BNT162b2 (COMIRNATY)

BLA STN 125742/0

Response to 27 July 2021 CBER Information Request Regarding

Assessment of Vaccine Effectiveness

30 July 2021

090177e197b1d030\Approved\Approved On: 30-Jul-2021 14:59 (GMT)

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LIST OF ABBREVIATIONS

Abbreviation	Term
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
COVID-19	coronavirus disease 2019
FDA	United States Food and Drug Administration
IR	Information Request
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

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1. INTRODUCTION

Reference is made to BLA STN 125742/0 for the Pfizer-BioNTech COVID-19 Vaccine 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 Information Request (IR) communicated from Captain Michael Smith, PhD (CBER) to Elisa Harkins Tull (Pfizer Inc.) via email on 27 July 2021, requesting information regarding the assessment of vaccine effectiveness.

CBER's comments/requests in ***bold italics*** are followed by the Sponsor's responses below.

2. CBER REQUESTS

2.1. CBER Request 1

1. Regarding the cumulative incidence rates, please calculate vaccine effectiveness with confidence intervals during the two intervals of interest separately from days 35-91 (i.e., 8 weeks of observation after dose 2) and from days 91-224 (more prolonged follow up post vaccination series).

Response

Additional feedback from CBER clarified that the two interval periods were 35-90 and 91-224 days. The requested vaccine effectiveness data for days 35-90 and days 91-224 is included below in Table 1.

Subjects enrolled in the study were to receive two doses of BNT162b2 or placebo approximately 21 days apart. The timing of second vaccination varied across subjects, and some subjects did not receive the second dose. Therefore, using days relative to Dose 1 to approximate time after Dose 2 is not as precise as using days relative to Dose 2, as presented in Table 18 of the Interim Clinical Study Report Body for Study C4591001 (the table is also included below as Table 2).

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Table 1. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 and Within Specific Time Interval – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=23040)		Placebo (N[a]=23037)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	131	8.412 (22505)	1034	8.124 (22434)	87.8	(85.3, 89.9)
Day 35 to Day 90	25	3.305 (22290)	392	3.249 (22117)	93.7	(90.6, 96.0)
Day 91 to Day 224	59	3.023 (19854)	467	2.798 (19268)	88.3	(84.6, 91.2)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of the range stated for each time interval.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 29JUL2021 (16:56)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adc19ef_ve_cov_cber_pd1_aai

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2.2. CBER Request 2

2. We also request assessment of vaccine effectiveness during a time period that is entirely further out from vaccination (e.g., starting at 4 months post-dose 2). We acknowledge though that at some point unblinding and placebo cross-over started, and there may have been differential loss between the two groups from blinded follow-up that could introduce bias and/or confound the analyses.

Response

As communicated via email by Elisa Harkins Tull on 27 July 2021, the requested information is included in Table 18 of the Interim Clinical Study Report Body for Study C4591001 in Module 5.3.5.1 submitted to BLA 125742, which provides efficacy data from a placebo controlled, randomized, blinded trial, not real world effectiveness data. This table is also included below as Table 2.

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Table 2. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=23040)		Placebo (N[a]=23037)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	131	8.412 (22505)	1034	8.124 (22434)	87.8	(85.3, 89.9)
After Dose 1 to before Dose 2	46	1.339 (22505)	110	1.331 (22434)	58.4	(40.8, 71.2)
After Dose 1 to <11 days after Dose 1	41	0.677 (22505)	50	0.675 (22434)	18.2	(-26.1, 47.3)
≥11 Days after Dose 1 to before Dose 2	5	0.662 (22399)	60	0.656 (22369)	91.7	(79.6, 97.4)
Dose 2 to 7 days after Dose 2	3	0.424 (22163)	35	0.422 (22057)	91.5	(72.9, 98.3)
≥7 Days after Dose 2	82	6.649 (22132)	889	6.371 (22001)	91.2	(88.9, 93.0)
≥7 days after Dose 2 to <2 Months after Dose 2	12	2.923 (22132)	312	2.884 (22001)	96.2	(93.3, 98.1)
≥2 Months after Dose 2 to <4 Months after Dose 2	46	2.696 (20814)	449	2.593 (20344)	90.1	(86.6, 92.9)
≥4 Months after Dose 2	24	1.030 (12670)	128	0.895 (11802)	83.7	(74.7, 89.9)

Abbreviation: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 19APR2021 (17:34)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA/adc19ef_ve_cov_pd1_aai

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2.3. CBER Request 3

3. Sorry, but the below question was inadvertently omitted from the earlier IR. Additionally, the review team has requested a response to this question by Friday, July 30, 2021.

