Application Type	Original BLA
STN	125742/0
CBER Received Date	May 18, 2021
PDUFA Goal Date	January 16, 2022
Division / Office	OVRR
Committee Chair	Ramachandra Naik
Product Reviewer	Xiao Wang
Project Manager	Mike Smith and Laura Gottschalk
Priority Review	Yes
Reviewer Name	Xinyu Tang
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, VEB, DB, OBE
	Tsai-Lien Lin, Branch Chief, VEB, DB, OBE
	John A. Scott, Director, DB, OBE
Applicant	BioNTech Manufacturing GmbH in partnership with Pfizer, Inc.
Established Name	COVID-19 Vaccine, mRNA
Trade Name	COMIRNATY®
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	After preparation, each 0.3 mL dose contains 30 µg modified mRNA encoding SARS-CoV-2 spike glycoprotein
Dosage Form and Route of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Two 0.3 mL doses, 3 weeks apart
Indication and Intended Population	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

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GLOSSARY

BLA	biologics license application
CI	confidence interval
COVID-19	Coronavirus Disease 2019
DL	detection limit
dLIA	direct Luminex assay
DP	drug product
DPC	drug product control
DS	drug substance
GMT	geometric mean titer
IR	information request
LLOQ	lower limit of quantitation
IM	intramuscular
IND	Investigational New Drug application
LNP	lipid nanoparticle
LOD	limit of detection
(b) (4)	
mRNA	messenger RNA
(b) (4)	
RSD	relative standard deviation
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SARS-CoV-2 mNG NT	SARS-CoV-2 mNeonGreen virus microneutralization assay
S/N	signal-to-noise
TDV	Titer Determining Value
ULOQ	upper limit of quantitation
VCA	variance components analysis

1. Executive Summary

BioNTech and Pfizer submitted an original Biologics License Application (BLA) on May 18, 2021 for BNT162b2. BNT162b2 is a prophylactic vaccine that prevents Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The proposed indication is active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age. The proposed dosage is 30 µg via intramuscular (IM) injection following a dosing regimen of two 0.3-mL doses given three weeks apart.

This review memo focuses on the statistical review of the non-clinical aspects of this submission, including the validation of the clinical immunogenicity assay as well as the in-vitro potency assay. Specifically, this review memo covers:

- the validation of the SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT) for the detection of serum antibodies capable of neutralizing SARS-CoV-2 (VR-MVR-10083), and
- the validation of Test Method TM100010380 v5.0 for determination of the (b) (4) of PF-07302048 (BNT162b2 construct, Drug Product) by (b) (4) (VAL100147509)

based on the validation reports submitted in Module 5.3.1.4 of BLA125742/0.0 and Module 3.2.R of BLA125741/0.19, which have not been reviewed previously.

With respect to the validation of the SARS-CoV-2 mNG NT assay, results from the validation study suggest acceptable accuracy and precision. The limit of detection (LOD), lower limit of quantitation (LLOQ), and upper limit of quantitation (ULOQ) were determined to be (b) (4), respectively. The LOD study demonstrated an acceptable false positive rate but did not evaluate the false negative rate at the LOD. Because this assay was not used in the determination of serostatus in clinical studies included in this BLA submission, the unknown false negative rate does not impact the approval of this BLA. However, the false negative rate may be a concern in the future, depending on future use of this assay.

With respect to the validation of Test Method TM100010380 v5.0 (referred to as the (b) (4) assay hereafter), results from the validation study suggest acceptable specificity and robustness to (b) (4). The detection limit (DL) was determined to be (b) (4) The repeatability and reproducibility of the assay were estimated to be (b) (4) relative standard deviation (RSD), respectively. Since the (b) (4) assay was validated as a limit test, the repeatability and reproducibility results were evaluated for information only.

In conclusion, I consider both the SARS-CoV-2 mNG NT and (b) (4) assays adequate for their intended uses in support of this BLA.

2. Regulatory Background

The Investigational New Drug Application (IND19736) for BNT162b2 was submitted on April 29, 2020. Fast Track Designation was granted on July 7, 2020 for individuals 18 years of age and older. On December 11, 2020, Emergency Use Authorization (EUA 27034) of BNT162b2 for active immunization to prevent COVID-19 in individuals 16 years of age and older was granted (EUA product identified as Pfizer-BioNTech COVID-19 Vaccine). BioNTech and Pfizer submitted this BLA on May 18, 2021 for BNT162b2.

