,

Reference is made to BB-IND 19736 for the COVID-19 Vaccine (BNT162; PF-07302048), which Pfizer and BioNTech are developing for the indication of active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The IND was effective on 29 April 2020.

Reference is also made to the following:

- Study C4591001 protocol entitled, "*A Phase 1/2/3, Placebo Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals"* and the current C4591001 Clinical Protocol incorporating Amendment 17 submitted to the IND on 20 July 2021 (SN 0413).
- The Biologics License Application (BLA) 125742 submitted 19 May 2021 for the COVID-19 mRNA Vaccine (BNT162; PF-07302048), developed by BioNTech and Pfizer under BB-IND 19736 for the prevention of COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age currently under review.
- Phase 1 Booster Safety and Immunogenicity Data up to 1 Month Post-Dose 3 of BNT162b2 30 µg in Study C4591001 which provide preliminary safety and immunogenicity data for C4591001 Phase 1 participants who completed the two-dose BNT162b2 30 µg series and then received a third (booster) dose of BNT162b2 30 µg,

including SARS-CoV-2 serum neutralizing titers against wild-type (USA-WA1/2020) and B.1.351 lineage target strains determined before and after booster vaccination submitted to BB-IND 19736 on 14 July 2021 (SN 0406).

The purpose of this submission is to provide additional preliminary immunogenicity data for C4591001 Phase 1 participants (same participants included in the Phase 1 Booster Safety and Immunogenicity Data up to 1 Month Post-Dose 3 of BNT162b2 30 µg in Study C4591001 submitted on 14 July 2021;SN 0406), who completed the two-dose BNT162b2 30 µg series and then received a third (booster) dose of BNT162b2 30 µg approximately 6 to 12 months later, with SARS-CoV-2 serum neutralizing titers against the **B.1.617.2 (Delta) variant lineages**. The report, entitled Phase 1 Booster (Dose 3) Immunogenicity at 1 Month Post-Dose 3 in Study C4591001: SARS-CoV-2 Wild-Type and Delta Variant Neutralization Data, is provided in Module 1.11.3. These initial immunogenicity data (wild-type (USA-WA1/2020), B.1.351, and B.1.617.2 (Delta)), along with the Phase 3 safety and immunogenicity results, will be included in the planned sBLA to request licensure of a third, or booster dose of BNT162b2 for use in individuals 16 years of age and older. The planned Booster Dose sBLA will be submitted immediately following the full approval of BLA 125742.

This submission has been scanned for viruses using McAfee VirusScan Enterprise Version 8.8 and is virus free. The submission is being sent via the Gateway.

Should you have any questions regarding this submission, or require additional information, please contact me via phone at (b) (6); via facsimile at 845-474-3500; or via e-mail at (b) (6).

Sincerely,

Neda Aghajani Memar, Pharm.D.
Director
Pfizer Global Regulatory Affairs

CC: Ramachandra S. Naik, Ph.D.
CC: Laura Gottschalk, Ph.D.
CC: Captain Michael Smith, Ph.D.

Next Page | Export Data | Import Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
BioNTech SE

2. Date of Submission *(mm/dd/yyyy)*
08/16/2021

3. Sponsor Address

Address 1 *(Street address, P.O. box, company name c/o)*
An der Goldgrube 12

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City
Mainz

State/Province/Region
N/A

Country
Germany

ZIP or Postal Code
55131

4. Telephone Number *(Include country code if applicable and area code)*
215-280-5503

6A. IND Number *(If previously assigned)*
019736

6B. Select One: ☑ Commercial ☐ Research

5. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
COVID-19 Vaccine (BNT162, PF-07302048)

Continuation Page for #5

7A. (Proposed) Indication for Use
Active immunization to prevent COVID-19 caused by SARS-CoV-2

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☑ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☑ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #7

7B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*

8. Phase of Clinical Investigation to be conducted ☑ Phase 1 ☑ Phase 2 ☑ Phase 3 ☐ Other *(Specify)*:

9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
BB-IND 013812, BB-IND 013278, BLA 125549

10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..