Please calculate the cumulative incidence rates of vaccine and placebo arms at Day 57 and Day 224 and estimate the Risk Difference and Risk Ratio with their 95% CI.

Response

The incidence rates, Risk Ratio, and Risk Difference of the vaccine and placebo arms at Day 57 and Day 224 are provided below in Table 3 and Table 4.

Also included in this response is Table 18 of the Interim Clinical Study Report Body, included above (Table 2). As shown in Table 2, during the period of 'after Dose 1 to <11 days after Dose 1', the observed vaccine efficacy is very low (18.2%), as the most of the vaccine effect has not been achieved. Therefore, the cumulative incidence after Dose 1 to Day 57 and Day 224 requested (as shown in Table 3 and Table 4) is a combination of periods before and after meaningful vaccine effectiveness is observed and should be interpreted with caution.

In particular, estimates of vaccine efficacy corresponding to the risk ratios in Table 3 are 82.7% for Day 1 to Day 57 and 87.8% for Day 1 to Day 224. The apparent increase in vaccine efficacy over the much longer time interval compared to the early time interval is an artifact of the inclusion of the first 10 days (where there is minimal efficacy) in these calculations, as 10 days represents 17.5% of the interval from Day 1 to Day 57, but only 4.5% of the interval from Day 1 to Day 224.

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Table 3. Incidence Rates and Risk Ratio of First COVID-19 Occurrence After Dose 1– Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)							
	BNT162b2 (30 µg) (N[a]=23040)			Placebo (N[a]=23037)			Risk Ratio	
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	IR (/1000 PY)[e]	n1[b]	Surveillance Time[c] (n2[d])	IR (/1000 PY)[e]	IRR (/1000 PY)[f]	(95% CI[g])
First COVID-19 occurrence after Dose 1	131	8.412 (22505)	15.573	1034	8.124 (22434)	127.279	0.122	(0.101, 0.147)
After Dose 1 to Day 57	55	3.482 (22505)	15.796	315	3.459 (22434)	91.073	0.173	(0.128, 0.232)
After Dose 1 to Day 224	131	8.412 (22505)	15.573	1034	8.124 (22434)	127.280	0.122	(0.101, 0.147)

a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of the range stated for each time interval.
d. n2 = Number of subjects at risk for the endpoint.
e. Incidence rate (IR) is calculated as number of subjects meeting the endpoint definition/total surveillance time across all subjects at risk for the endpoint within the specific group.
f. Ratio of incidence rates (BNT162b2 [30 µg]/placebo).
g. 2-sided CI for the incidence rate difference based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 28JUL2021 (15:13)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adc19ef_ve_cov_irr_pd1_aai

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Table 4. Incidence Rates and Risk Difference of First COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)							
	BNT162b2 (30 µg) (N[a]=23040)			Placebo (N[a]=23037)			Difference	
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	IR (/1000 PY)[e]	n1[b]	Surveillance Time[c] (n2[d])	IR (/1000 PY)[e]	IRD (/1000 PY)[f]	(95% CI[g])
First COVID-19 occurrence after Dose 1	131	8.412 (22505)	15.573	1034	8.124 (22434)	127.279	-111.707	(-119.910, -103.503)
After Dose 1 to Day 57	55	3.482 (22505)	15.796	315	3.459 (22434)	91.073	-75.277	(-86.166, -64.388)
After Dose 1 to Day 224	131	8.412 (22505)	15.573	1034	8.124 (22434)	127.280	-111.707	(-119.910, -103.503)

a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of the range stated for each time interval.
d. n2 = Number of subjects at risk for the endpoint.
e. Incidence rate (IR) is calculated as number of subjects meeting the endpoint definition/total surveillance time across all subjects at risk for the endpoint within the specific group.
f. Difference in incidence rate (BNT162b2 [30 µg] - placebo).
g. 2-sided Wald CI for the incidence rate difference.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (19:19) Source Data: adc19ef Table Generation: 28JUL2021 (15:14)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adc19ef_ve_cov_ird_pd1_aai

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Document Approval Record

Document Name:	July 2021 COVID-19 Vaccine Response to 27Jul2021 CBER BLA Request -Vaccine Effectiveness
Document Title:	July 2021 COVID-19 Vaccine Response to 27Jul2021 CBER BLA Request -Vaccine Effectiveness

Signed By:	Date(GMT)	Signing Capacity
Devlin, Carmel M	30-Jul-2021 14:58:59	Regulatory Affairs Approval
Perez, John	30-Jul-2021 14:59:07	Final Approval

090177e197b1d030\Approved\Approved On: 30-Jul-2021 14:59 (GMT)