The following documents regarding clinical assays were submitted in Module 5.3.1.4 of BLA125741/0.0:

- Report on Method Validation of a Cepheid Xpert® Xpress PCR Assay to Detect SARS-CoV-2 (VR-MVR-10080, Version 3.0),
- Method Validation Report for the Elecsys Anti-SARS-CoV-2 Assay (VR-MVR-10081, Version 2.0),
- Qualification Report for a (b) (4) Direct Luminex Assay (dLIA) for Quantitation of IgG Antibodies to SARS-CoV-2 S1 Protein in Human Sera (VR-MQR-10211, Version 2.0),
- Qualification Report for a (b) (4) Direct Luminex Assay (dLIA) for Quantitation of IgG Antibodies to SARS-CoV-2 RBD Protein in Human Sera (VR-MQR-10212, Version 2.0),

- Qualification of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (VR-MQR-10214, Version 2.0), and
- Method Validation of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (VR-MVR-10083, Version 1.0).

All these qualification and validation reports have been reviewed during the IND stage, except for the validation report for the SARS-CoV-2 mNG NT assay, which is covered in this review memo.

The following document regarding the potency assay was submitted in Module 3.2.R of BLA125741/0.19:

- Report for Co-Validation of Test Method TM100010380 – Determination of the (b) (4) of PF-07302048 (BNT162b2 Construct, Drug Product) by (b) (4) (VAL100147509, Version 1.0).

This validation report has not been previously reviewed during the IND stage and is covered in this review memo as well.

3. Sources of Data and Other Information Considered in the Review

The following documents submitted to the BLA are reviewed:

- Method Validation of the SARS-CoV-2 mNeonGreen virus microneutralization assay used for the detection of serum antibodies capable of neutralizing SARS-CoV-2 (VR-MVR-10083, Version 1.0) (BLA125742/0.0, dated February 9, 2021, received May 6, 2021),
- Report for Co-Validation of Test Method TM100010380 – Determination of the (b) (4) of PF-07302048 (BNT162b2 Construct, Drug Product) by (b) (4) (VAL100147509, Version 1.0) (BLA125742/0.19, Module 3.2.R, dated July 16, 2021, received July 28, 2021).
- Response to 04 Aug 2021 FDA Information Request (IR) (BLA125742/0.34, Module 1.11.1, dated August 6, 2021, received August 6, 2021), and
- Validation of Analytical Procedure – (b) (4) (BLA125742/0.34, Module 3.2.P.5.3, dated August 6, 2021, received August 6, 2021).

The following document submitted to the IND is also referred to when reviewing the validation of the SARS-CoV-2 mNG NT assay:

- Validation Protocol for the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (VR-MVP-10074, Version 2.0) (IND19736/157, Module 5.3.1.4, dated December 2, 2020, received December 4, 2020).

4. Review of the Method Validation of the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay

4.1 Introduction

The SARS-CoV-2 mNG NT assay is a biofunctional assay that measures neutralizing antibodies against SARS-CoV-2. This assay is described in Test Method VR-TM-10298. Briefly, (b) (4)

(b) (4)

This validation study evaluated assay (b) (4) linearity, precision, limit of detection, and intermediate precision. The (b) (4) linearity and precision results were used to define the limits of quantitation and extravariability criterion.

4.2 Experimental Design

Validation of the SARS-CoV-2 mNG NT assay was performed as described in the validation protocol (VR-MVP-10074). (b) (4)

(b) (4)

4 pages have been determined to be not releasable: (b)(4)

(b) (4)

[redacted]

5.1 Introduction

Test Method TM100010380 "Determination (b) (4) PF-07302048 (b) (4)

[redacted]

(b) (4)

5.2 Validation Outline

This validation report contains the results of validation study conducted according to the following method validation protocols:

- VAL100138078, V1.0 Protocol for co-validation of test method TM100010380, which was the original method validation protocol to evaluate repeatability, reproducibility, specificity, and detection limit,
- INX100459445, V1.0 Amendment for protocol for co-validation of test method TM100010380, which was an amendment to original method validation protocol VAL100138078 to evaluate the robustness of (b) (4) during reproducibility studies.

In routine tests, the assay is analyzed (b) (4)

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(b) (4)

6. CONCLUSIONS

This review memo focuses on the validation of the SARS-CoV-2 mNG NT assay for the detection of serum antibodies capable of neutralizing SARS-CoV-2 and the validation of the (b) (4) potency assay, TM100010380 v5.0, for determination of the (b) (4) of PF-07302048 by (b) (4).

With respect to the validation of the SARS-CoV-2 mNG NT assay, results from the validation study suggest acceptable accuracy and precision. The LOD, LLOQ, and ULOQ were determined to be (b) (4), respectively. The LOD study demonstrated (b) (4)

With respect to the validation of the (b) (4) assay, results from the validation study suggest acceptable specificity and is robust to (b) (4). The detection limit (DL) was determined to be (b) (4). The repeatability and reproducibility of the assay were estimated to be (b) (4), respectively. Since the (b) (4) assay was validated as a limit test, the repeatability and reproducibility results were evaluated for information only.

In conclusion, I consider both the SARS-CoV-2 mNG NT and (b) (4) assays adequate for their intended uses in support of this BLA.