DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS

DATE: **July 22, 2021** **PAGES: 17**

TO: **BioNTech RNA Pharmaceuticals GmbH/Pfizer. Inc.**
Attention: Elisa Harkins
500 Arcola Road
Collegeville, PA 19426
Phone: 215-280-5503
Fax number: 845-474-3500
E-mail: Elisa.HarkinsTull@pfizer.com

FROM: **Laura Gottschalk, Ph.D.**
Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone number: 301-796-2640
Fax number: 301-595-1244

CBER Reference: BLA STN 125742/0

SUBJECT: Information request regarding clinical shell tables for study C4591001

Dear Ms. Harkins:

Reference is made to your original BLA STN 125742/0 for COVID-19 mRNA Vaccine (COMIRNATY), for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age. Our review of your application is ongoing and we have the following information requests at this time.

Information Requests, regarding Study C4591001:

1. Please provide the number and percentage of clinical COVID cases that meet the case definition but not confirmed by PCR for any reason (e.g., not done, sample lost, out of window), by study arm.

2. Please provide the cumulative incidence rates for the vaccine group as compared to the placebo group at 2, 4, and 6 months post dose 1 to complement the cumulative incidence curve submitted (Figure 2, pg 104, from c4591001-interim-mth6-report-body.pdf).

3. It appears that you have included Subject 10941002 in the efficacy analysis for first COVID-19 occurrence from 7 days after dose 2 over blinded placebo-controlled follow-up period in subjects without evidence of infection prior to 7 days after dose 2 (e.g. Table 16 of C4591001-interim-6-Month Report Body). However, this subject reported "covid-19 antibody test positive" in medical history, and the baseline COVID status was categorized as positive, as indicated in the ADSL data set. Please confirm whether this subject is included in the VE analysis in subjects without evidence of infection prior to 7 days after dose 2, and if yes, please provide a rationale for including this subject in the analysis.

4. It appears that Subject 10031167 was considered to have a confirmed COVID case, with an onset date 11/02/2020, in your efficacy analysis. We note that this subject reported three episodes of symptoms (from 10/08/2020 to 10/16/2020, 11/2/2020 to 12/11/2020, and 12/17/2020 to 01/16/2021, respectively), and the PCR tests were negative for the first two episodes and positive for the third episode. In Appendix 3 of the SAP, it is stated that "if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness." Since the second and third episodes were more than 4 days apart, it appears that they should be counted as separate episodes. Hence, the subject would be considered to have a COVID case with an onset on 12/17/2020. Since this subject was unblinded on 12/16/2020, this case occurred after unblinding and should not be included in the efficacy analysis during the blinded placebo-controlled follow up period. Please comment.

5. In the efficacy analyses, subjects at risk were determined (in part) by the "PDRMUPFL='N'" condition, which would exclude all subjects who had reported COVID symptoms but had missing or unknown PCR results at any time. It may be reasonable to exclude subjects who had reported COVID symptoms but had missing/unknown PCR results prior to 7 days after dose 2 for the efficacy analyses in subjects without evidence of infection, as this would define a more specific group of subjects without evidence of infection. However, based on your analyses, subjects who reported symptoms and had missing/unknown PCR results after 7 days post dose 2 were also excluded from the efficacy analyses, while these subjects were in fact at risk for the efficacy endpoint starting from 7 days post dose 2. For example, Subject 10011087 was excluded since he/she reported symptoms on 01/09/2021 without any associated PCR result, which was ~144 days post dose 2.

    a. Please explain why these subjects were not considered at risk for the respective efficacy endpoints, and comment on the impact of the exclusion on the VE results.

    b. In Section 6.1.3.1.2 of the SAP, it is stated that "with MAR assumption, a missing efficacy endpoint (laboratory-confirmed COVID-19 results) may be imputed based on predicted probability using the fully conditional specification method." Please clarify whether this sensitivity analysis was conducted and the location of the sensitivity analyses if they were submitted. If not, please perform such a sensitivity analysis for subjects who reported COVID symptoms but had missing/unknown PCR results.

