BNT162b2 (COMIRNATY)

BLA STN 125742/0

Response to CBER 22 July 2021 Information Request Regarding Clinical Shell Tables for Study C4591001

July 2021

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1. INTRODUCTION

Reference is made to 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.

The purpose of this document is to respond to CBER's 22 July 2021 Information Request to Pfizer, received via email from Laura Gottschalk, PhD (CBER). The requests are regarding clinical shell tables for Study C4591001 that correspond to data filed in the BLA, which is in ongoing CBER review.

CBER requests are provided below in ***bold italics*** with Sponsor responses in plain text. Note that Questions 7, 8, and 9 were duplicates of Questions 3, 4, and 5. Sponsor requests clarification as to whether additional questions from CBER were intended.

2. CBER INFORMATION REQUESTS AND SPONSOR RESPONSES

2.1. CBER Request 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.

Sponsor Response

Pfizer/BioNTech will provide this information by 28 July 2021.

2.2. CBER Request 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).

Sponsor Response

Pfizer/BioNTech will provide this information by 28 July 2021.

2.3. CBER Request 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

Sponsor Response

Subject 10941002 is included in the VE analysis in subjects without evidence of infection prior to 7 days after Dose 2. As illustrated by the flowchart in Appendix 3 of the Statistical Analysis Plan (SAP) and clarified in the footnote of VE tables, "subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2," were included in the analysis of subjects without evidence of infection. This subject had negative results on all required N-binding antibody and NAAT tests prior to 7 days after Dose 2, thus being included in the analysis. We based our "without evidence of infection" definition solely on objective serological and virological parameters due to the potential uncertainty of a medical history entry without knowledge of circumstances, assay performed etc. However, as requested in the FDA EUA guidance document, baseline COVID-19 status categorization did take account of the medical history.

2.4. CBER Request 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.

Sponsor Response

While the regular COVID-19 symptoms do have the start and stop dates specified by CBER, this subject has the severe symptom of hospitalization for COVID-19 starting on 22 November 2020 and ending on 23 December 2020. As the hospitalization spans both the COVID B and COVID C symptoms, they were merged into a single COVID-19 case.

2.5. CBER Request 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.

Sponsor Response

a. Subjects who reported symptoms and had missing/unknown PCR results do not have a chance to be counted in the numerator (confirmed cases). Including them in the denominator only (surveillance time among subjects at risk) would implicitly assume that all PCR results for these subjects were negative, and thus could underestimate the incidence rate. Therefore, such subjects were excluded from both numerator and denominator in the calculation of incidence rates for both active vaccine and placebo groups. As the percentages of subjects who reported symptoms but has missing/unknown PCR results were small and slightly higher in the placebo group, excluding them from the analyses had negligible impact on VE results. Sensitivity analysis through imputing the missing/unknown PCR results and including such subjects in the VE calculation (results presented in response b below), further support that main conclusions for vaccine efficacy will not be altered even under some extreme MNAR assumptions.

b. A sensitivity analysis with missing data imputation described in the SAP was performed using the final efficacy analysis of at least 164 cases data (original EUA database) based upon a request from the European Medicines Agency (EMA). A total of 348 subjects (141 and 207 participants in BNT162b2 group and placebo group, respectively) had protocol defined symptoms but missing laboratory results 7 days after Dose 2 as of the data cutoff of 14 November 2020. Sensitivity analysis of missing laboratory data was performed for the primary endpoint.

   Under the missing at random (MAR) assumption for the missing data mechanism, missing efficacy endpoint (laboratory-confirmed COVID-19 results) was imputed based on predicted probability from logistic regression model using the fully conditional specification method. In addition, a conservative approach was applied to the model by assuming a higher than the observed case rate when imputing missing

efficacy endpoints from participants in the BNT162b2 group only, to reflect potentially unknowable missing not at random (MNAR) effects that are unfavorable for efficacy results of the study.

As shown in Table 1, average VE after imputation was over 80% even with up to 15-fold increase of positivity rate applied to the BNT162b2 group. This further demonstrated robust vaccine efficacy of BNT162b2.

In the updated descriptive analyses included in the BLA, similarly high VE (91%) of BNT162b2 was observed with up to 6 months blinded follow up. The sensitivity analysis was not repeated. We will perform the sensitivity analysis using BLA data and provide the result by 02 August 2021. It's expected that missing data will have minimal impact on the overall result.

Table 1. Sensitivity and Robustness Analysis of Missing Laboratory Results for Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Assumed Missing Data Mechanism	Average Positive Rate (%) Across all Imputations (BNT162b2:Placebo)[a]	Infection Rates Based on Existing and Imputed Values (BNT162b2:Placebo)[b]	Average Posterior Probability of VE > 30%	Median Posterior Probability of VE > 30%	Number of Posterior Probability of VE > 30% greater than 98.6%	Percentage of Posterior Probability of VE > 30% greater than 98.6%	Average VE (%)
MAR	1.3:16.2	0.56:11.03	100.00	100.00	500	100.00	94.93
MNAR1	3.6:16.2	0.74:11.03	100.00	100.00	500	100.00	93.33
MNAR2	9.0:16.2	1.18:11.03	100.00	100.00	500	100.00	89.39
MNAR3	21.4:16.2	2.17:11.03	100.00	100.00	500	100.00	80.46
MNAR4	41.9:16.2	3.82:11.03	99.98	100.00	498	99.60	65.67

Abbreviations: MAR = missing at random; MNAR = missing not at random; VE = vaccine efficacy.
Note: Each row of this table represents summary results from 500 imputations that were generated using SAS PROC MI Fully Conditional Specification (FCS) method. Each imputation filled in the missing laboratory results based on a logistic regression model at the subject level, under the assumed missing data mechanism.
a. Average positive rate for each vaccine group was calculated as the mean of positive rates across all imputations among subjects with missing data after each imputation. Under the MAR assumption, the imputation model assumes the probability of positive cases for each vaccine group to be the same as observed from subjects with no missing data in that group. Under each MNAR assumption, while keeping the imputation model for placebo group unchanged, an increase in the positive rate for the BTN162b2 group was assumed to reflect a potential conservative and unknowable MNAR scenario for efficacy results of the study.
b. Infection rate in each vaccine group was the number of cases divided by a total number of subjects in that vaccine group times 1000.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adc19ef Table Generation: 09DEC2020 (10:27)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_EUA_FAEF_RR/adc19ef_ve_7pd2_wo_sen_eval_eua

2.6. CBER Request 6

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

Sponsor Response

The requested 508-complaint tables will require extensive customization and significant amount of changes to our existing standard macros and programming code. Considering the complexity of this task, we will need up to 3 weeks to complete these. Accordingly, we will provide the requested tables by 13 August 2021.

2.7. CBER Request 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.

Sponsor Response

Please refer to the Sponsor Response to CBER Request 3 (Section 2.3).

2.8. CBER Request 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.

Sponsor Response

Please refer to the Sponsor Response to CBER Request 4 (Section 2.4).

2.9. CBER Request 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.

Sponsor Response

Please refer to the Sponsor Response to CBER Request 5 (Section 2.5).

Document Approval Record

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