



BNT162b2 (COMIRNATY)

BLA STN 125742/0

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

Follow-Up #2

August 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 and to CBER's 22 July 2021 Information Request received via email from Laura Gottschalk, PhD, CBER, OVR, regarding the request to provide additional sensitivity analysis in question 5b if it was not previously provided or conducted. This request was made initially on 22 July 2021 and Pfizer agreed to provide the results of the additional sensitivity analysis by 02 August 2021 in the 26 July 2021 responses submitted to CBER.

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 and to CBER's 22 July 2022 Information Request received via email from Laura Gottschalk, PhD (CBER) regarding clinical shell tables for Study C4591001.

Further reference is made to the [Response to CBER 22 July 2021 Information Request](#) submitted to BLA 125742/0 on 26 July 2021 (Sequence Number 0018) and to the [Response to CBER 22 July 2021 Information Request Follow-up #1](#) submitted to BLA 125549/0 on 28 July 2021 (Sequence Number 0020)

Please note the following:

- Responses to CBER 22 July 2021 Information Request Items 3, 4, 5, 7, 8 and 9 were submitted to BLA 125742/0 on 26 July 2021. **The present submission provides further follow-up to the information provided in this document for Item 5(b).**
- Response to CBER 22 July 2021 Information Request Items 1 and 2 were submitted to BLA 125742/0 on 28 July 2021.
- CBER 22 July 2021 Information Request Item 6 will be the subject of separate, future, follow-up Response.

CBER requests are provided below in ***bold italics*** with Sponsor responses in plain text.

2. REQUESTS

2.1. 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

The response to Item 5(a) and an initial response to Item 5(b) was previously submitted to CBER on 26 July 2021 ([Response to 22 July 2021 Information Request](#); Sequence Number 0018).

The additional sensitivity analysis to respond to Item 5(b) is provided in [Table 1](#).

A total of 648 subjects (279 in BNT162b2 group and 369 in placebo group) in the evaluable population reported COVID-19 symptoms from 7 days post Dose 2 but had PCR results missing/unknown as of data cutoff 13 Mar 2021 ([Table 2](#) of the Response to CBER 22 July 2021 Information Request Follow-up #1 submitted on 28 July 2021). Sensitivity analysis with missing data imputation described in the SAP, using the same methods as the original EUA database, was performed using the updated data.

It was expected that the missing data had minimal impact on the overall result. As shown in [Table 1](#) below, average VE after imputation was over 70% even with up to 16-fold increase of positivity rate applied to the BNT162b2 group. With over 20-fold increase of positivity rate applied to the BNT162b2 group, median lower bound of the 95% CI for VE is still >60% and the percentage of times the posterior probability of VE >30% was greater than 98.6% is 100%.

Table 1. Table 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 | Median Posterior Probability of VE > 30% | Percentage of Posterior Probability of VE >30% greater than 98.6% | Median of Lower Limit of 95% CI for VE | Median VE (%) | Average VE (%) |
|--------------------------------|--|--|--|---|--|---------------|----------------|
| MAR | 4.0:28.5 | 4.21:45.31 | 100.00 | 100.00 | 88.56 | 90.78 | 90.76 |
| MNAR1 | 10.1:28.5 | 5.01:45.31 | 100.00 | 100.00 | 86.55 | 88.97 | 88.98 |
| MNAR2 | 23.3:28.5 | 6.76:45.31 | 100.00 | 100.00 | 82.30 | 85.12 | 85.14 |
| MNAR3 | 45.3:28.5 | 9.69:45.31 | 100.00 | 100.00 | 75.36 | 78.79 | 78.69 |
| MNAR4 | 69.1:28.5 | 12.85:45.31 | 100.00 | 100.00 | 67.71 | 71.78 | 71.75 |
| MNAR5 | 85.9:28.5 | 15.08:45.31 | 100.00 | 100.00 | 62.36 | 66.81 | 66.85 |

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 BNT162b2 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: 25MAR2021 (19:22) Source Data: adc19ef Table Generation: 30JUL2021 (12:35)

(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adc19ef_ve_7pd2_wo_sen1_eval_bla

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3. REFERENCES

None

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