6. Please complete the following tables, based on the Study C4591001 Phase 2/3 populations, limited to participants 16 years of age and older (<u>please exclude participants 12-15 years of age)</u> from the March data cutoff, unless otherwise specified. Please add rows, as needed to list additional items.

Table A: Please complete with data from the All-available efficacy analysis population, Participants 16 years of age and Older

RT-PCR NP Swab Results and Serostatus at Different Time Points	**BNT162b2** N= Cases n Attack Rate or other measure (%)	**Placebo** N= Cases n Attack Rate or other measure (%)	**Vaccine Efficacy (if applicable)**
Pre-Dose 1 SARS-CoV-2 RT-PCR (NP swab)			
Positive			
Negative			
Pre-Dose 2 SARS-CoV-2 RT-PCR (NP swab)			
Positive			
Negative			
Subjects with negative PCR pre-dose 1 and positive PCR pre-dose 2			
Subjects with documented COVID-19 symptoms between dose 1 and 2			
Subjects with no documented COVID-19 symptoms between dose 1 and 2			
Pre-Dose 1 N-binding antibody			
Positive			
Negative			

Subject Disposition

Table B: Study Disposition of All Randomized Participants 16 years of age and Older, through March data cut off

	BNT162b2 (N=) n (%)	**Placebo (N=) n (%)**	**Total (N=) n (%)**
Randomized			
Vaccinated: Original blinded follow up period			
Completed 1 dose			
Completed 2 doses			
Discontinued from original blinded follow up period			
Reason for discontinuation			
Lost to follow up			
Withdrawal by subject			
Adverse Event			
Other (list…)			
Withdrawn from Study			

After Dose 1 and before Dose 2			
After Dose 2 and before 1-month post Dose 2			
After 1-month post Dose 2			
Reason for Withdrawal			
Adverse Event			
Death			
Withdrawal by Subject			
Lost to Follow-up			
Protocol Deviation			
Other (list)			
Open Label Follow-up Period			
Originally randomized to BNT162b2			
Completed 6-month post Dose 2 visit			
Withdrawn from the study			
Reason for withdrawal (list..)			
Originally randomized to placebo			
Completed 6-month post Dose 2 visit			
Received Dose 3 (Dose 1 of BNT162b2)			
Received Dose 4 (Dose 2 of BNT162b2)			
Completed 1-month post-Dose 4 visit			
Discontinued from open-label follow up period			
Reason for discontinuation (list…)			
Withdrawn from the study			
Reason for withdrawal (list…)			

Table C. Disposition of Participants 16 Years of age and Older, Safety Populations

Treatment Group	**BNT162b2 (N=) n (%)**	**Placebo (N=) n (%)**	**Total (N=) n (%)**
Randomized (N)[a]			
Not vaccinated			
Vaccinated			
Completed 1 dose			
Completed 2 doses			
Safety population			
Reactogenicity subset			
HIV-positive			
Participants excluded from safety population			
Reason for exclusion[b]			
Did not receive study vaccination			
Other (list)			
Completed at least 6 months follow-up after Dose 2			
Completed 1-month after Dose 2 visit (vaccination period)			

Treatment Group	BNT162b2 (N=) n (%)	Placebo (N=) n (%)	Total (N=) n (%)
Discontinued from vaccination period but continued in the study up to 1-month after Dose 2 visit			
Discontinued after Dose 1 and before Dose 2			
Discontinued after Dose 2 and before 1-month post-Dose 2 visit			
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria			
Withdrawal by subject			
Pregnancy			
Adverse event			
Physician decision			
Protocol deviation			
Lost to follow-up			
Other			
Withdrawn from study before 1-month post-Dose 2 visit			
Withdrawn after Dose 1 and before Dose 2			
Withdrawn after Dose 2 and before 1-month post-Dose 2 visit			
Reason for withdrawal			
Adverse event			
Death			
Withdrawal by subject			
Lost to follow-up			
Protocol deviation			
Withdrawal by parent/guardian			
Physician decision			
Other (list)			

Table D. Disposition of Participants 16 years of age and older, Efficacy Populations

	BNT162b2 n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]			
Dose 1 all-available efficacy population			
Participants without evidence of infection before Dose 1			
Participants excluded from Dose 1 all-available efficacy population			
Reason for exclusion[c]			
Did not receive at least 1 vaccination			
Did not provide informed consent			