Serial Number: 0 4 5 3

11. This submission contains the following *(Select all that apply)*

☐ Initial Investigational New Drug Application (IND)
☐ Response to Clinical Hold
☐ Response To FDA Request For Information
☐ Request For Reactivation Or Reinstatement
☐ Annual Report
☐ General Correspondence
☐ Development Safety Update Report (DSUR)
☐ Other *(Specify)*:

Protocol Amendment
☐ New Protocol
☐ Change in Protocol
☐ New Investigator
☐ PMR/PMC Protocol
☐ Human Factors Protocol

Information Amendment
☐ Chemistry/Microbiology
☐ Pharmacology/Toxicology
☑ Clinical/Safety
☐ Statistics
☐ Clinical Pharmacology

Request for
☐ Meeting
☐ Proprietary Name Review
☐ Special Protocol Assessment
☐ Formal Dispute Resolution

IND Safety Report
☐ Initial Written Report
☐ Follow-up to a Written Report

12. For Originals, is the product a combination product (21 CFR 3.2(e))? ☐ Yes ☐ No

Combination Product Type *(See instructions)*

Request for Designation (RFD) Number

13. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*

☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8

Expanded Access Use, 21 CFR 312.300

☐ Individual Patient, Non-Emergency 21 CFR 312.310
☐ Intermediate Size Patient Population, 21 CFR 312.315
☐ Individual Patient, Emergency 21 CFR 312.310(d)
☐ Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only

CBER/DCC Receipt Stamp	DDR Receipt Stamp	Division Assignment
		IND Number Assigned

14. Contents of Application – This application contains the following items *(Select all that apply)*

- ☑ 1. Form FDA 1571 *(21 CFR 312.23(a)(1))*
- ☐ 2. Table of Contents *(21 CFR 312.23(a)(2))*
- ☐ 3. Introductory statement *(21 CFR 312.23(a)(3))*
- ☐ 4. General Investigational plan *(21 CFR 312.23(a)(3))*
- ☐ 5. Investigator's brochure *(21 CFR 312.23(a)(5))*
- ☐ 6. Protocol *(21 CFR 312.23(a)(6))*
  - ☐ a. Study protocol *(21 CFR 312.23(a)(6))*
  - ☐ b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
  - ☐ c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
- 6. Protocol *(Continued)*
  - ☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *(21 CFR 312.23(a)(7))*
  - ☐ Environmental assessment or claim for exclusion *(21 CFR 312.23(a)(7)(iv)(e))*
- ☐ 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
- ☑ 9. Previous human experience *(21 CFR 312.23(a)(9))*
- ☐ 10. Additional information *(21 CFR 312.23(a)(10))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

15. Is any part of the clinical study to be conducted by a contract research organization? ☑ Yes ☐ No

If Yes, will any sponsor obligations be transferred to the contract research organization? ☐ Yes ☑ No

If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred *(use continuation page)*.

Continuation Page for #15

16. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations

Özlem Türeci, MD, Chief Medical Officer, BioNTech SE

17. Name and Title of the person responsible for review and evaluation of information relevant to the safety of the drug

Özlem Türeci, MD, Chief Medical Officer, BioNTech SE

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

18. Name of Sponsor or Sponsor's Authorized Representative

Neda Aghajani Memar, Pharm.D., Director, Pfizer Global Regulatory Affairs - Vaccines

19. Telephone Number *(Include country code if applicable and area code)*

(b) (6)

20. Facsimile (FAX) Number *(Include country code if applicable and area code)*

(845) 474-3500

21. Address

Address 1 *(Street address, P.O. box, company name c/o)*

235 East 42nd Street

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

219/9/69

City: New York

State/Province/Region: NY

Country: United States of America

ZIP or Postal Code: 10017

22. Email Address

(b) (6)

23. Date of Sponsor's Signature *(mm/dd/yyyy)*

08/14/2021

24. Name of Countersigner

25. Address of Countersigner

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City

State/Province/Region

Country: United States of America

ZIP or Postal Code

26. Email Address

WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

27. Signature of Sponsor or Sponsor's Authorized Representative

Neda Aghajani Memar

Digitally signed by Neda Aghajani Memar
DN: cn Neda Aghajani Memar o ou
email (b) (6) c US
Reason: I attest to the accuracy and integrity of this document
Date: 2021.08.14 10:48:01 -04'00'

Sign

28. Signature of Countersigner

Sign

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

Please do NOT send your completed form to this PRA Staff email address.