	BNT162b2 n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Dose 2 all-available efficacy population			
Participants without evidence of infection prior to 7 days after Dose 2			
Participants excluded from Dose 2 all-available efficacy population			
Reason for exclusion[c]			
Did not receive 2 vaccinations			
Unblinded prior to 7 days after Dose 2			
Evaluable efficacy (7 days) population			
Participants without evidence of infection prior to 7 days after Dose 2			
Participants excluded from evaluable efficacy (7 days) population			
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria			
Did not provide informed consent			
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)			
Had other important protocol deviations on or prior to 7 days after Dose 2			
Had other important protocol deviations on or prior to 14 days after Dose 2			
Other (list…)			

Table E. Demographics and Other Baseline Characteristics, Participants 16 Years of age and Older, Safety Populations

Characteristic	BNT162b2 N= n[a] (%)	Placebo N= n[a] (%)	Total N= n[a] (%)
Sex: Female			
Sex: Male			
Age: Mean years (SD)			
Age: Median (years)			
Age at Vaccination: Min, max (years)			
Age Group: 16 to <18 years			
Age Group: 18 to <55 years			
Age Group: >55 years			
Age Group: ≥65 years			
Race: American Indian or Alaska Native			
Race: Asian			
Race: Black or African American			
Race: Native Hawaiian or other Pacific Islander			
Race: Multiracial			
Race: White			

Characteristic	BNT162b2 N= n[a] (%)	Placebo N= n[a] (%)	Total N= n[a] (%)
Race: Not reported			
Race: Other			
Ethnicity: Hispanic or Latino			
Ethnicity: Not Hispanic or Latino			
Ethnicity: Not reported			
Obese: Yes			
Obese: No			
Comorbidities: Yes			
Comorbidities: No			
Baseline evidence of prior SARS-CoV-2 infection: Negative			
Baseline evidence of prior SARS-CoV-2 infection: Positive			
Baseline evidence of prior SARS-CoV-2 infection: Missing			
Country: Argentina			
Country: Brazil			
Country: Germany			
Country: South Africa			
Country: Turkey			
Country: United States of America			
Other (list)			

Table F. Demographics and Other Baseline Characteristics, Participants 16 Years of age and Older, Evaluable Efficacy Population

Characteristic	BNT162b2 N= n[a] (%)	Placebo N= n[a] (%)	Total N= n[a] (%)
Sex: Female			
Sex: Male			
Age: Mean years (SD)			
Age: Median (years)			
Age at Vaccination: Min, max (years)			
Age Group: 16 to <18 years			
Age Group: 18 to <55 years			
Age Group: >55 years			
Age Group: ≥65 years			
Race: American Indian or Alaska Native			
Race: Asian			
Race: Black or African American			
Race: Native Hawaiian or other Pacific Islander			
Race: Multiracial			
Race: White			
Race: Not reported			

Characteristic	BNT162b2 N= n[a] (%)	Placebo N= n[a] (%)	Total N= n[a] (%)
Race: Other			
Ethnicity: Hispanic or Latino			
Ethnicity: Not Hispanic or Latino			
Ethnicity: Not reported			
Obese: Yes			
Obese: No			
Comorbidities: Yes			
Comorbidities: No			
Baseline evidence of prior SARS-CoV-2 infection: Negative			
Baseline evidence of prior SARS-CoV-2 infection: Positive			
Baseline evidence of prior SARS-CoV-2 infection: Missing			
Country: Argentina			
Country: Brazil			
Country: Germany			
Country: South Africa			
Country: Turkey			
Country: United States of America			
Other (list)			

Efficacy Results:

***Provide all vaccine efficacy analyses using the evaluable efficacy population, limited to participants 16 years of age and older (excluding participants 12 through 15 years of age).**

Table G. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population, 16 Years and Older (data cutoff November 2020)

Pre-specified Age Group	BNT162b2 N[a] = Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] = Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants				
16 to 55 years				NA
> 55 years and older				NA

Table H. Updated Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population, 16 Years and Older (data cutoff March 13, 2021)

Pre-specified Age Group	BNT162b2 N[a] = Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] = Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
All participants			
16 to 55 years			
> 55 years and older			

Table I. Updated Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With and Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population, 16 Years and Older (data cutoff March 13, 2021)

Pre-specified Age Group	BNT162b2 N[a] = Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] = Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
All participants			
16 to 55 years			
> 55 years and older			

Table J. Subgroup Analyses of Updated Second Primary Endpoint: First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup, Participants With and Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy Population (data cutoff March 13, 2021)

Efficacy Endpoint Subgroup	BNT162b2 N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Overall			
Age group: 16 to <18 years			
Age group: 18 to <65 years			
Age group: ≥65 years			
Age group: 65 to 74 years			
Age group: ≥75 years			
At risk: Yes			
At risk: No			
Age group and Risk: 16-64 and not at risk			
Age group and Risk: 16-64 and at risk			
Age group and Risk: ≥65 and not at risk			
Age group and Risk: ≥65 and at risk			
Obese: Yes			

Efficacy Endpoint Subgroup	BNT162b2 N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Obese: No			
Age group and obese:16-64 and not obese			
Age group and obese: 16-64 and obese			
Age group and obese: ≥65 and not obese			
Age group and obese: ≥65 and obese			
Sex: Female			
Sex: Male			
Ethnicity: Hispanic or Latino			
Ethnicity: Not Hispanic or Latino			
Race: American Indian or Alaska native			
Race: Asian			
Race: Black or African American			
Race: Native Hawaiian or other Pacific Islander			
Race: White			
Race: Multiracial			
Race: Not reported			
Baseline SARS-CoV-2 Status:Positive			
Baseline SARS-CoV-2 Status:Negative			
Baseline SARS-CoV-2 Status:Unknown			
Country: Argentina			
Country: Brazil			
Country: Germany			
Country: South Africa			
Country: Turkey			
Country: United States			

Table K. Demographic Characteristics, Participants 16 years of age and Older, With Protocol-Defined Case (Without Evidence of Infection Prior to 7 Days After Dose 2) (data cutoff March 13, 2021)

Characteristic	BNT162b2 N[a]= n[b] (%)	Placebo N[a]= n[b] (%)	Total N[a]= n[b] (%)
Age at Vaccination: Mean years (SD)			
Age at Vaccination: Median (years)			
Age at Vaccination: Min, max (years)			
Age Group: 16 to < 18 years			
Age Group: 18 to < 65 years			
Age group: ≥65 years			
Age Group: ≥ 65 to < 75 years			
Age Group: ≥ 75 years			
Race: American Indian or Alaska Native			
Race: Asian			

Characteristic	BNT162b2 N[a]= n[b] (%)	Placebo N[a]= n[b] (%)	Total N[a]= n[b] (%)
Race: Black or African American			
Race: Native Hawaiian or Other Pacific Islander			
Race: White			
Race: Multiracial			
Race: Not reported			
Sex: Female			
Sex: Male			
Ethnicity: Hispanic or Latino			
Ethnicity: Not Hispanic or Latino			
Ethnicity: Not reported			
Comorbidities: Yes			
Comorbidities: No			
Comorbidity: Obesity			
Country: Argentina			
Country: Brazil			
Country: Germany			
Country: South Africa			
Country: Turkey			
Country: United States			

Table L. Updated Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy Population. Participants 16 Years of age and Older (data cutoff March 13, 2021)

Efficacy Endpoint Subgroup	BNT162b2 N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall			
Comorbidity			
No comorbidity			
Any comorbidity[f]			
Any malignancy			
Cardiovascular			
Chronic pulmonary disease			
Diabetes			
Obese (BMI≥30.0 kg/m^2)			
Hypertension			
Diabetes (including gestational diabetes)			

Table M. First Severe COVID-19 Occurrence from 7 Days after Dose 2 - Evaluable Efficacy Population (data cutoff March 13, 2021)

Secondary Efficacy Endpoint	BNT162b2 N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection			

Table N. First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population (data cutoff March 13, 2021)

Secondary Efficacy Endpoint	BNT162b2 N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe case occurrence after Dose 1			
After Dose 1 to before Dose 2			
Dose 2 to 7 days after Dose 2			
≥7 Days after Dose 2			

Table O. Primary Efficacy Endpoint – All-Available Efficacy Population (data cutoff March 13, 2021)

Efficacy Endpoint	BNT162b2 N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]= Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after Dose 1 – Dose 1			
After Dose 1 to before Dose 2			
Dose 2 to 7 days after Dose 2			
≥7 Days after Dose 2			

Safety Results:

Table P. Safety Overview, Participants 16 Years of Age and older, Phase 2/3 Safety Population

Event	BNT162b2 n/N (%)	Placebo n/N (%)
Immediate unsolicited AE within 30 minutes after vaccination[a]		
Dose 1		
Dose 2		
Solicited injection site reaction within 7 days[a]		
Dose 1		
Dose 2		
Solicited systemic AE within 7 days[a]		
Dose 1		
Dose 2		
From Dose 1 through 1 month after Dose 2[b]		
Unsolicited non-serious AE		
SAE		
From Dose 1 to cutoff date or participant unblinding (whichever is earlier)[b]		
SAE		
Withdrawal due to AEs		
Deaths		

Table Q. Characteristics of Solicited Local and Systemic Adverse Reactions, Participants 16 Years of age and older, Safety Population

Event	BNT162b2 Dose 1 n[a]/N[b] (%)	Placebo Dose 1 n[a]/N[b] (%)	BNT162b2 Dose 2 n[a]/N[b] (%)	Placebo Dose 2 n[a]/N[b] (%)
Any solicited local reaction				
Day of onset: median (min, max)	Day (min, max)	Day (min, max)	Day (min, max)	Day (min, max)
Duration: median (min, max)	Days (min, max)	Days (min, max)	Days (min, max)	Days (min, max)
Persisted beyond 7 days				
e.g., Pain				
Day of onset: median (min, max)	Day (min, max)	Day (min, max)	Day (min, max)	Day (min, max)
Duration: median (min, max)	Days (min, max)	Days (min, max)	Days (min, max)	Days (min, max)
Persisted beyond 7 days				
Any solicited systemic reaction				
Day of onset: median (min, max)	Day (min, max)	Day (min, max)	Day (min, max)	Day (min, max)

Event	BNT162b2 Dose 1 n[a]/N[b] (%)	Placebo Dose 1 n[a]/N[b] (%)	BNT162b2 Dose 2 n[a]/N[b] (%)	Placebo Dose 2 n[a]/N[b] (%)
Duration: median (min, max)	Days (min, max)	Days (min, max)	Days (min, max)	Days (min, max)
Persisted beyond 7 days				
e.g., Myalgia				
Day of onset: median (min, max)	Day (min, max)	Day (min, max)	Day (min, max)	Day (min, max)
Duration: median (min, max)	Days (min, max)	Days (min, max)	Days (min, max)	Days (min, max)
Persisted beyond 7 days				

Table R. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in Any Treatment Group From Dose 1 to One Month After Dose 2, Participants 16 Years of age and Older, Safety Population

Primary System Organ Class (CODE)	Preferred Term (CODE)	BNT162b2 (N=) Any % (Severe %)	Placebo (N=) Any % (Severe %)
Each SOC	Adverse events in any PT Any PT (% severe) Any PT (% severe)		
Each SOC	Adverse events in any PT Any PT (% severe) Any PT (% severe)		

****Please repeat Table R for the following time periods:**

1. **From Dose 1 to Match data cutoff/participant unblinding (whichever is earlier) and**
2. **From participant unblinding to March data cutoff**

SMQ analyses
***narrow SMQs: vasculitis, hypersensitivity, arthritis, angioedema, peripheral neuropathy, demyelinating disease of central nervous system, convulsions

We may send additional SMQ requests as we review the data.

Table S. Name of Standard MedDRA Query, Participants 16 Years of age and Older, Safety Population

Dictionary Derived Term Number of Subjects (%)	BNT162b2 (n=)	Placebo (n=)
Subjects with any unsolicited adverse events within SMQ	xx (xx%)	x (x%)
DDT	x (x%)	-

Table T. SAEs considered related by Investigator- Participants 16 Years of age and Older, Safety Population

Product (Vaccine or Placebo)	SAE	Onset (Days After Vaccination)	Demographics: Age/Sex/Risk Factors	Resolution	Related per Investigator/ Pfizer
	e.g., brachial nerve neuritis	0 (day of vaccination)	30 M; no relevant medical history	Resolving	Yes/Yes

Table U. Deaths, Participants 16 Years of age and Older, Safety Population, through March data cutoff

-Product (BNT162b2 or Placebo) -Number of doses received	Subject Number	Onset (Days After Vaccination)	Cause of Death	Positive COVID-19 test (Y/N)	Age/Sex Race/Ethnicity	Demographics: Risk Factors from Charlson Index
e.g., placebo/BNT162b2 2/1		4	e.g., myocardial infarction	N	65 F B/NH	

Table V. Clinical Trials Submitted in Support of Safety and Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	Description	BNT162b2 (30 µg) Participants (N)	Placebo participants (N)	Study Status
C4591001 Argentina, Brazil, Germany, South Africa, Turkey, United States		Phase 1: Phase 2/3:	Phase 1: Phase 2/3:	Ongoing
BNT162-01 Germany				Ongoing

N= total number of randomized participants 16 years of age and older, as of March 13, 2020.

Please also respond to the following information requests regarding Study C4591001:

7. It appears that you have included Subject 10941002 in the efficacy analysis for first COVID-19 occurrence from 7 days after dose 2 over blinded placebo-controlled follow-up period in subjects without evidence of infection prior to 7 days after dose 2 (e.g. Table 16 of C4591001-interim-6-Month Report Body). However, this subject reported "covid-19 antibody test positive" in medical history, and the baseline COVID status was categorized as positive, as indicated in the ADSL data set. Please confirm whether this subject is included in the VE analysis in subjects without evidence of infection prior to 7 days after dose 2, and if yes, please provide a rationale for including this subject in the analysis.

8. It appears that Subject 10031167 was considered to have a confirmed COVID case, with an onset date 11/02/2020, in your efficacy analysis. We note that this subject reported three episodes of symptoms (from 10/08/2020 to 10/16/2020, 11/2/2020 to 12/11/2020, and 12/17/2020 to 01/16/2021, respectively), and the PCR tests were negative for the first two episodes and positive for the third episode. In Appendix 3 of the SAP, it is stated that "if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness." Since the second and third episodes were more than 4 days apart, it appears that they should be counted as separate episodes. Hence, the subject would be considered to have a COVID case with an onset on 12/17/2020. Since this subject was unblinded on 12/16/2020, this case occurred after unblinding and should not be included in the efficacy analysis during the blinded placebo-controlled follow up period. Please comment.

9. In the efficacy analyses, subjects at risk were determined (in part) by the "PDRMUPFL='N'" condition, which would exclude all subjects who had reported COVID symptoms but had missing or unknown PCR results at any time. It may be reasonable to exclude subjects who had reported COVID symptoms but had missing/unknown PCR results prior to 7 days after dose 2 for the efficacy analyses in subjects without evidence of infection, as this would define a more specific group of subjects without evidence of infection. However, based on your analyses, subjects who reported symptoms and had missing/unknown PCR results after 7 days post dose 2 were also excluded from the efficacy analyses, while these subjects were in fact at risk for the efficacy endpoint starting from 7 days post dose 2. For example, Subject 10011087 was excluded since he/she reported symptoms on 01/09/2021 without any associated PCR result, which was ~144 days post dose 2.

    a. Please explain why these subjects were not considered at risk for the respective efficacy endpoints, and comment on the impact of the exclusion on the VE results.

    b. In Section 6.1.3.1.2 of the SAP, it is stated that "with MAR assumption, a missing efficacy endpoint (laboratory-confirmed COVID-19 results) may be imputed based on predicted probability using the fully conditional specification method." Please clarify whether this sensitivity analysis was conducted and the location of the sensitivity analyses if they were submitted. If not, please perform such a sensitivity analysis for subjects who reported COVID symptoms but had missing/unknown PCR results.

Please provide your responses in an amendment to STN 125742/0 by COB Monday, July 26, 2021. We recommend that you restate each item and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference.