

### 1.6.3 CORRESPONDENCE REGARDING MEETINGS

The following is a brief summary of the significant meetings and communications between Pfizer and FDA regarding IND 19736. Copies of these correspondences are also provided.

<b>Key US Regulatory Interactions</b>		
<b>Date</b>	<b>Regulatory Communication</b>	<b>Additional Information</b>
26 June 2020	FDA Type C Meeting	<p>CRMTS #12645</p> <p>The purpose of this Type C Meeting was to present the proposed Clinical Development Program, including the revised Phase 1/2/3 Study C4591001, intended to support licensure in the US and globally as well as potential use of the candidate vaccine under an Emergency Use Authorization, if authorized by HHS.</p> <p><a href="#">Pfizer/BioNTech Meeting Request and Briefing Document Submitted 11 June 2020 (SN 0015)</a></p> <p><a href="#">Pfizer/BioNTech response to CBER's June 25, 2020 preliminary meeting responses and Meeting Minutes Submitted 09 July 2020 (SN 0028)</a></p> <p><a href="#">FDA Meeting Summary (Including Preliminary Meeting responses) Received 15 July 2020</a></p> <p><a href="#">FDA Teleconference Summary Received 06 July 2020</a></p>
14 October 2020	Request for Proprietary and Non-proprietary Name Review	<p>The purpose of this request was for the Agency to consider a new proprietary name: COMIRNATY.</p> <p><a href="#">Request for Proprietary Name Review submitted 14 October 2020 (SN 0108)</a></p> <p><a href="#">Proprietary Name Acceptable At this Time Letter Received from FDA 20 November 2020</a></p>

14 August 2020	FDA Type C Meeting	<p>CRMTS #12714</p> <p>The purpose of this Type C Meeting was to describe the proposed CMC and facilities information package intended to support licensure in the US and globally as well as potential use of the candidate vaccine under an Emergency Use Authorization, if authorized by HHS.</p> <p><a href="#">Pfizer/BioNTech Meeting Request and Briefing Document Submitted 13 July 2020 (SN 0031)</a></p> <p><a href="#">FDA Written Responses Received 14 August 2020</a></p> <p><a href="#">Response to FDA August 14 and September 18, 2020 Information Request Submitted 08 October 2020 (SN 0102)</a></p>
14 August 2020	Request for Comments and Advice (Nonclinical)	<p>The purpose of this Request for Comments and Advice was to seek FDA feedback and approval on sufficiency of the planned nonclinical absorption, disposition, metabolism, and excretion (ADME) and toxicology packages and timing of study data submissions to support the BLA for the COVID-19 Vaccine (BNT162, PF-07302048).</p> <p><a href="#">Request for Comments &amp; Advice Submitted 27 July 2020 (SN 0045)</a></p> <p><a href="#">FDA Comments Regarding Request for Advice on Sufficiency of Nonclinical Package for BLA Received on 14 August 2020</a></p>

<p>23 September 2020</p>	<p>FDA Type C Meeting</p>	<p>CRMTS# 12822</p> <p>The purpose of this Type C Meeting was to describe the proposed CMC and facilities information package intended to support licensure in the US and globally as well as the facilities utilized for the potential use of the candidate vaccine under an Emergency Use Authorization, if authorized by HHS.</p> <p><a href="#">Pfizer/BioNTech Briefing Document Submitted 02 September 2020 (SN 0074)</a></p> <p><a href="#">Response to Type C Facilities Meeting, September 23, 2020</a>  <a href="#">Response to CBER October 1, 2020 Information Request Submitted 14 October 2020 (SN 0106)</a></p> <p><a href="#">FDA Meeting Summary (Including Preliminary Meeting responses) Received 14 October 2020</a></p>
<p>28 September 2020</p>	<p>Request for Comments and Advice (Clinical, Nonclinical, Pre-Authorization Safety Pre-BLA)</p>	<p>The purpose of this Request for Comments and Advice was to seek CBER feedback regarding the practical (not data related) aspects of the planned BLA submission.</p> <p><a href="#">Request for Comments &amp; Advice Submitted 15 September 2020 (SN 0084)</a></p> <p><a href="#">FDA Comments Regarding Planned BLA Received 28 September 2020</a></p> <p><a href="#">Response to CBER September 28, 2020 Information Request (Practical aspects of the planned BLA submission) Submitted 16 October 2020 (SN 0112)</a></p>

27 November 2020	Request for Comments and Advice (C4591001 Placebo Subjects)	<p>The purpose of this Request for Comments and Advice was to seek CBER feedback regarding administration of BNT162b2 to participants in C4591001 who originally received placebo.</p> <p>Request for Comments &amp; Advice Submitted 18 November 2020 (SN 0139)</p> <p>FDA Comments Regarding Administration of BNT162b2 to Participants in C4591001 Who Originally Received Placebo (Placebo Cross-Over) Received 27 November 2020</p> <p>Request for Comments &amp; Advice Submitted 21 January 2021 (SN 0188)</p> <p>FDA Comments Regarding the Follow-up of BNT162b2 Recipients Who Originally Received Placebo Received 29 January 2021</p> <p>Response to FDA 29 January 2021 IR (Regarding Follow-up of BNT162b2 Recipients Who Originally Received Placebo) Submitted 08 February 2021 (SN 0205)</p> <p>Follow-up to 8 February 2021 Response to FDA 29 January 2021 Comments – Question for the Agency Submitted 15 March 2021 (SN 0243)</p> <p>FDA Comments Regarding a Follow-Up Question on Pfizer’s Response Regarding Follow-Up of Placebo Crossover Subjects Received 02 April 2021</p>
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<p>01 February 2021</p>	<p>Email Correspondence Regarding content of Nonclinical Package and Timelines of Rolling BLA</p>	<p>The purpose of this Request was to seek Agency Feedback regarding the nonclinical package to include in the BLA and the timelines regarding submission of nonclinical, CMC and clinical information to the rolling BLA for Pfizer-BioNTech COVID-19 Vaccine.</p> <p>Email Correspondence on January 13, 2021 and January 22, 2021 between Dr. Ramachandra Naik (CBER) and Ms. Elisa Harkins Tull (Pfizer)</p> <p>FDA Comments Regarding Content of Nonclinical Package and Timelines of Rolling BLA Received 01 February 2021</p>
<p>09 March 2021</p>	<p>Request for Comments and Advice (Proposal for Clinical and Post-Authorization Safety Data Package for Biologics License Application)</p>	<p>The purpose of this Request for Comments and Advice was to seek CBER feedback regarding the Clinical and Post-Authorization Safety Questions submitted in lieu of a pre-BLA meeting.</p> <p>Request for Comments &amp; Advice Submitted 04 February 2021 (SN 0200)</p> <p>FDA Comments Regarding the Proposal for Clinical and Post-EUA Safety Data Package for BLA Received 09 March 2021</p> <p>FDA Comments Regarding CMC Contents of the BLA and Additional Comments on Clinical/Statistical and CMC/Facilities Information to be Included in the BLA Received 31 March 2021</p> <p>FDA Clarification to a Few of the Comments Sent on March 9, 2021 Regarding the Proposal for Clinical and Post-EUA Safety Data Package for BLA Received 01 April 2021</p>

		<p>Response to FDA 09 and 31 March 2021 IR (regarding the proposal for clinical and post-EUA safety data package for BLA) Submitted 07 April 2021 (SN 0278)</p> <p>Additional Response to CBER Comments Received on 09 March 2021, 31 March 2021, and 01 April 2021, Regarding eSUB/CDISC data Submitted 14 April 2021 (SN 0285)</p> <p>FDA Teleconference Summary Received 26 April 2021</p>
<p>31 March 2021</p>	<p>Request for Comments and Advice (Plans for Submitting the CMC Portions of the BLA)</p>	<p>The purpose of this Request for Comments and Advice was to seek CBER feedback regarding the strategy for submitting the contents related to chemistry, manufacturing, and controls (CMC).</p> <p>Request for Comments &amp; Advice Submitted 01 March 2021 (SN 0229)</p> <p>FDA Comments Regarding CMC Contents of the BLA and Additional Comments on Clinical/Statistical and CMC/Facilities Information to be Included in the BLA Received 31 March 2021</p> <p>Response to FDA 31 March 2021 IR (regarding CMC package for BLA) Submitted 07 April 2021 (SN 0278)</p> <p>FDA Teleconference Summary Received 26 April 2021</p>

**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 019736**

**Type C Meeting Request**



**June 2020**

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## 1. PRODUCT DESCRIPTION AND APPLICATION NUMBER

Pfizer and BioNTech are developing an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus, SARS-CoV-2. The goal of the development program is to rapidly develop and license a vaccine for use in adults  $\geq 18$  years of age, followed by a pediatric indication. The vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048). Initially, four different clinical candidates were considered based on evaluation of emerging preclinical and clinical data. An Investigational New Drug Application (IND) for the COVID-19 Vaccine was submitted to the US FDA on April 22, 2020. On April 29, 2020 Pfizer was notified by CBER that there were no clinical hold issues identified and the evaluation of this vaccine in the US could proceed. The COVID-19 candidate vaccine formulations are investigational medicinal products (IMPs) and have not been submitted for marketing approval in any country. A Request for Fast Track Designation was submitted on May 15, 2020 (Serial Number 0005) and is currently under review by CBER.

BioNTech is conducting a German first-in-human (FIH) dose level-finding Phase 1/2 study (BNT162-01) to gather safety and immunogenicity data to enable evaluation of each of the vaccines individually to inform the overall clinical development of a COVID-19 Vaccine. This study is not conducted under the IND but is being conducted under a German Clinical Trial Agreement (CTA). The protocol for this study has been provided previously in Module 5 (Module 5.3.5.1 Clinical Study Protocol BNT162-01).

Pfizer and BioNTech are conducting a large Phase 1/2 clinical study in the US (C4591001) using a flexible and stepwise study design to evaluate the safety and immunogenicity of the same prophylactic COVID-19 vaccine candidates also being evaluated in the German study, using a range of dosage levels and dosing regimens, with the intent to select the most appropriate final vaccine candidate for Phase 3 development. To gather appropriate dose level information quickly, some dose levels evaluated in German or US studies were not the same. In addition, Pfizer has chosen not to evaluate currently unmodified RNA (uRNA) or self-amplifying RNA (saRNA) candidates in the US study. The protocol for this study is provided in Module 5 (Module 5.3.5.1 Clinical Study Protocol C4591001).

On May 15, 2020 (Serial Number 0007), Pfizer submitted the synopsis for a Phase 2/3 randomized, placebo-controlled, observer-blinded study of the efficacy and safety of one or more COVID-19 vaccine candidates in individuals  $\geq 18$  years of age (Module 5.3.5.1 Clinical Study Synopsis C4591002). On May 29, 2020, following their review, CBER provided comments and information requests on this synopsis via email. These comments have been considered and addressed in Response to CBER May 29, 2020 Comments and Information Requests provided in Module 1.11.3, and are also addressed in Briefing Document included with this meeting request.

Upon further consideration, specifically study site logistics and protocol efficiencies, a decision has been taken to incorporate this efficacy study design as an amendment to the ongoing Phase 1/2 study (C4591001) to create a Phase 1/2/3 study. Reference is made to

CBER's May 29, 2020 feedback regarding the efficacy study synopsis. CBER's feedback has been considered will be addressed in a revised Phase 1/2/3 study protocol for C4591001. A description of the revised protocol design, including plans for incorporation of Phase 2/3 based on CBER's May 29, 2020 feedback from CBER, is provided in the briefing document included with this request. It is Pfizer's intent to initiate the Phase 2/3 portion of the study in July 2020.

The purpose of this Type C Meeting is to present the proposed Clinical Development Program, including the revised Phase 1/2/3 Study C4591001, intended to support licensure in the US and globally as well as potential use of the candidate vaccine under an Emergency Use Authorization, if authorized by HHS. This Type C meeting package will explain our rationale to select a nucleoside-modified RNA (modRNA) vaccine candidate and dose level to progress into the Phase 3 part of Study C4591001. A separate meeting will be requested in the near future to present the CMC and facilities data package proposed for licensure.

## 2. CHEMICAL NAME AND STRUCTURE

BioNTech has developed three RNA-LNP platforms with different features, as follows:

- **nonmodified uridine containing mRNA (uRNA)**, with high intrinsic adjuvanticity;
- **nucleoside-modified mRNA (modRNA)**, with blunted innate immune sensor activating capacity and thus augmented antigen expression; and
- **self-amplifying mRNA (saRNA)**, from which higher amounts of protein per injected RNA template could be produced and thus immunogenicity enhanced.

The RNA-based vaccines are formulated in the same LNPs. Each platform RNA encodes either a full-length SARS-CoV-2 S glycoprotein, the P2 mutant S glycoprotein (P2 S), and/or the receptor binding domain (RBD) of the S glycoprotein. Each candidate is also given a V number that indicates the specific version of the optimized insert genomic sequence. BNT162 vaccine candidates based on these platforms have been (or may be) tested at the following dose ranges in the German Study BNT162-01 and/or US Study C4591001:

- **BNT162a1** (RBL063.3) uRNA encoding RBD (V5): 0.1 to 3 µg, German study only
- **BNT162b1** (RBP020.3) modRNA encoding RBD (V5): 1 to 100 µg
  - German study (1, 10, 30, 50, 60 µg) and US study (10, 20, 30, 100 µg)
- **BNT162b2** (RBP020.2) modRNA encoding P2 S (V9): 1 to 100 µg
  - German study (1, 10, 30, 100 µg) and US study (10, 20, 30 µg)
- **BNT162c2** (RBS004.2) saRNA encoding P2 S (V9): 0.1 to 3 µg, German study only.

Dosing with BNT162a1 and BNT162c2 is currently not planned in the US study; accordingly, these have been removed from Study C4591001 in protocol Amendment 3.

### 3. PROPOSED INDICATION(S)

The proposed indication for the COVID-19 Vaccine is:

- Active immunization against COVID-19 in adults  $\geq 18$  years of age.

Full clinical development of the COVID-19 Vaccine for a pediatric indication will also be pursued. The proposed indication for the pediatric population is:

- Active immunization against COVID-19 in children 12 months to 17 years of age.

The COVID-19 Vaccine will also be evaluated in pregnant women. Currently, these evaluations are planned for 2021. The proposed indication would be:

- Active immunization against COVID-19 in pregnant women 18-45 years of age.

### 4. TYPE OF MEETING BEING REQUESTED

This is a Type C meeting request; Pfizer respectfully requests a meeting with CBER by the end of June 2020.

### 5. PURPOSE OF THE MEETING

The purpose of this Type C Meeting is to present the proposed Clinical Development Program, including the proposed revisions to ongoing Study C4591001, as well as high level pediatric and maternal immunization plans. It is our intention to complete an efficacy study within C4591001 to support Traditional Approval; (b) (4)

(b) (4)

(b) (4)

(b) (4)

Specific CBER

feedback is requested on the clinical data requirements to support (b) (4) Traditional Approval, as well as requirements for use under an Emergency Use Authorization should one be authorized by HHS and FDA.

### 6. SPECIFIC OBJECTIVES/OUTCOMES EXPECTED

To obtain rapid CBER feedback on the questions included herein.

### 7. PRELIMINARY AGENDA, PRESENTER, TIME

Introduction – 10 minutes  
Discussion – 45 minutes  
Closure – 5 minutes

## 8. SPECIFIC QUESTIONS GROUPED BY DISCIPLINE

### Clinical

- 1) Does CBER have any comments on the overall Clinical Development Plan and timeline proposed to support (b) (4) [REDACTED] Traditional Approval? Specifically,
  - a) Does CBER agree with the proposed revisions to the ongoing Phase 1/2 US Study C4591001 that would add a Phase 2/3 efficacy phase to the study, to evaluate efficacy in an expanded number of participants? Does CBER agree with the proposed Phase 3 safety, immunogenicity, and efficacy endpoints and case definitions?
  - b) (b) (4) [REDACTED]
  - c) Does CBER agree with the proposed plan for progression of vaccine candidates from Phase 2 to Phase 3?
  - d) Does CBER agree with the proposed inclusion of global sites (eg, EU, South America, Turkey) in the efficacy phase of the study with at least 30% of participants coming from US assuming current state of the pandemic?
- 2) Does CBER agree that revised Study C4591001 is adequate to serve as the single pivotal study to demonstrate adequate safety, immunogenicity, and efficacy of the candidate vaccine for the proposed indication and may be used to support (b) (4) [REDACTED] Traditional Approval?
- 3) Does CBER agree with Pfizer/BioNTech's plans to evaluate the BNT162b3 candidate expressing the RBD domain with a short transmembrane tail and two amino acids added to the signal peptide for more homogenous cleavage in Study C4591001, as described in Section 6.2?

### Regulatory

(b) (4) [REDACTED]

(b) (4) [REDACTED]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Traditional Approval

- 1) Does CBER agree that the proposed study design, including a Phase 2/3 efficacy portion, and the planned persistence evaluations from Phase 1 sentinel and Phase 2 cohorts are adequate to support Traditional Approval?
- 2) Does CBER agree that the planned clinical lot consistency study may be conducted in parallel with the planned Phase 3 efficacy study and results submitted as a post-approval commitment under the Traditional Approval Pathway?

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Emergency Use Authorization

- 1) The Sponsor is currently manufacturing vaccine at-risk and is targeting to have US-manufactured and released vaccine doses of approximately (b) (4) available by year-end 2020 with initial deliveries projected for late November. Does CBER agree that the proposed (b) (4) (b) (4) (b) (4) ? The Emergency Use Authorization request package could be submitted for CBER review in parallel with the initial BLA.

Pediatric and Maternal Immunization Study Plans

- 1) Does CBER have any comments on the high-level pediatric study plan? Does CBER agree (b) (4) ?
- 2) Does CBER agree with the proposed inclusion of global sites (eg, EU, South America, Turkey) in the pediatric study with at least 30% of participants coming from US?
- 3) Does CBER have any comments on the proposed plan for evaluating maternal immunization?
- 4) The developmental and reproductive toxicology (DART) study will be initiated (b) (4) (b) (4) (b) (4) . Does CBER agree that the results of the DART study can be provided during review of the initial BLA (b) (4) (b) (4) ?

Please refer to the Pre-IND Briefing Document included in the submission for background information on the questions.

**9. SPONSOR ATTENDEES**

Mark Boaz	Program Director, Vaccine Research and Development, Pfizer Inc.
Donna Boyce	Vice President, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Carmel Devlin	Global Regulatory Portfolio Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Philip R. Dormitzer, MD, PhD	Vice President and Chief Scientific Officer, Viral Vaccines, Vaccines Research and Development, Pfizer Inc.
(b) (6), PhD	Regulatory Consultant for BioNTech SE
William C. Gruber, MD	Senior Vice President, Vaccine Clinical Research and Development, Pfizer Inc.
Elisa Harkins	Global Regulatory Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Kathrin U. Jansen, PhD	Senior Vice President and Head, Vaccine Research and Development, Pfizer Inc.
Luis Jodar, PhD	Vaccines Chief Medical and Scientific Affairs Officer, Pfizer Inc.
Nicholas Kitchin, MD	Senior Director, Vaccines Clinical Research and Development, Pfizer Ltd.

Kenneth Koury	Head of Statistics and Modeling, Vaccine Clinical Research and Development, Pfizer Inc.
Stephen Lockhart, MD	Head EU/AP, Vaccines Clinical Research and Development, Pfizer Ltd.
David Swerdlow, MD	Senior Director, Medical Development and Clinical/Scientific Affairs, Pfizer Inc.
Ruben Rizzi, PhD	Regulatory Affairs Strategist, BioNTech SE
Satrajit Roychoudhury, PhD	Senior Director, Statistical Research and Data Science Center, Pfizer Inc.
Ugur Sahin, MD, PhD	Chief Executive Officer, BioNTech, SE

## 10. AGENCY STAFF

Pfizer respectfully requests participation of appropriate personnel from the Division of Vaccines and Related Drug Products, the Office of Biostatistics and Epidemiology and the Division of Bacterial, Parasitic and Allergenic Products.

## 11. ANTICIPATED DATE OF SUPPORTING DOCUMENTATION

The Type C Briefing Document is included in this submission.

## 12. SUGGESTED MEETING DATES AND TIME

A meeting is requested by the end of June, morning or early afternoon time if possible.

## Document Approval Record

<b>Document Name:</b>	COVID-19 Vaccine Type C Clinical Meeting Request
<b>Document Title:</b>	COVID-19 Vaccine Type C Clinical Meeting Request

<b>Signed By:</b>	<b>Date(GMT)</b>	<b>Signing Capacity</b>
Boyce, Donna	10-Jun-2020 20:25:50	Regulatory Affairs Approval

**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 019736**

**Type C Meeting Briefing Document**



**June 2020**

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## ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BLA	Biologics License Application
CDER	(US Food and Drug Administration) Center for Drug Evaluation and Research
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CTA	Clinical Trial Agreement
DART	developmental and reproductive toxicology (study)
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECMO	extracorporeal membrane oxygenation
EU	European Union
FiO <sub>2</sub>	fraction of inspired oxygen
GLP	Good Laboratory Practice
FIH	first-in-human
HHS	(US Department of) Health and Human Services
HR	heart rate
IM	intramuscular(ly)
IMP	investigative medicinal product
iPSP	initial Pediatric Study Plan
IND	Investigational New Drug application
LL	lower limit (of confidence interval)
LNP	lipid nanoparticle
mNG	mNeonGreen
modRNA	nucleoside modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification test
NHP	non-human primate
PaO <sub>2</sub>	arterial oxygen pressure
P/B	prime/boost: dosing regimen of a priming immunization and a booster immunization
POS	probability of trial success

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<b>Abbreviation</b>	<b>Definition</b>
RNA-LNP	RNA lipid nanoparticle
RR	respiratory rate
saRNA	self-amplifying messenger RNA
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
sBLA	supplemental Biologics License Application
SBP	systolic blood pressure
S glycoprotein	Spike glycoprotein
SpO <sub>2</sub>	peripheral oxygen saturation
TdaP	Tetanus toxoid, low dose diphtheria toxoid, acellular pertussis (vaccine)
uRNA	non-modified uridine containing mRNA
US	United States
VE	vaccine efficacy
WHO	World Health Organization

## 1. EXECUTIVE SUMMARY

Pfizer and BioNTech are developing an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus, SARS-CoV-2. The goal of the development program is to rapidly develop and license a vaccine for use in adults  $\geq 18$  years of age, followed by a pediatric indication. The vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048). Initially, four different clinical candidates were considered based on evaluation of emerging preclinical and clinical data. An Investigational New Drug Application (IND) for the COVID-19 Vaccine was submitted to the US FDA on April 22, 2020. On April 29, 2020 Pfizer was notified by CBER that there were no clinical hold issues identified and the evaluation of this vaccine in the US could proceed. The COVID-19 candidate vaccine formulations are investigational medicinal products (IMPs) and have not been submitted for marketing approval in any country. A Request for Fast Track Designation was submitted on May 15, 2020 (Serial Number 0005) and is currently under review by CBER.

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## 2. PRODUCT IDENTIFICATION AND APPLICATION

### 2.1. Chemical Name and Structure

BioNTech has developed three RNA-LNP platforms with different features, as follows:

- **nonmodified uridine containing mRNA (uRNA)**, with high intrinsic adjuvanticity;
- **nucleoside-modified mRNA (modRNA)**, with blunted innate immune sensor activating capacity and thus augmented antigen expression; and
- **self-amplifying mRNA (saRNA)**, from which higher amounts of protein per injected RNA template could be produced and thus immunogenicity enhanced.

The RNA-based vaccines are formulated in the same LNPs. Each platform RNA encodes either a full-length SARS-CoV-2 S glycoprotein, the P2 mutant S glycoprotein (P2 S), and/or the receptor binding domain (RBD) of the S glycoprotein. Each candidate is also given a V number that indicates the specific version of the optimized insert genomic sequence. BNT162 vaccine candidates based on these platforms have been (or may be) tested at the following dose ranges in the German Study BNT162-01 and/or US Study C4591001:

- **BNT162a1** (RBL063.3) uRNA encoding RBD (V5): 0.1 to 3 µg, German study only
- **BNT162b1** (RBP020.3) modRNA encoding RBD (V5): 1 to 100 µg
  - German study (1, 10, 30, 50, 60 µg) and US study (10, 20, 30, 100 µg)
- **BNT162b2** (RBP020.2) modRNA encoding P2 S (V9): 1 to 100 µg
  - German study (1, 10, 30, 100 µg) and US study (10, 20, 30 µg)
- **BNT162c2** (RBS004.2) saRNA encoding P2 S (V9): 0.1 to 3 µg, German study only.

Dosing with BNT162a1 and BNT162c2 is currently not planned in the US study; accordingly, these have been removed from Study C4591001 in protocol Amendment 3.

## 2.2. Dosage Form, Route of Administration, and Dosing Regimen

The vaccine candidates being evaluated in clinical studies are liquid formulations stored frozen at -80 °C in a 2 ml Type 1 glass vial to be thawed on the day of administration and stored at 2-8 °C until administration, as described in Module 3.2 of the IND. The Sponsor intends to commercialize the current formulation and initially plans to provide a single vial from which multiple doses (depending on final dose level) would be drawn. The multi-dose vial presentation is planned to be preservative-free.

The candidate vaccine is administered intramuscularly (IM) in the upper arm (musculus deltoideus) using single dose or prime/boost (P/B) regimens. The currently planned P/B regimen is two injections given at 0 and 21 days.

## 2.3. Proposed Indication

The proposed indication for the COVID-19 Vaccine is:

- Active immunization against COVID-19 in adults  $\geq 18$  years of age.

Full clinical development of the COVID-19 Vaccine for a pediatric indication will also be pursued (see [Section 6.3](#)). The proposed indication for the pediatric population is:

- Active immunization against COVID-19 in children 12 months to 17 years of age.

The COVID-19 Vaccine will also be evaluated in pregnant women (see [Section 6.4](#)). Currently, these evaluations are planned for 2021. The proposed indication would be:

- Active immunization against COVID-19 in pregnant women 18-45 years of age.

## 3. PURPOSE OF MEETING

The purpose of this Type C Meeting is to present the proposed Clinical Development Program, including the proposed revisions to ongoing Study C4591001, as well as high-level pediatric and maternal immunization plans. It is our intention to complete an efficacy study within C4591001 to support Traditional Approval; (b) (4)

(b) (4)

(b) (4)

(b) (4)

. Specific CBER

feedback is requested on the clinical data requirements to support (b) (4)

Traditional Approval, as well as requirements for use under an Emergency Use Authorization should one be authorized by HHS and FDA.

## 4. PROPOSED AGENDA AND LIST OF PARTICIPANTS

### 4.1. Proposed Agenda

Introduction – 10 minutes

Discussion – 45 minutes

Closure – 5 minutes

#### 4.2. List of Pfizer Inc. and BioNTech SE Participants

Mark Boaz	Program Director, Vaccine Research and Development, Pfizer Inc.
Donna Boyce	Vice President, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Carmel Devlin	Global Regulatory Portfolio Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Philip R. Dormitzer, MD, PhD	Vice President and Chief Scientific Officer, Viral Vaccines, Vaccines Research and Development, Pfizer Inc.
(b) (6), (b) (4), PhD	Regulatory Consultant for BioNTech SE
William C. Gruber, MD	Senior Vice President, Vaccine Clinical Research and Development, Pfizer Inc.
Elisa Harkins	Global Regulatory Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Kathrin U. Jansen, PhD	Senior Vice President and Head, Vaccine Research and Development, Pfizer Inc.
Luis Jodar, PhD	Vaccines Chief Medical and Scientific Affairs Officer, Pfizer Inc.
Nicholas Kitchin, MD	Senior Director, Vaccines Clinical Research and Development, Pfizer Ltd.
Kenneth Koury, PhD	Head of Statistics and Modeling, Vaccine Clinical Research and Development, Pfizer Inc.
Stephen Lockhart, MD	Head EU/AP, Vaccines Clinical Research and Development, Pfizer Ltd.
David Swerdlow, MD	Senior Director, Medical Development and Clinical/Scientific Affairs, Pfizer Inc.
Ruben Rizzi, PhD	Regulatory Affairs Strategist, BioNTech SE
Satrajit Roychoudhury, PhD	Senior Director, Statistical Research and Data Science Center, Pfizer Inc.
Ugur Sahin, MD, PhD	Chief Executive Officer, BioNTech SE

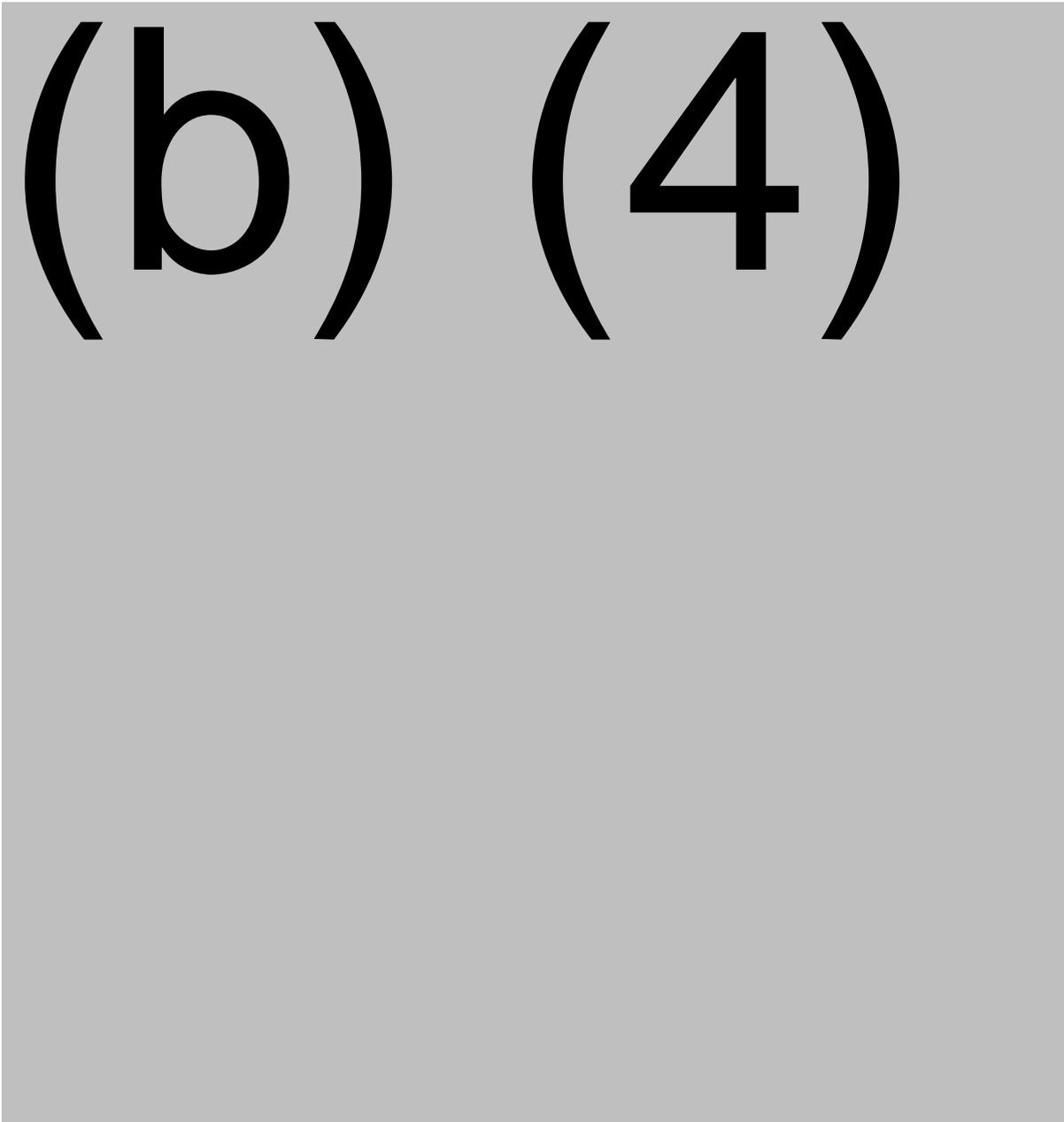
#### 5. LIST OF SPECIFIC QUESTIONS FOR DISCUSSION

##### Clinical

- 1) Does CBER have any comments on the overall Clinical Development Plan and timeline proposed to support (b) (4) [REDACTED] Traditional Approval? Specifically,
  - a) Does CBER agree with the proposed revisions to the ongoing Phase 1/2 US Study C4591001 that would add a Phase 2/3 efficacy phase to the study, to evaluate efficacy in an expanded number of participants? Does CBER agree with the proposed Phase 3 safety, immunogenicity, and efficacy endpoints and case definitions?
  - b) (b) (4) [REDACTED]
  - c) Does CBER agree with the proposed plan for progression of vaccine candidates from Phase 2 to Phase 3?
  - d) Does CBER agree with the proposed inclusion of global sites (eg, EU, South America, Turkey) in the efficacy phase of the study with at least 30% of participants coming from the US assuming current state of the pandemic?

- 2) Does CBER agree that revised Study C4591001 is adequate to serve as the single pivotal study to demonstrate adequate safety, immunogenicity, and efficacy of the candidate vaccine for the proposed indication and may be used to support (b) (4) Traditional Approval?
- 3) Does CBER agree with Pfizer/BioNTech's plans to evaluate the BNT162b3 candidate expressing the RBD domain with a short transmembrane tail and two amino acids added to the signal peptide for more homogenous cleavage in Study C4591001, as described in [Section 6.2](#)?

**Regulatory**



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(b) (4)

Traditional Approval

- 1) Does CBER agree that the proposed study design, including a Phase 2/3 efficacy portion, and the planned persistence evaluations from Phase 1 sentinel and Phase 2 cohorts are adequate to support Traditional Approval?
- 2) Does CBER agree that the planned clinical lot consistency study may be conducted in parallel with the planned Phase 3 efficacy study and results submitted as a post-approval commitment under the Traditional Approval Pathway?

Emergency Use Authorization

- 1) The Sponsor is currently manufacturing vaccine at-risk and is targeting to have US-manufactured and released vaccine doses of approximately (b) (4) available by year-end 2020 with initial deliveries projected for late November. Does CBER agree that (b) (4) (b) (4) (b) (4) (b) (4) ? The Emergency Use Authorization request package could be submitted for CBER review in parallel with the initial BLA.

Pediatric and Maternal Immunization Study Plans

- 1) Does CBER have any comments on the high-level pediatric study plan? Does CBER agree (b) (4) (b) (4) ?
- 2) Does CBER agree with the proposed inclusion of global sites (eg, EU, South America, Turkey) in the pediatric study with at least 30% of participants coming from US?
- 3) Does CBER have any comments on the proposed plan for evaluating maternal immunization?
- 4) The developmental and reproductive toxicology (DART) study will be initiated (b) (4) (b) (4) (b) (4) Does CBER agree that the results of the DART study can be provided during review of the initial BLA (b) (4) (b) (4) ?

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## 6. CLINICAL DEVELOPMENT PLAN

### 6.1. Introduction

#### 6.1.1. Background on the Target Indication

SARS-CoV-2 infections and the resulting COVID-19 disease have spread globally. On March 11, 2020 the World Health Organization (WHO) characterized the COVID-19 outbreak as pandemic. At the time of this communication, the number of confirmed cases exceeds 7 million and continues to rise globally.

There are currently no vaccines to prevent SARS-CoV-2 infections or the disease it causes, COVID-19 ([Habibzadeh & Stoneman 2020](#)).

#### 6.1.2. Rationale for Development

The rationale for development of BNT162 candidate vaccines based on mRNA technology was covered in the Clinical Overview with the initial IND application (Module 2.5).

### 6.2. Status of Ongoing and Planned Clinical Studies

German Study BNT162-01 is the FIH, Phase 1/2 dose level-finding study, in which all participants are 18-55 years of age and receive active vaccine; the number of participants who have received dose 1 and dose 2 of the first three candidates tested (BNT162b1, BNT162a1, and BNT162c2) is shown in Table 1.

**Table 1. Number of Participants Vaccinated in Study BNT162-01 as of June 8, 2020**

	BNT162b1		BNT162a1		BNT162c2
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1
0.1 µg dose level			N=12	Timepoint not reached	N=6
0.3 µg dose level			N=12	N=12	-
1 µg dose level	N=12	N=12	-	-	-
3 µg dose level			N=6	Not applicable	-
10 µg dose level	N=12	N=11			
30 µg dose level	N=12	N=12			
50 µg dose level	N=12	N=12			
60 µg dose level	N=12	Not applicable			

Not applicable = decision made by Safety Review Committee not to administer dose 2.

US Study C4591001 is a randomized and placebo-controlled study, in which participants in Stage 1 are randomized 4:1 to receive active vaccine or placebo; the number of participants who have received dose 1 and dose 2 of the first two candidates tested (BNT162b1 and BNT162b2) are shown in [Table 2](#).

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**Table 2. Number of Participants Vaccinated in Study C4591001 as of June 8, 2020**

	BNT162b1		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
18-55 years of age				
10 µg dose level	N=12	N=12	N=3	N=3
30 µg dose level	N=12	N=12	N=3	N=3
100 µg dose level	N=12	Not applicable	N=3	Not applicable
65-85 years of age				
10 µg dose level	-	-	-	-
20 µg dose level	-	-	-	-
30 µg dose level	-	-	-	-
	BNT162b2		Placebo	
	Dose 1	Dose 2	Dose 1	Dose 2
18-55 years of age				
10 µg dose level	N=2	-	-	-
20 µg dose level	-	-	-	-
30 µg dose level	-	-	-	-
65-85 years of age				
10 µg dose level	-	-	-	-
20 µg dose level	-	-	-	-
30 µg dose level	-	-	-	-

Not applicable = decision made by Internal Review Committee not to administer dose 2.

Pfizer/BioNTech intend to evaluate a slightly modified BNT162b1 candidate expressing the RBD domain with a short transmembrane tail and two amino acids added to the signal peptide for more homogenous cleavage (BNT162b3) in Study C4591001. BNT162b3 in mice has shown superior immunogenicity to BNT162b1. It will be assessed in non-human primates (NHP) and may replace BNT162b1 during its early evaluation in the Phase 2 portion of the Phase 2/3 study after confirmation of a similar (to BNT162b1 or BNT162b2) safety/tolerability profile expected for this modRNA/LNP platform. Pfizer plans to modify the protocol accordingly once a decision is made. This decision is planned by end June 2020.

Additional planned studies are listed in Table 3.

**Table 3. Additional Planned Clinical Studies**

Lot consistency study	Refer to Section <a href="#">6.2.3</a>
Pediatric study	Refer to Section <a href="#">6.3</a>
Maternal immunization study	Refer to Section <a href="#">6.4</a>

### 6.2.1. Ongoing German Phase 1/2 FIH Clinical Study BNT162-01

BioNTech is currently conducting a German FIH dose level-finding Phase 1/2 study (BNT162-01) to gather safety and immunogenicity data for each of the vaccine candidates noted above individually, and to inform the overall clinical development of a COVID-19 Vaccine. This study is not under an IND but is being conducted under a German CTA. The

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protocol for this study has been provided previously in Module 5 (Module 5.3.5.1 Clinical Study Protocol BNT162-01).

In Study BNT162-01, 60 participants have been administered a first dose of candidate BNT162b1 in five cohorts of 12 participants each at doses of 1, 10, 30, 50 and 60 µg. Eleven participants have received a second dose of 10 µg and 12 each a second dose at 1 µg, 30 µg, and 50 µg. Most participants report mild or moderate flu-like symptoms and/or injection site reactions. Approximately 25% of participants have reported fever. Onset of systemic or local symptoms may begin around 6 hours post vaccination but they more typically present 10-12 hours post administration, with fever usually starting 16-24 hours post vaccination. All events resolve spontaneously or with simple medical management, primarily acetaminophen, typically within 24-48 hours of onset. No serious adverse events (SAEs) have been reported. There was some increase in frequency and intensity of symptoms from the 1 µg to 10 µg cohorts; for 10 µg to 60 µg there is no clear dose dependency. On laboratory examination, transitory depression of the lymphocyte count and mild elevation of CRP are seen, consistent with the expected mode of action for the modRNA platform with no associated clinical consequence. Overall tolerability of P/B dosing is comparable at each dose level. No participants have withdrawn from the study due to related events. Overall the risk-benefit for this candidate within the dose range explored remains unchanged.

In Study BNT162-01, 6 participants have been administered the vaccine candidate BNT162a1 at the 3 µg dose. All participants reported flu-like symptoms within 24 hours of dosing, mostly of moderate intensity. One participant experienced vomiting and a second participant experienced an episode of hypotension, but this was not an SAE. A more marked elevation to CRP was noted, with a similar pattern of transient lymphocyte depression to that described above for the BNT162b1 candidate. All events resolved; however, some participants remained symptomatic for a number of days. No SAEs have been reported and no participants withdrew due to adverse events (AEs). Subsequently, 12 participants have been dosed at 0.3 µg and demonstrate a similar pattern of reactogenicity as described for the BNT162b1 candidate at the 1 µg to 10 µg doses, with almost exclusively mild effects reported to date. Twelve participants have recently been dosed at 0.1 µg.

BNT162a1 and BNT162b1 represent different mRNA platforms (unmodified and modified mRNA, respectively) and encode the same antigen (RBD). The difference in the reactogenicity profile between BNT162a1 and BNT162b1 candidates highlights that the reactogenicity profile is dependent on the type of RNA platform (eg, unmodified versus modified). Given the extensive clinical experiences with regard to safety and tolerability of the RNA platforms in the context of oncology programs (see Module 2.5 Clinical Overview) it is not anticipated that changes to the viral antigen sequence expressed by the RNA platform will affect the safety and tolerability profile.

As of June 8, 2020, dosing with BNT162b2 in the German Study BNT162-01 is planned to commence imminently, and the first 6 subjects have been dosed with BNT162c2.

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### 6.2.2. Ongoing US Phase 1/2 Clinical Study C4591001

Pfizer and BioNTech are currently conducting a large Phase 1/2 clinical study (C4591001) in the US. The current protocol for this study is provided in Module 5 (Module 5.3.5.1 Clinical Study Protocol C4591001). The study currently consists of three stages. Stage 1 is to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration; Stage 2 is an expanded-cohort stage; and Stage 3 is a final candidate/dose large-scale stage. Of note, Pfizer/BioNTech have de-selected evaluation of the BNT162a1 and BNT162c2 candidates for Study C4591001. As noted in [Section 6.2](#), however, Pfizer/BioNTech reserve the option to include an additional modRNA candidate similar to BNT162b1, a very slightly modified vaccine candidate BNT162b3.

Two amendments to the protocol for study C4591001 have been submitted to BB-IND 19736 as follows. A summary of the changes included in these amendments is located in the Protocol Amendment Summary of Changes Table within Module 5.3.5.1 Clinical Study Protocol C4591001.

- Protocol Amendment 1 was submitted on May 15, 2020 (Serial Number 0006). CBER acknowledged acceptance of the changes included in this protocol amendment via email to Pfizer on May 28, 2020.
- Protocol Amendment 2 was submitted on June 2, 2020 (Serial Number 0014). This submission also included 3 documents supportive of the changes made in this amendment (C4591001 Protocol Amendment 2 Briefing Document; C4591001 IRC 29May2020 Safety Tables BNT162b1 Stage 1, 2 Dose, 21 Days Apart – 18-55 Years of Age; C4591001 IRC 29May2020 Safety Listings BNT162b1 Stage 1, 2 Dose, 21 Days Apart – 18-55 Years of Age). CBER acknowledged acceptance of the revised plan for enrollment and dosing of elderly subjects included in this protocol amendment via email to Pfizer on June 3, 2020.
- Protocol Amendment 3 is being finalized in parallel with this Briefing Document and includes CBER requested revisions, following review of Amendment 2, to remove BNT162b3 and BNT162a1 from the C4591001 Protocol.

Pfizer also previously submitted a synopsis for review for a large Phase 2/3 study (C4591002) on May 15, 2020 (Serial Number 0007). This study was designed to allow further down-selection of candidate vaccines in the Phase 2 portion of the study and investigate the efficacy of BNT162 vaccine candidates (Module 5.3.5.1 Clinical Study Synopsis C4591002). On May 29, 2020, following their review, CBER provided comments and information requests on this synopsis via email. The Response to CBER May 29, 2020 Comments and Information Requests is provided in Module 1.11.3.

Pfizer now proposes to replace Stage 3 of C4591001 in its entirety with the Phase 2/3 components previously outlined as C4591002, with changes based on CBER review.

### 6.2.2.1. Current Status in Stage 1

A total of 45 participants have been enrolled and received a first dose of the BNT162b1 vaccine candidate (modRNA encoding RBD) or placebo. Of these, 12 participants received 10 µg, 12 received 30 µg, 12 received 100 µg, and 9 received placebo. A second dose of 10 µg (12), 30 µg (12) or placebo (6) has been administered to 30 participants. An expected degree of reactogenicity for the modRNA platform is evident, with local and systemic reactions similar to those reported in German Study BNT162-01. Reactogenicity is generally transient and of mild or moderate intensity. Grade 3 reactogenicity events have been reported by 5 participants: 3 after a single dose of 100 µg, 1 after the second dose of 10 µg, and 1 after the second dose of 30 µg. This, alongside an apparent increase in reactogenicity after the second dose of 30 µg, led to the Internal Review Committee (IRC) to decide not to give a second dose at 100 µg. No grade 4 reactogenicity has been reported. No stopping rules have been met and no SAEs have been reported to date.

Dosing with candidate BNT162b2 began on June 8, 2020.

### 6.2.2.2. Proposed Amendment to Replace Stage 3 of Protocol

It is proposed to replace Stage 3 of the current protocol with a Phase 2b/3 section similar to that proposed in the submitted synopsis C4591002.

To avoid confusion over terminology about sections of the study used in the initial protocol and in protocol Amendment 3, the sections are summarized in Table 4.

**Table 4. Current versus Revised Study C4591001 Sections**

Current				Revised			
Section name	Number of participants	Randomization (active:placebo)	Age groups (years)	Section name	Number of participants	Randomization (active:placebo)	Age groups (years)
Stage 1	15/cohort	4:1	18-55 65-85	Phase 1	15/cohort	4:1 unblinded	18-55 65-85
Stage 2	225/cohort	4:1	Stratified: 18-55 56-85	Phase 2a (if needed)	225/cohort	4:1 unblinded	Stratified: 18-55 56-85
Stage 3	3000/age group	1:1	Stratified: 18-55 56-85	Phase 2b/3 <sup>a</sup>	19,642 total	1:1 blinded	Stratified: 18-55 >55

<sup>a</sup> Anticipated 3000 in Phase 2b, will contribute to the 19,642 total for efficacy.

**Stage 1 is renamed Phase 1.** It is unchanged since Amendment 2. It is a classical Phase 1 stage with escalating dose levels in small cohorts in two different age groups.

As reactogenicity is dependent on the type of mRNA platform (ie, unmodified, modified, or self-amplifying), and both the unmodified (uRNA, BNT162a1) and self-amplifying (saRNA, BNT162c1) platforms have been de-selected for progression in the US study already, it is proposed that in the future a Phase 1 dose level escalation will not be required for new candidates encoding different S glycoprotein sequences if based on a the platform type that has already been in studied Phase 1 (ie, modRNA). As an example, a new candidate BNT162b3 encodes a revised RBD antigen, but otherwise is the same modRNA platform as

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BNT162b1. If BNT162b1 in Phase 1 leads to a selected dose level to proceed into Phase 2 for both younger and older adults, this same dose level would be appropriate to take directly into Phase 2 for both age groups for BNT162b3.

A vaccine candidate will be considered Phase 2-ready if, as determined by the IRC, safety (reactogenicity and AEs) and immunogenicity (binding and neutralizing antibody responses) are both considered acceptable in the Phase 1 sentinel cohorts (ie, 12 participants enrolled to receive active vaccine per dose level and age category) through 7 days after dose 2. As described below, progression may be to Phase 2a or directly to Phase 2b. In our submission accompanying Protocol Amendment 2, we committed that these data, including Th1/Th2 profile data for the platform (ie, modRNA and a single dose level), will be part of the package submitted for CBER review prior to initiation of Phase 2a or Phase 2b.

**Stage 2 is renamed Phase 2a.** This step allows further examination of safety and immunogenicity in larger numbers of participants (up to 225; 180 active, 45 placebo) and is likely to be particularly useful where it is not possible to define a single dose level from Phase 1 data to proceed into later development.

In Phase 1 and Phase 2a the emphasis is on rapid understanding of safety and immunogenicity for selection and deselection of dose levels to progress for further clinical development. To achieve this, most participants receive active vaccine, with a randomization ratio of 4:1 active:placebo. Additionally, although the study is observer-blinded, the Sponsor is unblinded to facilitate rapid decision making. If it is clear from Phase 1, or from the German Study BNT162-01, that a dose level can be selected, then a candidate vaccine may progress directly to Phase 2b.

A vaccine candidate studied in Phase 2a will be considered Phase 3-ready if, as determined by the IRC, the following are both considered acceptable in the 90 participants enrolled to receive active vaccine per dose level and age category:

- Safety (reactogenicity and AEs) through 7 days after dose 2; and
- Immunogenicity (binding and neutralizing antibody responses) through 21 days after dose 1.

These data will be submitted for CBER review prior to initiation of Phase 3.

**Stage 3 is renamed Phase 2b/3.** The main purpose of Phase 2b/3 is to provide pivotal assessment of efficacy. For this purpose, we anticipate enrollment of at least 20,000 subjects, with the possibility of enrolling more if required according to observed rates of disease. For that reason, the Phase 2b/3 section will be observer-blinded at site, and the Sponsor staff will also be blinded except for named unblinded staff. The randomization ratio will be 1:1 active:placebo to optimize power to detect efficacy.

If a vaccine candidate progresses directly from Phase 1 to Phase 2b/3, the following data will be analyzed by defined unblinded staff for the first 90 participants enrolled to receive active vaccine per age category per dose level (if more than one dose level enters Phase 2b/3):

- Safety (reactogenicity and AEs) through 7 days after dose 2; and
- Immunogenicity (binding and neutralizing antibody responses) through 21 days after dose 1. (Post-dose 2 immunogenicity data will not be required for decision making to progress but will be submitted to the IND once available.)

These data will be reviewed by the unblinded external Data Monitoring Committee (DMC) to determine suitability of the candidate to continue being studied in Phase 2b and through Phase 3 and will be submitted for CBER review. Enrollment, which is anticipated to be rapid, may continue during the accrual, analysis, and submission of these data. To assure the safety of study participants in this period, the DMC will review unblinded safety data weekly and, if an untoward safety finding arises, will have the authority to pause further enrollment whilst it is assessed.

In Phase 2b, 6000 participants (3000 active, 3000 placebo) will be enrolled. It is intended that this should include around 50% younger adults 18-55 years of age and 50% older adults >55 years of age, although the ratio may depend on when enrollment of older adults can start. The safety data from the first 3000 subjects in Phase 2b and immunogenicity data from a total of approximately 300 subjects (number to be confirmed; combined from earlier phases, German study BNT162-01, and subsets from Phase 2b) (b) (4) (b) (4) . Safety data from the remaining 3000 subjects would be submitted within 60 days of the initial application. The Phase 2b analysis will be undertaken by defined unblinded staff and resulting decisions on risk-benefit to continue taken by the study governance committee. Enrollment will continue in Phase 3 in parallel with the Phase 2b analysis.

It is anticipated that Phase 2b/3 will commence in July 2020.

#### 6.2.2.2.1. Rationale for Phase 2b/3 Enrollment

A broad adult population will be enrolled, comparable to that for which a vaccine is required. Of note, adults aged  $\geq 18$  years will be enrolled with no upper age limit.

In order to perform the study at sites where SARS-CoV-2 is circulating, the study will be performed at sites across the US where there is evidence of recent disease activity. We will also plan to include sites in the EU (possibly Germany, UK, Sweden, Netherlands) and Turkey. We anticipate at least 30% of participants being enrolled in the US, and enrollment will commence in the US.

Participants will be generally healthy at the time of enrollment, but those with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Immunocompromised persons will be excluded as vaccine immunogenicity is not yet defined in such conditions. In a large clinical trial of adults  $\geq 65$  years of age this has resulted in about half of enrolled participants having “at-risk” conditions such as chronic cardiopulmonary disease, chronic renal disease, diabetes, etc. (Suaya et al. 2018). Healthcare workers and

other front-line workers and care staff will be eligible, as will be participants in long-term care facilities.

Participants will not be screened at entry for SARS-CoV-2 infection or for antibody evidence of prior infection. This is for two reasons. Firstly, screening at entry would severely impact the ability to perform a large efficacy assessment. Secondly, such screening will not be possible in a routine immunization program and so it is important to assess immunogenicity and safety in such participants. It will be possible to identify previously infected participant based on baseline immunogenicity assays and to identify most participants infected at entry by presentation with COVID-19 before completing study vaccination. The primary analysis will exclude participants with evidence of previous infection or presentation with COVID-19 before 14 days after the last dose of study vaccine.

Age groups will be stratified by age between younger adults 18-55 years of age and older adults >55 years of age. It is possible that enrollment may commence in the younger stratum, as data to support progression in this age group may be available before data to support progression in older adults.

#### **6.2.2.2.2. Rationale for Efficacy Assessments and Case Definitions**

The case definitions for COVID-19 were described in the Clinical Overview for the initial IND (Module 2.5) as participants in all stages may be followed for COVID-19 for up to 24 months. The case definitions for COVID-19 and severe COVID-19 have been modified in accordance with CBER's suggestions.

Subjects with the following symptoms, which trigger either an illness visit or a telehealth visit with self-swabbing, and SARS-CoV-2 NAAT-positive at Pfizer's central laboratory or locally with a validated nucleic acid amplification test (NAAT) are defined as having COVID-19:

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat; and/or
- Diarrhea and vomiting.

Diarrhea and vomiting have been added to this list as requested by CBER as there have been reports of presentation with gastrointestinal symptoms alone ([Pan et al. 2020](#)). Consideration was given to adding nausea as a defining symptom, but as nausea is too common for many people in daily life, it has not been included.

Note that microbiological diagnosis may be by NAAT performed at Pfizer's central laboratory or a locally performed NAAT using a validated method. The use of local results may be particularly important for sites outside the US, due to transport limitations during the

current pandemic. It will also be important where participants present to emergency healthcare without contact with the investigator site.

The sample tested for by NAAT will generally be mid-turbinate swabs as COVID-19 most commonly presents with respiratory symptoms and these are readily provided for self-swabbing. However, positive NAAT testing from other samples will be considered to contribute to defining a case. This is most likely to be the case for local testing as emergency room procedures may vary in which samples are taken in suspected cases. For example, saliva or other upper respiratory tract samples may be acquired, and stool samples may be taken if gastrointestinal symptoms are prominent.

A definition for severe disease was added based on reports of factors associated with poor outcomes (Richardson S et al. 2020; Guan W-j et al. 2020). In addition, we have taken account of CBER's comments on the definition and updated it such that participants with confirmed COVID-19 and the following will be defined as having severe COVID-19:

- Clinical signs at rest indicative of severe systemic illness (RR  $\geq$ 30 per minute, HR  $\geq$ 125 per minute, SpO<sub>2</sub>  $\leq$ 93% on room air at sea level, or PaO<sub>2</sub>/FiO<sub>2</sub> <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an intensive care unit; or
- Death.

#### 6.2.2.2.3. Analyses During Phase 2b/3

Objectives, estimands and endpoints were presented in the synopsis for a Phase 2/3 randomized, placebo-controlled, observer-blinded study of the efficacy and safety of one or more COVID-19 Vaccine candidates in individuals  $\geq$ 18 years of age (C4591002). At CBER's suggestion, additional objectives and associated estimands and endpoints will be included to assess safety, immunogenicity, and efficacy in subjects with evidence of prior infection at baseline.

Three types of analyses are proposed during the Phase 2b/3 portion of the study:

- Phase 2b safety and immunogenicity analysis to support continuation of a vaccine candidate/dose level in Phase 3;
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- Efficacy interim and final analyses to support Traditional Approval.

### **Phase 2b safety and immunogenicity analysis to support continuation of a vaccine candidate/dose level in Phase 3**

If a vaccine candidate progresses directly from Phase 1 to Phase 2b/3, the following data will be analyzed by defined unblinded staff for the first 90 participants enrolled to receive active vaccine per age category per dose level (if more than one dose level enters Phase 2b/3):

- Safety (reactogenicity, AEs) through 7 days after dose 2; and
- Immunogenicity (binding, neutralizing antibody responses) through 21 days after dose 1. (Post-dose 2 immunogenicity data will not be required for decision making to progress but will be submitted to the IND once available.)

These data will be reviewed by the unblinded external DMC to determine suitability of the candidate to continue being studied in Phase 3 and will be submitted for CBER review. Enrollment will continue while this analysis is performed.

### **Phase 2b safety and immunogenicity analysis**

It is anticipated that up to 3000 subjects (1500 active, 1500 placebo) will have completed a 1-month post-dose 2 visit in September 2020 for at least one candidate vaccine, and that clinical data together with immunogenicity (including virus neutralizing assay results) on a subset would be available within a few weeks. As enrollment would continue during this analysis at a substantial rate, this could be supplemented by safety data on an additional 3000 participants (1500 active, 1500 placebo) within 60 days. This analysis would be performed and reported by a defined unblinded team separate from staff managing the clinical study as blinded assessment of efficacy would continue.

### **Efficacy interim and final analyses**

The primary efficacy analysis will be efficacy against COVID-19 at least 14 days after the last dose of vaccine in participants without evidence of prior SARS-CoV-2 infection at baseline, as such infection induces strong neutralizing antibody responses likely to prevent further infection ([Okba et al. 2020](#)).

Pfizer acknowledges CBER's position that the criterion of success for efficacy should be based on demonstrating vaccine efficacy (VE) >30%, and a statistical framework corresponding to this criterion is described below. Pfizer's preference, however, is to retain a criterion based on demonstrating VE >20% in the protocol because results from this study will be used to seek licensure from other global regulatory authorities who may accept a threshold of 20% for VE. We acknowledge that CBER may ultimately require VE >30% for US licensure. We look forward to additional discussions and alignment with CBER on this topic prior to unblinding.

Also, as shown below, using VE >30% rather than VE >20% requires approximately 50% more cases (under current design assumptions), which is likely to extend the length and/or increase the complexity of the study. From a practical perspective, both approaches would require an observed VE of approximately 50% to meet the respective success criteria, based on the proposed number of cases. For these reasons, Pfizer maintains that the original threshold is appropriate.

Given the large number of cases required, uncertainty in the rate of case accrual, as well as the true level of vaccine efficacy and the likely need to provide data to CBER as the study progresses, Pfizer proposes that a more flexible statistical framework be considered since it may be more appropriate for this setting than the more traditional frequentist approach described previously. Specifically, Bayesian sequential designs provide a formal framework for updating information about the vaccine effect as new data are observed, and consequently these designs are well suited to interim analyses with accumulating information. Results of Bayesian analyses may also be easier to interpret than frequentist analyses as they provide direct probabilistic statements about the unknown VE using the posterior distribution. The posterior distribution drives key decisions at each interim analysis, such as stopping for study success or futility. Predictive probabilities can also be obtained from the posterior, such as the probability that the study will be successful if it continues to completion. These measures are more informative than confidence intervals, and they can provide the probability of interest corresponding to various thresholds for VE.

The maximum number of cases is specified to be N=110 (corresponding to a VE threshold of 20%; [Table 5](#)) or N=150 (corresponding to a VE threshold of 30%; [Table 6](#)). Stopping for success will not occur before accruing at least 40% of the target or maximum number of cases, and the number of interim analyses is limited to four based on practical considerations. Bayesian sequential designs with interim analyses are proposed, although the boundaries for efficacy and futility in [Table 5](#) and [Table 6](#) may be further modified to ensure good operating characteristics (type I error and power).

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, Beta(0.700102, 1), is proposed for  $\theta$  ( $= (1-VE)/(2-VE)$ ). The prior is centered at 0.4118 (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for  $\theta$  is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

#### Decision criteria based on VE threshold = 20%

Study success is defined as demonstrating efficacy of a candidate vaccine. The study will be deemed successful at the final analysis if the posterior probability of VE >20% is at least 0.975. This value is chosen based on power and simulated type I error considerations. An observed estimate of VE  $\geq$ 47.2% (case split 38:72 for vaccine:placebo) is required to meet this criterion.

The stopping criteria for futility are based on the posterior predictive probability of trial success (POS) at the end of the study. POS incorporates accumulated complete data, as well as the uncertainty associated with future cases. The study will be stopped early for futility if demonstrating VE at the end of the study is unlikely (ie, POS <5%).

The stopping criteria for success at an interim analysis are based on the posterior probability at the current number of cases. If this probability is greater than the success threshold at an interim analysis, the study will stop for overwhelming efficacy. The success threshold for each interim analysis is specified as 99%, that is,  $P(VE \geq 20\% | \text{data}) > 0.99$ .

Efficacy and futility boundaries are calculated in a nonbinding way.

Table 5 summarizes the design with four interim analyses using a VE threshold of 20%.

**Table 5. Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 20%)**

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries	Futility Boundaries
1	22/110 (1/5)	No	Yes	NA	$VE \leq -20\%$ and $Y \geq 12$
2	44/110 (2/5)	Yes	Yes	$VE \geq 62.5\%$ and $Y \leq 12$	$VE \leq 16.7\%$ and $Y \geq 20$
3	66/110 (3/5)	Yes	Yes	$VE \geq 56.5\%$ and $Y \leq 20$	$VE \leq 26.3\%$ and $Y \geq 28$
4	88/110 (4/5)	Yes	No	$VE \geq 53.3\%$ and $Y \leq 28$	NA

Boundaries are provided in terms of VE and number of cases in the active vaccine arm (Y).

With assumptions of true VE of 60% after the last dose of investigational product, a total of approximately 110 first confirmed COVID-19 illness cases will be sufficient to demonstrate  $VE > 20\%$ . This would be achieved with 7857 evaluable participants per group or 9821 vaccine recipients randomized in a 1:1 ratio with placebo, based on the assumption of a 1.0% incidence rate in the placebo group, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2. Pfizer may investigate the possibility of enrolling a larger number of participants to accrue the cases in shorter time.

Decision criteria based on VE threshold = 30%

Using the threshold proposed by CBER, the study would be deemed successful at the final analysis if the posterior probability of  $VE > 30\%$  is at least 0.975. One hundred and fifty (150) would be accrued, and an observed estimate of  $VE \geq 50\%$  (case split 50:100 for vaccine:placebo) would be required to meet this criterion.

The stopping criteria for futility are based on the posterior predictive POS at the end of the study. The study will be stopped early for futility if demonstrating VE at the end of the study is unlikely (ie, POS <5%).

The stopping criteria for success at an interim analysis are based on the posterior probability at the current number of cases. If this probability is greater than the success threshold at an

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interim analysis, the study will stop for overwhelming efficacy. The success threshold for each interim analysis is specified as 99%, that is,  $P(VE \geq 30\% | \text{data}) > 0.99$ .

Table 6 summarizes the design with four interim analyses using a VE threshold of 30%.

**Table 6. Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 30%)**

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries	Futility Boundaries
1	30/150 (1/5)	No	Yes	NA	$VE \leq 0\%$ and $Y \geq 15$
2	60/150 (2/5)	Yes	Yes	$VE \geq 63.6\%$ and $Y \leq 16$	$VE \leq 28.6\%$ and $Y \geq 25$
3	90/150 (3/5)	Yes	Yes	$VE \geq 59.5\%$ and $Y \leq 26$	$VE \leq 36.4\%$ and $Y \geq 35$
4	120/150 (4/5)	Yes	No	$VE \geq 55.4\%$ and $Y \leq 37$	NA

Boundaries are provided in terms of VE and number of cases in the active vaccine arm (Y).

### 6.2.3. Clinical Lot Consistency Study

The BNT162 vaccine candidate active antigenic components are manufactured in a controlled chemical process and the LNPs contain defined components. To fulfill CBER's clinical lot consistency study requirement, a randomized safety and immunogenicity study will compare three lots of the vaccine candidate manufactured with a process suitable for large-scale manufacture and will be performed in 2021. The primary immunogenicity endpoint will be antigen-specific IgG. The number of participants will be based upon emerging data on vaccine immunogenicity and assay characteristics. Due to the urgency of the current pandemic and the desire to have a US-licensed vaccine as quickly as possible, the Sponsor proposes that this study be conducted as a post-approval commitment.

### 6.3. Pediatric Plan

Within family clusters children were noted to be infected as often as adults (Bi et al. 2020). Pediatric and adolescent SARS-CoV-2 infections have generally been asymptomatic or mild (Lu et al. 2020; Liu et al. 2020; Zimmermann & Curtis 2020; Qiu et al. 2020), which is likely the reason why far fewer cases were identified in these age groups than in adults (Wu & McGoogan 2020; Guan et al. 2020; Richardson et al. 2020). However, some infected children have required intensive care support (Lu et al. 2020). There is also a possible relationship between SARS-CoV-2 infection and a Kawasaki-like syndrome (Verdoni et al. 2020). The role of children and adolescents in transmission is unknown, but more common seasonal coronaviruses are frequently found in the upper respiratory tract of symptomatic and non-symptomatic children (Zimmermann & Curtis 2020), suggesting that transmission might be common.

In accordance with regulations, we intend to submit an initial Pediatric Study Plan (iPSP) in July 2020, at about the time we plan to start rapid enrollment of participants into the Phase 2/3 component of Study C4591001 and at which point we expect to be moving forward in adults with a specific vaccine candidate at a defined dose-level. The iPSP will

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outline the planned pediatric studies in children 12 months through 17 years of age which will proceed in a stepwise manner.

Currently, a waiver is planned for children <12 months of age to avoid interfering with delivery of existing vaccine schedules which are of known public health importance (Nelson 2020), and due to the infrequency and general mild and self-limiting nature of disease in children in the first year of life (Lu et al. 2020; Liu et al. 2020; Zimmermann & Curtis 2020; Qiu et al. 2020; Wu & McGoogan 2020; Guan et al. 2020; Richardson et al. 2020).

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(b) (4) safety will be demonstrated in approximately 3000 pediatric subjects. Licensure via Traditional Approval in the pediatric population will therefore be dependent on Traditional Approval of the adult indication (following demonstration of clinical endpoint efficacy). Details of the pediatric study plan will be included in the iPSP.

#### 6.4. Pregnancy

COVID-19 infections have been described in pregnant women, generally with good outcomes following Caesarean section (Yu et al. 2020). Neonatal infection has followed in some but generally without adverse outcomes (Yu et al. 2020; Zeng et al. 2020). Nonetheless, it would be desirable to protect women with a vaccine during the second half of pregnancy and this may also have the advantage of protecting neonates from COVID-19, even though neonatal disease has not generally been severe. Therefore, the Sponsor plans to seek licensure for use in pregnant women 18-45 years of age. Licensure will be sought based on demonstration of adequate safety and effectiveness (b) (4) sed (b) (4) (b) (4) (b) (4) (b) (4) .

Before starting a study of vaccination in pregnancy, results from a DART study will be submitted. The results of this would also be reassuring for advising women following accidental exposure in early pregnancy, which is very likely to occur in the event of a large-scale general population immunization program.

A two-step safety and immunogenicity study is anticipated, bridging to immunogenicity data in age-matched non-pregnant adults in Study C4591001. Initially up to 40 pregnant women 18-40 years of age would be randomized to receive a first dose of COVID-19 vaccine or Tdap (Tetanus toxoid, low dose diphtheria toxoid, acellular pertussis vaccine) between 27 0/7 and 35 6/7 weeks gestation and a second dose 3 weeks later, with the control group receiving placebo.

In a second step, the study would expand to 200 participants randomized to two doses of COVID-19 vaccine candidate or Tdap followed by placebo. Numbers may be adjusted based on assay characteristics and risk of safety events. Consideration would be given to including some participants to receive their first dose from 24 0/7 gestational age.

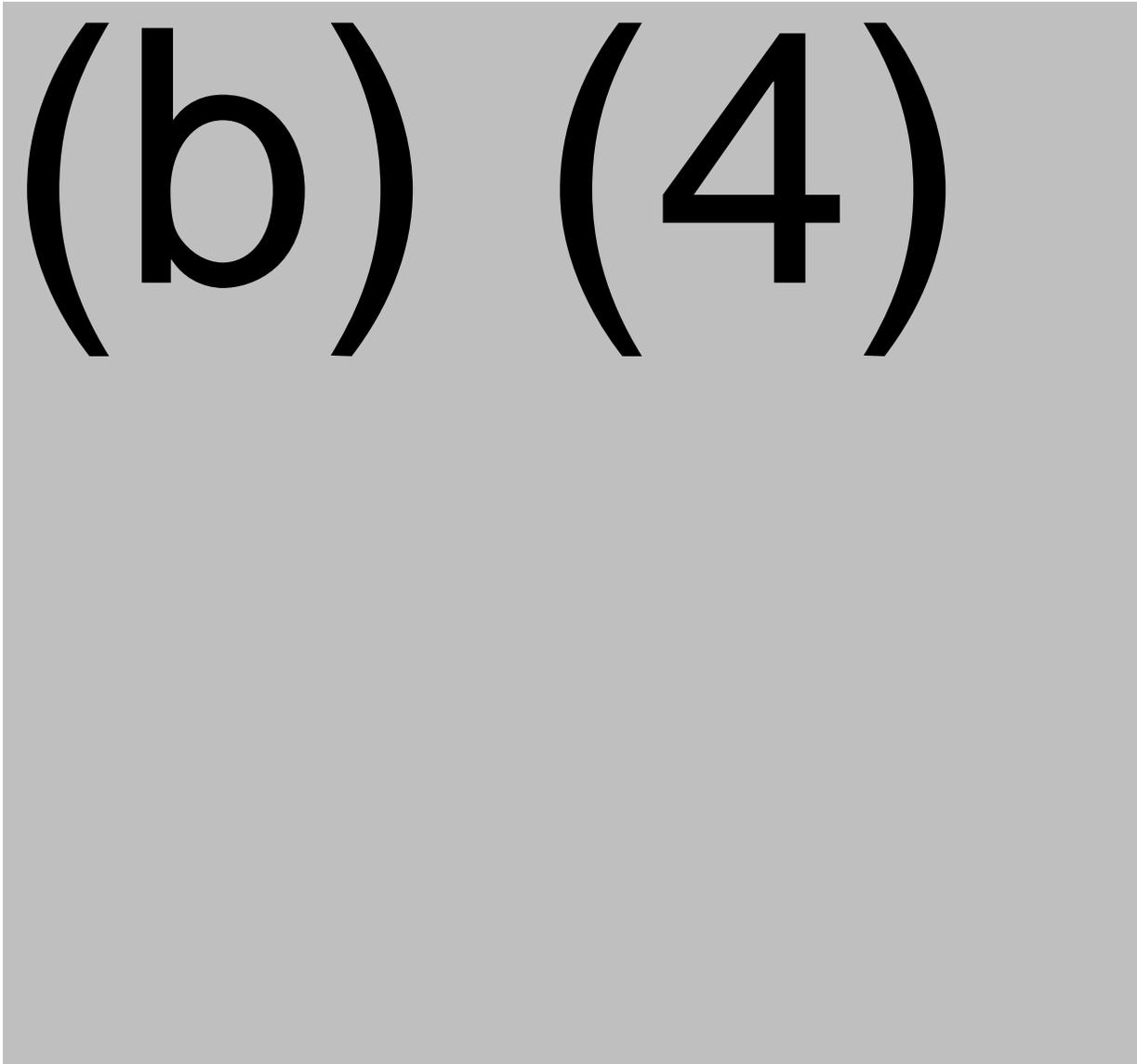
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In addition to safety, reactogenicity, and immunogenicity assessments in maternal participants we would record pregnancy and neonatal outcome, with cord blood and 6-month infant blood for SARS-CoV-2 serology. Mothers and neonates would be followed for up to 6 months after birth for SAEs and clinical COVID-19 episodes.

Similar to the pediatric population, licensure for use in pregnancy would follow Traditional Approval of the candidate vaccine in adult subjects following demonstration of acceptable clinical efficacy.

A pregnancy register capturing maternal, birth, and infant outcomes will be created for inadvertently exposed pregnant women during development but particularly for anticipated exposures in pregnancy during post-approval use of the vaccine.

## 7. REGULATORY PATHWAYS



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## 7.2. Emergency Use Authorization

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(b) (4) . The Emergency Use Authorization request package could be submitted for CBER review in parallel with the initial BLA.

## 7.3. Traditional Approval

The clinical data anticipated for Traditional Approval application in 2021 for the first BNT162 candidate is summarized in Table 8. The timeline for clinical development and regulatory submissions is shown below.

**Table 8. Clinical Data for Traditional Approval Pathway**

	Study	Safety 1-month post-dose 2 (active/placebo)	Immunogenicity (active)	Efficacy (total)
Traditional Approval based on final efficacy analysis	C4591001 Phase 1	24/6 <sup>a</sup>	24 <sup>a</sup>	NA
	C4591001 Phase 2a	180/45 <sup>b</sup>	180 <sup>b</sup>	NA
	C4591001 Phase 2b/3	9821/9821 <sup>c</sup>	9821 <sup>d</sup> (subset)	19,642 <sup>c</sup> 110 cases <sup>e</sup>

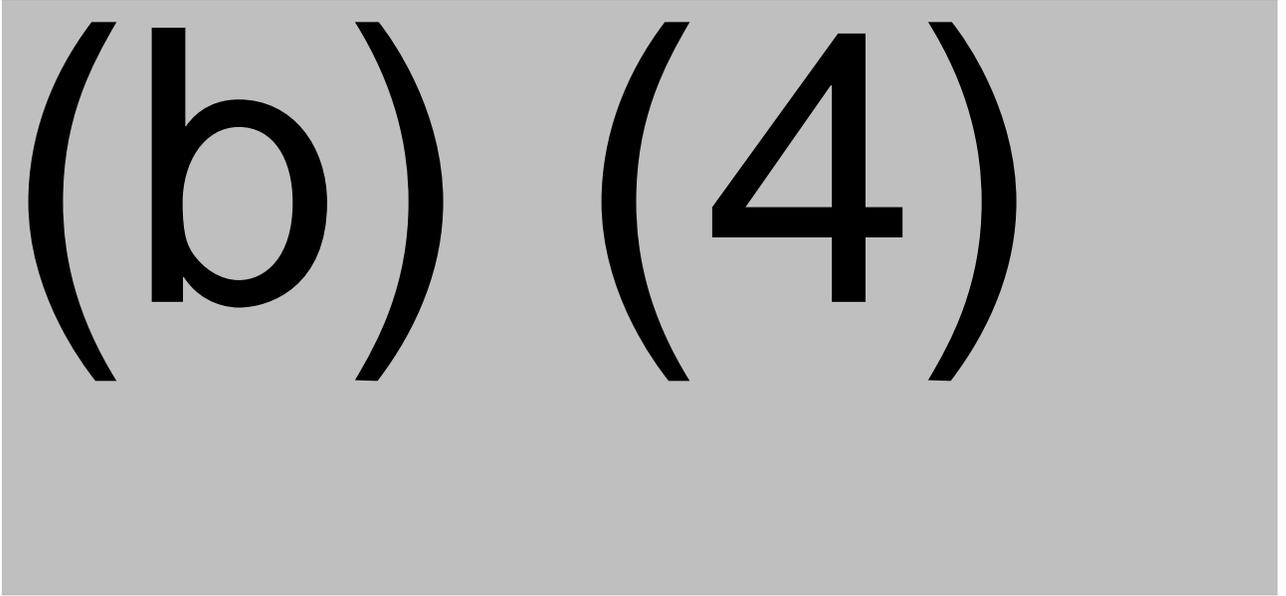
<sup>a</sup> Half 18-55 years of age, half 65-85 years of age.

<sup>b</sup> Half 18-55 years of age, half 56-85 years of age, if Phase 2a is performed.

<sup>c</sup> Stratified to 18-55 and >55 years of age. Not equal by age, depends on enrollment capability in older adults.

<sup>d</sup> Subset sizes for immunogenicity will depend on assay characteristics and Phase 1 data.

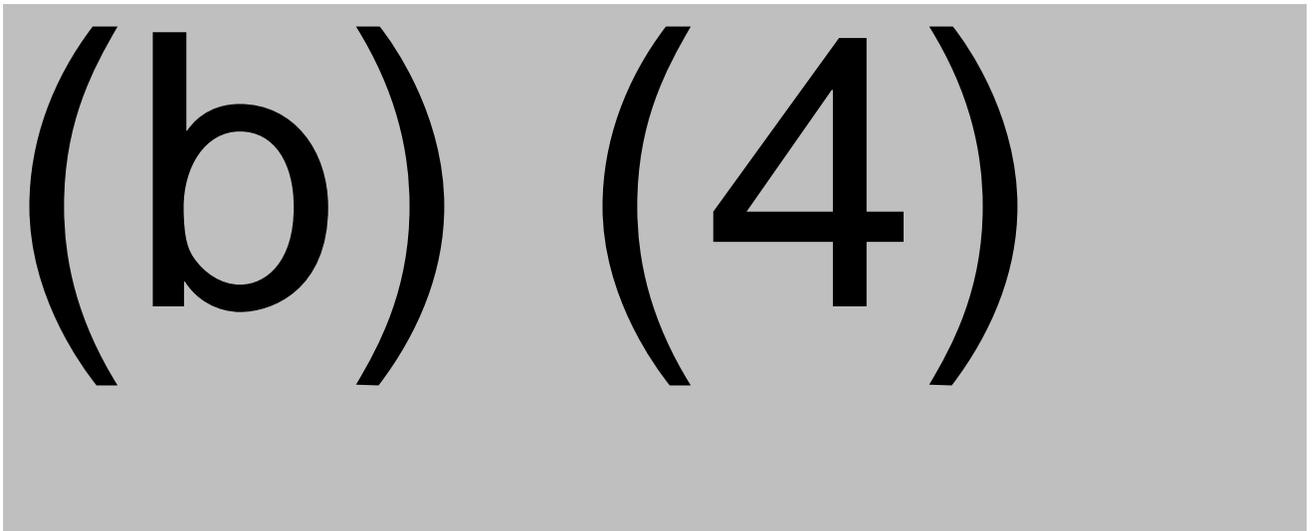
<sup>e</sup> 110 cases at final analysis but interim efficacy analyses at 44, 66, and 88 cases.



## 8. SUMMARY

In summary, the Sponsor respectfully requests CBER feedback on the following:

- The overall Clinical Development Plan and timeline proposed to support (b) (4) (b) (4) Traditional Approval.
- The adequacy of Study C4591001 to serve as the single pivotal study to demonstrate safety, immunogenicity, and efficacy of the candidate vaccine for the proposed indication and the use of Study C4591001 to support (b) (4) Traditional Approval.
- Pfizer/BioNTech's plans to evaluate the BNT162b3 candidate expressing the RBD domain with a short transmembrane tail and two amino acids added to the signal peptide for more homogenous cleavage in Study C4591001, as described in [Section 6.2](#).



- The proposal that study success criteria using the identified protective threshold may be defined in parallel with the Phase 2/3 study, as long as the study will continue fully blinded.

(b) (4)

- Providing additional safety data for 1500 vaccinated participants (additional 3000 vaccine and placebo combined), that is split approximately equally across cohorts 18-55 and >55 years of age during review, within 60 days of BLA submission.

(b) (4)

- Conducting the planned clinical lot consistency study in parallel with the planned Phase 3 efficacy study and submitting the results as a post-approval commitment.
- The adequacy of the proposed study design, including Phase 2b/3 efficacy portion, and the planned persistence evaluations to support Traditional Approval.

(b) (4)

- Pediatric Study Plans.
- Maternal Immunization Study Plans.

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*(All references are available upon request)*

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## Document Approval Record

<b>Document Name:</b>	COVID-19 Vaccine (BNT162 PF-07302048) 2020 FDA Type C Meeting Request Briefing Document
<b>Document Title:</b>	COVID-19 Vaccine (BNT162 PF-07302048) 2020 FDA Type C Meeting Request Briefing Document

<b>Signed By:</b>	<b>Date(GMT)</b>	<b>Signing Capacity</b>
Boyce, Donna	10-Jun-2020 17:38:10	Regulatory Affairs Approval



**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 19736**

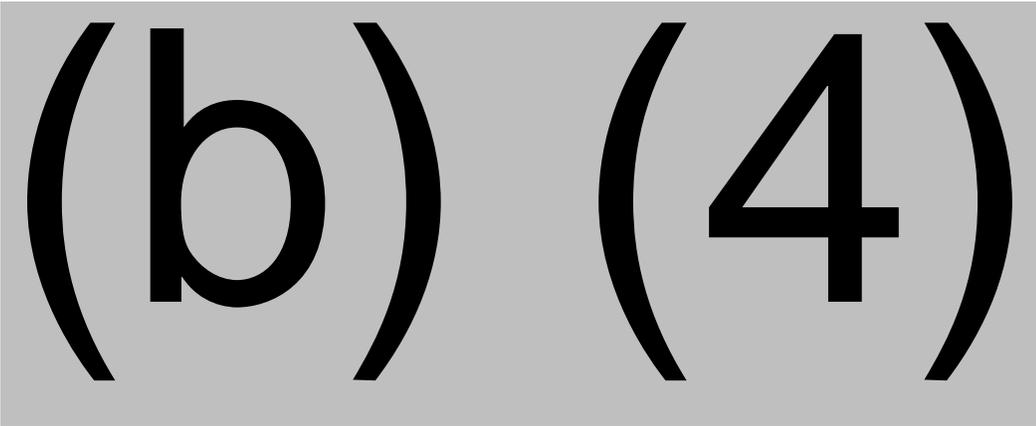
**Response to CBER 25 June 2020 Preliminary Type C Meeting  
Comments and Requests /Meeting Minutes**

**July 8, 2020**

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## 1. INTRODUCTION

Reference is made to BB-IND 19736 for the COVID-19 Vaccine (BNT162; PF-07302048) that Pfizer and BioNTech are developing for the prevention of COVID-19 in adults  $\geq 18$  years of age. On 26 June 2020, a Type C meeting was held to gain CBER feedback regarding Pfizer/BioNTech's proposed Clinical Development Program, including revisions to the ongoing Study C4591001, as well as high-level pediatric and maternal immunization plans. CBER feedback was also requested regarding the clinical data requirements to support (b) (4) Traditional Approval, as well as requirements for use under an Emergency Use Authorization.

CBER provided preliminary meeting responses to Pfizer/BioNTech's pre-meeting questions, along with additional comments and requests, via email on 25 June 2020. On 26 June 2020, in advance of the meeting, Pfizer requested to walk through each item during the meeting for clarity. The information below provides minutes of the discussion between CBER and Pfizer/BioNTech per item during the Type C Meeting. The Sponsor's original questions, as well as CBER's pre-meeting comments and requests are noted in *bold italics* and followed by the discussion per topic.

At the start of the meeting Pfizer/BioNTech acknowledged CBER's feedback regarding

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based

upon CBER's feedback we plan to seek Traditional Approval so we will focus the meeting on what will be required for that.

## 2. CBER REQUESTS AND SPONSOR RESPONSES

### 2.1. Clinical

#### 2.1.1. Sponsor Clinical Question 1

*Does CBER have any comments on the overall Clinical Development Plan and timeline proposed to support (b) (4)*

*Traditional Approval? Specifically,*

##### 2.1.1.1. Sponsor Clinical Question 1a

*Does CBER agree with the proposed revisions to the ongoing Phase 1/2 US Study C4591001 that would add a Phase 2/3 efficacy phase to the study, to evaluate efficacy in an expanded number of participants? Does CBER agree with the proposed Phase 3 safety, immunogenicity, and efficacy endpoints and case definitions?*

#### FDA Response to Clinical Question 1a

*We agree with your general proposal to add a Phase 2/3 efficacy phase to the study [C4591001] and evaluate efficacy in an expanded number of participants.*

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#### **2.1.1.1.1. CBER Clinical Request 1a(i)**

*We note that you state, “the Phase 2b/3 section will be observer-blinded at site, and the Sponsor staff will also be blinded except for named unblinded staff.” We request that the blinding procedures be updated in the revised protocol, with appropriate justifications included, to ensure study integrity.*

#### **Meeting Discussion**

Pfizer/BioNTech acknowledged CBER’s request and agreed to make the update to the protocol for study C4591001. We informed CBER that the submission of the updated protocol for study C4591001 is anticipated for the end of next week. [Post-meeting Note: Protocol C4591001 Amendment 4 including this update was submitted on 02 July 2020 (SN0025)].

#### **2.1.1.1.2. CBER Clinical Request 1a(ii)**

*We recommend the case definition described below, which is similar to your proposed primary efficacy endpoint case definition, to standardize evaluation of efficacy across COVID-19 vaccine studies. You may choose to evaluate the standardized case definition as your primary efficacy endpoint or as a secondary endpoint to be analyzed with or without formal hypothesis testing. We recommend defining a positive case as virologic confirmation by RT-PCR for SARS-CoV-2, along with any symptom for COVID-19 as listed by the CDC (<https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>): fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.*

#### **Meeting Discussion**

Pfizer/BioNTech acknowledged CBER’s request. We proposed to retain our case definition as currently described in the protocol for study C4591001 and add the CDC case definition as a secondary endpoint in the updated protocol. CBER agreed. [Post-meeting Note: Protocol C4591001 Amendment 4 including this change was submitted on 02 July 2020 (SN0025)].

#### **2.1.1.1.3. CBER Clinical Request 1a(iii)**

*We acknowledge your agreement to modify your case definition for severe COVID-19 as previously requested.*

#### **Meeting Discussion**

There was no discussion of this item during the meeting.

#### **2.1.1.1.4. CBER Clinical Request 1a(iv)**

*Please propose a study stopping rule for severe disease as an indicator of enhanced disease to be assessed by the DMC with each prespecified interim analysis. An acceptable*

*approach would be to pause study enrollment for further data review, as well as notification of OVR, if the number of severe COVID-19 cases is greater among vaccine versus placebo recipients. You may propose alternative rules based on reasonable statistical criteria.*

### **Meeting Discussion**

Pfizer/BioNTech acknowledged CBER's comment and stated that a stopping rule will be provided in the updated C4591001 protocol for CBER's review. CBER agreed with this approach. [Post-meeting Note: Protocol C4591001 Amendment 4 including the stopping rule was submitted on 02 July 2020 (SN0025)].

#### **2.1.1.1.5. CBER Clinical Request 1a(v)**

*The briefing document did not include defined safety and immunogenicity endpoints for Phase 3. However, we agree in general with the safety and immunogenicity endpoints described in the previously submitted Phase 3 protocol synopsis (in amendment 7, sequence 0007, dated May 15, 2020), including the plan to assess the serologic response at baseline, 14 days, and 1, 6, 12, and 24 months after completion of vaccination in all study subjects in Phase 3. The immunologic assays described in item 2.13.1 of your responses to CBER comments dated May 29, 2020 are appropriate, provided the assay validation data to be submitted prior to the testing of Phase 3 samples are acceptable.*

### **Meeting Discussion**

Pfizer/BioNTech sought clarification on the applicability of this request to the initial BLA since we would now be seeking Traditional Approval. We explained that while these would be supportive data, for example, for subsequent immunobridging, they will probably not be relevant for the initial BLA filing and licensure which will likely be based upon efficacy data, and hence would not be required in the initial BLA. CBER agreed. We also stated that the (b) (4) immunogenicity sampling beyond 1 month post-dose 2 to a subset of participants in Phase 2b/3.

It was also agreed that Pfizer will provide CBER the assay validation data prior to testing of Phase 3 samples.

#### **2.1.2. Sponsor Clinical Question 1b**

*Does CBER agree with the proposed study success criteria for Phase 3 (b) (4) (b) (4) ?*

##### **2.1.2.1. CBER Clinical Request 1b(i)**

*As communicated previously, we do not agree with a success criterion defined as the lower limit of VE being >20%. To ensure that a widely deployed vaccine is more than modestly effective, we request that the success criterion be defined equivalent to a primary efficacy*

*endpoint point estimate of at least 50% and the lower limit of the alpha-adjusted 95% CI around that point estimate being >30%. In principle, the four interim analyses proposed in Table 6 of the briefing document, using a VE threshold of 30%, would be acceptable if the criteria were adjusted to preserve the type I error rate at 2.5%. In addition, the proposed efficacy boundaries are based solely on case split, which presumes that the numbers of evaluable subjects and duration of follow-up in both groups are equivalent. Please clarify how you plan to adjust the boundaries for potential difference in numbers of evaluable subjects.*

### **Meeting Discussion**

On 24 June 2020 Pfizer provided a set of slides to CBER via email that were utilized for the discussion of this topic (See Attachment A). With reference to slide numbers 8 and 9 Pfizer explained how we intend to potentially identify vaccine efficacy at 32 cases. CBER conveyed that conceptually, the design seems appropriate, however they will review this carefully and provide post-meeting feedback on this topic. [Post-meeting Note: Protocol C4591001 Amendment 4 was submitted on 02 July 2020 (SN0025)].

#### **2.1.2.2. CBER Clinical Request 1b(ii)**

*Given that current COVID-19 epidemiology is permissive for conducting clinical disease endpoint efficacy trials, (b) (4)*

(b) (4)  
(b) (4)  
(b) (4)

(b) (4)

approval will need

*to be based on demonstration of clinical disease endpoint efficacy.*

### **Meeting Discussion**

Acknowledged by Pfizer/BioNTech at the start of the meeting.

#### **2.1.3. Sponsor Clinical Question 1c**

*Does CBER agree with the proposed plan for progression of vaccine candidates from Phase 2 to Phase 3?*

##### **2.1.3.1. CBER Clinical Request 1c**

*We agree with the proposal that includes review of unblinded safety data through 7 days after dose 2 and immunogenicity data through 21 days after dose 1 of each vaccine candidate by the internal review committee. With the submission of these data to CBER, we request that you include a summary of the data that includes the rationale for dose selection.*

### **Meeting Discussion**

On 26 June 2020 Pfizer provided 2 tables to CBER via email that were utilized for the discussion of this topic (See Attachment B). Pfizer explained that we are getting a much better understanding of the dosage from the US and German studies, have eliminated some of the initial candidates, and that going forward the dose levels are likely to be 10 or 20 mcg. We anticipate being able to have a decision on the Ph2b/3 candidate which would be either BNT162b1 or BNT162b2, and the dosage decision should be made by July 17<sup>th</sup>. Pfizer representatives walked through the tables provided with details regarding when relevant nucleoside-modified mRNA (modRNA) platform data from US Study C4591001 will become available for decisions and for submission to CBER, including plans to provide CBER data in real time. BioNTech representatives added information regarding when additional data will also be available from German Study BNT162-01.

Pfizer further explained that the intention is to make the decision on candidate and dosage based on data from the sentinel subjects in Stage 1 such that we are ready to have 1 vaccine candidate, at 1 dose level, to start Phase 2b/3 and enroll rapidly while there are still significant cases in the US, to be able to potentially identify vaccine efficacy as early as when 32 cases have accrued, as described during the discussion of the statistical design.

Pfizer/BioNTech offered to send further information regarding data availability from both studies to CBER to assist in their review. CBER conveyed that they will review and provide post-meeting feedback on this topic.

[Post Meeting Note: On 30 June 2020 Pfizer provided additional information via email for clarification and timing around the data to be provided to CBER in advance of Phase 2b/3 study start planned for 20 July 2020. This information was also submitted to BB-IND 19736 on 1 July 2020 (Module 1.12.14 Request for Comments and Advice SN0024).]

#### **2.1.4. Sponsor Clinical Question 1d**

***Does CBER agree with the proposed inclusion of global sites (e.g., EU, South America, Turkey) in the efficacy phase of the study with at least 30% of participants coming from the US assuming current state of the pandemic?***

#### **FDA Response to Clinical Question 1d**

***We agree with the proposal to include global sites in the efficacy phase of the study, with at least 30% of participants coming from the US.***

### **Meeting Discussion**

There was no discussion on this item during the meeting.

### 2.1.5. Sponsor Clinical Question 2

*Does CBER agree that revised Study C4591001 is adequate to serve as the single pivotal study to demonstrate adequate safety, immunogenicity, and efficacy of the candidate vaccine for the proposed indication and may be used to support (b) (4) Traditional Approval?*

#### FDA Response to Clinical Question 2

*Please see our responses to your other questions. We agree that a single, well-designed and well-conducted clinical disease endpoint efficacy study that is able to meet our requested pre-specified success criterion would likely provide substantial evidence of effectiveness and an adequately sized safety database to support licensure of your product via the Traditional Approval Pathway. (b) (4)*

(b) (4)  
(b) (4)  
(b) (4)  
(b) (4)

#### Meeting Discussion

Acknowledged by Pfizer/BioNTech at the start of the meeting.

### 2.1.6. Sponsor Clinical Question 3

*Does CBER agree with Pfizer/BioNTech's plans to evaluate the BNT162b3 candidate expressing the RBD domain with a short transmembrane tail and two amino acids added to the signal peptide for more homogeneous cleavage in Study C4591001, as described in Section 6.2?*

#### FDA Response to Clinical Question 3

*We agree that the clinical data from BNT162b1, which uses the same nucleoside-modified mRNA (modRNA) platform as your new BNT162b3 vaccine candidate, could support the use of BNT162b3 in the proposed Phase 1/2/3 study. As previously communicated on June 3, 2020, you may submit a revised protocol to include the new vaccine candidate with supportive CMC and nonclinical data.*

#### 2.1.6.1. CBER Clinical Request 3a

*Please provide the CMC drug substance and drug product information for the BNT162b3 clinical lot and the non-clinical immunogenicity data for this new vaccine candidate (including assessment of Th1/Th2 markers and cellular responses) to the IND prior to the initiation of the Phase 2 portion of your Study C4591001. In addition, please provide a summary of CMC comparability between BNT162b1 and BNT162b3.*

#### Meeting Discussion

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Pfizer/BioNTech acknowledged CBER’s request and conveyed that a CMC amendment to provide information for BNT162b3 is planned to be submitted to CBER next week. [Post-meeting Note: The CMC amendment was submitted to BB-IND 19736 on 29 June 2020 (SN 0021)].

### 2.1.6.2. CBER Clinical Request 3b

*We note that if Phase 1 evaluation of BNT162b1 leads to a selected dose level to proceed into Phase 2 for both younger and older adults, you plan to take BNT162b3 directly to Phase 2 for both age groups at the same dose selected for BNT162b1. However, your rationale for inclusion of BNT162b3 is that it has shown superior immunogenicity to BNT162b1 in mice, which suggests that the immunologic response to these vaccine candidates, and by extension the optimal dose, might not be the same. As such, we request that if you introduce BNT162b3 directly into Phase 2 based on a dose chosen for BNT162b1, you introduce it into the Phase 2a portion of your study, rather than the Phase 2b portion, so that the safety and immunogenicity of that dose level can be evaluated in a smaller group prior to dosing 3,000 subjects.*

#### Meeting Discussion

Pfizer/BioNTech acknowledged CBER’s request.

### 2.2. Regulatory Comments

(b) (4)

#### Meeting Discussion

Acknowledged by Pfizer/BioNTech at the start of the meeting.

(b) (4)

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(b) (4)

**Meeting Discussion**

Acknowledged by Pfizer/BioNTech at the start of the meeting.

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(b) (4)

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(b) (4)

**Meeting Discussion**

Acknowledged by Pfizer/BioNTech at the start of the meeting.

**2.2.2. Traditional Approval**

**2.2.2.1. Sponsor Traditional Approval-Related Question 1**

*Does CBER agree that the proposed study design, including a Phase 2/3 efficacy portion, and the planned persistence evaluations from Phase 1 sentinel and Phase 2 cohorts are adequate to support Traditional Approval?*

**2.2.2.1.1. CBER Traditional Approval-Related Request 1a**

*We agree that the proposed study design may be adequate to support Traditional Approval using the success criteria specified in our response to Question 1.b, contingent on our review and assessment of the submitted data. It is not clear from your briefing material what you mean by the planned persistence evaluations from Phase 1 sentinel and Phase 2 cohorts.*

**Meeting Discussion**

Pfizer explained that all subjects in Stage 1 will be followed for 24 months. For Phase 2/3 it is still intended to follow subjects for 24 months. However, if we achieve sufficient cases to be successful sooner, we may need to vaccinate subjects receiving placebo. These subjects would still be followed for safety but the persistence evaluations would be impacted. CBER acknowledged understanding and agreement.

**2.2.2.1.2. CBER Traditional Approval-Related Request 1b**

*Ideally, your BLA submission would include blinded 6-month safety data from at least 3,000 subjects who have received the vaccine at the dose intended for licensure. Please comment on how many subjects from whom you anticipate to provide 6-month safety data in your licensure application (including in the initial submission and potentially in a safety update submitted during our review) in the event that an interim efficacy analysis meets the study success criterion. Further discussion may be needed on the acceptability of the safety database, depending on the data you plan to have available.*

**Meeting Discussion**

Pfizer explained that we would have 1-month safety data from at least 3,000 subjects who have received the vaccine at the dose intended for licensure, but we would only have 6-month safety data from a few subjects enrolled near the start of the C4591001 study.

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### 2.2.2.1.3. CBER Traditional Approval-Related Request 1c

*We agree with your plan to continue to follow subjects through Month 24 to enable assessment of longer-term safety and durability of vaccine efficacy. Please discuss your contingency plans for continuing longer-term follow up and analysis of safety and effectiveness outcomes in the event that early demonstration of efficacy sufficient to support wide use of the vaccine raises ethical arguments to break the blind and offer vaccine to placebo recipients.*

#### Meeting Discussion

Discussed in the context of Traditional Approval Request 1a (See above [Section 2.2.2.1.1](#)).

### 2.2.2.2. Sponsor Traditional Approval-Related Question 2

#### 2.2.2.2.1. CBER Traditional Approval-Related Request 2

*Clinical lot consistency studies are traditionally performed as a component of the Phase 3 efficacy study. Data from these studies are used to support product consistency in the clinic and are typically designed using three independently manufactured lots. Data from these studies are used to support product licensure and therefore should be included in the BLA. If you are not able to complete a lot to lot consistency study as part of your Phase 3 study, please propose an analytical comparability study to support the consistent manufacture and quality of the product batches used in your Phase 3 study.*

#### Meeting Discussion

Pfizer/BioNTech acknowledged CBER's comment and conveyed that a Type C Meeting to discuss Chemistry, Manufacturing and Controls is planned for the end of July. We will provide a proposal within the context of that meeting.

### 2.2.3. Emergency Use Authorization (EUA)

#### 2.2.3.1. Sponsor EUA-Related Question 1

*The Sponsor is currently manufacturing vaccine at-risk and is targeting to have US-manufactured and released vaccine doses of approximately (b) (4) available by year-end 2020 with initial deliveries projected for late November. Does CBER agree that*

(b) (4)

(b) (4)

(b) (4)

*The Emergency Use Authorization request package could be submitted for CBER review in parallel with the initial BLA.*

#### FDA Response to EUA-Related Question 1

(b) (4)

(b) (4)

### **Meeting Discussion**

Pfizer/BioNTech requested clarification of our understanding that clinical efficacy data are needed to support Emergency Use Authorization. CBER confirmed that a signal of efficacy is needed to support Emergency Use Authorization.

Pfizer expressed agreement with CBER and explained that this is the reason we are planning to start the efficacy phase of the study in July, we are attempting to demonstrate efficacy as soon as possible while we are still able to in the US.

### **2.2.4. Pediatric and Maternal Immunization (P&MI) Study Plans**

#### **2.2.4.1. Sponsor P&MI Study Plans-Related Question 1**

*Does CBER have any comments on the high-level pediatric study plan? Does CBER agree that* (b) (4)

#### **FDA Response to P&MI Study Plans-Related Question 1**

*We have the following comments on the high-level pediatric study plan.*

##### **2.2.4.1.1. CBER P&MI Study Plan-Related Request 1a**

*Please provide a statutory rationale to support the planned waiver for children less than 12 months of age. We disagree with your statement that COVID-19 is generally mild and self-limiting in children in the first year of life as several large pediatric case series have demonstrated a higher proportion of severe disease in children less than 12 months of age versus other pediatric age groups (Dong Y, Mo X, Hu Y, et al. *Epidemiology of COVID-19 Among Children in China. Pediatrics.* 2020;145(6):e20200702. *Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep* 2020;69:422–426. DOI: <http://dx.doi.org/10.15585/mmwr.mm6914e4>)*

### **Meeting Discussion**

Pfizer/BioNTech acknowledged CBER's comment and will provide pediatric plans for CBER review in the Pediatric Study Plan that we plan to submit mid-July.

##### **2.2.4.1.2. CBER P&MI Study Plans-Related Request 1b**

*It is premature to agree on the applicability of immunobridging studies to infer effectiveness for all pediatric age groups; clinical disease endpoint efficacy studies may be*

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*required for some age groups pending better understanding of SARS-CoV-2 immunology and pathogenesis.*

### **Meeting Discussion**

Pfizer/BioNTech acknowledged CBER's comment and will provide pediatric plans for CBER review in the Pediatric Study Plan that we plan to submit mid-July.

#### **2.2.4.2. Sponsor P&MI Study Plans-Related Question 2**

*Does CBER agree with the proposed inclusion of global sites (eg, EU, South America, Turkey) in the pediatric study with at least 30% of participants coming from US?*

### **FDA Response to P&MI Study Plans-Related Question 2**

*We agree with the proposal to include global sites in the pediatric study, with at least 30% of participants coming from the US.*

### **Meeting Discussion**

There was no discussion of this item during the meeting.

#### **2.2.4.3. Sponsor P&MI Study Plans-Related Question 3**

*Does CBER have any comments on the proposed plan for evaluating maternal immunization?*

### **FDA Response to P&MI Study Plans-Related Question 3**

*We acknowledge your plans to assess your product in pregnant women, and we would encourage an ongoing dialogue regarding inclusion of pregnant women in your planned studies and how safety and effectiveness data obtained with your vaccine may be used. Please note that initiation of studies in this population is contingent on our review of data to support the safety of this approach, particularly your planned DART study. We have the following comments and requests for clarification:*

##### **2.2.4.3.1. CBER P&MI Study Plans-Related Request 3a**

*Please provide a detailed proposal for how you intend to label the data from studies conducted in pregnant women (or the subanalyses of the data from pregnant women, if they are included in broader studies).*

### **Meeting Discussion**

Pfizer/BioNTech acknowledged CBER's request and will defer this discussion for a later date.

#### 2.2.4.3.2. CBER P&MI Study Plans-Related Request 3b

*Please clarify whether you intend to seek an indication for vaccination during pregnancy to protect the infant from SARS CoV-2 infection. Please note that cord blood immune assays are unlikely to be adequate to support this indication in the absence of establishing a biomarker reasonably likely to predict protection.*

##### Meeting Discussion

Pfizer/BioNTech acknowledged CBER's request and will defer this discussion for a later date.

#### 2.2.4.3.3. CBER P&MI Study Plans Request 3c

*With respect to other vaccines recommended for administration during pregnancy (i.e., Tdap and influenza vaccines), please comment on the potential for immunologic interference and discuss your plans to address this issue.*

##### Meeting Discussion

Pfizer/BioNTech acknowledged CBER's request and will defer this discussion for a later date.

#### 2.2.4.3.4. CBER P&MI Study Plans Request 3d

*Further discussion on your proposed immunobridging study may be needed after you provide responses to our questions above to clarify your intentions for labeling of data from this study and claims related to the data, and after more data are available to determine the acceptability of immune markers that you would propose for immunobridging.*

##### Meeting Discussion

Pfizer/BioNTech acknowledged CBER's request and will defer this discussion for a later date.

#### 2.2.4.4. Sponsor P&MI Study Plans-Related Question 4

(b) (4)

(b) (4) . Does CBER agree that the results of the DART study can be provided during review of the initial BLA (b) (4)

(b) (4) ?

#### **FDA Response to P&MI Study Plans-Related Question 4**

*We agree that the results of the DART study can be provided during review of the initial BLA that will include data from Study C4591001. (b) (4)*

*(b) (4)*

#### **Meeting Discussion**

Pfizer conveyed that we plan to start the DART study in July and anticipate that we will be able to submit the results of it while the [Traditional Approval] BLA is under review.

### **2.3. Additional FDA Comments**

#### **2.3.1. Additional FDA Comment 1**

*Consistent with the FDA Guidance for Industry on Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (<https://www.fda.gov/media/127712/download>), we encourage you to adopt enrollment and retention practices that enhance inclusiveness so that the clinical trial population reflects the diversity of the people who will be using the vaccine, if approved. Specifically, racial and ethnic minority persons should be represented in clinical trials. We suggest that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minorities to recruit a diverse study population.*

#### **Meeting Discussion**

There was no discussion of this item during the meeting. Pfizer/BioNTech acknowledge CBER's comment.

#### **2.3.2. Additional FDA Comment 2**

*All study data generated from trials initiated after December 17, 2016, that will be submitted with applications for new drugs/biologics must be in conformance with the standards listed in the FDA Data Standards Catalog. As you intend to initiate your Phase 1/2/3 clinical trial in the near future, we request that you provide as soon as possible, a Study Data Standardization Plan (SDSP) with CBER appendix proposing the specific use of the Clinical Data Interchange Standards Consortium (CDISC), including Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) formats. We also request that the associated annotated case report form (aCRF) for SDTM be provided. Please refer to the CDISC Vaccine Therapeutic Area User Guide (TAUG) and Guidance for Industry "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review" for details on standardizing your data.*

#### **Meeting Discussion**

There was no discussion of this item during the meeting. Pfizer/BioNTech acknowledge CBER's comment.

# COVID -19 Design Details

# Design 1: Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 20%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries	Futility Boundaries
1	22/110 (1/5)	No	Yes	NA	VE $\leq$ -20% and Y $\geq$ 12
2	44/110 (2/5)	Yes	Yes	VE $\geq$ 62.5% and Y $\leq$ 12	VE $\leq$ 16.7% and Y $\geq$ 20
3	66/110 (3/5)	Yes	Yes	VE $\geq$ 56.5% and Y $\leq$ 20	VE $\leq$ 26.3% and Y $\geq$ 28
4	88/110 (4/5)	Yes	No	VE $\geq$ 53.3% and Y $\leq$ 28	NA
Final	110/110			VE $\geq$ 47.2% and Y $\leq$ 38	

# Design 1: Operating Characteristics

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Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				VE= 20%	VE= 55%	VE= 60%	VE= 20%	VE= 55%	VE= 60%
<b>1</b>	22/110 (1/5)	No	Yes	0%	0%	0%	22.9%	1.8%	0.1%
<b>2</b>	44/110 (2/5)	Yes	Yes	1.4%	36.0%	50.0%	52.8%	4.1%	1.9%
<b>3</b>	66/110 (3/5)	Yes	Yes	2.2%	54.8%	70.9%	72.9%	5.9%	2.5%
<b>4</b>	88/110 (4/5)	Yes	No	2.7%	69.2%	84.5%	-	-	-
<b>Final</b>	110/110			<b>3.8%</b>	90.2	99.0%	-	-	-

## Design 2: Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 30%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries	Futility Boundaries
1	30/150 (1/5)	No	Yes	NA	VE $\leq$ 0% and Y $\geq$ 15
2	60/150 (2/5)	Yes	Yes	VE $\geq$ 63.6% and Y $\leq$ 16	VE $\leq$ 28.6 % and Y $\geq$ 25
3	90/150 (3/5)	Yes	Yes	VE $\geq$ 59.5% and Y $\leq$ 26	VE $\leq$ 36.4 % and Y $\geq$ 35
4	120/150 (4/5)	Yes	No	VE $\geq$ 55.4% and Y $\leq$ 37	NA
Final	150/150			VE $\geq$ 50.0% and Y $\leq$ 50	

# Design 2: Operating Characteristics

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				VE= 30%	VE= 55%	VE= 60%	VE= 30%	VE= 55%	VE= 60%
<b>1</b>	30/150 (1/5)	No	Yes	0%	0%	0%	21.2%	2.3%	1.1%
<b>2</b>	60/150 (2/5)	Yes	Yes	1.4%	28.1%	43.5%	53.7%	6.3%	2.6%
<b>3</b>	90/150 (3/5)	Yes	Yes	2.0%	42.6%	62.1%	75.1%	10.0%	3.9%
<b>4</b>	120/150 (4/5)	Yes	No	2.7%	60.3%	80.7%	-	-	-
<b>Final</b>	150/150			<b>4.1%</b>	<b>84.3%</b>	<b>98.0%</b>	-	-	-

## Design 3: **Calibrated** Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 30%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries* , **	Futility Boundaries
<b>1</b>	32/164	No	Yes	NA	VE ≤11.8% and Y ≥15
<b>2</b>	62/164	Yes	Yes	VE ≥ 70.8% and Y ≤14	VE ≤27.8 % and Y ≥26
<b>3</b>	92/164	Yes	Yes	VE ≥62.7% and Y ≤25	VE ≤36.8 % and Y ≥36
<b>4</b>	120/164	Yes	No	VE ≥60.5% and Y ≤34	NA
<b>Final</b>	164/164			VE ≥50.9% and Y ≤54	

\*Using efficacy boundary at interim: ,  $P(\text{VE} \geq 30\% | \text{data}) > 0.9975$

\*\*Using success criteria at the final analysis: ,  $P(\text{VE} \geq 30\% | \text{data}) > 0.98$ .

# Design 4: Operating Characteristics

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				VE= 30%	VE= 55%	VE= 60%	VE= 30%	VE= 55%	VE= 60%
<b>1</b>	32/164	No	Yes	0%	0%	0%	31.5%	4.4%	2.1%
<b>2</b>	62/164	Yes	Yes	0.2%	9.4%	18.4%	62.7%	9.6%	4.3%
<b>3</b>	92/164	Yes	Yes	0.5%	26.0%	44.7%	81.4%	13.9%	5.9%
<b>4</b>	120/164	Yes	No	0.6%	35.4%	57.9%	-	-	-
<b>Final</b>	164/164			<b>2.2%</b>	78.8%	96.2%	-	-	-

# Design 4: Frequentist Sequential Design with Four Interim Analyses (VE Threshold = 30%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries*	Futility Boundaries
1	32/164	Yes	Yes	$VE \geq 81.5\%$ and $Y \leq 5$	$VE \leq 11.8\%$ and $Y \geq 15$
2	62/164	Yes	Yes	$VE \geq 70.8\%$ and $Y \leq 14$	$VE \leq 27.8\%$ and $Y \geq 26$
3	92/164	Yes	Yes	$VE \geq 62.7\%$ and $Y \leq 25$	$VE \leq 36.8\%$ and $Y \geq 36$
4	120/164	Yes	No	$VE \geq 57.1\%$ and $Y \leq 36$	NA
Final	164/164			$VE \geq 52.3\%$ and $Y \leq 53$	

\*Efficacy boundary is calculated using Gamma(-2) family

# Design 4: Operating Characteristics

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				VE= 30%	VE= 55%	VE= 60%	VE= 30%	VE= 55%	VE= 60%
<b>1</b>	32/164	Yes	Yes	0.1%	3.9%	7.2%	31.5%	4.4%	2.1%
<b>2</b>	62/164	Yes	Yes	0.3%	11.0%	20.4%	54.6%	7.1%	3.2%
<b>3</b>	92/164	Yes	Yes	0.6%	27.5%	46.7%	76.3%	10.4%	4.2%
<b>4</b>	120/164	Yes	No	1.1%	48.7%	72.0%	-	-	-
<b>Final</b>	164/164			<b>1.9%</b>	72.9%	92.4%	-	-	-

**Harkins Tull, Elisa**

**From:** Harkins Tull, Elisa  
**Sent:** Friday, June 26, 2020 12:51 PM  
**To:** Naik, Ramachandra  
**Subject:** IND 19736 Type C Meeting - Tables for use in meeting

**Importance:** High

Dear Ram,

Would you mind to kindly distribute these tables to your colleagues who are attending the meeting today? They are just intended as a tool to help discuss data availability. We thought this would be more clear than just describing verbally.

Best regards,  
 Elisa

**Projected serological Data following dose 1**

Construct	Age Cohort	Dose Level	Post Dose 1	
			IgG	Neut
	18-55	10ug	completed	completed
	18-55	30ug	completed	completed
<b>BNT162b1</b>	18-55	20ug	30-Jul	
	65-85	10ug	9-Jul	11-Jul
	65-85	20ug	16-Jul	17-Jul
	65-85	30ug	16-Jul	18-Jul
	18-55	10ug	9-Jul	11-Jul
	18-55	20ug	15-Jul	17-Jul
	18-55	30ug	23-Jul	
<b>BNT162b2</b>				
	65-85	10ug	30-Jul	3-Aug
	65-85	20ug	15-Jul	17-Jul
	65-85	30ug	16-Jul	

**Projected number of subjects**

<b>By 17-Jul-20</b>
<b>BNT162b1 total</b>
18-55yrs
65-85yrs
<b>BNT162b2 total</b>
18-55yrs
65-85yrs
<b>Grand Total</b>

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*Elisa Harkins Tull*  
 Senior Director  
 Global Regulatory Affairs - Vaccines  
 Pfizer, Inc.

500 Arcola Road  
Collegeville, PA 19426

Mobile – 215-280-5503  
Fax – 845-474-3500

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Our Reference: Type C Meeting Request: IND 19736, Amendment 15; CRMTS 12645

**MEETING SUMMARY**

Date: July 15, 2020

BioNTech RNA Pharmaceuticals GmbH  
Attention: Elisa Harkins  
Pfizer, Inc.  
500 Arcola Road  
Collegeville, PA 19436

Dear Ms. Harkins:

Attached is a copy of the memorandum summarizing your June 26, 2020, IND meeting (teleconference) with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to IND 19736, Amendment 15; CRMTS 12645 in your future submissions related to the subject product.

If you have any questions, please contact me at 301-796-2640.

Sincerely,

**Ramachandra Naik**

-S

Ramachandra S. Naik, PhD

Primary Reviewer

Division of Vaccines and Related Products Applications

Office of Vaccines Research and Review

Center for Biologics Evaluation and Research

Digitally signed by Ramachandra Naik -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, 0.9.2342.19200300.100.1.1=2001232361,  
cn=Ramachandra Naik -S  
Date: 2020.07.15 11:37:05 -04'00'

**Meeting Summary**  
**(Includes Preliminary Meeting Responses)**

**Meeting ID #:** CRMTS 12645  
**Submission type & #:** IND 19736, Amendment 15  
**Product name:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); and BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)  
**Proposed indication:** Active immunization against COVID-19 in adults 18 years of age and older  
**Sponsor:** BioNTech RNA Pharmaceuticals GmbH  
Sponsor Agent: Pfizer, Inc.  
**Meeting type:** Type C  
**Meeting category:** IND - Other  
**Meeting date & time:** June 26, 2020, 1:30 – 3:00 PM  
**Meeting format:** Teleconference  
**Meeting Leader:** Ramachandra Naik, PhD  
**RPM:** Ramachandra Naik, PhD  
**Preliminary Meeting Responses Sent:** June 25, 2020

**FDA Attendees:**

Nabil Al-Humadi, PhD	OVRP/DVRPA
Maria Allende, MD	OVRP/DVRPA
Brenda Baldwin, PhD	OVRP/DVRPA
Anissa Cheung, MSc	OVRP/DVP
Carmen Collazo, PhD	OVRP/DVRPA
Dennis Cato, MD	OBE/DIS
Nicolette Devore, PhD	OD
Karen Farizo, MD	OVRP
Doran Fink, MD, PhD	OVRP/DVRPA
Sara Gagneten, PhD	OVRP/DVP
Martin (Dave) Green, PhD	OVRP/DVRPA
Marion Gruber, PhD	OVRP
Lei Huang, PhD	OBE/DB
Bhanu Kannan	OBE/DIS
Philip Krause, MD	OVRP
Robin Levis, PhD	OVRP/DVP
Tsai-Lien Lin, PhD	OBE/DB
Carrie Mampilly	OCBQ/DIS
Valerie Marshall	OVRP
Loris McVittie, PhD	OVRP/DVRPA
Ramachandra Naik, PhD	OVRP/DVRPA
Manuel Osorio, PhD	OD

Keith Peden, PhD	OVRD/DVP
Douglas Pratt, MD	OVRD/DVRPA
Jeff Roberts, MD	OVRD
David Rouse	OD
Elizabeth Sutkowski, PhD	OVRD/DVRPA
Stephanie Troy, MD	OVRD/DVRPA
Jerry Weir, PhD	OVRD/DVP
Susan Wollersheim, MD	OVRD/DVRPA

**Sponsor Attendees:**

Mark Boaz	Program Director, Vaccine Research and Development, Pfizer Inc.
Donna Boyce	Vice President, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Carmel Devlin	Global Regulatory Portfolio Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Philip R. Dormitzer, MD, PhD	Vice President and Chief Scientific Officer, Viral Vaccines, Vaccines Research and Development, Pfizer Inc.
(b) (6), (b) (4), PhD	Regulatory Consultant for BioNTech SE
William C. Gruber, MD	Senior Vice President, Vaccine Clinical Research and Development, Pfizer Inc.
Elisa Harkins	Global Regulatory Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Kathrin U. Jansen, PhD	Senior Vice President and Head, Vaccine Research and Development, Pfizer Inc.
Luis Jodar, PhD	Vaccines Chief Medical and Scientific Affairs Officer, Pfizer Inc.
Nicholas Kitchin, MD	Senior Director, Vaccines Clinical Research and Development, Pfizer Ltd.
Kenneth Koury, PhD	Head of Statistics and Modeling, Vaccine Clinical Research and Development, Pfizer Inc.
Stephen Lockhart, MD	Head EU/AP, Vaccines Clinical Research and Development, Pfizer Ltd.
David Swerdlow, MD	Senior Director, Medical Development and Clinical/Scientific Affairs, Pfizer Inc.
Ruben Rizzi, PhD	Regulatory Affairs Strategist, BioNTech SE
Satrajit Roychoudhury, PhD	Senior Director, Statistical Research and Data Science Center, Pfizer Inc.
Ugur Sahin, MD, PhD	Chief Executive Officer, BioNTech SE

**Background and Objectives:**

The Sponsor submitted a meeting request on June 11, 2020, to gain CBER feedback regarding (1) the proposed Clinical Development Program, including revisions to the ongoing Study C4591001, as well as high-level pediatric and maternal immunization plans, and (2) the clinical data requirements to support (b) (4) Traditional

Approval, as well as requirements for use under an Emergency Use Authorization. The pre-meeting materials were submitted on June 11, 2020.

FDA provided its preliminary meeting responses to the Sponsor's questions on June 25, 2020. After reviewing the preliminary meeting responses, the Sponsor notified FDA on June 26, 2020, of its decision to proceed with the agenda as planned. In addition, on June 24, 2020, Pfizer sent a slide deck (Attachment 1; page 20), to facilitate the discussion, that describes their Phase 3 designs with 4 interim analyses with VE threshold = 20% or 30%, and their operating characteristics. On June 26, 2020, Pfizer sent two tables (Attachment 2; page 24) with Projected available serological data following dose 1 and Projected number of subjects receiving 1 or 2 doses by July 17, 2020. This slide deck/information was presented at the meeting.

### **Sponsor Questions:**

#### **Clinical**

##### ***Sponsor Question 1:***

Does CBER have any comments on the overall Clinical Development Plan and timeline proposed to support (b) (4) Traditional Approval? Specifically,

##### ***Sponsor Question 1.a:***

Does CBER agree with the proposed revisions to the ongoing Phase 1/2 US Study C4591001 that would add a Phase 2/3 efficacy phase to the study, to evaluate efficacy in an expanded number of participants? Does CBER agree with the proposed Phase 3 safety, immunogenicity, and efficacy endpoints and case definitions?

##### **FDA Preliminary Meeting Response to Sponsor Question 1.a:**

We agree with your general proposal to add a Phase 2/3 efficacy phase to the study and evaluate efficacy in an expanded number of participants.

- i. We note that you state, "the Phase 2b/3 section will be observer-blinded at site, and the Sponsor staff will also be blinded except for named unblinded staff." We request that the blinding procedures be updated in the revised protocol, with appropriate justifications included, to ensure study integrity.

##### **Meeting Discussion for Sponsor Question 1.a.i:**

Pfizer stated that they acknowledge CBER's concern regarding blinding and the ethical dilemma regarding breaking the blind and offering vaccine to placebo recipients in the event of early demonstration of efficacy sufficient to support wide use of the vaccine. They will include their justification in the revised protocol and submit for CBER review. CBER acknowledged.

- ii. We recommend the case definition described below, which is similar to your proposed primary efficacy endpoint case definition, to standardize evaluation of efficacy across COVID-19 vaccine studies. You may choose to evaluate the standardized case definition as your primary efficacy endpoint or as a secondary endpoint to be analyzed with or without formal hypothesis testing. We recommend defining a positive case as virologic confirmation by RT-PCR for SARS-CoV-2, along with any symptom for COVID-19 as listed by the CDC (<https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>):

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

**Meeting Discussion for Sponsor Question 1.a.ii:**

Pfizer indicated that they would keep their definition for COVID-19 described in the briefing document. However, they proposed to include OVRP's recommended definition using the symptoms listed on the CDC website as a secondary efficacy endpoint analysis without formal hypothesis testing. CBER agreed.

- iii. We acknowledge your agreement to modify your case definition for severe COVID-19 as previously requested.

**Meeting Discussion for Sponsor Question 1.a.iii:**

There was no discussion of this question during the meeting. This response is now considered final.

- iv. Please propose a study stopping rule for severe disease as an indicator of enhanced disease to be assessed by the DMC with each prespecified interim analysis. An acceptable approach would be to pause study enrollment for further data review, as well as notification of OVRP, if the number of severe COVID-19 cases is greater among vaccine versus placebo recipients. You may propose alternative rules based on reasonable statistical criteria.

**Meeting Discussion for Sponsor Question 1.a.iv:**

Pfizer understood and stated that they would include the alternative stopping rules in the revised protocol. CBER acknowledged.

- v. The briefing document did not include defined safety and immunogenicity endpoints for Phase 3. However, we agree in general with the safety and immunogenicity endpoints described in the previously submitted Phase 3 protocol synopsis (in amendment 7, sequence 0007, dated May 15, 2020), including the plan to assess the serologic response at baseline, 14 days, and 1, 6, 12, and 24 months after completion of vaccination in all study subjects in Phase 3. The immunologic assays described in item 2.13.1 of your responses to CBER comments dated May 29, 2020 are appropriate, provided the assay validation data to be submitted prior to the testing of Phase 3 samples are acceptable.

**Meeting Discussion for Sponsor Question 1.a.v:**

Pfizer stated that they (b) (4)

(b) (4)

(b) (4) collecting samples at baseline, 1-, 6-, 12-, and 24- month timepoints for immunogenicity assessments, but they may only conduct the assays in an immunogenicity subset of the study population. They believe that in principle, the serological data are not required for BLA filing and for licensure under Traditional Approval pathway.

CBER acknowledged and stated that although data from serological assessment at the above-stated timepoints will not be required for primary efficacy endpoints or for licensure under a Traditional pathway, these data will be important/useful, e.g., for immunobridging to populations not included in the efficacy trial. Pfizer acknowledged, and stated that for these reasons, they will collect samples at various timepoints, and they will keep these sample collections in the protocol. However, they commit to validating the immunological assays before testing these samples.

CBER asked how many different age groups Pfizer will have for adults. Pfizer replied that currently they stratify by age only two groups – 18-55 years of age and >55 years of age. Currently, there are no plans for additional subgroups. They plan to enroll 30,000 subjects split equally between age groups, 18-55 and >55 years of age, and half of them will receive placebo.

CBER asked when Pfizer will complete qualification and validation of the immunological assays and asked if the assays are adequately qualified to measure the immune response (e.g., antigen-binding IgGs and virus

neutralization titers) from Phase 1 studies. Pfizer stated that their assay to measure antigen-binding IgG antibodies (for determining which cases were infected before vaccination so they can be excluded from the primary efficacy analysis) has already been qualified. The virus neutralization assay (b) (4)

(b) (4). Both of these immunological assays are robust, and Pfizer can provide the details to CBER, if needed. Pfizer asked if that is acceptable. Pfizer also stated that they are planning to initiate the Phase 3 study on July 20, 2020. CBER stated that the plan for validating the assays is acceptable but stressed that the assays need to be validated prior to assessing the samples from the Phase 3 efficacy study. Pfizer understood.

**Sponsor Question 1.b:**

(b) (4)

(b) (4)

?

**FDA Preliminary Meeting Response to Sponsor Question 1.b:**

As communicated previously, we do not agree with a success criterion defined as the lower limit of VE being >20%. To ensure that a widely deployed vaccine is more than modestly effective, we request that the success criterion be defined equivalent to a primary efficacy endpoint point estimate of at least 50% and the lower limit of the alpha-adjusted 95% CI around that point estimate being >30%. In principle, the four interim analyses proposed in Table 6 of the briefing document, using a VE threshold of 30%, would be acceptable if the criteria were adjusted to preserve the type I error rate at 2.5%. In addition, the proposed efficacy boundaries are based solely on case split, which presumes that the numbers of evaluable subjects and duration of follow-up in both groups are equivalent. Please clarify how you plan to adjust the boundaries for potential difference in numbers of evaluable subjects.

Given that current COVID-19 epidemiology is permissive for conducting clinical disease endpoint efficacy trials, (b) (4)

(b) (4)

**Meeting Discussion for Sponsor Question 1.b.:**

Pfizer stated that they agree with defining the success criterion to be equivalent to a primary efficacy endpoint point estimate of at least 50% and the lower limit of the alpha-adjusted 95% CI around that point estimate being >30%. Also, they acknowledged CBER's comment regarding controlling the type I error rate at 2.5%. CBER indicated conceptual agreement with Pfizer's study designs 3 and 4 included in the slide deck sent to CBER on June 24, 2020, which control the overall type I error at nominal level; however, CBER had not fully evaluated and

discussed those designs internally. Therefore, CBER will provide comments on those designs in the meeting summary, as post-meeting notes. Pfizer acknowledged.

Regarding boundaries for efficacy, Pfizer stated that they will calculate boundaries in terms of VE for number of person-years in evaluable population, and VE analysis based on that population. CBER acknowledged and will provide feedback, if any, on the protocol when submitted.

**Post-meeting Comment:**

The proposed study designs 3 and 4 included in the slide deck sent to CBER on June 24, 2020 are acceptable.

***Sponsor Question 1.c.:***

Does CBER agree with the proposed plan for progression of vaccine candidates from Phase 2 to Phase 3?

**FDA Preliminary Meeting Response to Sponsor Question 1.c:**

We agree with the proposal that includes review of unblinded safety data through 7 days after dose 2 and immunogenicity data through 21 days after dose 1 of each vaccine candidate by the internal review committee. With the submission of these data to CBER, we request that you include a summary of the data that includes the rationale for dose selection.

**Meeting Discussion for Sponsor Question 1.c:**

Pfizer explained that in the initial IND submission, they proposed to evaluate multiple doses and dosing regimens of 4 vaccine candidates in their Phase 1/2 study. However, they have plans to eliminate some of the vaccine candidates. They are planning to initiate the Phase 2b/3 study on July 20, 2020, and will select only one construct, at one dose level. By that time, a total of 252 subjects will have received 1 dose and 180 subjects will have received 2 doses (all doses) of BNT162b1 or BNT162b2, and safety data on these subjects will be available. Pfizer has decided to eliminate the 50 µg and the 100 µg doses, and they believe they will go forward with either 10 µg or 20 µg of one of the two vaccine candidates, based on their safety profile. Post-dose 1 immunogenicity data for 10 µg and 30 µg of BNT162b1 in younger adults (18-55 years of age), for 10 µg and 20 µg of BNT162b1 in older adults (65-85 years of age), for 10 µg and 20 µg of BNT162b2 in younger adults, and for 20 µg of BNT162b2 in older adults, will be available by July 17, 2020. As reactogenicity is benign in older adults compared with that in younger adults, Pfizer feels comfortable dosing older adults based on the safety and tolerability profile of these doses in the younger adults.

CBER acknowledged Pfizer's plan to initiate the Phase 2b/3 study on July 20, 2020, but stated that further internal discussion is needed on whether the proposed clinical immunogenicity data that will be available then are sufficient

to support Phase 2b/3 initiation or whether additional clinical immunogenicity data will be required. CBER asked when the immunogenicity data will be available to Pfizer and to CBER for review. Pfizer replied that antigen-binding IgG data will be available on July 13, 2022, and virus neutralization data will be available by July 17, 2020. Pfizer will include all available immunogenicity data for the modRNA platform (BNT162b1 and BNT162b2). This includes T-cell (CD4 and CD8) data from the German study from all 12 subjects. All assays used in these evaluations are the same as those that are/will be used by Pfizer to analyze the serum samples from this study.

CBER acknowledged and expressed the need to discuss internally and provide feedback to Pfizer in post-meeting notes. Pfizer acknowledged.

**Post-meeting Comment:**

CBER held a follow-up teleconference on July 6, 2020, to clarify Pfizer's plans for the Phase 2b/3 portion of the study and the clinical data, non-clinical data, and immunogenicity assay information that would be submitted to support those plans. A summary of that teleconference will be provided in a separate communication.

**Sponsor Question 1.d:**

Does CBER agree with the proposed inclusion of global sites (e.g., EU, South America, Turkey) in the efficacy phase of the study with at least 30% of participants coming from the US assuming current state of the pandemic?

**FDA Preliminary Meeting Response to Sponsor Question 1.d:**

We agree with the proposal to include global sites in the efficacy phase of the study, with at least 30% of participants coming from the US.

**Meeting Discussion for Sponsor Question 1.d:**

There was no discussion of this question during the meeting. This response is now considered final.

**Sponsor Question 2:**

Does CBER agree that revised Study C4591001 is adequate to serve as the single pivotal study to demonstrate adequate safety, immunogenicity, and efficacy of the candidate vaccine for the proposed indication and may be used to support (b) (4) Traditional Approval?

**FDA Preliminary Meeting Response to Sponsor Question 2:**

Please see our responses to your other questions. We agree that a single, well-designed and well-conducted clinical disease endpoint efficacy study that is able to meet our requested pre-specified success criterion would likely provide substantial evidence of effectiveness and an adequately sized safety database to support licensure of your product via the Traditional Approval Pathway. (b) (4)

(b) (4)

**Meeting Discussion for Sponsor Question 2:**

There was no discussion of this question during the meeting. This response is now considered final.

**Sponsor Question 3:**

Does CBER agree with Pfizer/BioNTech's plans to evaluate the BNT162b3 candidate expressing the RBD domain with a short transmembrane tail and two amino acids added to the signal peptide for more homogeneous cleavage in Study C4591001, as described in Section 6.2?

**FDA Preliminary Meeting Response to Sponsor Question 3:**

We agree that the clinical data from BNT162b1, which uses the same nucleoside-modified mRNA (modRNA) platform as your new BNT162b3 vaccine candidate, could support the use of BNT162b3 in the proposed Phase 1/2/3 study. As previously communicated on June 3, 2020, you may submit a revised protocol to include the new vaccine candidate with supportive CMC and nonclinical data. Please provide the CMC drug substance and drug product information for the BNT162b3 clinical lot and the non-clinical immunogenicity data for this new vaccine candidate (including assessment of Th1/Th2 markers and cellular responses) to the IND prior to the initiation of the Phase 2 portion of your Study C4591001. In addition, please provide a summary of CMC comparability between BNT162b1 and BNT162b3.

We note that if Phase 1 evaluation of BNT162b1 leads to a selected dose level to proceed into Phase 2 for both younger and older adults, you plan to take BNT162b3 directly to Phase 2 for both age groups at the same dose selected for BNT162b1. However, your rationale for inclusion of BNT162b3 is that it has shown superior immunogenicity to BNT162b1 in mice, which suggests that the immunologic response to these vaccine candidates, and by extension the optimal dose, might not be the same. As such, we request that if you introduce BNT162b3 directly into Phase 2 based on a dose chosen for BNT162b1, you introduce it into the Phase 2a portion of your study, rather than the Phase 2b portion, so that the safety and immunogenicity of that dose level can be evaluated in a smaller group prior to dosing 3,000 subjects.

**Meeting Discussion for Sponsor Question 3.:**

There was no discussion of this question during the meeting. This response is now considered final.

**Regulatory**

**(b) (4)**

(b) (4)

(b) (4)

**Meeting Discussion for (b) (4) Sponsor Question 7:**  
There was no discussion of this question during the meeting. This response is now considered final.

Traditional Approval

***Traditional Approval-related Sponsor Question 1:***

Does CBER agree that the proposed study design, including a Phase 2/3 efficacy portion, and the planned persistence evaluations from Phase 1 sentinel and Phase 2 cohorts are adequate to support Traditional Approval?

**FDA Preliminary Meeting Response to Traditional Approval-related Sponsor Question 1:**

We agree that the proposed study design may be adequate to support Traditional Approval using the success criteria specified in our response to Question 1.b, contingent on our review and assessment of the submitted data. It is not clear from

your briefing material what you mean by the planned persistence evaluations from Phase 1 sentinel and Phase 2 cohorts.

Ideally, your BLA submission would include blinded 6-month safety data from at least 3,000 subjects who have received the vaccine at the dose intended for licensure. Please comment on how many subjects from whom you anticipate to provide 6-month safety data in your licensure application (including in the initial submission and potentially in a safety update submitted during our review) in the event that an interim efficacy analysis meets the study success criterion. Further discussion may be needed on the acceptability of the safety database, depending on the data you plan to have available.

We agree with your plan to continue to follow subjects through Month 24 to enable assessment of longer-term safety and durability of vaccine efficacy. Please discuss your contingency plans for continuing longer-term follow up and analysis of safety and effectiveness outcomes in the event that early demonstration of efficacy sufficient to support wide use of the vaccine raises ethical arguments to break the blind and offer vaccine to placebo recipients.

**Meeting Discussion for Traditional Approval-related Sponsor Question 1:**

Pfizer stated that all subjects in the Stage 1 sentinel groups will be followed for 24 months. Serological assessment is planned for the 24-month time point in Phase 2b/3. For long term effectiveness, the subjects will be followed for COVID-19 cases for the full 24-month period. Pfizer will address in the protocol the ethical dilemma regarding breaking the blind and offering vaccine to placebo recipients in the event of early demonstration of efficacy sufficient to support wide use of the vaccine. CBER acknowledged.

CBER asked how many subjects Pfizer is expecting to have 6-month safety data from at the time of submission of the BLA. Pfizer stated that they are confident to have 3,000 subjects in the vaccine group, and they will have abundant 7-day safety and 30-day immunogenicity data. However, Pfizer expressed concern that if their BLA is filed in October 2020, they will have very little 6-month safety data. CBER acknowledged and stated that this issue needs further discussion.

***Traditional Approval-related Sponsor Question 2:***

Does CBER agree that the planned clinical lot consistency study may be conducted in parallel with the planned Phase 3 efficacy study and results submitted as a post-approval commitment under the Traditional Approval Pathway?

**FDA Preliminary Meeting Response to Traditional Approval-related Sponsor Question 2:**

Clinical lot consistency studies are traditionally performed as a component of the Phase 3 efficacy study. Data from these studies are used to support product consistency in the clinic and are typically designed using three independently manufactured lots. Data from these studies are used to support product licensure

and therefore should be included in the BLA. If you are not able to complete a lot to lot consistency study as part of your Phase 3 study, please propose an analytical comparability study to support the consistent manufacture and quality of the product batches used in your Phase 3 study.

**Meeting Discussion for Traditional Approval-related Sponsor Question 2:**

Pfizer stated that they will propose an analytical comparability study to support the consistent manufacture and quality of the product batches in their Phase 3 study. Pfizer is planning to submit a Type C meeting request on July 13, 2020 to obtain CBER feedback regarding facilities and other CMC information. CBER acknowledged.

Emergency Use Authorization (EUA)

***EUA-related Sponsor Question 1:***

The Sponsor is currently manufacturing vaccine at-risk and is targeting to have US-manufactured and released vaccine doses of approximately (b) (4) available by year-end 2020 with initial deliveries projected for late November. Does CBER agree that

(b) (4)

(b) (4) ? The Emergency Use Authorization request package could be submitted for CBER review in parallel with the initial BLA.

**FDA Preliminary Meeting Response to EUA-related Sponsor Question 1:**

(b) (4)

**Meeting Discussion for EUA-related Sponsor Question 1:**

Pfizer asked whether clinical efficacy data would be considered to support an EUA in the event that declining COVID-19 disease activity precludes or significantly delays meeting the pre-specified study success criteria. CBER replied that the totality of data, including the clinical disease efficacy data, would be considered in the context of the specific circumstances of any EUA request. Pfizer acknowledged.

Pediatric and Maternal Immunization (P&MI) Study Plans

***P&MI Study Plans-related Sponsor Question 1:***

Does CBER have any comments on the high-level pediatric study plan? Does CBER agree (b) (4)

**FDA Preliminary Meeting Response to P&MI Study Plans-related Sponsor Question 1:**

We have the following comments on the high-level pediatric study plan:

- a. Please provide a statutory rationale to support the planned waiver for children less than 12 months of age. We disagree with your statement that COVID-19 is generally mild and self-limiting in children in the first year of life as several large pediatric case series have demonstrated a higher proportion of severe disease in children less than 12 months of age versus other pediatric age groups (Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020;145(6):e20200702. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422–426. DOI: <http://dx.doi.org/10.15585/mmwr.mm6914e4>)
- b. It is premature to agree on the applicability of immunobridging studies to infer effectiveness for all pediatric age groups; clinical disease endpoint efficacy studies may be required for some age groups pending better understanding of SARS-CoV-2 immunology and pathogenesis.

**Meeting Discussion for P&MI Study Plans-related Sponsor Question 1:**

Pfizer stated that they are planning to submit the Pediatric Study Plan (PSP) on July 15, 2020. They will include details of the deferred studies (and immunobridging) and justification of waiver in the PSP. CBER acknowledged.

***P&MI Study Plans-related Sponsor Question 2:***

Does CBER agree with the proposed inclusion of global sites (eg, EU, South America, Turkey) in the pediatric study with at least 30% of participants coming from US?

**FDA Preliminary Meeting Response to P&MI Study Plans-related Sponsor Question 2:**

We agree with the proposal to include global sites in the pediatric study, with at least 30% of participants coming from the US.

**Meeting Discussion for P&MI Study Plans-related Sponsor Question 2:**

There was no discussion of this question during the meeting. This response is now considered final.

***P&MI Study Plans-related Sponsor Question 3:***

Does CBER have any comments on the proposed plan for evaluating maternal immunization?

**FDA Preliminary Meeting Response to P&MI Study Plans-related Sponsor Question 3:**

We acknowledge your plans to assess your product in pregnant women, and we would encourage an ongoing dialogue regarding inclusion of pregnant women in

your planned studies and how safety and effectiveness data obtained with your vaccine may be used. Please note that initiation of studies in this population is contingent on our review of data to support the safety of this approach, particularly your planned DART study. We have the following comments and requests for clarification:

- a. Please provide a detailed proposal for how you intend to label the data from studies conducted in pregnant women (or the subanalyses of the data from pregnant women, if they are included in broader studies).
- b. Please clarify whether you intend to seek an indication for vaccination during pregnancy to protect the infant from SARS CoV-2 infection. Please note that cord blood immune assays are unlikely to be adequate to support this indication in the absence of establishing a biomarker reasonably likely to predict protection.
- c. With respect to other vaccines recommended for administration during pregnancy (i.e., Tdap and influenza vaccines), please comment on the potential for immunologic interference and discuss your plans to address this issue.
- d. Further discussion on your proposed immunobridging study may be needed after you provide responses to our questions above to clarify your intentions for labeling of data from this study and claims related to the data, and after more data are available to determine the acceptability of immune markers that you would propose for immunobridging.

**Meeting Discussion for P&MI Study Plans-related Sponsor Question 3:**

Pfizer stated that they will submit information related to maternal immunization studies later. CBER acknowledged.

***P&MI Study Plans-related Sponsor Question 4:***

The developmental and reproductive toxicology (DART) study will be initiated (b) (4)

(b) (4)

(b) (4) . Does CBER agree that the results of the DART study can be provided during review of the initial BLA (b) (4)

(b) (4)

?

**FDA Preliminary Meeting Response to P&MI Study Plans-related Sponsor Question 4:**

We agree that the results of the DART study can be provided during review of the initial BLA that will include data from Study C4591001. (b) (4)

(b) (4)

**Meeting Discussion for P&MI Study Plans-related Sponsor Question 4:**

Pfizer stated that they will submit the DART study protocol for CBER review in July 2020, and they plan to submit the DART study results during the review of the BLA. CBER acknowledged.

**FDA Questions/Comments sent in Preliminary Meeting Response:**

**FDA Comment 1:**

Consistent with the FDA Guidance for Industry on Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (<https://www.fda.gov/media/127712/download>), we encourage you to adopt enrollment and retention practices that enhance inclusiveness so that the clinical trial population reflects the diversity of the people who will be using the vaccine, if approved. Specifically, racial and ethnic minority persons should be represented in clinical trials. We suggest that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minorities to recruit a diverse study population.

**Meeting Discussion for FDA Comment 1:**

There was no discussion of this FDA comment during the meeting. This response is now considered final.

**FDA Comment 2:**

All study data generated from trials initiated after December 17, 2016, that will be submitted with applications for new drugs/biologics must be in conformance with the standards listed in the FDA Data Standards Catalog (<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

As you intend to initiate your Phase 1/2/3 clinical trial in the near future, we request that you provide as soon as possible, a Study Data Standardization Plan (SDSP) with CBER appendix (<https://www.phuse.eu/documents//sop/wp/phuse-tp001-study-data-standardization-plan-v1-8409.docx>) proposing the specific use of the Clinical Data Interchange Standards Consortium (CDISC), including Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) formats. We also request that the associated annotated case report form (aCRF) for SDTM be provided. Please refer to the CDISC Vaccine Therapeutic Area User Guide (TAUG) and Guidance for Industry “Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review” (<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM605147.pdf>) for details on standardizing your data.

**Meeting Discussion for FDA Comment 2:**

There was no discussion of this FDA comment during the meeting. This response is now considered final.

**Additional FDA Comment:**

1. Post Meeting Comments:

Please refer to the Post meeting comments provided regarding Sponsor Questions 1.b and 1.c that are located below the meeting discussion sections (above).

**Attachment 1:**

Slide deck that describes Pfizer’s Phase 3 designs with 4 interim analyses with VE threshold = 20% or 30%, and their operating characteristics.

Design 1: Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 20%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries	Futility Boundaries
1	22/110 (1/5)	No	Yes	NA	<u>VE</u> ≤ -20% and Y ≥ 12
2	44/110 (2/5)	Yes	Yes	VE ≥ 62.5% and Y ≤ 12	VE ≤ 16.7% and Y ≥ 20
3	66/110 (3/5)	Yes	Yes	VE ≥ 56.5% and Y ≤ 20	<u>VE</u> ≤ 26.3% and Y ≥ 28
4	88/110 (4/5)	Yes	No	<u>VE</u> ≥ 53.3% and Y ≤ 28	NA
<b>Final</b>	110/110			<u>VE</u> ≥ 47.2% and Y ≤ 38	

Design 1: Operating Characteristics

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				<u>VE</u> = 20%	<u>VE</u> = 55%	<u>VE</u> = 60%	<u>VE</u> = 20%	<u>VE</u> = 55%	<u>VE</u> = 60%
1	22/110 (1/5)	No	Yes	0%	0%	0%	22.9%	1.8%	0.1%
2	44/110 (2/5)	Yes	Yes	1.4%	36.0%	50.0%	52.8%	4.1%	1.9%
3	66/110 (3/5)	Yes	Yes	2.2%	54.8%	70.9%	72.9%	5.9%	2.5%
4	88/110 (4/5)	Yes	No	2.7%	69.2%	84.5%	-	-	-
<b>Final</b>	110/110			<b>3.8%</b>	90.2	99.0%	-	-	-

## Design 2: Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 30%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries	Futility Boundaries
1	30/150 (1/5)	No	Yes	NA	VE ≤0% and Y ≥15
2	60/150 (2/5)	Yes	Yes	VE ≥63.6% and Y ≤16	VE ≤28.6 % and Y ≥25
3	90/150 (3/5)	Yes	Yes	VE ≥59.5% and Y ≤26	VE ≤36.4 % and Y ≥35
4	120/150 (4/5)	Yes	No	<u>VE</u> ≥55.4% and Y ≤37	NA
Final	150/150			<u>VE</u> ≥50.0% and Y ≤50	

## Design 2: Operating Characteristics

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				<u>VE</u> = 30%	<u>VE</u> = 55%	<u>VE</u> = 60%	<u>VE</u> = 30%	<u>VE</u> = 55%	<u>VE</u> = 60%
1	30/150 (1/5)	No	Yes	0%	0%	0%	21.2%	2.3%	1.1%
2	60/150 (2/5)	Yes	Yes	1.4%	28.1%	43.5%	53.7%	6.3%	2.6%
3	90/150 (3/5)	Yes	Yes	2.0%	42.6%	62.1%	75.1%	10.0%	3.9%
4	120/150 (4/5)	Yes	No	2.7%	60.3%	80.7%	-	-	-
Final	150/150			<b>4.1%</b>	84.3%	98.0%	-	-	-

## Design 3: **Calibrated** Bayesian Sequential Design with Four Interim Analyses (VE Threshold = 30%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries*, **	Futility Boundaries
1	32/164	No	Yes	NA	<u>VE</u> ≤11.8% and Y ≥15
2	62/164	Yes	Yes	<u>VE</u> ≥ 70.8% and Y ≤14	<u>VE</u> ≤27.8 % and Y ≥26
3	92/164	Yes	Yes	<u>VE</u> ≥62.7% and Y ≤25	<u>VE</u> ≤36.8 % and Y ≥36
4	120/164	Yes	No	<u>VE</u> ≥60.5% and Y ≤34	NA
<b>Final</b>	164/164			<u>VE</u> ≥50.9% and Y ≤54	

\*Using efficacy boundary at interim: ,  $P(\underline{VE} \geq 30\% | \text{data}) > 0.9975$

\*\*Using success criteria at the final analysis: ,  $P(\underline{VE} \geq 30\% | \text{data}) > 0.98$ .

## Design 43: Operating Characteristics

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				<u>VE</u> = 30%	<u>VE</u> = 55%	<u>VE</u> = 60%	<u>VE</u> = 30%	<u>VE</u> = 55%	<u>VE</u> = 60%
1	32/164	No	Yes	0%	0%	0%	31.5%	4.4%	2.1%
2	62/164	Yes	Yes	0.2%	9.4%	18.4%	62.7%	9.6%	4.3%
3	92/164	Yes	Yes	0.5%	26.0%	44.7%	81.4%	13.9%	5.9%
4	120/164	Yes	No	0.6%	35.4%	57.9%	-	-	-
<b>Final</b>	164/164			<b>2.2%</b>	78.8%	96.2%	-	-	-

## Design 4: Frequentist Sequential Design with Four Interim Analyses (VE Threshold = 30%)

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Efficacy Boundaries*	Futility Boundaries
1	32/164	Yes	Yes	$VE \geq 81.5\%$ and $Y \leq 5$	$VE \leq 11.8\%$ and $Y \geq 15$
2	62/164	Yes	Yes	$VE \geq 70.8\%$ and $Y \leq 14$	$VE \leq 27.8\%$ and $Y \geq 26$
3	92/164	Yes	Yes	$VE \geq 62.7\%$ and $Y \leq 25$	$VE \leq 36.8\%$ and $Y \geq 36$
4	120/164	Yes	No	$VE \geq 57.1\%$ and $Y \leq 36$	NA
Final	164/164			$VE \geq 52.3\%$ and $Y \leq 53$	

\*Efficacy boundary is calculated using Gamma(-2) family

## Design 4: Operating Characteristics

Interim Analysis	Timing of Interim Analysis (Information Fraction)	Stop for Efficacy	Stop for Futility	Cumulative Probability of Stopping for Efficacy			Cumulative Probability of Stopping for Futility		
				VE= 30%	VE= 55%	VE= 60%	VE= 30%	VE= 55%	VE= 60%
1	32/164	Yes	Yes	0.1%	3.9%	7.2%	31.5%	4.4%	2.1%
2	62/164	Yes	Yes	0.3%	11.0%	20.4%	54.6%	7.1%	3.2%
3	92/164	Yes	Yes	0.6%	27.5%	46.7%	76.3%	10.4%	4.2%
4	120/164	Yes	No	1.1%	48.7%	72.0%	-	-	-
Final	164/164			<b>1.9%</b>	72.9%	92.4%	-	-	-

**Attachment 2:**

Projected available serological data following dose 1 and Projected number of subjects receiving 1 or 2 doses by July 17, 2020.

**Projected serological Data following dose 1**

Construct	Age Cohort	Dose Level	Post Dose 1	
			IgG	Neut
	18-55	10ug	completed	completed
	18-55	30ug	completed	completed
<b>BNT162b1</b>	18-55	20ug	30-Jul	
	65-85	10ug	9-Jul	11-Jul
	65-85	20ug	16-Jul	17-Jul
	65-85	30ug	16-Jul	18-Jul
	18-55	10ug	9-Jul	11-Jul
	18-55	20ug	15-Jul	17-Jul
	18-55	30ug	23-Jul	
<b>BNT162b2</b>				
	65-85	10ug	30-Jul	3-Aug
	65-85	20ug	15-Jul	17-Jul
	65-85	30ug	16-Jul	

**Projected number of subjects receiving 1 or 2 doses by 17 July 2020**

By 17-Jul-20	N dose 1	N dose 2
<b>BNT162b1 total</b>	<b>144</b>	<b>108</b>
18-55yrs	108	72
65-85yrs	36	36
<b>BNT162b2 total</b>	<b>108</b>	<b>72</b>
18-55yrs	72	48
65-85yrs	36	24
<b>Grand Total</b>	<b>252</b>	<b>180</b>

## Teleconference Summary

**Meeting date & time:** July 6, 2020, 2:00 – 3:00 PM  
**Submission:** IND 19736  
**Product name:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); and BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)  
**Proposed indication:** Active immunization against COVID-19 in adults 18 years of age and older  
**Sponsor:** BioNTech RNA Pharmaceuticals GmbH/Pfizer. Inc.  
Sponsor Agent: Pfizer, Inc.

### FDA Attendees:

Maria Allende, MD	OVRP/DVRPA
Sarah Browne, MD	OVRP/DVRPA
Carmen Collazo, PhD	OVRP/DVRPA
Doran Fink, MD, PhD	OVRP/DVRPA
Sara Gagneten, PhD	OVRP/DVP
Marion Gruber, PhD	OVRP
Lei Huang, PhD	OBE/DB
Robin Levis, PhD	OVRP/DVP
Keith Peden, PhD	OVRP/DVP
Douglas Pratt, MD	OVRP/DVRPA
Elizabeth Sutkowski, PhD	OVRP/DVRPA
Stephanie Troy, MD	OVRP/DVRPA
Jerry Weir, PhD	OVRP/DVP
Susan Wollersheim, MD	OVRP/DVRPA

### Pfizer Participants:

Donna Boyce	Vice President, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Carmel Devlin	Global Regulatory Portfolio Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Philip R. Dormitzer, MD, PhD	Vice President and Chief Scientific Officer, Viral Vaccines, Vaccines Research and Development, Pfizer Inc.
Kathrin U. Jansen, PhD	Senior Vice President and Head, Vaccine Research and Development, Pfizer Inc.

**Background and Objectives:**

After June 26, 2020 Type C meeting, CBER received clarification information from Pfizer's Donna Boyce regarding the construct and doses Pfizer is planning to use in Phase 3 (The same information was later submitted to IND 19736, in amendment 24 dated July 1, 2020). This information suggested, as discussed during the Type C meeting, that Pfizer will use either BNT162b1 and BNT162b2, at either a 10 or 20 µg dose. However, the clinical protocol amendment 4 submitted on July 2, 2020, includes the third candidate, i.e., BNT162b3, and the email sent by Pfizer's Donna Boyce on July 6, 2020, suggested that Pfizer may select a 30 µg dose (The same information was later submitted to IND 19736, in amendment 26 dated July 8, 2020). CBER requested a teleconference with Pfizer to obtain clarification regarding the construct and doses Pfizer is planning to use in Phase 3 as knowing this helps us to provide appropriate advice and response to Pfizer's questions.

**Teleconference summary:**

Pfizer stated it is too late for them to introduce BNT162b3, and therefore, they will remove this vaccine candidate from consideration for their study. They plan to make the decision by July 17, 2020, if they will move forward with either BNT162b1 or BNT162b2 and which dose level they will select.

CBER stated that less immunogenicity data have been submitted for older subjects as compared with younger subjects, and post-dose 2 immunogenicity data will be available only for the 10 µg dose of BNT162b1. In addition, Pfizer has not submitted details on the methodology or assays that used to measure antigen-binding IgG and authentic virus neutralization titers, to make sure that the data generated by using these assays are acceptable. Pfizer stated that they will submit the qualification reports for both assays next week. CBER acknowledged. Pfizer stated that they will submit complete post-dose 2 safety and immunogenicity data (including the CMI data) for the 10 µg dose from the German study by July 10, 2020. CBER acknowledged. Pfizer indicated that the immune responses from subjects from the German study are consistent with the immune responses from subjects in the US study. Pfizer also indicated that the immune responses are tightly distributed, post-dose 2 safety data from subjects that received 30 µg vaccine candidate also look promising, and that they believe that the risk-benefit considerations could favor moving forward with 10 µg, 20 µg or 30 µg doses, depending on the construct. CBER asked, for BNT162b2, as post-dose 2 immunogenicity data are available for only 10 µg dose, how Pfizer will choose the 20 µg or 30 µg dose to study in Phase 3 in the absence of post-dose 2 immunogenicity data. Pfizer replied that based on quality of the post-dose 2 immunogenicity data for 10 µg dose, they believe that post-dose 2 immunogenicity data for the other doses (20 µg or 30 µg) will be better, whether it is BNT162b1 or BNT162b2, based on the (same) platform, and T-cell response will be same.

CBER noted that Pfizer plans to analyze data for the first 360 subjects enrolled in the Phase 2b/3 portion of the study, and enrollment may continue during this period. CBER asked how many subjects will be enrolled in Phase 2b/3 before data from the planned interim assessment in the first 360 enrolled subjects (which will consist of post-dose 2

safety and post-dose 1 immunogenicity). Pfizer stated that they plan on enrolling 1,400 subjects/week. So, by the time of the interim assessment in the first 360 subjects, which would take 4-5 weeks, they may have already vaccinated close to 4,000 subjects given the 1:1 randomization. They will make sure to have oversight by IRC and DMC.

CBER also asked about the timing of the submission of the NHP challenge study data. Pfizer asked if submission of the data from the NHP challenge study is necessary before initiating the Phase 3 study, as they understood the data to be “nice to have” rather than “must have.” CBER stated that the animal challenge study data may not be absolutely necessary but would help to compensate for the relatively small amount of clinical immunogenicity data being proposed to support Phase 2b/3 initiation. Pfizer stated that the data from the NHP challenge study (including viral load and CAT scan) will be submitted by July 17, 2020; lung pathology information will be submitted later. CBER acknowledged.

CBER indicated that if Pfizer submits much of this information on July 17, 2020 with the plan of initiating Phase 3 trial on July 22, 2020, CBER may not have adequate time for reviewing the submitted information. Pfizer responded that they will provide the information to support Phase 2b/3 initiation as soon as it becomes available. Pfizer stated that they will submit the qualification reports for the two assays by the end of this week, and they will submit preliminary data (viral load and CT scans) from the macaque challenge studies by July 17, 2020. They will also submit the safety and immunogenicity data (including CMI data from 12 subjects in the German study) per the schedule they previously communicated.

Pfizer asked if CBER could instruct Pfizer, based on the planned available safety and immunogenicity data, if they can enroll younger and older adults concurrently in Phase 2b/3, or if they will need to enroll younger adults first and older adults later. CBER stated that we would need to at least receive the assay qualification data first to assess the quality of the immunogenicity data, before providing an answer. CBER stressed again that the animal challenge study data is important given the smaller size of safety and immunogenicity data from Phase 1. CBER committed to take all data into consideration, review and discuss internally the upcoming submissions, and provide feedback later. Pfizer agreed.

**Post-meeting Comment:**

Pfizer submitted the Qualification Information (assay method/manual and qualification report) for the Luminex Assay for Quantitation of IgG Antibodies and the Virus neutralization assay, in amendment 30 dated July 10, 2020, and it is under CBER review.

Ramachandra  
Naik -S

Digitally signed by Ramachandra Naik -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=2001232361,  
cn=Ramachandra Naik -S  
Date: 2020.07.15 12:30:35 -04'00'

COVID-19 Vaccine (BNT162, PF-07302048)  
IND #19736  
Request for Proprietary & Non-Proprietary Name Review



**REQUEST FOR PROPRIETARY &  
NON-PROPRIETARY NAME REVIEW**

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## 1. APPLICANT CONTACT INFORMATION

Name and title of contact	Elisa Harkins, Senior Director, Global Regulatory Affairs, Pfizer, Inc. – Authorized US Agent for: BioNTech RNA Pharmaceuticals GmbH
Company Name	Pfizer, Inc.
Address	500 Arcola Road Collegeville, PA 19426
Phone number	215-280-5503
Fax number	845-474-3500
Email address	Elisa.HarkinsTull@pfizer.com

## 2. PROPOSED PRIMARY AND ALTERNATE PROPRIETARY NAMES

The primary proposed proprietary name for Agency consideration is COMIRNATY.

The trademark application serial number is 88942267 (filed by BioNTech SE) for COMIRNATY. The application was filed at the United States Patent and Trademark Office on June 1, 2020 by BioNTech SE. The Notice of Allowance has not yet issued.

Should this name not be found acceptable, an alternate name will be provided at that time.

## 3. INTENDED PRONUNCIATION

koh-MER' nah-tee

## 4. DERIVATION OF PROPRIETARY NAME

The proposed proprietary name COMIRNATY is an invented word with no inherent meaning.

## 5. INTENDED MEANING OF PROPRIETARY NAME MODIFIERS

Not applicable.

## 6. PROPOSED ESTABLISHED NAME

Pfizer-BioNTech COVID-19 vaccine

## 7. PHARMACOLOGIC/ THERAPEUTIC CATEGORY

Prophylactic vaccine.

## 8. PROPOSED INDICATION FOR USE

Active immunization against COVID-19.

## 9. PRESCRIPTION STATUS

To be administered by a qualified healthcare professional.

## **10. DOSAGE FORM, PRODUCT STRENGTH(S)**

Concentrate for solution for injection.

5-Dose Vial is supplied as a white to off-white sterile frozen liquid, packaged in a clear glass 2 mL vial with a rubber stopper, aluminum overseal and flip off cap.

A single vial will be used to prepare a diluted dosing solution that is used to prepare doses for multiple individuals. The concentrated solution in the vial requires dilution with sterile 0.9% Sodium Chloride Injection, USP. After dilution, the vials contain a sufficient volume to supply 5 doses, where each 0.3 mL dose contains 30 µg vaccine for intramuscular injection.

## **11. ROUTE OF ADMINISTRATION**

For intramuscular injection only.

## **12. USUAL DOSAGE, FREQUENCY OF ADMINISTRATION, MAXIMUM DAILY DOSE**

Administered intramuscularly as a series of two 30 µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: A single 0.3 mL dose followed by a second 0.3 mL dose 21 days later.

## **13. DOSING IN SPECIFIC POPULATIONS**

No specific information will be provided for modifications that are dependent on renal and/or hepatic function. There will be no gender-based modifications.

## **14. INSTRUCTIONS FOR USE**

After thawing, each vial of vaccine must be diluted with 1.8 mL sterile 0.9% Sodium Chloride Injection, USP. After dilution, the vial contains five 30 µg doses of 0.3 mL per dose. Individual 0.3 mL doses should be withdrawn from the vial and administered intramuscularly in the deltoid muscle of the non-dominant arm.

## **15. STORAGE REQUIREMENT**

Vaccine vials must be immediately stored between -80 °C and -60 °C (-112 °F to -76 °F), protected from light and kept in the original packaging until ready for use.

## **16. HOW SUPPLIED AND PACKAGING CONFIGURATION**

The vaccine will be supplied frozen in -80 °C thermal containers with dry ice, in cartons each containing 195 vials.

## **17. LIKELY CARE ENVIRONMENT(S) FOR DISPENSING AND USE**

This vaccine will be administered by a qualified healthcare professional.

### **18. DELIVERY SYSTEM, MEASURING DEVICE**

After dilution, each 0.3 mL dose of vaccine should be withdrawn from the vial with a commercially available disposable sterile syringe with appropriate graduations and delivered with a needle appropriate for intramuscular injection.

### **19. ASSESSMENTS OF PROPRIETARY NAME, PACKAGING, AND/OR LABELING**

The Sponsor has evaluated the proposed primary proprietary name of COMIRNATY for this vaccine and considers the name safe, not misleading, or over-promising. However, no information of this nature is included in the current application.

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Our Reference: IND 19736

**PROPRIETARY NAME  
ACCEPTABLE AT THIS TIME**

BioNTech RNA Pharmaceuticals GmbH  
Attention: Ms. Elisa Harkins  
Pfizer, Inc.  
500 Arcola Road  
Collegetown, PA 19426

**November 20, 2020**

Dear Ms. Harkins:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "Human Coronavirus mRNA Vaccine (SARS-CoV-2 Spike Protein; BNT162b2 (modRNA; variant RBP020.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)."

We also refer to your amendment submitted and received on October 14, 2020, requesting a proprietary name review for COMIRNATY.

In consultation with the Center for Biologics Evaluation and Research's Advertising and Promotional Labeling Branch (CBER/APLB), we conclude that, under the FDCA and applicable regulations, COMIRNATY is *Acceptable at this time*.

Please provide a request for a re-review of your proposed proprietary name COMIRNATY within 14 days following submission of your Biologics License Application.

If you have any questions, please contact the Regulatory Project Manager, Ramachandra Naik, PhD, at 301-796-2640.

Sincerely,

Loris D.  
McVittie -S

Digitally signed by Loris D. McVittie -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=13000647  
81, cn=Loris D. McVittie -S  
Date: 2020.11.20 09:30:51 -05'00'

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FDA-CBER-2021-5683-1147762

**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 019736**

**Type C Meeting Request**



**July 2020**

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## 1. PRODUCT DESCRIPTION AND APPLICATION NUMBER

Pfizer and BioNTech are developing an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus, *SARS-CoV-2*. The goal of the development program is to rapidly develop and license a vaccine for use in adults  $\geq 18$  years of age, followed by a pediatric indication. The vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048).

An Investigational New Drug Application (IND) for the COVID-19 Vaccine was submitted to the US FDA on April 22, 2020. On April 29, 2020 Pfizer was notified by CBER that there were no clinical hold issues identified, and the evaluation of this vaccine in the US could proceed. The COVID-19 candidate vaccine formulations are investigational medicinal products (IMPs) and have not been submitted for marketing approval in any country. A Request for Fast Track Designation was submitted on May 15, 2020 (Serial Number 0005) and was granted on July 7, 2020.

BioNTech is conducting a German first-in-human (FIH) dose level-finding Phase 1/2 study (BNT162-01; 2020-001038-36) to gather safety and immunogenicity data to enable evaluation of each of the vaccines individually to inform the overall clinical development of a COVID-19 vaccine. This study is not conducted under the IND but is being conducted under a German Clinical Trial Authorization (CTA). The protocol for this study has been provided previously in Module 5 (Module 5.3.5.1 Clinical Study Protocol BNT162-01).

Pfizer and BioNTech are conducting a large Phase 1/2 clinical study in the US (C4591001) to evaluate the safety and immunogenicity of the prophylactic COVID-19 vaccine candidates using a range of dosage levels and dosing regimens, with the intent to select the most appropriate final vaccine candidate for Phase 3 development. To gather appropriate dose level information quickly, some dose levels evaluated in German or US studies were not the same. In addition, Pfizer has chosen not to evaluate currently unmodified RNA (uRNA) or self-amplifying RNA (saRNA) candidates in the US study. The protocol for this study is provided in Module 5 (Module 5.3.5.1 Clinical Study Protocol C4591001). Pfizer and BioNTech plan to convert this study to a large Phase 2b/3 safety and efficacy study by the end of July 2020.

A Type C Meeting was held on June 26, 2020 presenting the proposed Clinical Development Program intended to support Traditional licensure in the US and globally, as well as potential use of the candidate vaccine under an Emergency Use Authorization if authorized by HHS. The rationale to select a nucleoside-modified RNA (modRNA) vaccine candidate and dose level to progress into the Phase 3 part of Study C4591001 was also explained.

The purpose of this Type C Meeting is to present and obtain CBER agreement with the proposed CMC and facilities data package intended to support a BLA submission projected in the September 2020 timeframe in conjunction with the clinical program discussed with the Agency on June 26, 2020. CBER agreement is also sought regarding the proposed plan for providing additional and updated CMC information which will ensure an adequate and

consistent commercial supply chain as it comes available during late-2020 and throughout 2021. Finally, CBER feedback is requested regarding the proposed plans for manufacture, testing and release of vaccine which could be made available prior to material made by the intended commercial supply chain.

## 2. CHEMICAL NAME AND STRUCTURE

One of BioNTech's two nucleoside-modified RNA (modRNA) vaccine candidates will be selected as the final vaccine candidate to evaluate in Phase 3 and license. The **nucleoside-modified mRNA (modRNA) candidate platform** has blunted innate immune sensor activating capacity and thus augmented antigen expression. These RNA-based vaccines are formulated in the same LNPs. Each platform RNA encodes either a full-length SARS-CoV-2 S glycoprotein, the P2 mutant S glycoprotein (P2 S), and/or the receptor binding domain (RBD) of the S glycoprotein. Each candidate is also given a V number that indicates the specific version of the optimized insert genomic sequence. The two modRNA potential candidates are:

- **BNT162b1** (RBP020.3) modRNA encoding RBD (V5): 1 to 100 µg
  - German study (1, 10, 30, 50, 60 µg) and US study (10, 20, 30, 100 µg)
- **BNT162b2** (RBP020.2) modRNA encoding P2 S (V9): 1 to 100 µg
  - German study (1, 10, 30, 100 µg) and US study (10, 20, 30 µg)

The following are the details of the differences between the two expressed antigens.

- Nucleoside modified messenger RNA (modRNA), called BNT162b1, expresses the receptor binding domain of the SARS-CoV-2 S-glycoprotein.
- Nucleoside modified messenger RNA (modRNA), called BNT162b2, expresses a prefusion stabilized full-length variant of the SARS-CoV-2 S-glycoprotein.

## 3. PROPOSED INDICATION(S)

The proposed indication for the COVID-19 vaccine is:

- Active immunization against COVID-19 in adults  $\geq 18$  years of age.

## 4. TYPE OF MEETING BEING REQUESTED

This is a Type C meeting request; Pfizer respectfully requests a meeting with CBER by the end of July 2020.

## 5. PURPOSE OF THE MEETING

The purpose of this Type C Meeting is to present and obtain CBER agreement with the proposed CMC and facilities data package intended to support a BLA submission projected as early as September 2020, in conjunction with the clinical program discussed with the Agency on June 26, 2020. CBER agreement is also sought regarding the proposed plan for providing additional and updated CMC information which will ensure an adequate and

consistent commercial supply chain as it comes available during late-2020 and throughout 2021. Finally, CBER feedback is requested regarding the proposed plans for manufacture, testing and release of vaccine which we could be made available under an Emergency Use Authorization, should one be authorized.

## **6. SPECIFIC OBJECTIVES/OUTCOMES EXPECTED**

To obtain rapid CBER feedback on the questions included herein.

## **7. PRELIMINARY AGENDA, PRESENTER, TIME**

Introduction – 10 minutes

Discussion – 70 minutes

Closure – 10 minutes

## **8. SPECIFIC QUESTIONS GROUPED BY DISCIPLINE**

### **Chemistry, Manufacturing and Controls**

- 1) Does CBER have any comments on the overall CMC Development Plan, proposed BLA contents, and timeline proposed to support initial licensure via Traditional Approval? Specifically,
  - a) Does CBER agree with the proposed process confirmation and validation approach?
  - b) Does CBER agree with the proposed analytical validation approach?
  - c) Does CBER agree with the planned stability and shelf-life strategy?
  - d) Does CBER agree with the planned approach for the starting materials?
- 2) Does CBER agree with the plan for augmenting the CMC package further in late-2020 and into 2021?
- 3) Does CBER agree with the sponsor's plan to provide additional CMC/quality information frequently from continuous improvement and verification as well as results from confirmatory evaluations and studies, i.e., method and process validation, stability, etc., in order to provide additional evidence of batch to batch consistency and product stability?
- 4) Does CBER agree with the sponsor's proposal that the manufacturing process and analytical methods used for Phase 3 supplies are appropriately controlled, qualified and/or verified to ensure quality for initial commercial supply of the vaccine?
- 5) Does CBER agree with the sponsor's proposal that past inspection history be considered and that any pre-approval inspections be deferred, or should the Agency consider inspections as necessary that they be performed remotely?

- 6) Does CBER agree with the sponsor’s plan to demonstrate analytical comparability of the Drug Substance and Drug Product processes from clinical to commercial supply?
- 7) Does CBER agree with the sponsor’s plan to use an in vitro protein expression assay to assess potency of the drug product in lieu of an in vivo potency assay?
- 8) Does CBER agree with the Sponsor’s proposal for lot release process to expedite commercial release of drug product lots?

**Emergency Use Authorization**

- 1) An Emergency Use Authorization request package is currently planned for submission in parallel with the initial BLA. The Sponsor has initiated manufacturing activities to enable vaccine supply as early as October 2020 and potentially prior to Biologics License Application approval (see 1.6.2 Briefing Package, Section 6). Does CBER agree that Pfizer can continue to provide CMC amendments to the BB IND 19736 to support release of vaccine for supply under an Emergency Use Authorization, should one be granted for the candidate vaccine. prior to BLA approval?

**9. SPONSOR ATTENDEES**

Advait Badkar, PhD	Senior Director, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
(b) (6), PhD	Director, Manufacturing Science & Technology, Pfizer Inc.
Mark Boaz, PhD	Program Director, Vaccine Research and Development, Pfizer Inc.
Donna Boyce	Vice President, Global Regulatory Affairs, Vaccines, Pfizer Inc.
David Cirelli	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc.
Rodney Combs	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
(b) (6), PhD.	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc.
Carmel Devlin	Global Regulatory Portfolio Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Philip R. Dormitzer, MD, PhD	Vice President and Chief Scientific Officer, Viral Vaccines, Vaccines Research and Development, Pfizer Inc.
Elisa Harkins	Global Regulatory Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Michael Hripsak	Senior Manager, Technical Development Services, Pfizer Inc
Kathrin U. Jansen, PhD	Senior Vice President and Head, Vaccine Research and Development, Pfizer Inc.
(b) (6), PhD	Head of Regulatory Affairs CMC, BioNTech RNA Pharmaceuticals GmbH
Andreas Kuhn, PhD	Senior Vice President & Head of RNA Biochemistry & Manufacturing, BioNTech RNA Pharmaceuticals GmbH
Ulrich Blaschke, PhD	Vice President Technical Development; BioNTech RNA Pharmaceuticals GmbH
Julia Schlereth, PhD	Head of RNA Analytics; BioNTech RNA Pharmaceuticals GmbH
(b) (6), PhD	External Consultant for BioNTech RNA Pharmaceuticals GmbH
Lavinia M. Lewis, PhD	Senior Director, Pharmaceutical Sciences, Pfizer Inc.
Roger Nosal	Vice President, GCMC Regulatory Affairs, Pfizer Inc.

Roger H. Pak, PhD	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
Rich Pelt	Director, GCMC Vaccines Regulatory Affairs, Pfizer Inc.
Paul Rohlffing	Executive Director, GCMC Vaccines Regulatory Affairs, Pfizer Inc.
(b) (6)	Director, Pharmaceutical Sciences QA Biologics Portfolio Lead, Pfizer Inc.
Justin Sperry, PhD	Senior Director, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
Adrienne Stafford	Director, GCMC Vaccines Regulatory Affairs, Pfizer Inc.
Sriram Srinivasan, PhD	Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
Khurram M. Sunasara	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
(b) (6)	Manager, External Supply, Pfizer Inc.

**10. AGENCY STAFF**

Pfizer respectfully requests participation of appropriate personnel from the Division of Vaccines and Related Drug Products, Division of Manufacturing and Product Quality.

**11. ANTICIPATED DATE OF SUPPORTING DOCUMENTATION**

The Type C Briefing Document is included in this submission.

**12. SUGGESTED MEETING DATES AND TIME**

A meeting is requested by the end of July, morning or early afternoon time if possible.

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**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 019736**

**Type C Meeting Briefing Document**



**July 2020**

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## ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALC-0159	(2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide)
ALC-0315	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
BLA	Biologics License Application
BNT	BioNTech
CDER	(US Food and Drug Administration) Center for Drug Evaluation and Research
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CTA	Clinical Trial Authorization
DART	developmental and reproductive toxicology (study)
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECMO	extracorporeal membrane oxygenation
EU	European Union
FiO <sub>2</sub>	fraction of inspired oxygen
GLP	Good Laboratory Practice
FIH	first-in-human
HHS	(US Department of) Health and Human Services
HR	heart rate
IM	intramuscular(ly)
IMP	investigative medicinal product
iPSP	initial Pediatric Study Plan
IND	Investigational New Drug application
LL	lower limit (of confidence interval)
LNP	lipid nanoparticle
mNG	mNeonGreen
modRNA	nucleoside modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification test

<b>Abbreviation</b>	<b>Definition</b>
NHP	non-human primate
PaO <sub>2</sub>	arterial oxygen pressure
P/B	prime/boost: dosing regimen of a priming immunization and a booster immunization
POS	probability of trial success
RNA-LNP	RNA lipid nanoparticle
RR	respiratory rate
saRNA	self-amplifying messenger RNA
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
sBLA	supplemental Biologics License Application
SBP	systolic blood pressure
S glycoprotein	Spike glycoprotein
SpO <sub>2</sub>	peripheral oxygen saturation
Tdap	Tetanus toxoid, low dose diphtheria toxoid, acellular pertussis (vaccine)
uRNA	non-modified uridine containing mRNA
US	United States
VE	vaccine efficacy
WHO	World Health Organization

## 1. EXECUTIVE SUMMARY

Pfizer and BioNTech are developing an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus, SARS-CoV-2. The goal of the development program is to rapidly develop and license a vaccine for use in adults  $\geq 18$  years of age, followed by a pediatric indication. The vaccine is based on SARS-CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048).

An Investigational New Drug Application (IND) for the COVID-19 Vaccine was submitted to the US FDA on April 22, 2020. On April 29, 2020 Pfizer was notified by CBER that there were no clinical hold issues identified, and the evaluation of this vaccine in the US could proceed. The COVID-19 candidate vaccine formulations are investigational medicinal products (IMPs) and have not been submitted for marketing approval in any country. A Request for Fast Track Designation was submitted on May 15, 2020 (Serial Number 0005) and was granted on July 7, 2020.

BioNTech is conducting a German first-in-human (FIH) dose level-finding Phase 1/2 study (BNT162-01; 2020-001038-36) to gather safety and immunogenicity data to enable evaluation of each of the vaccines individually to inform the overall clinical development of a COVID-19 vaccine. This study is not conducted under the IND but is being conducted under a German Clinical Trial Authorization (CTA). The protocol for this study has been provided previously in Module 5 (Module 5.3.5.1 Clinical Study Protocol BNT162-01).

Pfizer and BioNTech are conducting a large Phase 1/2 clinical study in the US (C4591001) to evaluate the safety and immunogenicity of the prophylactic COVID-19 vaccine candidates using a range of dosage levels and dosing regimens, with the intent to select the most appropriate final vaccine candidate for Phase 3 development. To gather appropriate dose level information quickly, some dose levels evaluated in German or US studies were not the same. In addition, Pfizer has chosen not to evaluate currently unmodified RNA (uRNA) or self-amplifying RNA (saRNA) candidates in the US study. The protocol for this study is provided in Module 5 (Module 5.3.5.1 Clinical Study Protocol C4591001). Pfizer and BioNTech plan to convert this study to a large Phase 2b/3 safety and efficacy study by the end of July 2020.

A Type C Meeting was held on June 26, 2020 presenting the proposed Clinical Development Program intended to support Traditional licensure in the US and globally, as well as potential use of the candidate vaccine under an Emergency Use Authorization if authorized by HHS. The rationale to select a nucleoside-modified RNA (modRNA) vaccine candidate and dose level to progress into the Phase 3 part of Study C4591001 was also explained.

The purpose of this Type C Meeting is to present and obtain CBER agreement with the proposed CMC and facilities data package intended to support a BLA submission projected in the September 2020 timeframe in conjunction with the clinical program discussed with the Agency on June 26, 2020. CBER agreement is also sought regarding the proposed plan for providing additional and updated CMC information which will ensure an adequate and

consistent commercial supply chain as it comes available during late-2020 and throughout 2021. Finally, CBER feedback is requested regarding the proposed plans for manufacture, testing and release of vaccine which could be made available prior to material made by the intended commercial supply chain.

## 2. PRODUCT IDENTIFICATION AND APPLICATION

### 2.1. Chemical Name and Structure

One of BioNTech's two nucleoside-modified RNA (modRNA) vaccine candidates will be selected as the final vaccine candidate to evaluate in Phase 3 and license. The **nucleoside-modified mRNA (modRNA) candidate platform** has blunted innate immune sensor activating capacity and thus augmented antigen expression. These RNA-based vaccines are formulated in the same LNPs. Each platform RNA encodes either a full-length SARS-CoV-2 S glycoprotein, the P2 mutant S glycoprotein (P2 S), and/or the receptor binding domain (RBD) of the S glycoprotein. Each candidate is also given a V number that indicates the specific version of the optimized insert genomic sequence. The two modRNA potential candidates are:

- **BNT162b1** (RBP020.3) modRNA encoding RBD (V5): 1 to 100 µg
  - German study (1, 10, 30, 50, 60 µg) and US study (10, 20, 30, 100 µg)
- **BNT162b2** (RBP020.2) modRNA encoding P2 S (V9): 1 to 100 µg
  - German study (1, 10, 30, 100 µg) and US study (10, 20, 30 µg)

The following are the details of the differences between the two expressed antigens.

- Nucleoside modified messenger RNA (modRNA), called BNT162b1, expresses the receptor binding domain of the SARS-CoV-2 S-glycoprotein.
- Nucleoside modified messenger RNA (modRNA), called BNT162b2, expresses a prefusion stabilized full-length variant of the SARS-CoV-2 S-glycoprotein.

### 2.2. Dosage Form, Route of Administration, and Dosing Regimen

The vaccine candidate will be released as a concentrated liquid formulation stored frozen at -70 °C (+/- 10°C) in a 2 mL Type 1 glass vial to be thawed on the day of administration and subsequently diluted with sterile 0.9% sodium chloride Solution for Injection, USP, and stored at 2-8 °C until administration, as described in Module 3.2 of the IND. The Sponsor intends to commercialize the current formulation and initially plans to provide a single vial from which multiple doses would be drawn. The multi-dose vial presentation is planned to be preservative-free.

The candidate vaccine is administered intramuscularly (IM) in the upper arm (musculus deltoideus) using prime/boost (P/B) regimens. The P/B regimen is two injections given at 0 and 21 days.

### 2.3. Proposed Indication

The proposed indication for the COVID-19 vaccine is:

- Active immunization against COVID-19 in adults  $\geq 18$  years of age.

### 3. PURPOSE OF MEETING

The purpose of this Type C Meeting is to present and obtain CBER agreement with the proposed CMC and facilities data package intended to support a BLA submission projected as early as September 2020, in conjunction with the clinical program discussed with the Agency on June 26, 2020. CBER agreement is also sought regarding the proposed plan for providing additional and updated CMC information which will ensure an adequate and consistent commercial supply chain as it comes available during late-2020 and throughout 2021. Finally, CBER feedback is requested regarding the proposed plans for manufacture, testing and release of vaccine which we could be made available under an Emergency Use Authorization, should one be authorized.

### 4. PROPOSED AGENDA AND LIST OF PARTICIPANTS

#### 4.1. Proposed Agenda

Introduction – 10 minutes  
 Discussion – 70 minutes  
 Closure – 10 minutes

#### 4.2. List of Pfizer Inc. and BioNTech SE Participants

Advait Badkar, PhD	Senior Director, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
(b) (6), PhD	Director, Manufacturing Science & Technology, Pfizer Inc.
Mark Boaz, PhD	Program Director, Vaccine Research and Development, Pfizer Inc.
Donna Boyce	Vice President, Global Regulatory Affairs, Vaccines, Pfizer Inc.
David Cirelli	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc.
Rodney Combs	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
(b) (6), PhD.	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc.
Carmel Devlin	Global Regulatory Portfolio Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Philip R. Dormitzer, MD, PhD	Vice President and Chief Scientific Officer, Viral Vaccines, Vaccines Research and Development, Pfizer Inc.
Elisa Harkins	Global Regulatory Lead, Global Regulatory Affairs, Vaccines, Pfizer Inc.
Michael Hripcsak	Senior Manager, Technical Development Services, Pfizer Inc
Kathrin U. Jansen, PhD	Senior Vice President and Head, Vaccine Research and Development, Pfizer Inc.
(b) (6), PhD	Head of Regulatory Affairs CMC, BioNTech RNA Pharmaceuticals GmbH
Andreas Kuhn, PhD	Senior Vice President & Head of RNA Biochemistry & Manufacturing, BioNTech RNA Pharmaceuticals GmbH

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Ulrich Blaschke, PhD	Vice President Technical Development; BioNTech RNA Pharmaceuticals GmbH
Julia Schlereth, PhD	Head of RNA Analytics; BioNTech RNA Pharmaceuticals GmbH
(b) (6), PhD	External Consultant for BioNTech RNA Pharmaceuticals GmbH
Lavinia M. Lewis, PhD	Senior Director, Pharmaceutical Sciences, Pfizer Inc.
Roger Nosal	Vice President, GCMC Regulatory Affairs, Pfizer Inc.
Roger H. Pak, PhD	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
Rich Pelt	Director, GCMC Vaccines Regulatory Affairs, Pfizer Inc.
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(b) (6)	Director, Pharmaceutical Sciences QA Biologics Portfolio Lead, Pfizer Inc.
Justin Sperry, PhD	Senior Director, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
Adrienne Stafford	Director, GCMC Vaccines Regulatory Affairs, Pfizer Inc.
Sriram Srinivasan, PhD	Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
Khurram M. Sunasara	Associate Research Fellow, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc.
(b) (6)	Manager, External Supply, Pfizer Inc.

## 5. LIST OF SPECIFIC QUESTIONS FOR DISCUSSION

### Chemistry, Manufacturing and Controls

- 1) Does CBER have any comments on the overall CMC Development Plan, proposed BLA contents, and timeline proposed to support initial licensure via Traditional Approval? Specifically,
  - a) Does CBER agree with the proposed process confirmation and validation approach?
  - b) Does CBER agree with the proposed analytical validation approach?
  - c) Does CBER agree with the planned stability and shelf-life strategy?
  - d) Does CBER agree with the planned approach for the starting materials?
- 2) Does CBER agree with the plan for augmenting the CMC package further in late-2020 and into 2021?
- 3) Does CBER agree with the sponsor's plan to provide additional CMC/quality information frequently from continuous improvement and verification as well as results from confirmatory evaluations and studies, i.e., method and process validation, stability, etc., in order to provide additional evidence of batch to batch consistency and product stability?
- 4) Does CBER agree with the sponsor's proposal that the manufacturing process and analytical methods used for Phase 3 supplies are appropriately controlled, qualified and/or verified to ensure quality for initial commercial supply of the vaccine?

- 5) Does CBER agree with the sponsor's proposal that past inspection history be considered and that any pre-approval inspections be deferred, or should the Agency consider inspections as necessary that they be performed remotely?
- 6) Does CBER agree with the sponsor's plan to demonstrate analytical comparability of the Drug Substance and Drug Product processes from clinical to commercial supply?
- 7) Does CBER agree with the sponsor's plan to use an in vitro protein expression assay to assess potency of the drug product in lieu of an in vivo potency assay?
- 8) Does CBER agree with the Sponsor's proposal for lot release process to expedite commercial release of drug product lots?

### **Emergency Use Authorization**

- 1) An Emergency Use Authorization request package is currently planned for submission in parallel with the initial BLA. The Sponsor has initiated manufacturing activities to enable vaccine supply as early as October 2020 and potentially prior to Biologics License Application approval (see section 6). Does CBER agree that Pfizer can continue to provide CMC amendments to the BB IND 19736 to support release of vaccine for supply under an Emergency Use Authorization, should one be granted for the candidate vaccine, prior to BLA approval?

## **6. CMC DEVELOPMENT PLAN**

### **6.1. Introduction**

#### **6.1.1. Background on the Target Indication**

SARS-CoV-2 infections and the resulting COVID-19 disease have spread globally. On March 11, 2020 the World Health Organization (WHO) characterized the COVID-19 outbreak as pandemic. At the time of this communication, the number of confirmed cases exceeds 11 million and continues to rise globally.

There are currently no vaccines to prevent SARS-CoV-2 infections or the disease it causes, COVID-19 ([Habibzadeh & Stoneman 2020](#)).

#### **6.1.2. Rationale for Development**

The rationale for development of BNT162 candidate vaccines based on mRNA technology was covered in the Clinical Overview with the initial IND application (Module 2.5).

### **6.2. Terminology**

The following mRNA vaccine terms are used throughout this document:

RNA lipid nanoparticle (LNP): Used for enabling RNA delivery

Ancillary Material: A component, reagent or material used during the manufacture of an mRNA vaccine product that is not intended to be part of the final product.

(b) (4)

Drug Substance (DS): Bulk (b) (4) operations.

Drug Product (DP): Formulated, filled and finished (including cryopreserved) RNA Lipid Nanoparticle (LNP) in its primary package (container closure system).

Excipient: A component or reagent used in the formulation of the final mRNA vaccine product. (b) (4)

(b) (4)

Impurity: Process or product-related species that remain with the DS or develops during formulation or upon aging of DS or DP.

Process-related: Species derived from a manufacturing process. Examples: manufacturing reagents (b) (4)

Product-related: (b) (4)

(b) (4)

(b) (4)

Placebo: A substance or treatment which is designed to have no therapeutic value

Primary Package: Material that comes into direct contact with the drug product and may have an effect on the product itself. Examples include vials, stoppers, prefilled syringes, (b) (4), etc.

Primary Label: The label affixed to the primary packaged drug product.

Secondary Label (labeling): The label affixed to the secondary container (in which the primary packaged drug product is placed) for distribution to clinical and/or commercial sites.

Starting Material: A component, reagent or material used during the manufacture of an mRNA vaccine product that is intended to be part of the final product. (b) (4)

(b) (4)

(b) (4)

### 6.3. Manufacturing Process

(b) (4)

(b) (4)

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(b) (4)

**6.3.1. Drug Substance**

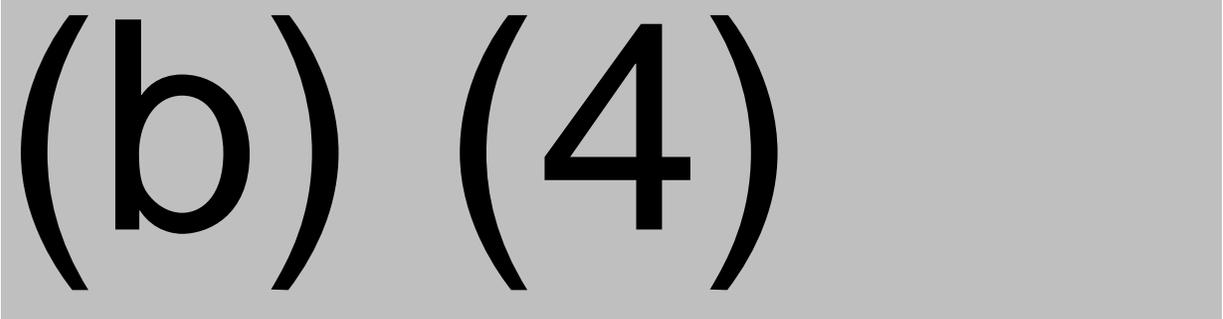
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### 6.3.2. Drug Product



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## 6.5. Comparability Strategy

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(b) (4)

**6.6. Overall Control Strategy and Process Validation/Verification Strategy**

(b) (4)

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(b) (4)

**6.7. Facilities and Personnel Information**

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(b) (4)

### 6.8. Equipment

(b) (4)

### 6.9. Materials

(b) (4)

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(b) (4)

## 7. REGULATORY PATHWAYS

### 7.1. Traditional Approval

The CMC information anticipated for inclusion in the Traditional Approval BLA targeted for September 2020 for the first BNT162 candidate is summarized in section 6.3 to section 6.15.

### 7.2. Emergency Use Authorization

The Sponsor has initiated supply activities to enable manufacture of vaccine supply as early as October 2020 and potentially prior to biologics license application approval (see section 6). The sponsor proposes to provide CMC amendments to the BB IND 19736 to support release of vaccine for supply under an Emergency Use Authorization, should one be approved, prior to BLA approval. The Emergency Use Authorization request package is currently planned for submission in parallel with the initial BLA.

## 8. SUMMARY

In summary, the Sponsor respectfully requests CBER feedback on the following:

- The overall CMC Development Plan and timeline proposed to support initial licensure via Traditional Approval.
- CMC/quality information from continuous improvement and verification as well as results from confirmatory evaluations and studies, i.e., method and process validation,

stability, etc., that substantiate batch to batch consistency and product expiry will be continually provided to the Agency.

- The manufacturing process and analytical methods used for the planned Phase 2b/3 study supplies are “fit-for-purpose” to ascertain efficacy and could be qualified for initial commercialization of the vaccine with continued verification/validation and continuous improvement to demonstrate robust and consistent quality assurance.

## 9. REFERENCES

*(All references are available upon request)*

Habibzadeh P, Stoneman EK. The novel coronavirus: a bird's eye view. *Int J Occup Environ Med* 2020;11(2):65-71.

## Written Responses

**Our Reference:** Type C Meeting Request: IND 19736, Amendment 31; CRMTS 12714

**DATE:** August 14, 2020 **PAGES:** 15

**TO:** Elisa Harkins  
BioNTech RNA Pharmaceuticals GmbH/Pfizer. Inc.  
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Phone: 215-280-5503  
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**FROM:** Ramachandra Naik, PhD  
Primary Reviewer  
Division of Vaccines and Related Products Applications  
Office of Vaccines Research and Review

**SUBJECT:** Type C meeting to obtain CBER agreement with: (1) the proposed CMC and Facilities data package intended to support a BLA submission, (2) the proposed plan for providing additional and updated CMC information, to ensure an adequate and consistent commercial supply chain, as it becomes available during late-2020 and throughout 2021, and (3) the proposed plans for manufacture, testing and release of vaccine which could be made available under an Emergency Use Authorization prior to BLA approval

**PRODUCT:** Human Coronavirus mRNA Vaccines [SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); and BNT162c2 (saRNA; variant RBS004.2)] in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**PROPOSED INDICATION:** Active immunization against COVID-19 in adults 18 years of age and older

### FDA Participants:

Nabil Al-Humadi, PhD	OVRP/DVRPA
Marie Anderson, PhD	OCBQ/DBSQC
Anissa Cheung, MSc	OVRP/DVP
Carmen Collazo, PhD	OVRP/DVRPA
Dennis Cato, MD	OBE/DIS

Anil Choudhary, PhD, MBA	OCBQ/DBSQC
Maryna Eichelberger, PhD	OCBQ/DBSQC
John Eltermann, PhD	OCBQ/DMPQ
Laura Fontan	OCBQ/DMPQ
Sara Gagneten, PhD	OVRD/DVP
Karla Garcia, M.S.	OCBQ/DBSQC
Martin (Dave) Green, PhD	OVRD/DVRPA
Marion Gruber, PhD	OVRD
Lei Huang, PhD	OBE/DB
Kathleen Jones, PhD	OCBQ/DMPQ
Bhanu Kannan	OBE/DIS
James Kenney, DSc	OCBQ/DBSQC
Philip Krause, MD	OVRD
Robin Levis, PhD	OVRD/DVP
Loris McVittie, PhD	OVRD/DVRPA
Haruhiko Murata, PhD	OVRD/DVP
Ramachandra Naik, PhD	OVRD/DVRPA
Tao Pan, PhD	OCBQ/DBSQC
Keith Peden, PhD	OVRD/DVP
Lori Peters, PhD	OCBQ/DMPQ
Douglas Pratt, MD	OVRD/DVRPA
Kirk Prutzman, PhD	OVRD/DVRPA
Carolyn Renshaw	OCBQ/DMPQ
Muhammad Shahabuddin, PhD	OCBQ/DBSQC
Li Sheng Fowler, PhD	OVRD/DVRPA
Elizabeth Sutkowski, PhD	OVRD/DVRPA
Deborah Trout, PhD	OCBQ/DMPQ
Swati Verma, PhD	OVRD/DVRPA
Hsiaoling Wang, PhD	OCBQ/DBSQC
Xiao Wang, PhD	OVRD/DVP
Jerry Weir, PhD	OVRD/DVP
Emnet Yitbarek, PhD	OCBQ/DBSQC

We completed our review of your meeting package for Human Coronavirus mRNA Vaccines and are providing the following Written Responses to the questions you posed in the package.

Please be aware that your future submission should include all components for a complete submission and should be in compliance with all appropriate statutes and regulations.

If you have any questions, please contact Ramachandra Naik, PhD, at 301-796-2640.

Please include a reference to IND 19736, Amendment 31; CRMTS 12714 in your future submissions related to the subject product.

## Written Responses

For a BLA, the manufacturing process, including the control of starting materials, and in-process and quality release tests are expected to be validated to ensure that after licensure, drug product lots are consistently manufactured and are comparable to the quality of lots used in the Phase 3 studies used to support licensure. Therefore, your projected timeframe of (b) (4) [REDACTED]. Please see our comments below.

## Chemistry, Manufacturing and Controls

### **Sponsor Question 1.a:**

Does CBER have any comments on the overall CMC Development Plan, proposed BLA contents, and timeline proposed to support initial licensure via Traditional Approval? Specifically, Does CBER agree with the proposed process confirmation and validation approach?

### **FDA Response to Question 1.a:**

The background information on the validation of the manufacturing process is insufficient to address this question.

- a. We acknowledge that you plan to execute drug substance (DS) and drug product (DP) process performance qualifications (PPQs) (b) (4) [REDACTED]

[REDACTED] Please provide the following information for our input:

- i. The timeline for the PPQ of DS and DP lots and submission of PPQ reports
  - ii. Identification of the DS and DP PPQ lots that will be produced at each site
  - iii. A timeline of the qualification and validation activities covering all aspects of DS and DP manufacture and controls, such as material and equipment qualification, analytical test validation, and manufacturing process validation.
- b. We acknowledge that you will perform assessments of “parameter set points/ranges and their initial criticality.” Please describe how criticality of parameter targets (set points) and ranges will be analyzed and which performance attributes will be evaluated as part of the PPQ. In the BLA, for each process step, please identify the critical process parameters (CPPs) with operational targets (i.e., set points) and ranges. Please also specify where the

in-process testing will be performed during the commercial manufacture of DS and DP and establish acceptance criteria.

- c. We note that you plan to conduct (b) (4)

Please note, all CPP operational ranges will need to be qualified prior to BLA submission.

Please see our responses to Questions 1.d, 5 and 6 for additional advice on starting materials, facilities and analytical comparability. Please also see Additional FDA Questions/Comments, regarding the information needed for facilities, product quality and manufacturing control.

**Sponsor Question 1.b:**

Does CBER agree with the proposed analytical validation approach?

**FDA Response to Question 1.b:**

The background information on the validation of analytical tests is insufficient to address this question.

- a. We agree with your proposed analytical validation approach for compendial Bioburden, LAL, and sterility methods. Please notify us about any changes to analytical test approaches as part of future regulatory submissions.
- b. Regarding non-compendial in-process and release tests for DS and DP, it appears some (b) (4)

Please note that test methods (i.e., SOPs) and validation protocols and reports will be needed for all in-process and DS and DP release tests. Please provide the following information:

- i. As requested in the response to Question 1.a, please provide a timeline of validation for in-process and release quality tests.
- ii. You indicated that testing developed or performed by Pfizer or their contract laboratories for DS and DP commercial release will be initially validated according to ICH Q2, (b) (4) will be used for validation.
- ii. You also indicated that if a test is used for in-process and/or final DS or DP characterization, then it will be (b) (4) For the characterization tests, please provide the test methods and clarify what qualification information may be available for each test. For the in-process tests, as we recommended above, all tests should be validated.

Please see Additional FDA Questions/Comments, regarding the quality test information.

**Sponsor Question 1.c:**

Does CBER agree with the planned stability and shelf-life strategy?

**FDA Response to Question 1.c:**

The background information on the stability plan and strategy is insufficient to address this question. Please provide:

- a. The analytical tests that will be used in the DS and DP stability plans,
- b. The container-closure system(s) used for the DS and DP stability studies and a description of how they compare with the containers used for commercial production,
- c. The lot numbers, manufacturing process (1 or 2) and manufacturing sites of the developmental and clinical lots for which stability data will be provided.

**Sponsor Question 1.d:**

Does CBER agree with the planned approach for the starting materials?

**FDA Response to Question 1.d:**

For the reference materials, the proposed strategy is acceptable. The background information on other starting materials is insufficient to fully address this question. We have the following recommendations:

(b) (4)

(b) (4)

(b) (4)

**Sponsor Question 3:**

Does CBER agree with the sponsor's plan to provide additional CMC/quality information frequently from continuous improvement and verification as well as results from confirmatory evaluations and studies, i.e., method and process validation, stability, etc., in order to provide additional evidence of batch to batch consistency and product stability?

**FDA Response to Question 3:**

- a. Regarding method and process validation, see our response to Question 1.a.
- b. Regarding submission of results for post-approval verifications, we will provide feedback after we receive the information requested in this communication. Any validation information that will not be submitted in the initial BLA (i.e., submitted during the BLA review cycle or post-licensure) will need to be agreed upon prior to submission of the BLA.
- c. Regarding post approval stability updates, please submit DS and DP stability data from PPQ lots when studies are completed as a product correspondence.

**Sponsor Question 4:**

Does CBER agree with the sponsor's proposal that the manufacturing process and analytical methods used for Phase 3 supplies are appropriately controlled, qualified and/or verified to ensure quality for initial commercial supply of the vaccine?

**FDA Response to Question 4:**

- a. The proposed manufacturing process and analytical methods used for Phase 3 supplies are appropriate for use of clinical lots under IND.
- b. Regarding manufacturing process controls to support commercial production, please see our response to Question 1.a.
- c. Regarding the quality release tests, the proposed DS release specifications and DS characterization of impurities are acceptable.
- d. Regarding the DP, please provide:

(b) (4)

(b) (4)

Please see our response to Question 1.b. on quality test methods and validation information.

**Sponsor Question 5:**

Does CBER agree with the sponsor's proposal that past inspection history be considered and that any pre-approval inspections be deferred, or should the Agency consider inspections as necessary that they be performed remotely?

**FDA Response to Question 5:**

(b) (4)

At this time, we cannot provide a definitive response regarding the performance of pre-license or pre-approval inspections that may be needed in support of your BLA or post approval supplement(s). However, we will use all resources available to assist us in determining if an onsite inspection will be required. Some considerations include requesting inspection reports from other trusted foreign regulatory partners (mutual recognition and confidentiality agreements), requesting records in advance or in lieu of an onsite inspection, and waiving inspections for facilities with acceptable FDA compliance histories. We will perform mission critical pre-license inspections on a case by case basis. Additional facility information was requested via information requests emailed on August 7, 2020 and August 11, 2020.

Please also see Additional FDA Questions/Comments, regarding the facilities information.

**Sponsor Question 6:**

Does CBER agree with the sponsor's plan to demonstrate analytical comparability of the Drug Substance and Drug Product processes from clinical to commercial supply?

**FDA Response to Question 6:**

The background information on the manufacturing changes and comparability approach is insufficient to address this question.

- a. Regarding your comparability approach, we have the following recommendations:

(b) (4)

(b) (4)

**Sponsor Question 7:**

Does CBER agree with the sponsor's plan to use an *in vitro* protein expression assay to assess potency of the drug product in lieu of an *in vivo* potency assay?

**FDA Response to Question 7:**

We agree with your plan to use an *in vitro* expression assay to assess potency of the drug product. In addition, while we appreciate your effort to develop an *in vitro*

(b) (4)

**Sponsor Question 8:**

Does CBER agree with the Sponsor's proposal for lot release process to expedite commercial release of drug product lots?

**FDA Response to Question 8:**

Vaccine lots to be distributed in the U.S. after licensure will need to be manufactured using the qualified processes, sites and equipment and be released according to the validated analytical methods described in the BLA.

Regarding CBER's lot-release procedures, we commit to a rapid review of lot-release protocols for vaccine lots to be distributed in the U.S.

**Emergency Use Authorization (EUA)**

**EUA-related Sponsor Question 1:**

An Emergency Use Authorization request package is currently planned for submission in parallel with the initial BLA. The Sponsor has initiated manufacturing activities to enable vaccine supply as early as October 2020 and potentially prior to Biologics License Application approval (see section 6). Does CBER agree that Pfizer can continue to provide CMC amendments to the BB IND 19736 to support release of

vaccine for supply under an Emergency Use Authorization, should one be granted for the candidate vaccine prior to BLA approval?

**FDA Response to EUA-related Question 1:**

We will provide recommendations regarding the information needed to support vaccine distribution under Emergency Use Authorization in a separate communication.

**Additional FDA Questions/Comments:**

We are providing additional product quality and microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your <351(a)> BLA submission:

1. All facilities should be registered with the FDA at the time of the <351(a)> BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the DS and DP should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.
2. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the <351(a)> BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- b. Bioburden and endotoxin data obtained during manufacture of the process qualification (PPQ) lots when available (3.2.S.2.5).
- c. If there are any holds for more than 24 hours, then microbial data from three successful product intermediate hold time validation runs at manufacturing scale should be provided. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

- d. Information and summary results from the shipping validation studies. Please indicate the placement of your temperature monitors for routine shipping, and rationale, as necessary, to explain leveraging validated shipping configurations as approved for other products. (3.2.S.2.5).
  - e. Drug substance bioburden and endotoxin release specifications (3.2.S.4).
3. The CMC Drug Product section of the <351(a)> BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry “*Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.
  4. The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.
    - a. Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.
    - b. Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
    - c. Parameters for filling and capping for the vials.
    - d. A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
    - e. Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
    - f. Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. For final sterile filtration of drug product, pre-sterile filtration bioburden limits typically do not exceed 10 CFU/100 mL.
  5. The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- a. Bacterial filter retention study for the final sterilizing filter. Please include a comparison of validation test parameters with routine sterile filtration parameters.
  - b. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Please provide summary data for the three validation studies and describe the equipment and component revalidation program.
  - c. In-process microbial controls and hold times over 24 hours. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
  - d. Isolator decontamination summary data and information, if applicable.
  - e. Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Please describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
  - f. Information and summary results from shipping validation studies. Please indicate the placement of your temperature monitors for routine shipping, and rationale, as necessary, to explain leveraging validated shipping configurations as approved for other products.
  - g. Validation of capping parameters, using a container closure integrity test.
6. The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:
- a. Regarding container closure:
    - i. Container closure integrity testing should be demonstrated initially and during stability assessment. Container closure integrity must be maintained through stability conditions (-70°C). Developmental studies may be submitted to support that container closure integrity may be maintained at stability conditions if stability data are not available. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress ( $\leq 20$  microns). It is recommended to perform container closure integrity testing *in lieu* of sterility whenever sterility assurance is assessed throughout your stability program.
    - ii. For the multi-dose vial, please provide results of testing per USP<381> Elastomeric Closures for Injections and ISO 8871-5, i.e., fragmentation (coring), penetrability (piercing force by hypodermic needle), self-sealing

capacity (container closure integrity testing after multiple punctures), etc. to demonstrate suitability of your container closure system.

- b. For microbiological studies in support of the post-dilution storage conditions, including multiple breaches of the container closure to simulate multiple dosing, please describe the test methods and results that employ a minimum countable inoculum (10-100 CFU in the product) to simulate potential microbial contamination that may occur during dilution or with multiple dosing. The test should be run at the label's recommended storage conditions with drug product, be conducted for the recommended storage period, include the maximum number of needle pierces, and use the label-recommended diluents. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections.

We have the following comments regarding physicochemical release assays and validation:

(b) (4)

(b) (4)

END



**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 19736**

**Response to CBER Comments Received on August 14, 2020 in Response to the  
Sponsor's Type C CMC Meeting Request IND 19746, Amendment 31  
CRMTS 12714**

**And**

**Response to CBER September 18, 2020 response to the Sponsor's clarification question  
sent via email on August 21, 2020 regarding items 1.d.d.ii and Additional FDA Comment  
11 listed in CBER's Type C meeting Written Responses sent to Pfizer on August 14, 2020.**

**October 8, 2020**

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## 1. BACKGROUND

Reference is made to BB-IND 19736 for the COVID-19 vaccine (BNT162; PF-07302048) which is being developed by Pfizer and BioNTech. The initial proposed indication is “active immunization against COVID-19 disease caused by SARS-CoV-2 virus in participants  $\geq 16$  years of age.” The IND was effective on April 29, 2020.

Further reference is made to the Sponsor’s Type C CMC Briefing Document (SN0031 submitted July 13, 2020) and to CBER’s written responses to the Briefing Document received August 14, 2020.

This submission provides responses to CBER’s comments. CBER’s comments are in bold italics and are followed by the Sponsor’s responses.

Additional information/detail is provided with this response taking into consideration CBER’s guidance regarding the expected requirements and process for the Emergency Use Authorization (EUA) application provided via email to Ms. Elisa Harkins on October 5, 2020.

Also provided are responses to CBER’s September 18, 2020 response to the Sponsor’s clarification question sent via email on August 21, 2020 regarding items 1.d.d.ii and Additional FDA Comment 11 listed in CBER’s Type C meeting Written Responses sent to Pfizer on August 14, 2020.

## 2. CBER CMC RESPONSES AND PFIZER RESPONSES

### 2.1. CBER Comment 1.a

***Sponsor Question 1.a:***

***Does CBER have any comments on the overall CMC Development Plan, proposed BLA contents, and timeline proposed to support initial licensure via Traditional Approval? Specifically, Does CBER agree with the proposed process confirmation and validation approach?***

***FDA Response to Question 1.a:***

***The background information on the validation of the manufacturing process is insufficient to address this question.***

- a. ***We acknowledge that you plan to execute drug substance (DS) and drug product (DP) process performance qualifications (PPQs) (b) (4)***



***. Please provide the following information for our input:***

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- i. The timeline for the PPQ of DS and DP lots and submission of PPQ reports*
  - ii. Identification of the DS and DP PPQ lots that will be produced at each site*
  - iii. A timeline of the qualification and validation activities covering all aspects of DS and DP manufacture and controls, such as material and equipment qualification, analytical test validation, and manufacturing process validation.*
- b. We acknowledge that you will perform assessments of “parameter set points/ranges and their initial criticality.” Please describe how criticality of parameter targets (set points) and ranges will be analyzed and which performance attributes will be evaluated as part of the PPQ. In the BLA, for each process step, please identify the critical process parameters (CPPs) with operational targets (i.e., set points) and ranges. Please also specify where the in-process testing will be performed during the commercial manufacture of DS and DP and establish acceptance criteria.*
- c. We note that you plan to conduct (b) (4)*

*Please note, all CPP operational ranges will need to be qualified prior to BLA submission.*

*Please see our responses to Questions 1.d, 5 and 6 for additional advice on starting materials, facilities and analytical comparability. Please also see Additional FDA Questions/Comments, regarding the information needed for facilities, product quality and manufacturing control.*

### **2.1.1. Pfizer Response to Comment 1.a Part a (i-iii)**

The sponsor has modified the timing of many activities relative to the information in the July 13, 2020 briefing document, considering the Agency’s feedback. A timeline for the manufacturing process validation (PPQ) activities for drug substance (DS) and drug product (DP) is provided in Table 1 below.

Critical process parameters and in-process controls have been defined and will be described in the BLA. Along with the DS and DP manufacturing process design and mRNA platform knowledge, these controls will ensure consistency of the manufacturing processes and the quality of the vaccine product. As detailed in the response 1b, process controls will be further confirmed through the planned PPQ studies and additional process characterization studies, including demonstration of comparability of the vaccine quality between the proposed DP manufacturing sites.

Regarding prerequisites to BLA submission listed in 1.a part a (iii):

(1) Material qualification. Raw materials are qualified for use in the manufacturing process and records are maintained in the Quality Management System (QMS), including identification of supply channel with appropriate Quality Agreements.

All raw materials are adequately controlled and will be qualified, including testing using validated test methods prior to the BLA submission.

All materials used in the manufacture have been investigated for the origin of animal material and have been determined to comply with “Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01).”

(2) Equipment qualification and manufacturing process validation. Qualification of equipment

(b) (4) will be completed (b) (4). The equipment to be used in the (b) (4)

(b) (4) The timeline for PPQ campaigns and availability of PPQ reports is provided in Table 1. At least 3 consecutive PPQ lots per manufacturing facility will be included in the respective DS and DP PPQ campaigns.

**Table 1. Timeline for PPQ Campaigns and Availability of PPQ Reports**

(b) (4)

(b) (4)

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(b) (4)

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(b) (4)

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### 2.1.2. Pfizer Response to Comment 1.a Part b

A Cause and Effect (C&E) risk assessment was performed on all process parameters to evaluate the impact of independent process parameters and their proposed ranges on drug substance (DS) and drug product (DP) quality and process performance. The scoring for the C&E tables was performed based upon (b) (4)

[REDACTED]

(b) (4)

[REDACTED]

Parameters criticality and associated ranges and settings will be reassessed following the completion of additional characterization and process validation studies.

The identified CPPs together with acceptable ranges and targets/set points, as applicable, for each process step will be provided in the BLA submission. For each process step, in-process testing performed during the commercial manufacture of drug substance and drug product will be also defined in the BLA, including specified acceptance criteria/control limits. This information will also be provided in IND amendments as appropriate to support EUA material.

### 2.1.3. Pfizer Response to Comment 1.a Part c

As stated in Section 2.1.2, CPP ranges have been identified and applied to the commercial DS and DP processes based on (b) (4)

[REDACTED] to ensure quality and consistency of the DS and DP.

## 2.2. CBER Comment 1.b

### *Sponsor Question 1.b:*

*Does CBER agree with the proposed analytical validation approach?*

### *FDA Response to Question 1.b:*

*The background information on the validation of analytical tests is insufficient to address this question.*

- a. *We agree with your proposed analytical validation approach for compendial Bioburden, LAL, and sterility methods. Please notify us about any changes to analytical test approaches as part of future regulatory submissions.*

- b. *Regarding non-compendial in-process and release tests for DS and DP, it appears (b) (4). Please note that test methods (i.e., SOPs) and validation protocols and reports will be needed for all in-process and DS and DP release tests. Please provide the following information:*
- i. *As requested in the response to Question 1.a, please provide a timeline of validation for in-process and release quality tests.*
  - ii. *You indicated that testing developed or performed by Pfizer or their contract laboratories for DS and DP commercial release will be initially validated according to ICH Q2, (b) (4). [redacted] will be used for validation.*
  - iii. *You also indicated that if a test is used for in-process and/or final DS or DP characterization, then it will be (b) (4). [redacted] For the characterization tests, please provide the test methods and clarify what qualification information may be available for each test. For the in-process tests, as we recommended above, all tests should be validated.*

*Please see Additional FDA Questions/Comments, regarding the quality test information.*

### **2.2.1. Pfizer Response to Comment 1.b Part a**

The sponsor confirms that any changes to compendial Bioburden, LAL, and sterility methods will be filed as part of future regulatory submissions.

### **2.2.2. Pfizer Response to Comment 1.b Part b (i-ii)**

The sponsor would like to clarify that test methods used for in-process and release tests for DS and DP have been validated according to a standard operating procedure (SOP) protocol and includes an assessment of all required elements of validation as defined in ICH Q2(R1) and 21 CFR § 211.194(a)(2). (b) (4)

[redacted]

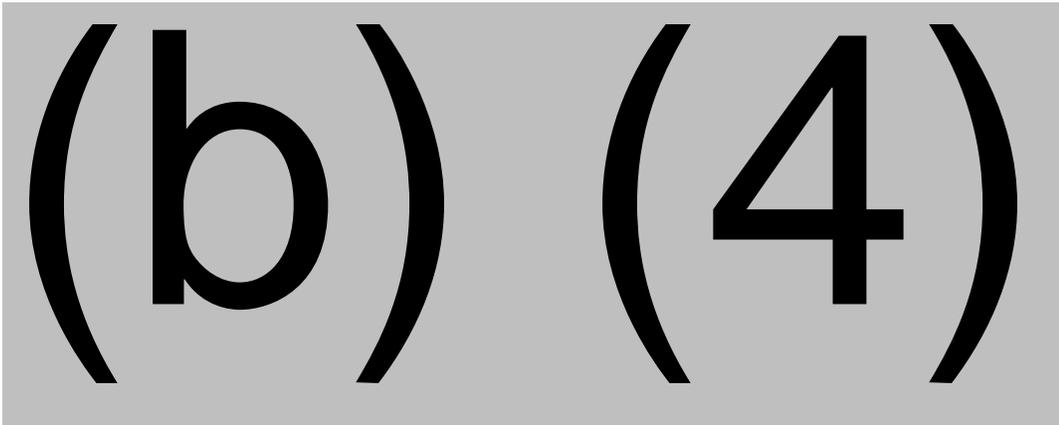
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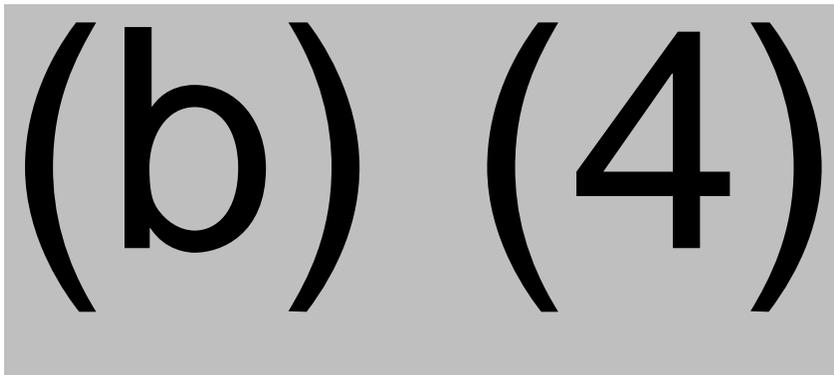


**2.2.3. Pfizer Response to Comment 1.b Part b (iii)**

The sponsor confirms that in-process test methods applied to the routine process control have been validated. Drug substance and drug product characterization methods are intended for non-routine applications, such as comparability studies. The panel of DS characterization assays that could be employed and the corresponding quality attributes include:



The panel of DP characterization assays that could be employed and the corresponding quality attributes include:



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(b) (4)

(b) (4)

For all the analytical methods used, appropriate system and method performance measures were instituted in the testing laboratory.

### 2.3. CBER Comment 1.c

***Sponsor Question 1.c:***

***Does CBER agree with the planned stability and shelf-life strategy?***

***FDA Response to Question 1.c:***

***The background information on the stability plan and strategy is insufficient to address this question. Please provide:***

- a. The analytical tests that will be used in the DS and DP stability plans,***
- b. The container-closure system(s) used for the DS and DP stability studies and a description of how they compare with the containers used for commercial production,***
- c. The lot numbers, manufacturing process (1 or 2) and manufacturing sites of the developmental and clinical lots for which stability data will be provided.***

#### 2.3.1. Pfizer Response to Comment 1.c Part a

The list of analytical tests that are used in the DS and DP stability protocols is provided in [Table 3](#) and [Table 4](#), respectively. These tests were selected based on the potential to be stability indicating. The on-going stability programs monitor quality attributes of development, clinical and the available commercial lots of DS and DP that are representative of the product. The

(b) (4)

(b) (4)

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(b) (4)

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### 2.3.2. Pfizer Response to Comment 1.c Part b



### 2.3.3. Pfizer Response to Comment 1.c Part c

The lot numbers, manufacturing process (1 or 2) and manufacturing sites of the stability lots will be provided in the BLA as well as IND amendments (as appropriate to support EUA material).

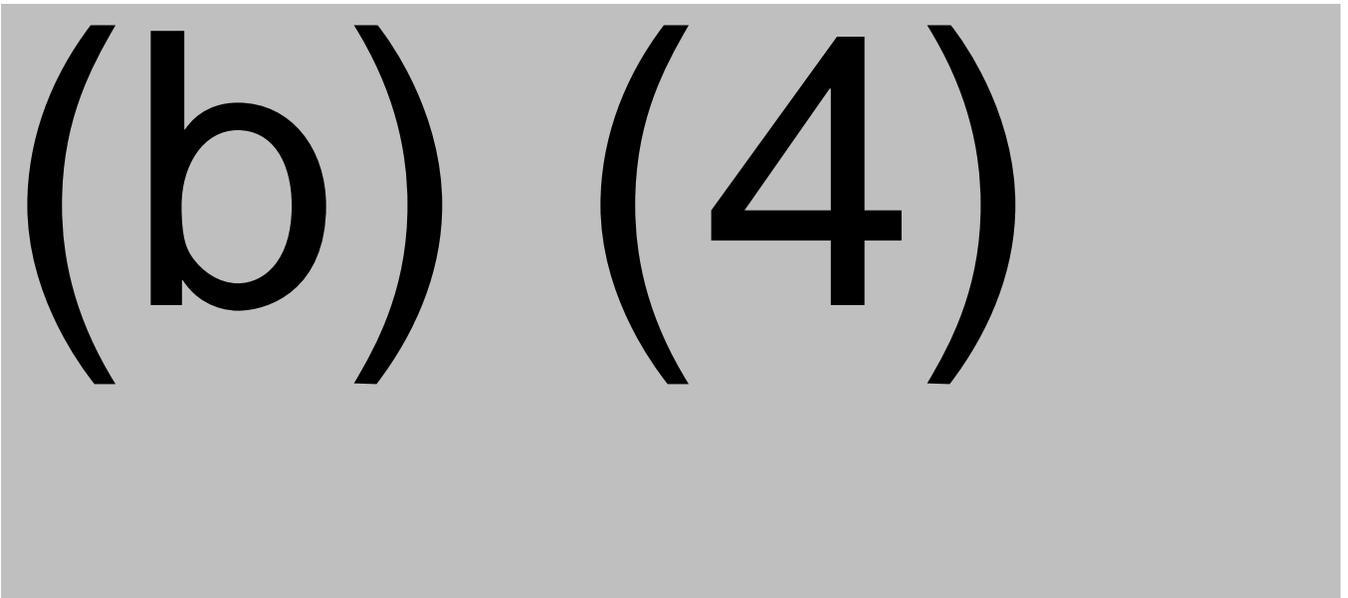
### 2.4. CBER Comment 1.d

*Sponsor Question 1.d:*

*Does CBER agree with the planned approach for the starting materials?*

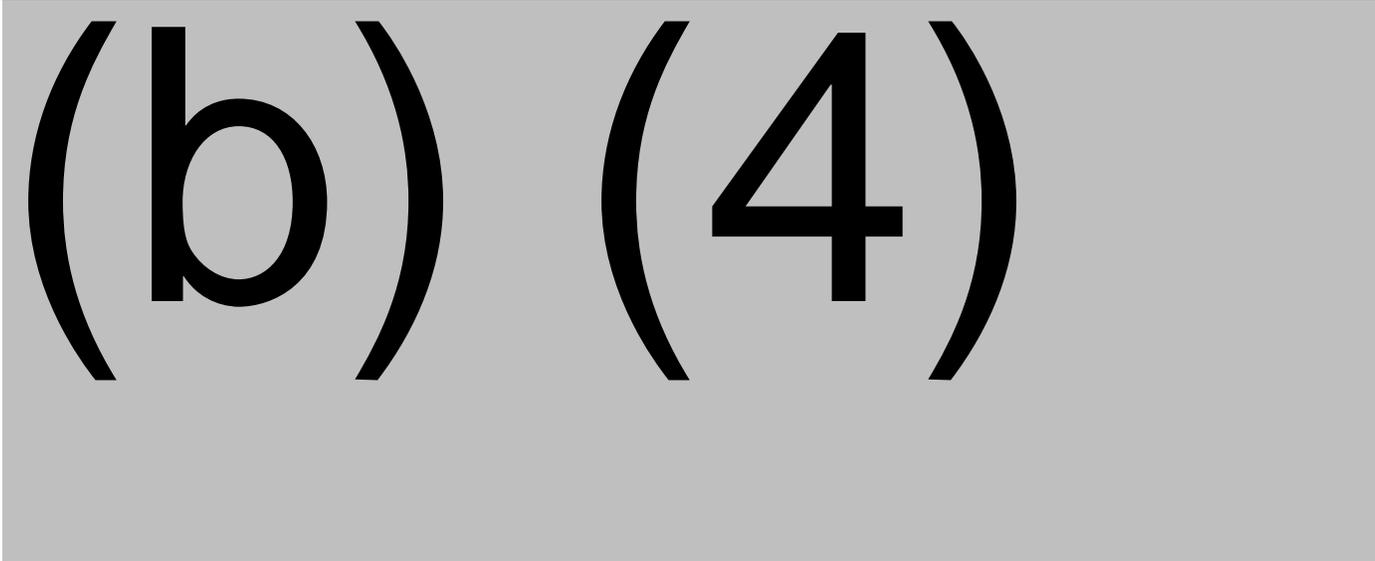
*FDA Response to Question 1.d:*

*For the reference materials, the proposed strategy is acceptable. The background information on other starting materials is insufficient to fully address this question. We have the following recommendations:*



(b) (4)

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(b) (4)

## 2.6. CBER Comment 3

### *Sponsor Question 3:*

*Does CBER agree with the sponsor's plan to provide additional CMC/quality information frequently from continuous improvement and verification as well as results from confirmatory evaluations and studies, i.e., method and process validation, stability, etc., in order to provide additional evidence of batch to batch consistency and product stability?*

### *FDA Response to Question 3:*

- a. Regarding method and process validation, see our response to Question 1.a.*
- b. Regarding submission of results for post-approval verifications, we will provide feedback after we receive the information requested in this communication. Any validation information that will not be submitted in the initial BLA (i.e., submitted during the BLA review cycle or post-licensure) will need to be agreed upon prior to submission of the BLA.*
- c. Regarding post approval stability updates, please submit DS and DP stability data from PPQ lots when studies are completed as a product correspondence.*

### 2.6.1. Pfizer Response to Comment 3

As detailed in [Section 2.2.2](#), analytical procedures are considered validated and the validation data will be provided in the BLA. DS and DP process validation studies have been initiated and the timeline for completion is provided in [Table 1](#). Post-approval stability updates will be provided as product correspondence as suggested.

### 2.7. CBER Comment 4

#### *Sponsor Question 4:*

*Does CBER agree with the sponsor's proposal that the manufacturing process and analytical methods used for Phase 3 supplies are appropriately controlled, qualified and/or verified to ensure quality for initial commercial supply of the vaccine?*

#### *FDA Response to Question 4:*

- a. *The proposed manufacturing process and analytical methods used for Phase 3 supplies are appropriate for use of clinical lots under IND.*
- b. *Regarding manufacturing process controls to support commercial production, please see our response to Question 1.a.*
- c. *Regarding the quality release tests, the proposed DS release specifications and DS characterization of impurities are acceptable.*
- d. *Regarding the DP, please provide:*
  - i. (b) (4)
  - ii. (b) (4)

*Please see our response to Question 1.b. on quality test methods and validation information.*

#### 2.7.1. Pfizer Response to Comment 4 Part a

The sponsor acknowledges FDA's response.

#### 2.7.2. Pfizer Response to Comment 4 Part b

See response in [Section 2.1.1](#).

#### 2.7.3. Pfizer Response to Comment 4 Part c

The sponsor acknowledges FDA's response.

#### 2.7.4. Pfizer Response to Comment 4 Part d (i)

Information on the control of (b) (4) components will be provided in the BLA as well as upcoming amendments to the IND to support EUA.

#### 2.7.5. Pfizer Response to Comment 4 Part d (ii)

The sponsor acknowledges FDA's comment and (b) (4)

#### 2.8. CBER Comment 5

##### *Sponsor Question 5:*

*Does CBER agree with the sponsor's proposal that past inspection history be considered and that any pre-approval inspections be deferred, or should the Agency consider inspections as necessary that they be performed remotely?*

##### *FDA Response to Question 5:*

*We note that for commercial manufacture, (b) (4)*

(b) (4).

- a. *As we indicated in the response to Question 1.d, (b) (4) should be manufactured in a GMP-compliant facility.*
- b. *Please describe the source and quality assurance of raw materials used for (b) (4) (b) (4) manufacture.*

*At this time, we cannot provide a definitive response regarding the performance of pre-license or pre-approval inspections that may be needed in support of your BLA or post approval supplement(s). However, we will use all resources available to assist us in determining if an onsite inspection will be required. Some considerations include requesting inspection reports from other trusted foreign regulatory partners (mutual recognition and confidentiality agreements), requesting records in advance or in lieu of an onsite inspection, and waiving inspections for facilities with acceptable FDA compliance histories. We will perform mission critical pre-license inspections on a case by case basis. Additional facility information was requested via information requests emailed on August 7, 2020 and August 11, 2020.*

*Please also see Additional FDA Questions/Comments, regarding the facilities information.*

#### 2.8.1. Pfizer Response to Comment 5 Part a

Details regarding all manufacturing facilities ((b) (4)) are provided in the meeting Briefing Package submitted on September 2, 2020 (SN0074).

The purpose of the Type C CMC Facilities Meeting, held on September 23, 2020, was to present facilities information and to gain FDA feedback regarding Pfizer/BioNTech’s facilities and equipment information and supporting data package for inclusion in the planned BLA and to support planned EUA.

All facilities will be registered with the FDA at the time of the BLA submission and will be ready for inspection. A complete list of the manufacturing and testing sites with their corresponding FEI numbers will be included in the BLA submission. A preliminary manufacturing schedule for the DS and DP will be provided in the BLA submission and manufacturing facilities will be in operation and manufacturing the product under review during the inspection.

Reference is made to Pfizer/BNT’s IND Submission SN0058 in response to CBER’s comments and requests dated August 7, 2020 and August 10, 2020 providing the following:

- Identification of the production areas/suites to be used for the manufacturing of the LNP’s, DS, DP, and filling operations of the SARS CoV-2 mRNA Vaccine.
- Information on the multi-product status and other products manufactured in these facilities that will be manufacturing SARS COV-2 mRNA vaccine.
- Information on the Regulatory inspection status of the facilities that will be manufacturing SARS COV-2 mRNA vaccine for EUA and commercial use.
- Information on the experience of the manufacturing sites relative to similar processes or manufacturing capabilities that will be manufacturing SARS COV-2 mRNA vaccine.
- Identification of locations to be used for Phase 2/3 supply, Initial EUA, and commercial/EUA supply.

In addition, CBER recommended that a Facilities Type C Meeting be requested. Subsequently, Mr. Paul Rohlfing, Executive Director, Pfizer GCMC, contacted Mr. James Crim on August 10, 2020 regarding scheduling a facilities Type C meeting. Initial advice was that the meeting package should concentrate on anticipated go-forward facilities, however subsequent e-mail from Mr. Crim, on Wednesday August 19, 2020, requested Pfizer to also include all manufacturing facilities that would be used for production under the EUA in the Briefing Document.

### **2.8.2. Pfizer Response to Comment 5 Part b**

A list of the raw materials used in the manufacture of the (b) (4) is provided in Table 14. All the materials used in the (b) (4) are of non-animal origin and sourced from approved suppliers. Visual inspection of materials received and examination of vendor certificate of analysis, are performed for non-compendial materials

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(b) (4)

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(b) (4)

## 2.9. CBER Comment 6

### *Sponsor Question 6:*

*Does CBER agree with the sponsor's plan to demonstrate analytical comparability of the Drug Substance and Drug Product processes from clinical to commercial supply?*

### *FDA Response to Question 6:*

*The background information on the manufacturing changes and comparability approach is insufficient to address this question.*

*a. Regarding your comparability approach, we have the following recommendations:*

- i. Please provide a detailed description of the DS and DP changes implemented for manufacture of clinical lots and changes that will be introduced for commercial manufacture, including assessment of the impact of the changes on the DP quality attributes such as DS and DP impurity profiles* (b) (4) (b) (4)

(b) (4)

(b) (4)

- ii. *Please provide a tabular listing of all clinical studies and DP lot numbers used in each study including DS lot genealogy, (b) (4) and manufacturing site.*
- iii. *Please provide the certificates of analysis (COAs) for all clinical lots used in clinical studies and information on any lots that were not accepted for release.*
- iv. *Please specify which DS and DP lots will be included in the comparability assessments.*

(b) (4)

- b. *Regarding the proposed analytical comparability approach of the DS, LNPs and DP, please distinguish the quality release tests from the supplementary tests.*
- c. *For the DS, we note the comparability approach will include the following DS supplementary characterization tests:*

(b) (4)

- d. *For the DP, we note the comparability approach will include the following supplementary characterization tests:*

(b) (4)

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(b) (4)

### 2.9.1. Pfizer Response to Comment 6 Part a

A detailed description of DS and DP changes and associated release and characterization testing results will be provided in the BLA as well as to the IND on an ongoing basis as new batches are manufactured and introduced for clinical and anticipated EUA purposes. CoAs will also be provided on an ongoing basis.

Comparability of immune responses to support the (b) (4) changes will be performed and data will be provided.

### 2.9.2. Pfizer Response to Comment 6 Part b

The sponsor acknowledges FDA's comment and confirms that the quality release tests will be distinguished from the supplementary tests regarding the proposed analytical comparability approach of the DS, LNPs and DP.

### 2.9.3. Pfizer Response to Comment 6 Part c

The following analytical procedures have been moved to the routine release and/or stability testing panel and are performed for every batch of DS; the results of these tests will be included in the comparability assessments:

(b) (4)

### 2.9.4. Pfizer Response to Comment 6 Part d

The following analytical procedures have been moved to the routine release and/or stability testing panel and are performed for every lot of DP; the results of these tests will be included in the comparability assessments:

(b) (4)

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(b) (4)

(b) (4)

## 2.10. CBER Comment 7

### *Sponsor Question 7:*

*Does CBER agree with the sponsor's plan to use an in vitro protein expression assay to assess potency of the drug product in lieu of an in vivo potency assay?*

### *FDA Response to Question 7:*

*We agree with your plan to use an in vitro expression assay to assess potency of the drug product. In addition, while we appreciate your effort to develop an in vitro potency assay based*

(b) (4)

### 2.10.1. Pfizer Response to Comment 7

The Sponsor acknowledges FDA's guidance on (b) (4)  
(b) (4).

## 2.11. CBER Comment 8

### *Sponsor Question 8:*

*Does CBER agree with the Sponsor's proposal for lot release process to expedite commercial release of drug product lots?*

### *FDA Response to Question 8:*

*Vaccine lots to be distributed in the U.S. after licensure will need to be manufactured using the qualified processes, sites and equipment and be released according to the validated analytical methods described in the BLA.*

***Regarding CBER’s lot-release procedures, we commit to a rapid review of lot-release protocols for vaccine lots to be distributed in the U.S.***

### **2.11.1. Pfizer Response to Comment 8**

The sponsor acknowledges FDA’s response and acknowledges FDA’s August 25, 2020 email communication to Ms. Donna Boyce regarding official lot release for products used under EUA. This communication stated “Title 21 Code of Federal Regulations section 610.2 outlines the requirements for official lot release. These requirements apply to *Licensed Biological Products*. The requirements **do not apply** to products used under an **Emergency Use Authorization**.”

### **2.12. CBER EUA-related Comment 1**

***Emergency Use Authorization (EUA)***

***EUA-related Sponsor Question 1:***

***An Emergency Use Authorization request package is currently planned for submission in parallel with the initial BLA. The Sponsor has initiated manufacturing activities to enable vaccine supply as early as October 2020 and potentially prior to Biologics License Application approval (see section 6). Does CBER agree that Pfizer can continue to provide CMC amendments to the BB IND 19736 to support release of vaccine for supply under an Emergency Use Authorization, should one be granted for the candidate vaccine prior to BLA approval?***

***FDA Response to EUA-related Question 1:***

***We will provide recommendations regarding the information needed to support vaccine distribution under Emergency Use Authorization in a separate communication.***

#### **2.12.1. Pfizer Response to EUA-related Comment 1**

The sponsor acknowledges FDA’s response.

### **3. ADDITIONAL FDA QUESTIONS/COMMENTS:**

***We are providing additional product quality and microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your <351(a)> BLA submission:***

#### **3.1. CBER Additional Comment 1**

***All facilities should be registered with the FDA at the time of the <351(a)> BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the DS and DP should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.***

### 3.1.1. Pfizer Response to Additional Comment 1

All facilities will be registered with the FDA at the time of the BLA submission and will be ready for inspection. A complete list of the manufacturing and testing sites with their corresponding FEI numbers will be included in the BLA submission. A preliminary manufacturing schedule for the DS and DP will be provided in the BLA submission and manufacturing facilities will be in operation and manufacturing the product under review during the inspection.

Reference is made to Pfizer/BNT's IND Submission SN0058 in response to CBER's comments and requests dated August 7, 2020 and August 10, 2020 providing the following:

- Identification of the production areas/suites to be used for the manufacturing of the LNP's, DS, DP, and filling operations of the SARS CoV-2 mRNA Vaccine.
- Information on the multi-product status and other products manufactured in these facilities that will be manufacturing SARS COV-2 mRNA vaccine.
- Information on the Regulatory inspection status of the facilities that will be manufacturing SARS COV-2 mRNA vaccine for EUA and commercial use.
- Information on the experience of the manufacturing sites relative to similar processes or manufacturing capabilities that will be manufacturing SARS COV-2 mRNA vaccine.
- Identification of locations to be used for Phase 2/3 supply, Initial EUA, and commercial/EUA supply.

In addition, CBER recommended that a Facilities Type C Meeting be requested. Subsequently, Mr. Paul Rohlfing, Executive Director, Pfizer GCMC, contacted Mr. James Crim on August 10, 2020 regarding scheduling a facilities Type C meeting. Initial advice was that the meeting package should concentrate on anticipated go-forward facilities, however subsequent e-mail from Mr. Crim, on Wednesday August 19, 2020, requested Pfizer to also include all manufacturing facilities that would be used for production under the EUA in the Briefing Document.

Details regarding all manufacturing facilities are provided in the meeting Briefing Package submitted on September 2, 2020 (SN0074).

The purpose of the Type C CMC Facilities Meeting, held on September 23, 2020, was to present facilities information and to gain FDA feedback regarding Pfizer/BioNTech's facilities and equipment information and supporting data package for inclusion in the planned BLA and to support planned EUA.

### 3.2. CBER Additional Comment 2

***Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.***

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***The CMC Drug Substance section of the <351(a)> BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:***

- a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).***
- b. Bioburden and endotoxin data obtained during manufacture of the process qualification (PPQ) lots when available (3.2.S.2.5).***
- c. If there are any holds for more than 24 hours, then microbial data from three successful product intermediate hold time validation runs at manufacturing scale should be provided. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).***
- d. Information and summary results from the shipping validation studies. Please indicate the placement of your temperature monitors for routine shipping, and rationale, as necessary, to explain leveraging validated shipping configurations as approved for other products. (3.2.S.2.5).***
- e. Drug substance bioburden and endotoxin release specifications (3.2.S.4).***

### **3.2.1. Pfizer Response to Additional Comment 2**

The sponsor acknowledges FDA’s comments, and these will be addressed in the BLA as suggested. Also, additional information, as requested to support EUA, will be provided in upcoming amendments to the IND.

### **3.3. CBER Additional Comment 3**

***The CMC Drug Product section of the <351(a)> BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry “Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.***

### **3.3.1. Pfizer Response to Additional Comment 3**

The sponsor acknowledges FDA’s comments, and these will be addressed in the BLA as suggested.

### 3.4. CBER Additional Comment 4

*The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.*

- a. Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.*
- b. Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.*
- c. Parameters for filling and capping for the vials.*
- d. A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.*
- e. Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.*
- f. Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. For final sterile filtration of drug product, pre-sterile filtration bioburden limits typically do not exceed 10 CFU/100 mL.*

#### 3.4.1. Pfizer Response to Additional Comment 4

The sponsor acknowledges FDA's comments, and these will be addressed in the BLA as suggested. Also, additional information, as requested to support EUA, will be provided in upcoming amendments to the IND.

### 3.5. CBER Additional Comment 5

*The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:*

- a. Bacterial filter retention study for the final sterilizing filter. Please include a comparison of validation test parameters with routine sterile filtration parameters.*
- b. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Please provide summary data for the three validation studies and describe the equipment and component revalidation program.*

- c. In-process microbial controls and hold times over 24 hours. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*
- d. Isolator decontamination summary data and information, if applicable.*
- e. Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Please describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.*
- f. Information and summary results from shipping validation studies. Please indicate the placement of your temperature monitors for routine shipping, and rationale, as necessary, to explain leveraging validated shipping configurations as approved for other products.*
- g. Validation of capping parameters, using a container closure integrity test.*

### **3.5.1. Pfizer Response to Additional Comment 5**

The sponsor acknowledges FDA's comments, and these will be addressed in the BLA as suggested. Also, additional information, as requested to support EUA, will be provided in upcoming amendments to the IND.

### **3.6. CBER Additional Comment 6**

*The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:*

- a. Regarding container closure:*
  - i. Container closure integrity testing should be demonstrated initially and during stability assessment. Container closure integrity must be maintained through stability conditions (-70°C). Developmental studies may be submitted to support that container closure integrity may be maintained at stability conditions if stability data are not available. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress ( $\leq 20$  microns). It is recommended to perform container closure integrity testing in lieu of sterility whenever sterility assurance is assessed throughout your stability program.*
  - ii. For the multi-dose vial, please provide results of testing per USP<381> Elastomeric Closures for Injections and ISO 8871-5, i.e., fragmentation (coring), penetrability (piercing force by hypodermic needle), self-sealing capacity (container closure*

*integrity testing after multiple punctures), etc. to demonstrate suitability of your container closure system.*

- b. For microbiological studies in support of the post-dilution storage conditions, including multiple breaches of the container closure to simulate multiple dosing, please describe the test methods and results that employ a minimum countable inoculum (10-100 CFU in the product) to simulate potential microbial contamination that may occur during dilution or with multiple dosing. The test should be run at the label's recommended storage conditions with drug product, be conducted for the recommended storage period, include the maximum number of needle pierces, and use the label-recommended diluents. Challenge organisms may include strains described in USP <51> Antimicrobial Effectiveness Testing, plus typical skin flora or species associated with hospital-borne infections.**

### 3.6.1. Pfizer Response to Additional Comment 6

The sponsor acknowledges FDA's comments, and these will be addressed in the BLA as suggested. Additional clarification is provided below on specific items.

#### 3.6.1.1. Pfizer Response to Additional Question 6.a(ii)

Regarding multiple penetrations of the stopper, the stoppers meet USP <381>, ISO 8871-5 and Ph. Eur. 3.2.9 requirements for function tests of penetrability, fragmentation, and self-sealing capacity. Testing has been performed and results demonstrating compliance are shown in Table 15.

**Table 15. Functional Testing**

A large grey rectangular area redacting the content of Table 15. The redaction consists of two large, bold, black characters: a lowercase 'b' enclosed in parentheses on the left, and the number '4' enclosed in parentheses on the right.

### 3.6.2. Pfizer Response to Additional Question 6.b

Results of microbiological studies in support of the post-dilution storage conditions were provided in IND amendment SN0080 submitted on September 4, 2020. The studies were

(b) (4)

*We have the following comments regarding physicochemical release assays and validation:*

#### 3.7. CBER Additional Comment 7

(b) (4)

*identity, specificity and sensitivity of the methods should be assessed and validated for BLA submission.*

#### 3.7.1. Pfizer Response to Additional Comment 7

The sponsor acknowledges FDA's comments and these will be addressed in the BLA as suggested and in upcoming amendments to the IND to support EUA.

#### 3.8. CBER Additional Comment 8

(b) (4)

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(b) (4)

### 3.8.1. Pfizer Response to Additional Comment 8

(b) (4)

### 3.9. CBER Additional Comment 9

*We acknowledge that* (b) (4)

*Please note that* (b) (4)  
*quality in-process or release tests will require method validation assessments.*

### 3.9.1. Pfizer Response to Additional Comment 9

The sponsor acknowledges FDA's comments and these will be addressed in the BLA and in upcoming amendments to the IND to support EUA as suggested.

*We have the following comments regarding the excipients used in the manufacture of the LNP/DP:*

### 3.10. CBER Additional Comment 10

*Please note that the approach described in FDA Response 1.d.ii to Question 1.d to submit detailed CMC information in your IND would simplify the submission of information necessary for completing Module 3 of a future BLA (along with the additional information and data necessary for licensure), since your BLA should be self-contained with regard to the chemistry, manufacturing and control information necessary for your product.*

### 3.10.1. Pfizer Response to Additional Comment 10

The sponsor acknowledges FDA's comments. Information regarding the lipids will be addressed in the BLA in alignment with CBER's Additional Comment 11 regarding ALC-0159 and ALC-0315 and additional Comment 12 regarding DSPC and cholesterol.

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### 3.11. CBER Additional Comment 11

(b) (4)

#### 3.11.1. Pfizer Response to Additional Comment 11

The sponsor acknowledges FDA's comments and these will be addressed in the BLA as suggested. (b) (4)

### 3.12. CBER Additional Comment 12

*For the non-novel DSPC and cholesterol excipients, you may submit to the BLA non-proprietary CMC information as well as the COAs for the lot(s) that you have used/plan to use in the formulation of LNP/DP as well as a listing of the control tests (and acceptance criteria) that are performed on the excipients once received at your facility prior to its use in the manufacture of the LNP/DP. In addition, you should provide in the BLA a cross-reference to a Master File for the facilities information for the DSPC and cholesterol excipients.*

#### 3.12.1. Pfizer Response to Additional Comment 12

The sponsor acknowledges FDA's comments and these will be addressed in the BLA as suggested. (b) (4)

### 3.13. CBER Additional Comment 13

(b) (4)

#### 3.13.1. Pfizer Response to Additional Comment 13

The sponsor acknowledges FDA's comments (b) (4) components will be controlled, evaluated, and reported according to our change control process.

## 4. CBER CLARIFICATION COMMENTS PROVIDED SEPTEMBER 18, 2020

### 4.1. CBER Comment 1.d.d.ii sent on August 14, 2020:

(b) (4)

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(b) (4)

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(b) (4)

**4.2.1. Pfizer Response to CBER Clarification Comments Provided September 18, 2020**

(b) (4)

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## **5. APPENDICES**

None

## **6. REFERENCES**

None

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**Request for Comments and Advice**

**SUFFICIENCY OF THE COVID-19 VACCINE (PF-07302048) NONCLINICAL  
PACKAGE TO SUPPORT THE BLA**

**JULY 2020**

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## 1. INTRODUCTION

The purpose of this communication is to obtain FDA feedback and approval on sufficiency of the planned nonclinical absorption, disposition, metabolism, and excretion (ADME) and toxicology packages and timing of study data submissions to support the BLA for the COVID-19 Vaccine (BNT162, PF-07302048).

### Nonclinical ADME

The lipid nanoparticles (LNP) in the COVID-19 vaccine are comprised of four lipids: 1) ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary ionizable aminolipid, 2) ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary PEG-lipid, 3) DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), and 4) cholesterol. ALC-0315 is the major lipid component in the BNT162 vaccines and is included in the LNP to confer distinct physicochemical properties that regulate particle formation, cellular uptake and endosomal release of the mRNA. ALC-0159 (PEG-lipid) stabilizes the particles, facilitating homogeneous particle sizes, and when administered, provides a transient steric barrier to minimize interactions with plasma proteins. DSPC and cholesterol are naturally-occurring lipids, present in mammalian cell membranes, and are included in the LNP as structural lipids.

Of the four lipids that form the LNP in the COVID-19 vaccine candidates, two are novel excipients (ALC-0315 [aminolipid] and ALC-0159 [PEG-lipid]). These lipid excipients have no known pharmacology and are integrated components of the drug product. As such, these excipients have been tested in toxicology studies (Table 1), wherein they are tolerated, and at the time of filing, clinical safety of these excipients will have been established as part of the phase 3 study. In addition, the overall clinical dose of these excipients is low and dose frequency is anticipated to be infrequent.

Preliminary *in vitro* metabolic evaluation of these novel excipients has demonstrated that the molecules appear to be poorly metabolized in liver microsomes and S9 in mouse, rat, monkey, and human.

Given the urgency with which this vaccine is being developed, the Applicant is committed to conducting the following studies and will provide updates and final reports during the BLA review process or shortly after its completion. Preliminary data could be available at the time of filing if requested.

- *In vitro* metabolism of ALC-0315 and ALC-0159 in S9, microsomes and hepatocytes in mouse, rat, monkey and human.
- A rat distribution study of the mRNA-containing lipid nanoparticles administered intramuscularly at a toxicologically relevant dose, using a non-diffusible, non-metabolizable radiolabeled lipid marker incorporated into the LNP to identify key organs into which the LNP distribute.

- Efforts will be made to identify key routes of metabolism / clearance of ALC-0315 and ALC-0159 in *in vitro* systems in which turnover is observed, or in *in vivo* animal experiments, including pharmacokinetic parameters, as available, for each novel excipient.

Given the low clinical dose and limited evidence of toxicological findings (as described below in the Nonclinical Toxicology section), the Sponsor believes that the above ADME package and the timing of the available data is sufficient to support the nonclinical package at filing.

### **Question for CBER**

*Pfizer is planning to conduct in vitro and in vivo studies to collect data on microsomal stability, metabolism, distribution and clearance of the two novel excipients and/or the lipid nanoparticles (LNP) of BNT162 vaccines. Does the FDA agree that this ADME information is sufficient to support the nonclinical package required for the BLA?*

### Nonclinical Toxicology

Several potential COVID-19 vaccine candidates have been evaluated in toxicity studies and/or in the clinic. At this time, only BNT162b2 (V9) is being considered for further development.

The toxicity studies supporting the BNT162b2 (V9) vaccine candidate in the planned BLA are listed in the table below. At the time of the BLA submission, the two ongoing studies (DART and repeat-dose toxicity study) will not have been completed. The Applicant previously proposed to submit the final DART study report during the BLA review period and this was agreed upon by the FDA. However, the timing of data submission and final reports for the ongoing repeat-dose toxicity study are discussed below. The ongoing repeat-dose toxicity is evaluating BNT162b2 (V9) among other COVID-19 vaccine candidates.

**Table 1. Overview of Toxicity Testing Program**

Study <sup>a</sup>	Study (Sponsor) No.	Dos Group/ Dose level	Total Volume (μL) <sup>b</sup>	No. of Animals/ Group	Study Status
<b>Repeat-Dose Toxicity</b>					
17-Day, 2 or 3 Dose (1 Dose/Week) <sup>c</sup> IM Toxicity in Rats With a 3-Week Recovery Period in Rats	38166	Control <sup>d</sup> , 0 μg	200 <sup>e</sup>	15/sex	Complete
		BNT162a1, 30 μg	60	15/sex	
		BNT162a1, 10 μg	20	15/sex	
		BNT162b1, 30 μg	60	15/sex	
		BNT162b1, 100 μg	200 <sup>e</sup>	15/sex	
		BNT162c1, 30 μg	70	15/sex	
17-Day, 3 Dose (1 Dose/Week) Toxicity With a 3 Week Recovery Period in Rats	20GR142	Saline <sup>f</sup> , 0 μg	60	15/sex	Ongoing
		BNT162b2 [V9] <sup>g</sup> , 30 μg	60	15/sex	
		BNT162b3, 30 μg	60	15/sex	
<b>Reproductive &amp; Developmental Toxicity</b>					
IM Combined Fertility and Developmental (Including Teratogenicity and Postnatal Investigations) in Rats	20256434 (RN9391 R58)	Saline <sup>f</sup> , 0 μg	60	44 F	Ongoing
		BNT162b1, 30 μg	60	44 F	
		BNT162b2 [V9], 30 μg	60	44 F	
		BNT162b3, 30 μg	60	44 F	

a. All studies are GLP-compliant and were conducted in an OECD mutual acceptance of data-compliant member state.

b. Doses were administered as 1 application at 1 site unless otherwise indicated.

c. QW x 3 (Days 1, 8, 15) for BNT162a1, BNT162b1, and BNT162b2 (V8); QW x 2 (Days 1, 8) for BNT162c1.

d. Phosphate buffered saline, 300 mM sucrose.

e. One application (100 μL) at 2 sites for a total dose volume of 200 μL.

f. Sterile saline (0.9% NaCl).

g. BNT162b2 (V8) and BNT162b2 (V9) both encode the spike protein antigen with two stabilizing amino acids in the stalk and have the same amino acid sequence. Different codon optimizations were used for their coding sequences, with the V9 variant having a higher Guanine-Cytosine content.

In the completed repeat-dose toxicity study (38166) in Wistar Han rats, administration of the vaccine candidates BNT162a1, BNT162b1, BNT162b2 (V8), or BNT162c1 using intramuscular (IM) injections was tolerated without evidence of systemic toxicity. Non-adverse inflammatory changes at the injection sites and the draining lymph nodes, increased hematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites were observed. The final study

report for the first repeat-dose toxicity study (38166) was submitted to the IND on 13 July 2020.

For the ongoing repeat-dose toxicity study (20GR142), the Applicant proposes to submit a dosing phase interim data set that will include all dosing phase in-life data, clinical pathology data, and organ weights and macroscopic observations from the terminal scheduled necropsy. The dosing phase interim data set and remaining study data from the dosing phase, which includes microscopic observations and serology, will be collected in an interim report and can be provided to the FDA when available. All data pertaining to the recovery phase will be submitted to the FDA as a final study report during the BLA review period. The BNT162b2 (V9) vaccine candidate being evaluated in this second repeat-dose toxicity study encodes the same antigen as the BNT162b2 (V8) candidate evaluated in the first repeat-dose toxicity study (38166), differing only in the ribonucleic acid content to support codon optimization of the modRNA. Therefore, we do not anticipate any new findings with the BNT162b2 (V9) vaccine candidate in the ongoing repeat-dose toxicity study.

Upon completion of the second repeat-dose toxicity study, along with the completed first repeat-dose toxicity study, COVID vaccine candidates BNT162a1, BNT162b1, BNT162b2 (V8), BNT162b2 (V9), BNT162b3 and BNT162c1 will have been assessed for potential toxicity in rats. Since the BNT162b2 (V9) vaccine candidate will be the final candidate in the BLA, no additional repeat-dose toxicity studies are planned. Following the completion of the DART study (Study 20256434), vaccine candidates BNT162b1, BNT162b2 (V9), and BNT162b3 will have been evaluated for developmental and reproductive toxicity in rats. As BNT162b2 (V9) will be the final candidate in the BLA and based on FDA feedback on the acceptable study design, no additional DART or juvenile toxicity studies are planned.

#### **Question for CBER**

*Does the FDA agree that the proposed nonclinical package is adequate to support licensure of BNT162b2 (V9) vaccine candidate without further toxicity studies? Specifically, the two repeat dose toxicity studies in rats and a developmental and reproductive toxicity in rats.*

#### **Question for CBER**

*Does the FDA agree that the proposed nonclinical study submission timeline is acceptable? Specifically, submission of a dosing phase interim dataset for the second repeat dose toxicity study at time of filing with the full study report being submitted during the BLA review period.*

---

**From:** Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>  
**Sent:** Friday, August 14, 2020 5:55 PM  
**To:** Harkins Tull, Elisa  
**Cc:** Devlin, Carmel M  
**Subject:** [EXTERNAL] Comments regarding IND 19736.45 submission (Request for advice ♦C sufficiency of nonclinical package for BLA)

Dear Ms. Harkins,

We refer to your Investigational New Drug Application (IND) received on April 22, 2020, for “Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol),” for the prevention of COVID-19 in adults  $\geq 18$  years of age, which included the protocol for your initial phase 1/2 clinical trial (C4591001), titled “*A Phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding study to describe the safety, tolerability, immunogenicity, and potential efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy adults.*”

We also refer to amendment 45 to your IND received on July 27, 2020, which included your request for comments and advice seeking CBER feedback and approval on sufficiency of the planned nonclinical absorption, disposition, metabolism, and excretion (ADME) and toxicology packages and timing of study data submissions to support the BLA for the COVID-19 Vaccine (BNT162, PF-07302048).

We have the following comments and requests for additional information:

**Sponsor Question 1:**

Pfizer is planning to conduct in vitro and in vivo studies to collect data on microsomal stability, metabolism, distribution and clearance of the two novel excipients and/or the lipid nanoparticles (LNP) of BNT162 vaccines. Does the FDA agree that this ADME information is sufficient to support the nonclinical package required for the BLA?

**FDA Response to Sponsor Question 1:**

We agree that the proposed ADME information is sufficient to support the nonclinical package required for the BLA.

**Sponsor Question 2:**

Does the FDA agree that the proposed nonclinical package is adequate to support licensure of BNT162b2 (V9) vaccine candidate without further toxicity studies? Specifically, the two repeat dose toxicity studies in rats and a developmental and reproductive toxicity in rats.

**FDA Response to Sponsor Question 2:**

We agree that the proposed nonclinical package is adequate to support licensure of BNT162b2 (V9) vaccine candidate without further toxicity studies.

**Sponsor Question 3:**

Does the FDA agree that the proposed nonclinical study submission timeline is acceptable? Specifically, submission of a dosing phase interim dataset for the second repeat dose toxicity study at time of filing with the full study report being submitted during the BLA review period.

**FDA Response to Sponsor Question 3:**

Your proposed timeline to submit a dosing phase interim dataset for the second repeat dose toxicity study at time of filing with the full study report being submitted during the BLA review period, is acceptable. However, to provide CBER adequate time for review, please submit the study reports for the second repeat toxicity study and the developmental and reproductive toxicity study as soon as they are ready.

In your response to this communication, we recommend that you submit an amendment to your IND in which you restate each item from the above list 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.

Please confirm receipt of this message and let me know if you have any questions or need additional information.

Regards,  
Ram

**Ramachandra S. Naik, Ph.D.**

*Chemist (Regulatory) / Primary Reviewer*  
Center for Biologics Evaluation and Research  
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(b) (4)



**COVID-19 VACCINE (BNT162, PF-07302048)**  
**REQUEST FOR COMMENTS AND ADVICE**  
**SEPTEMBER 2020**

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## ABBREVIATIONS

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
BLA	Biologics License Application
CBER	(US Food and Drug Administration) Center for Biologics Evaluation and Research
CMC	chemistry, manufacturing, and controls
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
DMC	Data Monitoring Committee
FDA	(US) Food and Drug Administration
FIH	first-in-human
GMP	Good Manufacturing Practice
IM	intramuscular(ly)
IMP	investigational medicinal product
IND	Investigational New Drug
IgG	Immunoglobulin G
iPSP	initial Pediatric Study Plan
LNP	lipid nanoparticle
MDV	multi-dose vial
modRNA	nucleoside-modified RNA
NAAT	nucleic acid amplification test
RBD	receptor binding domain
RNA-LNP	RNA lipid nanoparticle
RTOR	Real Time Oncology Review
SAE	serious adverse event
saRNA	self-amplifying RNA
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
S glycoprotein	spike glycoprotein
SPL	Structured Product Labeling
uRNA	nonmodified uridine-containing RNA
US	United States
USP	United States Pharmacopeia
USPI	United States Prescribing Information
US-PVP	United States Pharmacovigilance Plan
VAED	vaccine-induced enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VCRD	Vaccine Clinical Research and Development
VE	vaccine efficacy
WHO	World Health Organization

## 1. EXECUTIVE SUMMARY

Pfizer and BioNTech are developing an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus SARS-CoV-2. The vaccine is based on SARS CoV-2 spike glycoprotein (S) antigen encoded in RNA and formulated in lipid nanoparticles (LNPs).

The Investigational New Drug (IND) application was effective on 29 April 2020 and Pfizer initiated a United States (US) clinical study (Module 5.3.5.1 C4591001) on 04 May 2020.

The Phase 2/3 part of the study commenced on 27 July 2020 and is designed to evaluate the safety, efficacy and immunogenicity of BNT162b2 in participants  $\geq 16$  years of age. Phase 2/3 is currently being conducted in the US, Brazil, Argentina, and South Africa, with sites to be added in Germany and Turkey in the near future. A total of  $\sim 44,000$  participants,  $\geq 16$  years of age, randomized in a 1:1 ratio with placebo are planned to be enrolled.

Study C4591001 includes four planned Interim Analyses (to be conducted at accrual of 32, 62, 92, and 120 confirmed COVID-19 cases) and targets 164 cases in total at the Final Analysis. Based on anticipated enrollment rates and disease incidence of 0.9% per month in the placebo group, demonstration of the primary and key secondary study endpoints for safety and efficacy is anticipated by the end of November or mid December 2020. The projected timing of the event-driven planned Interim Analyses, Final Analysis, and the availability of safety data are shown in [Table 1](#).

Pfizer/BioNTech plan to seek US licensure of the candidate vaccine via Traditional Approval based on demonstration of an acceptable safety profile and clinical endpoint efficacy in Study C4591001. The initial proposed indication is “active immunization against COVID-19 disease caused by SARS-CoV-2 virus in participants  $\geq 16$  years of age.”

The purpose of this submission is to obtain the Agency’s feedback on questions related to the proposed contents, format and timing of the planned rolling BLA components regarding nonclinical, clinical, safety, and pharmacovigilance. Please note that the proposed content and format of the quality and facility BLA modules will be discussed separately. Center for Biologics Evaluation and Research (CBER) feedback on these questions is respectfully requested by 25 September 2020.

## 2. INTRODUCTION

### 2.1. Clinical Development

BioNTech is conducting a first-in-human (FIH), dose level-finding, Phase 1/2 study (BNT162-01) in Germany to gather safety and immunogenicity data for multiple vaccine candidates, to inform the overall clinical development of a COVID-19 Vaccine. This study is not being conducted under the IND but is being conducted under an approved German Clinical Trial Application. Preliminary results from this study are intended to be supportive of the global licensure of the candidate vaccine BNT162b2.

Pfizer and BioNTech are conducting an ongoing Phase 1/2/3 clinical study (C4591001) under the IND. The Phase 2/3 portion of the study evaluates the safety, immunogenicity and efficacy of BNT162b2.

- Phase 1 was conducted in the US and designed for candidate and dose level evaluation in younger and older adult age groups (18 to 55 years of age and 65 to 85 years of age). Based on review of safety and immunogenicity data from the Phase 1 part of the study, the final vaccine candidate BNT162b2 at the 30 µg dose level was selected and proceeded into Phase 2/3 on 27 July 2020. Phase 2/3 is intended to support licensure in the US and globally.
- Phase 2 was conducted in the US and designed to confirm the safety and immunogenicity of the first 360 participants enrolled in the Phase 2/3 study.
- Phase 2/3 is designed to enroll up to ~44,000 participants globally for an adequately powered efficacy assessment in addition to safety and exploratory immunogenicity assessments. Interim analysis dates are based upon projections of COVID-19 attack rates and successful enrollment of the study according to recruitment plan.

#### **2.1.1. First-in-Human Phase 1/2 Study BNT162-01**

German Study BNT162-01 is the FIH, Phase 1/2 dose level-finding study, in which all participants are 18 to 55 years of age and receive active vaccine with different vaccine candidates and dose levels defined in Section 5. This study is ongoing and has been amended to include older participants 55 to 85 years of age.

Dosing in this study with candidates other than BNT162b1 and BNT162b2, for example, BNT162a1 (uRNA) and BNT162c2 (saRNA), will not be discussed herein as it is not relevant to our final vaccine candidate BNT162b2.

#### **2.1.2. Registration Phase 1/2/3 Study C4591001**

Study C4591001 is a randomized and placebo-controlled study, in which participants in the Phase 1 part were randomized 4:1 to receive active vaccine (at each dose level and within each age group) or placebo.

Based on Pfizer/BioNTech and CBER review of Phase 1 safety and immunogenicity data in younger adults (age 18 to 55 years of age) and older adults (65 to 85 years of age) for US study vaccine candidates and dose levels defined in [Section 5](#), BNT162b2 at the 30 µg dose level was selected as the final vaccine candidate.

The Phase 2/3 part of the study is ongoing and enrolling adults  $\geq 16$  years of age 1:1 to receive active vaccine or placebo.

On 9 September 2020 (SN 0081 a C4591001 Protocol Amendment 6, was submitted. This amendment reduces the minimum age for participants to from 18 years to 16 years, it also increased the study size from ~33,000 to ~ 44,000.

As shown in Table 1, four Interim Analyses are planned to assess vaccine efficacy (VE) and futility (at each of the first three Interim Analyses). The first successful Interim Analysis would include the first primary efficacy endpoint only and supporting safety data. Subsequent Interim Analyses for efficacy would be descriptive in nature and would not impact the overall Type 1 error for the study. The next formal analysis would be the Final Analysis where the second primary endpoint and all the secondary endpoints would be evaluated.

Interim Analyses include participants  $\geq 16$  years of age. For efficacy analyses, participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of prior SARS-CoV-2 infection will be included. No serological evidence of prior SARS-CoV-2 infection (a sero-negative participant) is defined by an N-binding IgG level below the lower limit of quantitation in a serum sample drawn at Visit 1. No virological evidence of prior SARS-CoV-2 infection is defined by SARS-CoV-2 not detected by nucleic acid amplification test (NAAT) (nasal swab) at Visits 1 and 2.

Table 1. Interim Analysis and Final Analysis Timing and Data Availability

<b>Interim Analysis<sup>a</sup></b>	<b>Potential Efficacy Data Availability</b>	<b>Safety Data Availability for the Analysis<sup>b</sup></b>
#1 3 <sup>rd</sup> week of Oct 2020	32 COVID-19 cases; sero-negative participants only	Safety data through 1 month post-dose 2 from the first 6000 participants enrolled  All available safety data collected for participants enrolled
#2 Early Nov 2020	62 COVID-19 cases; sero-negative participants only	Updated safety data through 1 month post-dose 2 from the first 6000 participants enrolled  All available safety data collected for participants enrolled
#3 Mid Nov 2020	92 COVID-19 cases; sero-negative participants only	Updated safety data through 1 month post-dose 2 from the first 6000 participants enrolled  All available safety data collected for participants enrolled  Safety data 3 months post-dose 2 for the BNT162b2 construct from Phase 1 and safety data 4 months post-dose 2 for the BNT162b1 construct for individuals $\leq 55$ years of age.

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Table 1. Interim Analysis and Final Analysis Timing and Data Availability

Interim Analysis <sup>a</sup>	Potential Efficacy Data Availability	Safety Data Availability for the Analysis <sup>b</sup>
#4  Late Nov 2020	120 COVID-19 cases;  sero-negative participants only	Updated safety data through 2 months post-dose 2 from the first 6000 participants enrolled  All available safety data collected for participants enrolled  Safety data for BNT162b1 and BNT162b2 constructs from Phase 1 for individuals ≤ 55 years of age.
Final Analysis  End Nov/Mid Dec 2020	164 COVID-19 cases;  sero-negative and sero-positive participants	Updated safety data through 2 months post-dose 2 from the first 6000 participants enrolled  All available safety data collected for participants enrolled  Safety data for BNT162b1 and BNT162b2 constructs from Phase 1 for individuals ≤ 55 years of age.

a. Interim analysis timing is event-driven; represents projected timing.

b. Safety data presented in the table show the latest amount of safety data; the interim analysis package will contain earlier phases of safety data

### 2.1.3. Summary of Clinical Data Submitted Previously in Support of Final Candidate Selection

Clinical Information Amendment (SN 0020) submitted on 23 June 2020 provided an update on the available safety and tolerability profile of BNT162b1 in addition to available immunogenicity data including T cell responses. The safety and tolerability data, as well as the RBD-binding IgG and SARS-CoV-2 neutralization data, were from US Study C4591001; the T cell data were from German Study BNT162-01.

Clinical Information Amendment (SN 0027) submitted on 8 July 2020 provided RBD-binding IgG concentrations and SARS-CoV-2 neutralization titers elicited by BNT162b1 in participants 18 to 55 years of age through 7 days after Dose 2 at the 10, 30 and 50 µg dose levels from the German Study BNT162-01; RBD-binding IgG concentrations elicited by BNT162b1 in participants 18 to 55 years of age at Day 35 which is 14 days after Dose 2 from US Study C4591001; and IFN $\gamma$  ELISpot and intracellular cytokine staining data for BNT162b1 in participants 18 to 55 years of age before Dose 1 and 7 days after Dose 2 from German Study BNT162-01.

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Clinical Information Amendment (SN 0034) submitted on 15 July 2020 provided available safety and immunogenicity data from Stage 1 of US Study C4591001, as well as supporting safety data from German Study BNT162-01. This submission also provided a Summary of SARS-CoV-2 Challenge of BNT162b1-immunized Rhesus Macaques.

Clinical Information Amendment (SN 0038) submitted on 17 July 2020 provided additional available safety and tolerability data, as well as IgG binding and SARS-CoV-2 neutralization titer data, from Stage 1 of US Study C4591001.

Clinical Information Amendment (SN 0041) submitted on 24 July 2020 provided additional immunogenicity and safety and tolerability data, as well as IgG binding and SARS-CoV-2 neutralization titer data, from Stage 1 US Study C4591001.

Clinical Information Amendment (SN 0044) submitted on 27 July 2020 provided nonclinical and clinical data summarizing the T cell response following BNT162b2 immunization in mice and in humans enrolled in German Study BNT162-01.

### **3. PRODUCT IDENTIFICATION AND APPLICATION**

**Sponsor Compound Number:** BNT162, PF-07302048

### **4. PROPOSED PROPRIETARY AND ESTABLISHED NAME**

The proposed proprietary name for Agency consideration is Covuity™.

The proposed established name is “SARS-CoV-2 mRNA Vaccine” or “COVID-19 Vaccine.”

A Request for Proprietary and Non-proprietary Name Review was submitted to BB-IND 19738 on 30 July 2020 (SN 0047).

### **5. VACCINE COMPOSITION**

#### **5.1. Vaccine Platforms**

BioNTech has developed RNA-LNP platforms including nucleoside-modified RNA (modRNA), which has blunted innate immune sensor activating capacity and thus augmented antigen expression. Each modRNA candidate encodes either a P2 mutant S (P2 S) or the trimerized receptor binding domain (RBD) of the S glycoprotein.

BNT162 modRNA vaccine candidates have been tested at multiple dose levels in the German Study BNT162-01 and/or US Study C4591001:

- **BNT162b1** (RBP020.3) modRNA encoding RBD (V5)
  - German study (1, 3, 10, 20, 30, 50, 60 µg) and US study (10, 20, 30, 100 µg)
  - Note: 60 µg (German study) and 100 µg (US study) were discontinued after first dose
- **BNT162b2** (RBP020.2) modRNA encoding P2 S (V9)
  - German study (1, 3, 10, 20, 30 µg) and US study (10, 20, 30 µg)

Based on review of safety and immunogenicity data from Phase 1, BNT162b2 at the 30 µg dose level was selected as the final vaccine candidate and proceeded into Phase 2/3 of Study C4591001.

## 5.2. Dosage Form, Route of Administration, and Dosing Regimen

The vaccine is supplied as a preservative-free, multi-dose (5-dose) concentrate to be diluted for intramuscular (IM) administration with saline. A total of 195 vaccine vials are provided per carton. The carton resembles a pizza box.

The concentrated multi-dose vaccine is stored frozen at -70 °C (±10 °C) to be thawed on the day of administration, diluted with sterile 0.9% Sodium Chloride Injection, USP and stored at 2-8 °C until administration.

The 5-dose vial is supplied as a white to off-white sterile frozen liquid, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal and flip off cap. Note: the vial stopper is composed of Datwyler FM457 gray bromobutyl rubber that is not manufactured from dry natural rubber (latex).

The 1.8 mL of saline diluent is added directly to the concentrated multidose vaccine concentrate. After dilution, the vials contain a sufficient volume to supply 5 doses, where each 0.3-mL dose contains 30 µg vaccine for IM injection. The 0.9% Sodium Chloride Injection, USP will not be supplied with the vaccine. Healthcare professionals will be instructed to use locally sourced saline.

The vaccine will be administered as a series of two 30-µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single 0.3-mL dose followed by a second 0.3-mL dose 21 days later.

A justification and risk assessment for the non-preserved multi-dose vial (MDV) and use of locally sourced 0.9% Sodium Chloride Injection, USP was previously submitted to the IND on 10 July 2020 (SN 0029) and the Response to CBER's 17 July 2020 Information Request following review of the 10 July 2020 submission was provided on 27 July 2020 (SN 0043).

## 6. LIST OF SPECIFIC QUESTIONS FOR CBER

### 6.1. eCTD Content and Format Questions

#### 6.1.1. Question 1

**Does CBER agree with the proposed overall table of contents for the planned BLA for Pfizer/BioNTech's COVID-19 Vaccine?**

Sponsor Position:

The overall table of contents for the planned BLA is provided below in Table 2.

**Table 2. Draft Table of Contents for the COVID-19 Vaccine BLA**

<b>MODULE 1</b>
<b>1.1 Forms</b>
Form FDA 356h
Form FDA 3397
Form FDA 3674
<b>1.2 Cover Letter</b>
Cover Letter
<b>1.3 Administrative Information</b>
<b>1.3.1 Contact/sponsor/applicant information</b>
<b>1.3.1.4 Transfer of obligation</b>
Transfer of Obligation
<b>1.3.3 Debarment Certification</b>
Debarment Certification
<b>1.3.4 Financial Certification and Disclosure</b>
Financial Certification and Disclosure
<b>1.3.5 Patent and exclusivity</b>
<b>1.3.5.3 Exclusivity Claim</b>
Exclusivity Claim
<b>1.4 References</b>
<b>1.4.1 Letter of Authorization</b>
Letter of Authorization
<b>1.4.2 Statement of Right to Reference</b>
DMF Letters of Authorization
<b>1.4.4 Cross Reference to Previously Submitted Information</b>
Cross Reference to IND
<b>1.6 Meetings</b>
<b>1.6.3 Correspondence Regarding Meetings</b>
Relevant meeting minutes to be included
<b>1.7 Fast Track</b>
<b>1.7.4 Correspondence Regarding Fast Track/Rolling Review</b>
Fast Track Designation Grant letter
<b>1.9 Pediatric Administrative Information</b>
<b>1.9.1 Request for Waiver of Pediatric Studies</b>
Request for Waiver of Pediatric Studies
<b>1.9.2 Request for Deferral of Pediatric Studies</b>
Request for Deferral of Pediatric Studies
<b>1.9.4 Proposed Pediatric Study Request and amendments</b>
initial Pediatric Study Plan (iPSP)
<b>1.9.6 Other Correspondence Regarding Pediatric Exclusivity or Study Plans</b>

**Table 2. Draft Table of Contents for the COVID-19 Vaccine BLA**

Letter of FDA Agreement with iPSP
<b>1.12 Other Correspondence</b>
<b>1.12.5 Request for Waiver</b>
Waiver Request for FDA-Designated Suffix for Biologics
<b>1.12.14 Environmental Analysis</b>
Environmental Analysis
<b>1.14 Labeling</b>
<b>1.14.1 Draft Labeling</b>
<b>1.14.1.1 Draft Carton and Container Labels</b>
Draft Carton and Container Labels
<b>1.14.1.2 Annotated Draft Labeling Text</b>
Draft Annotated USPI
<b>1.14.1.3 Draft Labeling Text</b>
Draft USPI - PDF and Word format
Structured Product Labeling (SPL) - XML format
<b>1.16 Risk Management Plans</b>
Pharmacovigilance Plan
<b>1.18 Proprietary Names</b>
Request for Proprietary Name Review
<b>MODULE 2</b>
<b>2.2 Introduction Summary</b>
<b>2.3 Quality Overall Summary</b>
<b>2.4 Nonclinical Overview</b>
<b>2.5 Clinical Overview</b>
<b>2.6 Nonclinical Written &amp; Tabulated Summaries</b>
2.6.1 Introduction
2.6.2 Pharmacology Written Summary
2.6.3 Pharmacology Tabulated Summary
2.6.4 Pharmacokinetics Written Summary
2.6.5 Pharmacokinetics Tabulated Summary
2.6.6 Toxicology Written Summary
2.6.7 Toxicology Tabulated Summary
<b>2.7 Clinical Summary</b>
2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods
2.7.3 Summary of Clinical Efficacy
2.7.4 Summary of Clinical Safety
2.7.5 References
2.7.6 Synopses of individual Studies
<b>MODULE 3</b>
Module 3 contents will be the subject of a separate CMC pre-BLA meeting
<b>MODULE 4</b>
Module 4 contents are described in Section 10.4
<b>MODULE 5</b>
<b>5.2 Tabular Listing of All Clinical Studies</b>
Tabular Listing of All Clinical Studies
<b>5.3 Clinical Study Reports and Related Information</b>
<b>5.3.1 Reports of Biopharmaceutic Studies</b>
<b>5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies</b>
SARS-CoV-2 Neutralization Assay
SARS-CoV-2 S-Binding and RBD-Binding IgG Level Assays
SARS-CoV-2 N-Binding Antibody Assay

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**Table 2. Draft Table of Contents for the COVID-19 Vaccine BLA**

SARS-CoV-2 Cepheid PCR Assay
<b>5.3.5 Reports of Efficacy and Safety Studies</b>
<b>5.3.5.1 Study Reports and Related Information of Controlled Clinical Studies Pertinent to the Claimed Indication</b>
<b>C4591001</b>
Interim Clinical Study Report
Case Report Forms (for subjects with narratives)
Dataset eSUB Packages
<b>BNT162-01</b>
Interim Clinical Study Report
Case Report Forms (for subjects with narratives)
Dataset eSUB Packages
<b>5.4 Literature References</b>
Literature References

### 6.1.2. Question 2

**Does CBER agree that the results of the planned clinical lot consistency study may be submitted as a post-approval commitment?**

Sponsor Position:

Pfizer/BioNTech plans to initiate a clinical lot consistency study in December 2020 or January 2021, once clinical material from manufacturing scale lots are available. The study will evaluate and compare the immunogenicity and safety of three lots of BNT162b2. The statistical design and sample size and the final protocol will be submitted to the IND when available.

Please note, with respect to CBER’s feedback provided in advance of the 26 June 2020 Type C Meeting, *“If you are not able to complete a lot to lot consistency study as part of your Phase 3 study, please propose an analytical comparability study to support the consistent manufacture and quality of the product batches used in your Phase 3 study.”* and agreement that Pfizer/BioNTech would provide a proposal for analytical comparability in the briefing document for a planned Type C Meeting to discuss Chemistry, Manufacturing and Controls, the comparability strategy was presented in the briefing document submitted 13 July 2020 (SN 0031). CBER feedback on the 13 July 2020 Briefing Document was received 14 August 2020 via email and is being addressed separately.

### 6.1.3. Question 3

**Does CBER agree with our plans for a separate unblinded submissions team to submit the results of the Interim Analysis, if successful, to the BLA and IND?**

Sponsor Position:

The Phase 2/3 portion of Study C4591001 is an observer-blinded, randomized placebo-controlled study to evaluate safety and efficacy of the candidate COVID-19 vaccine BNT162b2 at a 30 µg dose level, in which participants are followed through 24 months after the second dose of vaccine. Due to the expected fast accumulation of COVID-19 cases given

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the current status of the pandemic in the US, the study could support efficacy long before 6 months after the last dose of vaccine and certainly before the 24-month timepoint. Hence, as specified in C4591001 Protocol Amendment 5, Pfizer/BioNTech have specified that a group of separate teams manage the study.

1. A **blinded study team** to support the normal conduct and management of the trial following all Pfizer SOPs that commences at the start of Phase 2/3 until a determination is made to unblind the study or final database release after study completion, whichever is first. This team will be blinded to safety, immunogenicity, and efficacy.
2. An **unblinded statistical team** supporting the external Data Monitoring Committee (DMC). It is essential to restrict knowledge of the randomized investigational product assignments (vaccine or placebo) to this small unblinded statistical team supporting the DMC. The unblinded statistician leading this team is part of a separate statistical organization within Pfizer that is not part of Vaccine Clinical Research and Development (VCRD), in order to reduce the possibility of inadvertently communicating sensitive information to VCRD personnel. This team will apply the randomization codes to the blinded data sets (including blinded cases) and run programs developed and validated by the blinded study team to provide the efficacy analyses and safety summaries for the DMC. To ensure that action is taken promptly if there is early evidence of an imbalance between vaccine and placebo suspecting vaccine induced disease enhancement per our pre-specified rules, a medical monitor with vaccine experience will be a member of this team to review cases of severe COVID-19 as they reported and, if required, will discuss the need for an ad hoc meeting with the DMC Chair. The DMC will then meet to review available COVID-19 cases to determine whether a potentially observed imbalance should result in modifications to the study. The details of this team are specified in the DMC charter.
3. The purpose of a separate **unblinded submissions team** is to submit the safety and immunogenicity results from the Phase 2/3 part of the study to regulatory agencies, as well as to provide timely safety summaries that will be submitted along with positive efficacy results if the DMC determines that the efficacy criterion is met at an Interim Analysis or a Final Analysis if the study remains blinded to the study team. The existence of this unblinded team will allow these submissions to happen in a timely manner while not potentially unblinding study team members. The unblinded submissions team will remain blinded to all efficacy analyses until the DMC communicates to Pfizer that an interim or final efficacy analysis met the success criteria as defined in the protocol. It is important to note that this submissions team would only be unblinded at the group level, that is, summaries of safety and immunogenicity by group will identify the group (vaccine or placebo), but this team will not have access to individual subject assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team (the only individuals with access to the randomization codes before formal unblinding). These group-level unblinded summary tables will be provided to the unblinded submissions team to create the required submission documents. Importantly, the unblinded submissions team will not have access to any unblinded data on COVID-19 cases until

formal unblinding has occurred. The unblinded submissions team charter is included with this briefing package for CBER to review.

The Operational and Unblinding Procedures for Study C4591001 (Amendment 5) was submitted to BB-IND 19736 on 20 August 2020 (SN0063).

## 6.2. Regulatory Questions

### 6.2.1. Question 4

The Sponsor plans to roll the BLA components. Does CBER agree with the proposed contents of each of the planned rolls (as depicted in Table 3, Table 4, [Table 5](#), and [Table 6](#))?

**Table 3. Roll 1: Nonclinical**

High Level Planned Content	
	<b>MODULE 1</b>
	Regional Information – Cover letter and form
	<b>MODULE 2</b>
2.4	Nonclinical Overview
2.6	Nonclinical Written and Tabulated Summaries
	<b>MODULE 4</b>
	Nonclinical Study Reports

**Table 4. Roll 2: 1<sup>st</sup> successful Interim Analysis – Clinical**

High Level Planned Content	
	<b>MODULE 1</b>
	Regional Information
	<b>MODULE 2</b>
2.7.1	Summary of Biopharmaceutics
	<b>MODULE 5</b>
5.3.1.4	SARS-CoV-2 Assays
5.3.5.1	C4591001 / Narratives / Appendices / CRFs / Datasets

**Table 5. Roll 3: Final Analysis –Clinical**

<b>High Level Planned Content</b>	
	<b>MODULE 1</b>
	Regional Information (Label, SmPC, PVP, RMP)
	<b>MODULE 2</b>
2.2	Introduction
2.3	Quality Overall Summary (BLA)
2.5	Clinical Overview
2.7	Clinical Summaries (SCE, SCS)
	<b>MODULE 4</b>
	Nonclinical Study Reports – Any updates
	<b>MODULE 5</b>
5.2	Tabular Listing of Clinical Studies
5.3.5.1	C4591001 / Narratives / Appendices / CRFs / Datasets
5.3.5.1	BNT162-01 / Appendices / CRFs / Datasets

**Table 6. Roll 4: CMC**

<b>High Level Planned Content</b>	
	<b>MODULE 3</b>
3.2.S	Drug Substance (BLA)
3.2.P	Drug Product (BLA)
3.2.A	Appendices (BLA)
3.2.R	Regional Information (BLA)

**6.2.2. Question 5**

**Does CBER agree that the safety results from the candidate vaccine evaluated in German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine?**

Sponsor Position:

Study BNT162-01, which is ongoing, supported the timely decisions required to help select the candidate and dose level with the most appropriate benefit-risk profile for the candidate vaccines under consideration in Phase 1 for Study C4591001, namely BNT162b1 and BNT162b2 even though the safety data collected from the Phase 1 portion of Study

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C4591001 were sufficient to select the final vaccine candidate and dose level to proceed into Phase 2/3 (BNT162b2 at 30 µg). Pfizer/BioNTech propose to include safety data from Study BNT162-01 as supportive information in the BLA.

### 6.2.3. Question 6

**Does CBER agree that the T cell data from German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine?**

Sponsor Position:

T cell data were only generated from German Study BNT162-01 and provided important, additional information on the functional immune response elicited by the candidate vaccine. These data show a robust SARS-CoV-2 S-specific Th1-type CD4+ and CD8+ T cell response following BNT162b2 vaccination; these were comparable to or higher than the memory responses in the same subjects when stimulated with influenza virus, cytomegalovirus, Epstein Barr virus, and tetanus toxoid-derived immuno-dominant peptide panels.<sup>1</sup> These T cell data contribute to our understanding of the vaccine's immunogenicity profile, complementing the clinical serology data that show similarly robust vaccine antigen-specific IgG levels and SARS-CoV-2 neutralizing titers following vaccination in both Study BNT162-01 and Study C4591001, and are therefore intended as supportive to the BLA and licensure.

### 6.2.4. Question 7

**Please comment on the acceptability of the proposed trade name (Covuity™) and established names [(SARS-CoV-2 mRNA Vaccine) or (COVID-19 Vaccine)].**

Sponsor Position:

Please see the Request for Proprietary and Non-proprietary Name Review submitted 30 July 2020 (SN 0047).

## 6.3. Clinical Questions

### 6.3.1. Question 8

**Does CBER agree for Study BNT162-01 that only an abbreviated Clinical Study Report is provided and that the safety data from this study be considered supportive of US licensure of the candidate vaccine?**

Sponsor Position:

Pfizer/BioNTech propose to submit an abbreviated Clinical Study Report for Study BNT162-01, which would contain only available data for vaccine candidates BNT162b1 and BNT162b2 (noting that other RNA platform vaccine candidates studied in BNT162-01 were not studied in C4591001). Pfizer/BioNTech propose that the safety data from this study be considered supportive of US licensure of the candidate vaccine.

### 6.3.2. Question 9

**Does CBER agree that an Integrated Summary of Safety and Integrated Summary of Efficacy for Studies BNT162-01 and C4591001 are not required to be included in the BLA?**

#### Sponsor Position:

German Study BNT162-01 is the FIH, Phase 1/2 dose level-finding study to evaluate the safety and immunogenicity of different vaccine candidates and dose levels as defined in [Section 5](#). This study is ongoing. Participants received 2 doses 21 days apart of regimens of modRNA candidate BNT162b1 or BNT162b2. For BNT162b1 dose levels of up to 60 µg were studied as two doses administered 21 days apart for all doses, except 60 µg for which only one dose was administered. Similarly, BNT162b2 was studied as two doses administered 21 days apart at dose levels up to 30 µg. The 20 µg dose level data analysis is currently ongoing. Reactogenicity data were collected in paper diaries and adverse events (AEs) were recorded in the database. Immune response data will be evaluated for these participants. These data were evaluated together with data from Study C4591001 supported the selection of BNT162b2 at the 30 µg dose level for Phase 2/3.

In Phase 2 of Study C4591001, Pfizer/BioNTech will obtain safety and immunogenicity data from 360 participants and submit these data to CBER for review. The expected timing of available data to 1 month post-dose 2 is approximately beginning of September 2020 for safety data and beginning of October for immunogenicity data. These participants will be included in the Phase 3 data described below.

In Phase 3 of Study C4591001, Pfizer/BioNTech intend to recruit up to ~44,000 participants and obtain safety data in the first 6000 participants and submit these data to CBER to review. Ultimately, safety data will be collected in all recruited participants. The immunogenicity data from all participants that may ultimately be generated in Phase 3 are exploratory.

Given the expected size of the Phase 2/3 safety database (N ~44,000) ultimately available and the methodological differences in the collection of reactogenicity data in Study BNT162-01 compared to C4591001, Pfizer/BioNTech propose to include the available safety data from Study BNT162-01 separately in the Summary of Clinical Safety, and therefore proposes not to include an Integrated Summary of Safety in the BLA. Similarly, C4591001 Phase 1 safety data would also not be integrated with Phase 2/3 safety data but would be presented separately due to small sample size and the data being unblinded.

Similarly, given the importance placed on efficacy rather than immunogenicity in determining whether the vaccine is licensable, Pfizer/BioNTech propose to present immunogenicity data from Study BNT162-01 separately in the Summary of Clinical Efficacy and not integrate the data in an Integrated Summary of Efficacy, similar for Study C4591001 Phase 1 immunogenicity data.

### 6.3.3. Question 10

**Pfizer/BioNTech propose to submit the eSUB (SDTM & ADaM) data packages (details described below) in this BLA. Does CBER agree?**

Sponsor Position:

Given the expected fast recruitment and the expanding pandemic as of August 2020, Pfizer/BioNTech believe that there is significant potential for demonstration of vaccine efficacy in the 4<sup>th</sup> quarter 2020.

Pfizer/BioNTech propose to submit the following eSUB data packages (SDTM, ADaM) in the BLA:

For the pivotal Study C4591001, we propose to submit eSUB per the following major milestones data cut to support the Real Time Review:

- An eSUB package will be submitted based on the 1<sup>st</sup> successful Interim Analysis with positive efficacy results data cut. It will include all SDTM datasets, relevant efficacy ADaM datasets, and related documents (eg, define.xml, reviewer's guide, aCRF) to support the efficacy analysis. An additional eSUB package will be submitted that corresponds to the safety data cut supporting the submission documents. SAS codes to support primary efficacy and key safety analysis will also be provided. The safety package included would correspond with the safety data available as outlined in [Table 1](#).
- An eSUB package will be based on the Final Analysis with 164 cases data cut. It will include all SDTM and ADaM datasets and related documents. The eSUB package will support the efficacy data summarized in the submission documents as outlined in Table 1. An additional eSUB package will be submitted that corresponds to the safety data cut supporting the submission document. SAS codes to support primary efficacy and key safety analysis will also be provided. The safety package included would correspond with the safety data available as outlined in Table 1.

For Study BNT162-01, we propose to submit one eSUB package:

- An eSUB package will be submitted based on the data cut for the abbreviated CSR of this BLA. It will include all SDTM datasets and relevant ADaM datasets to support the abbreviated CSR for both BNT162b1 and BNT162b2 constructs.

**6.3.4. Question 11**

**Does CBER agree with the proposed plan for submission of Safety Narratives, and the corresponding Case Report Forms (CRFs) for those participants in the safety narratives in studies to be included in the BLA for Pfizer/BioNTech's COVID-19 Vaccine?**

Sponsor Position:

Pfizer/BioNTech plan to include narratives in the BLA for:

- Deaths
- Treatment-related serious adverse events (SAEs)
- AEs resulting in permanent discontinuation from study treatment and/or study

- All COVID-19 cases (including severe COVID-19 cases).

The narratives will be provided:

- For the entirety of the Phase 1/2/3 study,
- As prose for the smaller Phase 1, and
- For the Phase 2/3 study part as a hybrid consisting of a programmatic header with supportive participant data and prose.

The narratives will be written in a blinded manner. In the event of a successful Interim Analysis or the Final Analysis, the programmed narrative header will be updated to include whether the participant received BNT162b2 or placebo. As specified in Question 5 (in [Section 6.1.3](#)), only the small unblinded statistical team supporting the DMC will have access to the randomization codes. Members of the unblinded submissions team will not have access to the narratives with treatment assignment included in the header. In order to support information provided in the safety narrative and to comply with the requirements in 21CFR 314.50(f)(2), Pfizer/BioNTech plan to submit copies of individual CRFs for each participant for which a safety narrative is provided. Pfizer/BioNTech do not plan to submit copies of CRFs for other participants.

## 6.4. Nonclinical Questions

### 6.4.1. Question 12

**Does CBER agree that the nonclinical package as summarized below is adequate for registration of Pfizer/BioNTech's COVID-19 Vaccine and that no additional studies are needed?**

#### Sponsor Position:

The nonclinical table of contents for the planned BLA is provided below ([Table 7](#)). The content is based on the studies that support the proposed indication, as well as feedback previously received from the Agency.

- During the 26 June 2020 Type C Meeting CBER agreed that DART study results could be submitted during initial BLA review [Pfizer/BioNTech Meeting Minutes Submitted 09 July 2020 (SN 0028)]
- 30 June 2020 Request for FDA Comments and Advice on the DART Study Protocol (20256434) Protocol and timing of data submission (SN 0023) – CBER agreed via email on 08 July 2020.
- 27 July 2020 Request for FDA Comments & Advice on sufficiency of the planned nonclinical absorption, disposition, metabolism, and excretion (ADME) and toxicology packages and timing of study data submissions (SN 0045) – CBER agreed via email on 14 August 2020.

**Table 7. Draft Nonclinical Table of Contents for the COVID-19 Vaccine BLA**

<b>MODULE 2</b>
<b>2.4 Nonclinical Overview</b>
<b>2.6 Nonclinical Written and Tabulated Summaries</b>
2.6.1 Introduction
2.6.2 Pharmacology Written Summary
2.6.3 Pharmacology Tabulated Summary
2.6.4 Pharmacokinetics Written Summary
2.6.5 Pharmacokinetics Tabulated Summary
2.6.6 Toxicology Written Summary
2.6.7 Toxicology Tabulated Summary
<b>MODULE 4</b>
<b>4.2 Nonclinical Study Reports</b>
<b>4.2.1 Pharmacology</b>
<b>4.2.1.1 Primary Pharmacology</b>
VR-VTR-10671 (COVID-19 vaccine candidate immunogenicity and evaluation of protection against SARS-CoV-2 challenge in rhesus macaques)
R-20-0211 (In vitro results for BNT162b2)
R-20-0085 (COVID-19: Immunogenicity Study of the LNP-Formulated ModRNA Encoding the Viral S Protein-V9)
R-20-0112 (Characterizing the Immunophenotype in Spleen and Lymph Node of Mice Treated with SARS-COV-2 Vaccine Candidates)
<b>4.2.2 Pharmacokinetics</b>
<b>4.2.2.3 Distribution</b>
R-20-0072 - Expression of Luciferase-Encoding ModRNA After I.M. Application of GMP-Ready Acuitas LNP Formulation
<b>4.2.2.4 Metabolism</b>
01049-20008 - In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Liver Microsomes
01049-20009 - In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Cynomolgus Monkey, and Human Liver S9 Fractions
01049-20010 - In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Hepatocytes
01049-20020 - In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Liver Microsomes
01049-20021 - In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Cynomolgus Monkey, and Human Liver S9 Fractions
01049-20022 - In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Hepatocytes
<b>4.2.3 Toxicology</b>
<b>4.2.3.2 Repeat-Dose Toxicity</b>
Study 38166 - Repeat-Dose Toxicity Study of Three LNP-Formulated RNA Platforms Encoding for Viral Proteins by Repeated Intramuscular Administration to Wistar Han Rats SEND Data Package
Study 20GR142 - 17-Day, 3 Intramuscular Toxicity Study of BNT162b2 (V9) and BNT162b3c in Wistar Han Rats With a 3-week Recovery <sup>a</sup> SEND Data Package <sup>a</sup>
<b>4.3 Literature References</b>
Literature References

a. For 20GR142, only a dosing phase interim data set will be submitted with the initial BLA. The final report will be submitted during BLA review.

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## 6.5. Pharmacovigilance

### 6.5.1. Question 13

**For post-marketing pharmacovigilance, Pfizer/BioNTech are considering short and long-term active surveillance and, potentially, comparative safety evaluation, with data partners that contribute to Sentinel. Does CBER agree? Is FDA able to comment further on safety concerns they expected to be included in the required pharmacovigilance plan?**

Sponsor Position:

Pfizer/BioNTech acknowledges FDA's requirement for a pharmacovigilance plan (US-PVP) to be included in the submission package for the vaccine and has begun preliminary work on the contents of the US-PVP based on available data, previously submitted vaccine US-PVPs, the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005) and the FDA Guidance for Industry Development and Licensure of Vaccines to prevent COVID-19.<sup>2,3</sup>

The US-PVP will include non-clinical information relevant to human usage of the vaccine and clinical trial exposure and limitations. It will also include proposed potential safety concerns and discussion of planned post-marketing pharmacovigilance and risk mitigation activities based on current knowledge of the efficacy and safety of the vaccine. As exposure to the vaccine increases and understanding of the safety profile evolves, the US-PVP will be updated appropriately.

At this time, Pfizer/BioNTech plan to include vaccine-associated enhanced disease (VAED), including vaccine-enhanced respiratory disease (VAERD) as an important potential risk. Missing information will include use in pregnancy and lactation, use in children, use in immunocompromised individuals, use in individuals with chronic disease and vaccine effectiveness. These safety concerns may be updated prior to submission based on data collected from the ongoing Phase 3 study.

For both active surveillance and comparative safety analyses, the ability to detect rare events will require a very large data source allowing quick accrual of exposure and long-term follow up of data. This can be accomplished by leveraging data from a consortium of secondary data sources or a distributed data network such as sites contributing data through the Sentinel system. Pfizer/BioNTech acknowledge that if more than one vaccine for COVID-19 is available to the public, the utility of this approach depends on the ability to differentiate the vaccines from each other via NDC, CPT, or J codes.

### 6.5.2. Question 14

**Does the Agency agree that Pfizer/BioNTech may submit Structured Product Labeling (SPL) during the course of BLA review?**

Sponsor Position:

SPL cannot be created until a final draft US Prescribing Information (USPI) is available. Pfizer/BioNTech propose to not delay submission of the Final Analysis for creation and

inclusion of the SPL, but rather, submit the SPL shortly after BLA filing during the course of review. The proposed draft USPI in both clean and annotated versions will be available at the time of BLA filing.

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## 7. APPENDICES

Minimum point size - 6.5pt.

NDC 0069-1000-02		<b>DOSAGE AND ADMINISTRATION:</b> After dilution, each vial contains 5 doses at 0.3 mL per dose. Each dose contains 30 mcg Covuity. See prescribing information for dosage, preparation and administration. Store -80°C to -60°C (-112°F to -76°F). Store in this carton to protect from light. <b>MUST BE DILUTED BEFORE USE.</b> After Dilution: Use within 6 hours. Any unused solution must be discarded. Contains no preservatives. Manufactured by BioNTech An der Goldgrube 12 55131 Mainz, Germany Distributed by Pfizer Labs Division of Pfizer Inc NY, NY 10017 U.S. License # XX
195 Multiple Dose Vials		
<b>Covuity™</b> (SARS-CoV-2-mRNA Vaccine) Concentrate for Injection		
<b>5-Dose Vials</b> For Intramuscular Injection Only		
		
Rx only		LOT/EXP:
		
300691000021	Drt CLAB1	
195 Multiple Dose Vials	Store -80°C to -60°C (-112°F to -76°F). <b>Protect from light.</b> <b>MUST BE DILUTED BEFORE USE.</b> After Dilution: Use within 6 hours.	LOT/EXP:
<b>Covuity™</b> (SARS-CoV-2-mRNA Vaccine) Concentrate for Injection		
<b>5-Dose Vials</b> For Intramuscular Injection Only		

Minimum point size - 6.5pt.

NDC 0069-1000-02		<b>DOSAGE AND ADMINISTRATION:</b> After dilution, each vial contains 5 doses at 0.3 mL per dose. Each dose contains 30 mcg Covuity. See prescribing information for dosage, preparation and administration. Store -80°C to -60°C (-112°F to -76°F). Store in this carton to protect from light. <b>MUST BE DILUTED BEFORE USE.</b> After Dilution: Use within 6 hours. Any unused solution must be discarded. Contains no preservatives. Manufactured by BioNTech An der Goldgrube 12 55131 Mainz, Germany Distributed by Pfizer Labs Division of Pfizer Inc NY, NY 10017 U.S. License # XX
195 Multiple Dose Vials		
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Rx only		LOT/EXP:
		
300691000021	Drt CLAB2	
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<b>Covuity™</b> (COVID-19 Vaccine) Concentrate for Injection		
<b>5-Dose Vials</b> For Intramuscular Injection Only		

## **8. REFERENCES**

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- <sup>1</sup> Sahin AR, Erdogan A, Agaoglu PM, et al. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. *Euroasian J Med Oncol* 2020;4(1):1-7.
- <sup>2</sup> Food and Drug Administration Guidance Document. E2E Pharmacovigilance Planning April 2005. Accessed 12 August 2020. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2e-pharmacovigilance-planning>.
- <sup>3</sup> Food and Drug Administration Development and Licensure of Vaccines to Prevent COVID 19 Guidance for Industry. June 2020. Available at: <https://www.fda.gov/media/139638/download>.

## Document Approval Record

<b>Document Name:</b>	1.12.14 COVID-19 Vaccine (BN162, PF-07302048) Request for Comments and Advice_September 2020
<b>Document Title:</b>	1.12.14 COVID-19 Vaccine (BN162, PF-07302048) Request for Comments and Advice_September 2020

<b>Signed By:</b>	<b>Date(GMT)</b>	<b>Signing Capacity</b>
Boyce, Donna	14-Sep-2020 17:05:34	Regulatory Affairs Approval

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Our Reference: IND 19736

**ADVICE**  
Date: September 28, 2020

BioNTech RNA Pharmaceuticals GmbH  
Attention: Elisa Harkins, Pfizer Inc.  
Global Regulatory Lead,  
Pfizer Global Regulatory Affairs - Vaccines  
500 Arcola Road  
Collegeville, PA 19426

Dear Ms. Harkins:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)” for the prevention of COVID-19 in adults  $\geq 18$  years of age.

We also refer to amendment 84 to your IND received on September 15, 2020, which included your request for comments and advice regarding the practical aspects of the planned BLA submission. Please see below for our responses and comments to your questions.

### **eCTD Content and Format:**

#### **Sponsor Question 1:**

Does CBER agree with the proposed overall table of contents for the planned BLA for Pfizer/BioNTech’s COVID-19 Vaccine?

#### **FDA Response to Sponsor Question 1:**

We agree with the proposed overall table of contents (regarding the nonclinical and clinical information) for the planned BLA for Pfizer/BioNTech’s COVID-19 Vaccine. As a clarification, please include all appendices (i.e., randomization schema, listing of participants receiving vaccine from specified batches, final protocol and SAP, etc.) and participant data listings for each clinical study report.

#### **Sponsor Question 2:**

Does CBER agree that the results of the planned clinical lot consistency study may be submitted as a post-approval commitment?

**FDA Response to Sponsor Question 2:**

In your position description to this question, you acknowledged our feedback provided in advance of the June 26, 2020 Type C meeting in which we indicated that if you are unable to complete a lot consistency study as part of your Phase 3 studies, you could provide a comparability package to support manufacturing consistency. In addition, in our written responses of August 14, 2020 [to questions in your Type C meeting submitted in amendment 31 (sequence 0032, July 13, 2020)] we indicated that to support manufacturing changes introduced during clinical development through commercial manufacture, analytical comparability based on results of in-process tests, release tests, and product characterization tests would be needed to support licensure. We have the following requests:

- a. Please provide data on the comparability of the clinical lots used under IND and commercial PPQ lots with the information requested in our written responses of August 14, 2020. If the results of supplemental characterization tests are not available, please include a timeframe for submission of those data.
- b. In the comparability submission, please include a description of all analytical tests and the qualification or validation status of each assay.
- c. Please note that a clinical lot consistency study will be needed in support of the license application, if adequate analytical comparability data are not provided.

**Sponsor Question 3:**

Does CBER agree with our plans for a separate unblinded submissions team to submit the results of the Interim Analysis, if successful, to the BLA and IND?

**FDA Response to Sponsor Question 3:**

We do not foresee the need for an unblinded submissions team to submit the results of the first successful Interim Analysis (IA) to the BLA or IND, because only final analyses contained in a full clinical study report will be sufficient to support your BLA submission. If the results of an IA are deemed successful by the Data Monitoring Committee, and an adequate safety database has been accumulated by that timepoint, then the results should be included as part of an EUA submission [for details, please refer to CBER's September 2, 2020, communication in response to your IND 19736.57 submission]. We would welcome the submission of topline results of an IA intended to support an EUA request to the IND at the time that you notify the FDA that preparation for the EUA request is underway.

Please see FDA Response to Question 4 (items 4.b and 4.c) regarding submission of type of Clinical Study Report and Analysis to the BLA.

**Sponsor Question 4:**

The Sponsor plans to roll the BLA components. Does CBER agree with the proposed contents of each of the planned rolls (as depicted in Table 3, Table 4, Table 5, and Table 6)?

**FDA Response to Sponsor Question 4:**

As per May 2014 FDA Guidance: Expedited Programs for Serious Conditions -Drugs and Biologics

<https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf>, for preliminary agreement on your rolling BLA approach, we request that you provide: (1) the data that will be used to support effectiveness, (2) the schedule for submission of each portion of the BLA, and (3) a description of portions of the application to be submitted separately (late components). Please note that the cited guidance recommends submissions of complete BLA sections such as the entire CMC section, toxicology section or clinical section. Although we may accept rolling sub-sections within these main sections, to reach preliminary agreement, we request that the number of rolling sub-sections be limited and that you describe the timeline and the information to be included in each.

We do not agree with your plans to start the rolling BLA submission on September 30, 2020, because no preliminary clinical endpoint efficacy data have been submitted to support BNT162b2 vaccine effectiveness. We are willing to discuss a timeline for rolling submission after evidence of preliminary effectiveness from a successful interim analysis, as assessed by the Data Monitoring Committee.

- a. We disagree with your proposed contents of Roll 1 (Nonclinical), since it will not include the final study reports for Study 20GR142 (repeat dose toxicity study for BNT162b2) or the Developmental and Reproductive Toxicity study. Please defer submission of Roll 1 until you are able to submit the complete Nonclinical module (with final study reports).
- b. We disagree with your proposed contents of Roll 2 (Clinical- Interim Analysis) and request that only the full Clinical Study Report containing the final efficacy analysis be submitted in the BLA. An intermediate submission containing an interim analysis is not necessary or helpful to facilitate approval.
- c. For the proposed contents of Roll 3 (Clinical – Final Analysis; full clinical study report), in addition to analyses of vaccine efficacy, we expect a BLA submitted for traditional approval of your vaccine to include safety data (reactogenicity, 6-month follow-up for SAEs) from at least 3,000 vaccine recipients, and assessment for potential vaccine-associated enhanced respiratory disease (ERD) based on a reasonable amount of follow-up in participants representative of all age cohorts (recognizing that an adequate number of subjects evaluated for ERD and duration of follow-up is based on the totality of the data available, number of severe COVID-19 cases and the quality of the data). Further discussions in the context of a pre-BLA meeting will be needed to further discuss requirements for the BLA content.
- d. Please include a list of late components in your pre-BLA meeting briefing package, for discussion and agreement at the pre-BLA meeting.

**Sponsor Question 5:**

Does CBER agree that the safety results from the candidate vaccine evaluated in German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine?

**FDA Response to Sponsor Question 5:**

We agree that the safety results from the final candidate vaccine, BNT162b2, evaluated in the German Study BNT162-01 may be considered supportive of US licensure of the same candidate vaccine.

**Sponsor Question 6:**

Does CBER agree that the T cell data from German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine?

**FDA Response to Sponsor Question 6:**

We agree that the T-cell immunogenicity data from German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine.

**Sponsor Question 7:**

Please comment on the acceptability of the proposed trade name (Covuity™) and established names [(SARS-CoV-2 mRNA Vaccine) or (COVID-19 Vaccine)].

**FDA Response to Sponsor Question 7:**

In consultation with the Center for Biologics Evaluation and Research's Advertising and Promotional Labeling Branch (CBER/APLB), we conclude that, under the FDCA and applicable regulations, COVUITY is Acceptable at this time. Please provide a request for a re-review of your proposed proprietary name COVUITY within 14 days following submission of your Biologics License Application.

We defer providing comment on established name for the COVID-19 Vaccine during review of the BLA.

**Clinical:**

**Sponsor Question 8:**

Does CBER agree for Study BNT162-01 that only an abbreviated Clinical Study Report is provided and that the safety data from this study be considered supportive of US licensure of the candidate vaccine?

**FDA Response to Sponsor Question 8:**

We agree that an abbreviated Clinical Study Report for Study BNT162-01 containing data from all subjects who received the final vaccine candidate BNT162b2 can be considered supportive of US licensure of the same candidate vaccine. Please see FDA Response to Sponsor Question 5 regarding consideration of safety data from Study BNT162-01.

**Sponsor Question 9:**

Does CBER agree that an Integrated Summary of Safety and Integrated Summary of Efficacy for Studies BNT162-01 and C4591001 are not required to be included in the BLA?

**FDA Response to Sponsor Question 9:**

We agree that an Integrated Summary of Safety and Integrated Summary of Efficacy for Studies BNT162-01 and C4591001 are not required to be included in the BLA since the summaries would largely be based on study C4591001 results.

**Sponsor Question 10:**

Pfizer/BioNTech propose to submit the eSUB (SDTM & ADaM) data packages (details described below) in this BLA. Does CBER agree?

**FDA Response to Sponsor Question 10:**

We agree with your proposal regarding submission of the eSUB (SDTM & ADaM) data packages in the BLA.

**Sponsor Question 11:**

Does CBER agree with the proposed plan for submission of Safety Narratives, and the corresponding Case Report Forms (CRFs) for those participants in the safety narratives in studies to be included in the BLA for Pfizer/BioNTech's COVID-19 Vaccine?

**FDA Response to Sponsor Question 11:**

We agree with the proposed plan to include case narratives for all deaths, treatment-related SAEs, AEs resulting discontinuation from study treatment and/or study, and that the treatment assignment for the narratives will be unblinded upon successful interim analysis or the final analysis. We may ask for additional safety narratives during the BLA review.

**Nonclinical:**

**Sponsor Question 12:**

Does CBER agree that the nonclinical package as summarized below is adequate for registration of Pfizer/BioNTech's COVID-19 Vaccine and that no additional studies are needed?

**FDA Response to Sponsor Question 12:**

We do not agree that the nonclinical package as summarized in Table 7 is adequate for licensure of Pfizer/BioNTech's COVID-19 Vaccine, as the final study report for the agreed-upon DART study is not included in the table. Please include your DART study in Table 7 and submit the final DART study report for our review at the time of the BLA submission.

## Pharmacovigilance:

### Sponsor Question 13:

For post-marketing pharmacovigilance, Pfizer/BioNTech are considering short and long-term active surveillance and, potentially, comparative safety evaluation, with data partners that contribute to Sentinel. Does CBER agree? Is FDA able to comment further on safety concerns they expected to be included in the required pharmacovigilance plan?

#### FDA Response to Sponsor Question 13:

Active surveillance studies in Sentinel may be acceptable as a component of your pharmacovigilance plan. Please provide the protocol for any post-marketing studies for FDA review in your BLA submission.

You propose to include pregnancy and lactation as missing information in your pharmacovigilance plan. We recommend a pregnancy registry for your product. Pregnancy registries provide data collected with a structured study design and may provide important product safety information for pregnant women. Therefore, please develop a pregnancy registry protocol and submit for FDA review with your BLA submission. Your pregnancy registry protocol should include study objectives, sample size calculations specifying the target number of pregnancy exposed cases, and milestones.

We are unable to comment on additional safety concerns without a full review of the clinical and safety data related to your product. Please ensure the pharmacovigilance plan submitted with your BLA contains the elements specified in the ICH E2E Pharmacovigilance Planning Guidance (<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073107.pdf>).

### Sponsor Question 14:

Does the Agency agree that Pfizer/BioNTech may submit Structured Product Labeling (SPL) during the course of BLA review?

#### FDA Response to Sponsor Question 14:

We agree with your proposal to submit your SPL during the BLA review. However, as stated in *Sponsor Position*, please submit the SPL soon after filing of your BLA.

## Additional FDA Questions/Comments:

1. In order to facilitate the Bioresearch Monitoring (BIMO) inspections, please provide in a tabular format the contact information of the responsible clinical investigator for each study site including the name, address, telephone number, and an email address in addition to the number of subjects screened and enrolled.

2. Please include the final versions of data management plan, and the technical/user manuals for TrialMax app and Trial Manager distributed to the subjects and/or sites during the study in your proposed BLA as Appendices.
3. In Section 6.1.3, Question 3, item 3 about the *unblinded submissions team*, states that “the unblinded submissions team charter is included with this briefing package for CBER to review.” However, this charter was not included with the briefing package. Please submit the unblinded submissions team charter to the IND for our review.

If you have any questions, please contact me by email at [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov).

Sincerely,

Ramachandra  
Naik -S

Digitally signed by Ramachandra Naik -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=2001232361,  
cn=Ramachandra Naik -S  
Date: 2020.09.28 12:08:50 -04'00'

Ramachandra S. Naik  
Primary Reviewer  
Division of Vaccines and  
Related Products Applications  
Office of Vaccines  
Research and Review  
Center for Biologics  
Evaluation and Research

**COVID-19 Vaccine**  
**Response to CBER September 28, 2020 Information Request**  
**IND 19736**  
**October 2020**

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## 1 INTRODUCTION

Reference is made to BB-IND 19736 for the COVID-19 vaccine (PF-07302048; BNT162), which Pfizer and BioNTech are developing for the prevention of COVID-19 in adults  $\geq 16$  years of age. The IND was effective on April 29, 2020.

Reference is also made to Request for Comment & Advice (SN 0084) submitted on 15 September to BB-IND 19736 for which the FDA subsequently provided the following comments on 28 September 2020. Please see Section 2 for responses from the Sponsor.

## 2 QUESTIONS AND RESPONSES

### 2.1 Question 1 eCTD Content and Format

*Does CBER agree with the proposed overall table of contents for the planned BLA for Pfizer/BioNTech's COVID-19 Vaccine?*

#### ***FDA Response to Sponsor Question 1:***

***We agree with the proposed overall table of contents (regarding the nonclinical and clinical information) for the planned BLA for Pfizer/BioNTech's COVID-19 Vaccine. As a clarification, please include all appendices (i.e., randomization schema, listing of participants receiving vaccine from specified batches, final protocol and SAP, etc.) and participant data listings for each clinical study report.***

#### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments and will include all appendices (i.e., randomization schema, listing of participants receiving vaccine from specified batches, final protocol and SAP, etc.) and participant data listings for each clinical study report.

### 2.2 Question 2

*Does CBER agree that the results of the planned clinical lot consistency study may be submitted as a post-approval commitment?*

#### ***FDA Response to Sponsor Question 2:***

***In your position description to this question, you acknowledged our feedback provided in advance of the June 26, 2020 Type C meeting in which we indicated that if you are unable to complete a lot consistency study as part of your Phase 3 studies, you could provide a comparability package to support manufacturing consistency. In addition, in our written responses of August 14, 2020 [to questions in your Type C meeting submitted in amendment 31 (sequence 0032, July 13, 2020)] we indicated that to support manufacturing changes introduced during clinical development through commercial manufacture, analytical comparability based on results of in-process tests, release tests,***

*and product characterization tests would be needed to support licensure. We have the following requests:*

- a. Please provide data on the comparability of the clinical lots used under IND and commercial PPQ lots with the information requested in our written responses of August 14, 2020. If the results of supplemental characterization tests are not available, please include a timeframe for submission of those data.*
- b. In the comparability submission, please include a description of all analytical tests and the qualification or validation status of each assay.*
- c. Please note that a clinical lot consistency study will be needed in support of the license application, if adequate analytical comparability data are not provided.*

**Sponsor's Response to CBER**

- a. The Sponsor acknowledges this request. As described in SN0102, submitted 08 October 2020, comparability against clinical lots and across EUA lots and commercial PPQ lots will be submitted to the IND once additional lots are manufactured and tested. Comparability will include a (b) (4) (b) (4) (b) (4). Additional supplemental PPQ data will be filed to the IND after completion of PPQ campaigns at each site and be provided in the BLA
- b. A description of the analytical tests and the qualification or validation status of each assay will be provided to the IND as well as to the BLA.
- c. The Sponsor acknowledges this comment. If, in addition to analytical comparability data, a clinical lot consistency study is required, a matrix approach is proposed to cover both US commercial supply nodes. (b) (4)

(b) (4) (b) (4)

(b) (4) (b) (4)

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Does CBER concur with the proposed clinical lot consistency matrix if needed?

### 2.3 Question 3

*Does CBER agree with our plans for a separate unblinded submissions team to submit the results of the Interim Analysis, if successful, to the BLA and IND?*

#### ***FDA Response to Sponsor Question 3***

***We do not foresee the need for an unblinded submissions team to submit the results of the first successful Interim Analysis (IA) to the BLA or IND, because only final analyses contained in a full clinical study report will be sufficient to support your BLA submission. If the results of an IA are deemed successful by the Data Monitoring Committee, and an adequate safety database has been accumulated by that timepoint, then the results should be included as part of an EUA submission [for details, please refer to CBER's September 2, 2020, communication in response to your IND 19736.57 submission]. We would welcome the submission of topline results of an IA intended to support an EUA request to the IND at the time that you notify the FDA that preparation for the EUA request is underway.***

***Please see FDA Response to Question 4 (items 4.b and 4.c) regarding submission of type of Clinical Study Report and Analysis to the BLA.***

#### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. Pfizer/BioNTech expects the EUA to be ready for CBER's evaluation before a final efficacy analysis is performed at 164 COVID-19 cases. The EUA may be supported by a prior successful interim analysis and as recommended by CBER while keeping the blind for the study intact. As the EUA will require the presentation of unblinded information to support safety and efficacy for CBER's review, the unblinded submissions team is still required for this purpose. Moreover, multiple regulatory agencies globally have agreed to the planned rolls presented to CBER in order to support local applications and hence the unblinded submissions team is required to satisfy requirements of these agencies.

### 2.4 Question 4

*The Sponsor plans to roll the BLA components. Does CBER agree with the proposed contents of each of the planned rolls (as depicted in Table 3, Table 4, Table 5, and Table 6)?*

#### ***FDA Response to Sponsor Question 4***

***As per May 2014 FDA Guidance: Expedited Programs for Serious Conditions -Drugs and Biologics <https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf>, for preliminary agreement on your rolling BLA***

*approach, we request that you provide: (1) the data that will be used to support effectiveness, (2) the schedule for submission of each portion of the BLA, and (3) a description of portions of the application to be submitted separately (late components). Please note that the cited guidance recommends submissions of complete BLA sections such as the entire CMC section, toxicology section or clinical section. Although we may accept rolling sub-sections within these main sections, to reach preliminary agreement, we request that the number of rolling sub-sections be limited and that you describe the timeline and the information to be included in each.*

*We do not agree with your plans to start the rolling BLA submission on September 30, 2020, because no preliminary clinical endpoint efficacy data have been submitted to support BNT162b2 vaccine effectiveness. We are willing to discuss a timeline for rolling submission after evidence of preliminary effectiveness from a successful interim analysis, as assessed by the Data Monitoring Committee.*

- a. We disagree with your proposed contents of Roll 1 (Nonclinical), since it will not include the final study reports for Study 20GR142 (repeat dose toxicity study for BNT162b2) or the Developmental and Reproductive Toxicity study. Please defer submission of Roll 1 until you are able to submit the complete Nonclinical module (with final study reports).*
- b. We disagree with your proposed contents of Roll 2 (Clinical- Interim Analysis) and request that only the full Clinical Study Report containing the final efficacy analysis be submitted in the BLA. An intermediate submission containing an interim analysis is not necessary or helpful to facilitate approval.*
- c. For the proposed contents of Roll 3 (Clinical – Final Analysis; full clinical study report), in addition to analyses of vaccine efficacy, we expect a BLA submitted for traditional approval of your vaccine to include safety data (reactogenicity, 6- month follow-up for SAEs) from at least 3,000 vaccine recipients, and assessment for potential vaccine-associated enhanced respiratory disease (ERD) based on a reasonable amount of follow-up in participants representative of all age cohorts (recognizing that an adequate number of subjects evaluated for ERD and duration of follow-up is based on the totality of the data available, number of severe COVID-19 cases and the quality of the data). Further discussions in the context of a pre-BLA meeting will be needed to further discuss requirements for the BLA content.*
- d. Please include a list of late components in your pre-BLA meeting briefing package, for discussion and agreement at the pre-BLA meeting.*

### **Sponsor's Response to CBER**

The Sponsor acknowledges the FDA's feedback for the rolling submission of the BLA components and will reassess the BLA strategy and provide a new proposal taking into account the requirements hereby set forth by the FDA. An updated proposal for the rolling submission of BLA components will be discussed with the FDA at a future pre-BLA meeting.

## 2.5 Question 5

*Does CBER agree that the safety results from the candidate vaccine evaluated in German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine?*

### ***FDA Response to Sponsor Question 5***

***We agree that the safety results from the final candidate vaccine, BNT162b2, evaluated in the German Study BNT162-01 may be considered supportive of US licensure of the same candidate vaccine.***

### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. No further discussion is required.

## 2.6 Question 6

*Does CBER agree that the T cell data from German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine?*

### ***FDA Response to Sponsor Question 6***

***We agree that the T-cell immunogenicity data from German Study BNT162-01 may be considered supportive of US licensure of the candidate vaccine.***

### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. No further discussion is required.

## 2.7 Question 7

*Please comment on the acceptability of the proposed trade name (Covuity™) and established names [(SARS-CoV-2 mRNA Vaccine) or (COVID-19 Vaccine)].*

### ***FDA Response to Sponsor Question 7***

***In consultation with the Center for Biologics Evaluation and Research's Advertising and Promotional Labeling Branch (CBER/APLB), we conclude that, under the FDCA and applicable regulations, COVUIITY is Acceptable at this time. Please provide a request for a re-review of your proposed proprietary name COVUIITY within 14 days following submission of your Biologics License Application.***

### **Sponsor's Response to CBER**

The proposed proprietary name, COVUIITY, was withdrawn for consideration on 29 September 2020, SN 0097. The new proposed proprietary name will be submitted to the IND in the near future.

## **2.8 Question 8**

*Does CBER agree for Study BNT162-01 that only an abbreviated Clinical Study Report is provided and that the safety data from this study be considered supportive of US licensure of the candidate vaccine?*

### ***FDA Response to Sponsor Question 8***

***We agree that an abbreviated Clinical Study Report for Study BNT162-01 containing data from all subjects who received the final vaccine candidate BNT162b2 can be considered supportive of US licensure of the same candidate vaccine. Please see FDA Response to Sponsor Question 5 regarding consideration of safety data from Study BNT162-01.***

### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. No further discussion is required.

## **2.9 Question 9**

*Does CBER agree that an Integrated Summary of Safety and Integrated Summary of Efficacy for Studies BNT162-01 and C4591001 are not required to be included in the BLA?*

### ***FDA Response to Sponsor Question 9***

***We agree that an Integrated Summary of Safety and Integrated Summary of Efficacy for Studies BNT162-01 and C4591001 are not required to be included in the BLA since the summaries would largely be based on study C4591001 results.***

### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. No further discussion is required.

## **2.10 Question 10**

*Pfizer/BioNTech propose to submit the eSUB (SDTM & ADaM) data packages (details described below) in this BLA. Does CBER agree?*

### ***FDA Response to Sponsor Question 10***

***We agree with your proposal regarding submission of the eSUB (SDTM & ADaM) data packages in the BLA.***

### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. No further discussion is required.

## 2.11 Question 11

*Does CBER agree with the proposed plan for submission of Safety Narratives, and the corresponding Case Report Forms (CRFs) for those participants in the safety narratives in studies to be included in the BLA for Pfizer/BioNTech's COVID-19 Vaccine?*

### ***FDA Response to Sponsor Question 11***

***We agree with the proposed plan to include case narratives for all deaths, treatment-related SAEs, AEs resulting discontinuation from study treatment and/or study, and that the treatment assignment for the narratives will be unblinded upon successful interim analysis or the final analysis. We may ask for additional safety narratives during the BLA review.***

### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. No further discussion is required.

## 2.12 Question 12 Nonclinical

*Does CBER agree that the nonclinical package as summarized below is adequate for registration of Pfizer/BioNTech's COVID-19 Vaccine and that no additional studies are needed?*

### ***FDA Response to Sponsor Question 12***

***We do not agree that the nonclinical package as summarized in Table 7 is adequate for licensure of Pfizer/BioNTech's COVID-19 Vaccine, as the final study report for the agreed-upon DART study is not included in the table. Please include your DART study in Table 7 and submit the final DART study report for our review at the time of the BLA submission.***

### **Sponsor's Response to CBER**

The final DART study report will be submitted for review at the time of the BLA submission.

## 2.13 Question 13: Pharmacovigilance

*For post-marketing pharmacovigilance, Pfizer/BioNTech are considering short and long-term active surveillance and, potentially, comparative safety evaluation, with data partners that contribute to Sentinel. Does CBER agree? Is FDA able to comment further on safety concerns they expected to be included in the required pharmacovigilance plan?*

### ***FDA Response to Sponsor Question 13***

***Active surveillance studies in Sentinel may be acceptable as a component of your pharmacovigilance plan. Please provide the protocol for any post-marketing studies for FDA review in your BLA submission.***

***You propose to include pregnancy and lactation as missing information in your pharmacovigilance plan. We recommend a pregnancy registry for your product. Pregnancy registries provide data collected with a structured study design and may provide important product safety information for pregnant women. Therefore, please develop a pregnancy registry protocol and submit for FDA review with your BLA submission. Your pregnancy registry protocol should include study objectives, sample size calculations specifying the target number of pregnancy exposed cases, and milestones.***

***We are unable to comment on additional safety concerns without a full review of the clinical and safety data related to your product. Please ensure the pharmacovigilance plan submitted with your BLA contains the elements specified in the ICH E2E Pharmacovigilance Planning Guidance (<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm073107.pdf>).***

### **Sponsor's Response to CBER**

A description of Pfizer/BioNTech's proposed post-marketing non-interventional safety studies, including protocols, will be provided in the Pharmacovigilance Plan submitted with the BLA application.

Pfizer/BioNTech agrees that monitoring vaccine safety in pregnant women is critical. Given that a pregnancy registry based on primary data collection is susceptible to non-participation, attrition, small sample size and limited or lack of comparator data, Pfizer would like to propose monitoring vaccine safety in pregnancy using electronic health care data, which could be conducted in a representative pregnant woman population exposed to the vaccine and minimize selection bias, follow-up bias, and reporting bias. In addition, internal comparison groups, such as contemporaneous unvaccinated pregnant women or women receiving other vaccine(s) to prevent COVID-19 (if available) could be included. Pfizer/BioNTech will provide a proposal for pregnancy surveillance in the Pharmacovigilance Plan submitted with the BLA application.

Pfizer/BioNTech will ensure the pharmacovigilance plan submitted with the BLA contains the elements specified in the ICH E2E Pharmacovigilance Planning Guidance ([https://database.ich.org/sites/default/files/E2E\\_Guideline.pdf](https://database.ich.org/sites/default/files/E2E_Guideline.pdf)).

### **2.14 Question 14**

***Does the Agency agree that Pfizer/BioNTech may submit Structured Product Labeling (SPL) during the course of BLA review?***

### ***FDA Response to Sponsor Question 14***

***We agree with your proposal to submit your SPL during the BLA review. However, as stated in Sponsor Position, please submit the SPL soon after filing of your BLA.***

### **Sponsor's Response to CBER**

The Sponsor thanks the Agency for its comments. No further discussion is required.

#### **2.15 Additional FDA Questions/Comments:**

- 1. In order to facilitate the Bioresearch Monitoring (BIMO) inspections, please provide in a tabular format the contact information of the responsible clinical investigator for each study site including the name, address, telephone number, and an email address in addition to the number of subjects screened and enrolled.***
- 2. Please include the final versions of data management plan, and the technical/user manuals for TrialMax app and Trial Manager distributed to the subjects and/or sites during the study in your proposed BLA as Appendices.***
- 3. In Section 6.1.3, Question 3, item 3 about the unblinded submissions team, states that "the unblinded submissions team charter is included with this briefing package for CBER to review." However, this charter was not included with the briefing package. Please submit the unblinded submissions team charter to the IND for our review.***

### **Sponsor's Response to CBER**

The Sponsor acknowledges Additional FDA Questions/Comments 1 and 2 and confirms the information will be provided with BLA submission.

For item 3, "the unblinded submissions team charter is included with this briefing package for CBER to review" noted in Section 6.1.3, Question 3 is the Operational and Unblinding Procedures for Study C4591001 which was submitted to BB-IND 19736 on 20 August 2020 (SN 0063).

### **3 REFERENCES**

None

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#### **4 SUPPORTING DOCUMENTATION**

##### **New, Appended, or Replaced Supporting Documentation**

None

##### **Previously Submitted Supporting Documentation**

None

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## Document Approval Record

**Document Name:** COVID-19 Vaccine (PF-07302048) 2020 Response to CBER September 28, 2020 Information Request

**Document Title:** COVID-19 Vaccine (PF-07302048) 2020 Response to CBER September 28, 2020 Information Request

<b>Signed By:</b>	<b>Date(GMT)</b>	<b>Signing Capacity</b>
Boyce, Donna	15-Oct-2020 14:47:17	Regulatory Affairs Approval



**Request for Comments and Advice**

**Administration of BNT162b2 To Participants in C4591001 Who Originally Received  
Placebo**

**17<sup>th</sup> November 2020**

090177e1958c386b\Approved\Approved On: 17-Nov-2020 21:55 (GMT)

Pfizer and BioNTech recognize the Agency's desire to continue blinded follow-up in COVID-19 vaccine studies and to ensure the ability to assess long-term safety and efficacy, as described in the EUA guidance:

“FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for stopping blinded follow-up in an ongoing clinical trial. An EUA request should include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated ERD as well as decreased effectiveness as immunity wanes over time) in sufficient numbers of subjects to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.”

Pfizer and BioNTech have considered how to manage participants in the C4591001 study, balancing the need to collect data that is as informative and unbiased as possible with the ethical imperative to not disadvantage participants who have put themselves forward to further COVID-19 vaccine research and who may themselves be eligible for vaccination.

We therefore propose a two-step approach for participants enrolled in all countries involved in the study, implemented through a protocol amendment.

### **Step 1**

Participants eligible for receipt of a COVID-19 vaccine in accordance with local or national recommendations (including under EUA) will need to be unblinded to determine whether they received BNT162b2 or placebo. In this situation our preference is that such individuals are vaccinated within the study in order that both safety and efficacy data can continue to be collected. We therefore plan the following:

- Site writes to all participants with template letter informing them to contact the site if they are eligible for receipt of a COVID-19 vaccine
- Eligible participants contact site if they want to receive COVID-19 vaccine
- Site conducts phone visit to confirm eligibility and unblinds to determine whether they received BNT162b2 or placebo
- If they originally received placebo, an in-person visit is arranged for re-consent and vaccination

### **Step 2**

All participants that have not been unblinded in Step 1 by 6 months post-dose 2:

- Site unblinds at scheduled visit to determine whether they received BNT162b2 or placebo

- If they originally received placebo and wish to receive BNT162b2, they are reconsented and vaccinated

In both scenarios adverse event (AE) follow-up will be as for the initial vaccinations i.e. to 1-month post-vaccination 4 for non-serious and 6 months for serious AEs. In addition, Illness/convalescent visits for COVID-19 surveillance will continue for all participants. Those participants who originally received BNT162b2 will continue with study visits as currently specified in the protocol.

We believe this approach will minimize the number of current participants who choose to withdraw from the study once a vaccine is available and will maximize the collection of data that can inform the long-term efficacy and safety of BNT162b2.

With this 2-step approach, it is expected that a sufficient number of subjects will continue on the study blinded until 6 months post-dose 2 to allow for comparative assessment of safety and efficacy. Vaccine efficacy comparing to placebo through 6 months post-dose 2 will be evaluated using the current exposure adjusted analysis method and time to event data analysis methods. Statistical models accounting for cross over, e.g. rank-preserving structural failure time (RPSFT) model, may also be explored to assess vaccine efficacy. After step 2 the control group will be eliminated, but it will allow the subjects who received vaccine to continue to be followed for long-term safety and efficacy. Incidence rate and cumulative incidence over time through the end of the study (up to 24 months post-dose 2) for active vaccine group will be descriptively summarized and plotted.

**Does the agency agree with the proposed approach? In order to be prepared for the possible need to unblind EUA eligible individuals, and potentially offer vaccination, soon after an EUA is granted, we would appreciate a response by 25<sup>th</sup> November 2020.**



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DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS**

**DATE:** November 27, 2020 **PAGES:** 3

**TO:** **BioNTech RNA Pharmaceuticals GmbH/Pfizer. Inc.**  
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**FROM:** **Ramachandra Naik, Ph.D.**  
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Office of Vaccines Research and Review  
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**CBER Reference:** IND 19736.140

**IND Title:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:** CBER comments regarding administration of BNT162b2 to participants in C4591001 who originally received placebo (placebo cross-over)

Dear Ms. Harkins:

Reference is made to the amendment 140 (dated November 18, 2020) to your IND 19736 that contained your Request for Comments and Advice seeking (1) FDA feedback regarding administration of BNT162b2 to participants in C4591001 who originally received placebo, and (2) FDA endorsement for continued use of clinical supplies through expiry without label revision for the transfer of sponsorship from BioNTech RNA Pharmaceuticals GmbH to BioNTech SE, where the IMP label is impacted by this change. We provided feedback on item 2 in a separate communication. Below are our comments on item 1.

***Item 1 (Administration of BNT162b2 To Participants in C4591001 Who Originally Received Placebo):***

Pfizer and BioNTech recognize the Agency's desire to continue blinded follow-up in COVID-19 vaccine studies and to ensure the ability to assess long-term safety and efficacy, as described in the EUA guidance:

“FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for stopping blinded follow-up in an ongoing clinical trial. An EUA request should include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated ERD as well as decreased effectiveness as immunity wanes over time) in sufficient numbers of subjects to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.”

Pfizer and BioNTech have considered how to manage participants in the C4591001 study, balancing the need to collect data that is as informative and unbiased as possible with the ethical imperative to not disadvantage participants who have put themselves forward to further COVID-19 vaccine research and who may themselves be eligible for vaccination.

We therefore propose a two-step approach for participants enrolled in all countries involved in the study, implemented through a protocol amendment.

...

With this 2-step approach, it is expected that a sufficient number of subjects will continue on the study blinded until 6 months post-dose 2 to allow for comparative assessment of safety and efficacy. Vaccine efficacy comparing to placebo through 6 months post-dose 2 will be evaluated using the current exposure adjusted analysis method and time to event data analysis methods. Statistical models accounting for cross over, e.g. rank-preserving structural failure time (RPSFT) model, may also be explored to assess vaccine efficacy. After step 2 the control group will be eliminated, but

it will allow the subjects who received vaccine to continue to be followed for long-term safety and efficacy. Incidence rate and cumulative incidence over time through the end of the study (up to 24 months post-dose 2) for active vaccine group will be descriptively summarized and plotted.

**Does the agency agree with the proposed approach? In order to be prepared for the possible need to unblind EUA eligible individuals, and potentially offer vaccination, soon after an EUA is granted, we would appreciate a response by 25th November 2020.**

**CBER Response to Item 1:**

We agree with that if an EUA is issued for your product, subjects in ongoing studies should be informed about the availability of the vaccine under the EUA, including relevant conditions for use under EUA and recommendations for vaccine prioritization and distribution issued by local or national recommendations. While we acknowledge that subjects may request to know their treatment assignment to inform their decision-making, we remain concerned that a standing offer to unblind subjects may not be ethically necessary and could influence subjects to request unblinding even when they may be willing to continue blinded follow-up, with or without the option to receive vaccine based on eligibility under conditions of the EUA. These concerns will be a topic for further VRBPAC discussion during the upcoming meeting on December 10, 2020.

We also request that study participants who are willing to continue blinded, placebo-controlled follow-up beyond 6 months post-dose 2 be allowed to continue their blinded follow-up. The information obtained from continued blinded, placebo-controlled follow-up, even with a smaller placebo group cohort, would be important to continued assessment of risk-benefit considerations for your vaccine, including but not limited to evaluating late adverse reactions, duration of protection and risk of vaccine-induced enhanced disease.

We therefore request that you maintain blinded, placebo-controlled follow-up for as long as feasible. We also recommend that subjects who choose to pursue vaccination with BNT162b2 under an EUA should continue follow-up for safety and effectiveness outcomes, as you have proposed.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.



**Request for Comments and Advice**

**Follow-up of BNT162b2 Recipients in C4591001 Who Originally Received Placebo**

**20 January 2021**

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## 1. BACKGROUND

C4591001 protocol amendment 10 introduced the ability for those study participants who originally received placebo to be able to receive BNT162b2 within the study. As described in the protocol, in this circumstance, participants moved to a new visit schedule as follows:

Visit Number	101	102	103	104	105
Visit Description	Vaccination 3	Vaccination 4	1-Month Telephone Contact	6-Month Telephone Contact	18-Month Telephone Contact
Visit Window (Days)	From Recommendation or At Least 175 Days After Vaccination 2	19 to 23 Days After Visit 101	28 to 35 Days After Visit 102	175 to 189 Days After Visit 102	532 to 560 Days After Visit 102
Obtain informed consent	X				
Collect blood sample for immunogenicity assessment	~20 mL				
Obtain nasal (midturbinate) swab	X	X			
Administer BNT162b2	X	X			
Collect AEs and SAEs as appropriate	X	X	X	X	

As well as following the above schedule, such participants are also expected to report symptoms that could represent a potential COVID-19 illness.

## 2. PROPOSAL

All follow-up in these participants is unblinded, no blood draws are taken after vaccination as there are already data accruing from the large number of participants originally randomized to BNT162b2. In addition, since data are accruing from real world use of the vaccine in multiple countries, Pfizer and BioNTech propose to remove Visits 104 and 105 from the protocol. Consequently, the follow-up of those receiving open-label BNT162b2 would finish 1 month after their second dose of vaccine.

The implications for the study's objectives would be limited:

- With respect to adverse events, it is already planned to summarize those collected during blinded follow-up and those collected during open-label follow-up separately. The proposed change would result in open-label follow-up of serious adverse events (SAEs) between 1 and 6 months after a second dose of BNT162b2 being from those originally randomized to BNT162b2, and not from those originally randomized to placebo who later received open-label BNT162b2.

- With respect to COVID-19, once there is no longer a control group, COVID-19 will be evaluated descriptively. Instead of “To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization or subsequently” the wording would be revised to “To describe the incidence of confirmed COVID-19 through the entire study follow-up period in participants who received BNT162b2 at initial randomization ~~or subsequently~~”.

In light of the limited scientific value of the open-label follow-up of placebo recipients who later received BNT162b2, and the volume of data expected to accrue from other studies and post-authorization activities, Pfizer and BioNTech believe this approach is reasonable.

As is standard in Pfizer clinical study protocols, if an investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer.

**Does the agency agree with the proposed approach?**



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OFFICE OF VACCINES RESEARCH AND REVIEW  
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS**

**DATE:** January 29, 2021                      **PAGES:** 3

**TO:**                      **BioNTech RNA Pharmaceuticals GmbH/Pfizer. Inc.**  
**Attention: Neda Aghajani Memar, Pharm.D.**  
235 East 42<sup>nd</sup> Street  
219/9/69  
New York, NY 10017  
Phone: 212-733-2613  
Fax number: 845-474-3500  
E-mail: [neda.aghajanimemar@pfizer.com](mailto:neda.aghajanimemar@pfizer.com)

**FROM:**                      **Ramachandra Naik, 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 References:** IND 19736 amendment 189

**IND Title:**                      Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein;  
BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA;  
variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2);  
BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles  
(ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:**                      CBER comments regarding the follow-up of BNT162b2 recipients  
who originally received placebo

Dear Ms. Memar:

Reference is made to the amendment 189 (dated January 21, 2021) to your IND 19736 that contained a Request for Comments and Advice seeking FDA feedback regarding follow-up of BNT162b2 recipients in C4591001 who originally received placebo.

We have the following comments:

**Sponsor’s Question 1:**

C4591001 protocol amendment 10 introduced the ability for those study participants who originally received placebo to be able to receive BNT162b2 within the study. As described in the protocol, in this circumstance, participants moved to a new visit schedule as follows:

...

As well as following the above schedule, such participants are also expected to report symptoms that could represent a potential COVID-19 illness.

...

All follow-up in these participants is unblinded, no blood draws are taken after vaccination as there are already data accruing from the large number of participants originally randomized to BNT162b2. In addition, since data are accruing from real world use of the vaccine in multiple countries, Pfizer and BioNTech propose to remove Visits 104 and 105 from the protocol. Consequently, the follow-up of those receiving open-label BNT162b2 would finish 1 month after their second dose of vaccine.

...

In light of the limited scientific value of the open-label follow-up of placebo recipients who later received BNT162b2, and the volume of data expected to accrue from other studies and post-authorization activities, Pfizer and BioNTech believe this approach is reasonable.

...

**Does the agency agree with the proposed approach?**

**FDA Response to Sponsor Question 1:**

We disagree with your proposal to limit the follow up of placebo recipients who receive BNT162b2 at 1 month post dose 2, and we continue to encourage follow up for as long as possible. Although real-world data is accumulating following the Emergency Use Authorization of BNT162b2, the protocol-driven follow up would allow for continued systematic evaluation of safety and effectiveness beyond what might be accomplished in observational studies. We note that approaches to continued evaluation of vaccine effectiveness following crossover of placebo recipients have been presented in the literature and other public forums.

**Additional FDA Comments:**

1. Please clarify if the NAAT and N-binding antibody assays you plan to use for diagnosis of SARS CoV-2 infection are able to detect the circulating variant strains. Please submit supportive data and/or alternative methods you plan to use to diagnose these variant strains.
2. Because the implications of asymptomatic infection in terms of shedding and transmission are unknown, and to support the fitness for purpose (i.e., sensitivity) of the N-binding antibody assay to assess asymptomatic infection, please consider frequent surveillance for shedding, via NAAT assessments from NP samples collected at multiple time points, as part of your evaluation of asymptomatic infection, along with serological assessment of N-binding antibodies.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.

**Pfizer-BioNTech COVID-19 Vaccine**

**Response to 29 January 2021 FDA Information Request Regarding  
The Follow-up of BNT162b2 Recipients in C4591001 Who Originally Received Placebo**

**February 2021**

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## INTRODUCTION

Reference is made to BB-IND 19736 for Pfizer-BioNTech COVID-19 Vaccine (BNT162; PF-07302048) and to amendment 189 (dated January 21, 2021), which contained a Request for Comments and Advice seeking FDA feedback regarding the follow-up of BNT162b2 recipients in C4591001 who originally received placebo.

The following information are provided in response to FDA's January 29, 2021:

- response to the request for feedback regarding the proposed follow-up of BNT162b2 recipients who originally received placebo in C4591001;
- additional 2 comments.

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

## FDA RESPONSE TO SPONSOR QUESTION 1

***We disagree with your proposal to limit the follow up of placebo recipients who receive BNT162b2 at 1 month post dose 2, and we continue to encourage follow up for as long as possible. Although real-world data is accumulating following the Emergency Use Authorization of BNT162b2, the protocol-driven follow up would allow for continued systematic evaluation of safety and effectiveness beyond what might be accomplished in observational studies. We note that approaches to continued evaluation of vaccine effectiveness following crossover of placebo recipients have been presented in the literature and other public forums.***

### **Sponsor Response**

Pfizer/BioNTech understand the Agency's objective to continue to collect safety and effectiveness data in vaccinated individuals; however, we would propose that this can be done more efficiently with real world data and with data from those who were not randomized to placebo originally. This will limit the burden on investigator sites, allowing them to focus on the multiple competing aspects of our COVID-19 vaccine development: for example, serial swab collection for assessment of asymptomatic infection; continued study of participants 12 to 15 years of age; evaluation of a booster dose of BNT162b2; potential evaluation of a modified vaccine candidate encoding the spike protein from new SARS-CoV-2 variants of concern; evaluation of multiple vaccine lots; evaluation of formulations with increased thermal stability; evaluation in children; evaluation in pregnant women and evaluation in immunocompromised individuals.

The fidelity of the safety and efficacy data collected from the ~23,000 study participants originally randomized to BNT162b2 will not be significantly enhanced by long-term collection of a similar data set during unblinded follow-up of participants who originally received placebo followed by open-label BNT162b2. This is particularly so in the context of the observational assessment of safety and effectiveness during large-scale global deployment of the vaccine:

- Safety surveillance by spontaneous reports and formal studies, for which the potential denominator is very large: the total number of BNT162b2 doses shipped through 22 January 2021 was (b) (4). During this period, an estimated (b) (4) doses of BNT162b2 have been administered for an estimated (b) (4) total person-years of follow-up.
- Per the US Pharmacovigilance Plan, we are conducting 3 post-authorization safety studies. C4591008, a primary data collection study, will capture safety information in 20,000 health care workers vaccinated post-EUA. Secondary data studies C4591011 and C4591012 will capture all documented vaccinations within the source populations of 10 million (Department of Defense) and 18 million (Veterans Health Administration) with a 2-year follow-up period. Additionally, safety information will be collected in studies described in the EU Risk Management Plan. C4591010 is a primary data collection study of 10,000 vaccinated persons in the EU. C4591021 is a secondary data study of vaccinated persons in several electronic health care databases in Europe covering over 60 million individuals. These protocol-driven, active surveillance studies are designed to characterize and evaluate the risk of adverse events of special interest via comparative methods that account for the non-randomized allocation of vaccine. Outcomes will be identified systematically using pre-defined definitions described in the protocol or statistical analysis plan.
- With respect to vaccine effectiveness, we plan to conduct studies in at least 3 locations using population-based test-negative design methodology in the United States and UK. One of the sites will also assess effectiveness in a large HMO using cohort methodology. We are also assessing vaccine effectiveness in country-wide population assessments in Israel and perhaps several other countries. In total we will be assessing effectiveness in millions of vaccinees.

#### **ADDITIONAL FDA COMMENT #1**

***Please clarify if the NAAT and N-binding antibody assays you plan to use for diagnosis of SARS CoV-2 infection are able to detect the circulating variant strains. Please submit supportive data and/or alternative methods you plan to use to diagnose these variant strains.***

#### **Sponsor Response**

Regarding the SARS-CoV-2 NAAT, Pfizer/BioNTech will continue to use the Cepheid Xpert Xpress SARS-CoV-2 test. The test amplifies SARS-CoV-2 N and E genes through specific complementary primers and probes. Two gene targets are detected by the assay, but detection of only 1 target is required to report a SARS-CoV-2 positive result. The use of two gene targets in the assay provides redundancy which helps ensure that SARS-CoV-2 infections will be identified throughout the planned duration of the study. [Table 1](#) describes the 4 frequently mentioned SARS-CoV-2 variants in global circulation. Of these 4 variants, there are no sequence disruptions in the N or E primer or probe binding regions that would impact PCR amplification in the Xpert Xpress SARS-CoV-2 test. Regarding the N-binding

assay, variant B.1.429 (CAL.20C) has no documented changed gene sequences to the original Wuhan reference isolate and, therefore, would code the same N protein as the original sequence. The mutations in B.1.1.7 (UK), B 1.351 (South Africa) and P.1 (Brazil) are sparse and would not likely impact the sensitivity of the N-binding assay (Roche Elecsys Anti-SARS-CoV-2 Assay).

**Table 1. Summary of 4 Frequently Referenced SARS-CoV-2 Variants**

Variant Name	ORF1a/b	ORF8	N	E	S
B.1.1.7 (UK) <sup>1</sup>	T1001I A1708D I2230T C3267T C5388A T6954C 11288-11296 deletion, 3675-3677 deletion	C27972T, G28048T A28111G Q27stop R52I Y73C	28280 GAT- >CTA, C28977T D3L S235F		21765-21770 deletion, 21991-21993 deletion, A23063T A23604A C23709T T24506G G24914C C23271A ΔH69-V70 ΔY144 N501Y A570D D614G P681H T716I S982A D1118H
B.1.351 (South Africa) <sup>2,3,4</sup>	11288-11296 deletion S1188L K1795Q E5665D K1655N		T205I	P71L	L18F D80A D215G R246I Δ242-244 K417N E484K N501Y A701V I1227V
P.1 (B.1.1.28.1) (Brazil) <sup>5,6</sup>	11288-11296 deletion	E92K Ins28269- 28273	P80R		L18F T20N P26S D138Y R190S E484K, K417T N501Y H655Y T1027I
B.1.429 / CAL.20C (California) <sup>7</sup>	I4205V, D1183Y				S13I, W152C, L452R

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## **ADDITIONAL FDA COMMENT #2**

***Because the implications of asymptomatic infection in terms of shedding and transmission are unknown, and to support the fitness for purpose (i.e., sensitivity) of the N-binding antibody assay to assess asymptomatic infection, please consider frequent surveillance for shedding, via NAAT assessments from NP samples collected at multiple time points, as part of your evaluation of asymptomatic infection, along with serological assessment of N-binding antibodies.***

### **Sponsor Response**

Pfizer/BioNTech has a two-pronged approach to assess vaccine protection against asymptomatic infection. In the first approach, Pfizer/BioNTech use seroconversion by N-protein-binding antibody assessment (Roche Elecsys Anti-SARS-CoV-2 assay) as described in the 31 July 2020 (SN0049) submission. Pfizer/BioNTech provided detailed responses and required data to CBER questions concerning the sensitivity of the Roche Elecsys Anti-SARS-CoV-2 assay that we believe support the fitness of the assay for its intended use. In the second approach, Pfizer/BioNTech use the frequent nasal swabbing (every 2 weeks) for testing by NAAT in consenting participants as proposed in Protocol amendment 11 (submitted 04 January 2021 [SN0177]), section 8.17 (Surveillance for Asymptomatic SARS-CoV-2 Infection) that was previously reviewed by the Agency.

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## REFERENCES

- <sup>1</sup> Rambaut A, Loman N, Pybus O, et al. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations. Available at <https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563>. Accessed 2 Feb 2021.
- <sup>2</sup> O'Toole A, Hill V, Pybus OG, et al. Tracking the international spread of SARS-CoV-2 lineages B.1.1.7 and B.1.351/501Y-V2. Available at <https://virological.org/t/tracking-the-international-spread-of-sars-cov-2-lineages-b-1-1-7-and-b-1-351-501y-v2/592>. Accessed 2 Feb 2021.
- <sup>3</sup> O'Toole A and Hill V. B.1.351 report. Available at [https://cov-lineages.org/global\\_report\\_B.1.351.html](https://cov-lineages.org/global_report_B.1.351.html). Accessed 2 Feb 2021.
- <sup>4</sup> Naveca F, Nascimento V, Victor Souza V, et al. Phylogenetic relationship of SARS-CoV-2 sequences from Amazonas with emerging Brazilian variants harboring mutations E484K and N501Y in the Spike protein. Available at <https://virological.org/t/phylogenetic-relationship-of-sars-cov-2-sequences-from-amazonas-with-emerging-brazilian-variants-harboring-mutations-e484k-and-n501y-in-the-spike-protein/585>. Accessed 2 Feb 2021.
- <sup>5</sup> Faria NR, Claro IM, Candido D, et al. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. Available at <https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586>. Accessed 2 Feb 2021.
- <sup>6</sup> Tegally H, Wilkinson E, Giovanetti M, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. MedRxiv preprint doi: <https://doi.org/10.1101/2020.12.21.20248640>.
- <sup>7</sup> Zhang W, Davis B, Chen SS, et al. Emergence of a novel SARS-CoV-2 strain in Southern California, USA. MedRxiv preprint doi: <https://doi.org/10.1101/2021.01.18.21249786>.

## Document Approval Record

**Document Name:**

COVID-19 Response to FDA - C4591001 - Follow-up of BNT162b2 Recipients Who Originally Received Placebo - Feb 2021

**Document Title:**

COVID-19 Response to FDA - C4591001 - Follow-up of BNT162b2 Recipients Who Originally Received Placebo - Feb 2021

**Signed By:**

**Date(GMT)**

**Signing Capacity**

Boyce, Donna

08-Feb-2021 17:16:37

Regulatory Affairs Approval

090177e19637b9cf\Approved\Approved On: 08-Feb-2021 17:16 (GMT)



## Global Product Development

15 March 2021

Marion Gruber, Ph.D.  
Director  
Office of Vaccines Research and Review  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
Document Control Center  
10903 New Hampshire Avenue  
WO71, G112  
Silver Spring, MD 20993-0002

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**SN0243**

**Re: Covid-19 Vaccine (BNT162/PF-07302048) BB-IND 19736**

**Follow-up to 8 February 2021 Response to FDA 29 January 2021 Comments –  
Question for the Agency**

Dear Dr. Gruber,

Reference is made to BB-IND 19736 for BioNTech's COVID-19 Vaccine (BNT162; PF-07302048) for the prevention of COVID-19 in adults  $\geq 16$  years of age. The IND was effective on April 29, 2020.

Reference is made to the Request for Comments and Advice regarding follow-up of BNT162b2 recipients in C4591001 who originally received placebo that was submitted on 21 January 2021 (SN0188), CBER's 29 January 2021 response to the Request for Comments and Advice and Pfizer/BioNTech Response to FDA 29 January 2021 comments submitted 8 February 2021 (SN 0205).

Regarding Item #1 of the 8 February Response, does CBER agree that continued collection of safety and effectiveness data in vaccinated individuals could be done more efficiently with real world data than with data from those who were randomized to placebo originally and that follow-up of the latter could therefore be modified in line with our original proposal? Pfizer/BioNTech respectfully request CBER response by 22 March 2021.

This submission has been scanned for viruses using McAfee VirusScan Enterprise Version 8.8 and is virus free. The submission is being sent via the Gateway.

Should you have any questions regarding this submission, or require additional information, please contact me via phone at 212-733-2613; via facsimile at 845-474-3500; or via e-mail at [neda.aghajanimemar@pfizer.com](mailto:neda.aghajanimemar@pfizer.com).

Sincerely,

Neda Aghajani Memar, Pharm.D.  
Director  
Pfizer Global Regulatory Affairs

CC: Ramachandra S. Naik, Ph.D.



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

**DATE:** April 2, 2021 **PAGES:** 2

**TO:** **BioNTech SE/Pfizer. Inc.**  
**Attention: Neda Aghajani Memar**  
235 East 42<sup>nd</sup> Street, 219/9/69  
New York, NY 10017  
Phone: 212-733-2613  
Fax number: 845-474-3500  
E-mail: [Neda.Aghajani.Memar@pfizer.com](mailto:Neda.Aghajani.Memar@pfizer.com)

**FROM:** **Ramachandra Naik, 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:** IND 19736.244

**IND Title:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:** CBER comments regarding a follow-up question on Pfizer's response regarding follow-up of placebo crossover subjects

Dear Ms. Aghajani Memar:

Reference is made to the amendment 244 (dated March 15, 2021) to your IND 19736 that contained a follow-up question regarding your response submitted in IND 19736 amendment 206 dated February 8, 2021 regarding follow-up of placebo crossover subjects. We have the following response to your question:

***Sponsor Question 1:***

Regarding Item #1 of the February 8, Response (amendment 206), does CBER agree that continued collection of safety and effectiveness data in vaccinated individuals could be done more efficiently with real world data than with data from those who were randomized to placebo originally and that follow-up of the latter could therefore be modified in line with our original proposal?

**FDA Response to Sponsor Question 1:**

We disagree with your proposal, for reasons stated in our response to amendment 189 submission sent on January 29, 2021, and continue to recommend follow-up for all participants who originally received placebo for protocol-driven follow up, which includes potential COVID-19 illness visits, through 18 months after BNT162b2 (30ug) Dose #2.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.

---

**From:** Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>  
**Sent:** Monday, February 1, 2021 2:53 PM  
**To:** Harkins Tull, Elisa  
**Cc:** Aghajani Memar, Neda  
**Subject:** [EXTERNAL] IND 19736 - Pfizer-BioNTech COVID-19 Vaccine - CBER comments regarding content of nonclinical package and timelines of rolling BLA  
**Attachments:** IND 19736\_Advice\_Timelines reg rolling BLA\_Content of nonclinical info.pdf

Dear Ms. Harkins,

Please see the attached pdf for CBER comments regarding content of nonclinical package and timelines of rolling BLA.

Please confirm receipt of this message and let me know if you have any questions or need additional information.

Regards,  
Ram

**Ramachandra S. Naik, Ph.D.**

*Biologist (Regulatory) / Primary Reviewer*  
Center for Biologics Evaluation and Research  
Office of Vaccines Research and Review  
U.S. Food and Drug Administration  
Tel: 301-796-2640

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**From:** Harkins Tull, Elisa  
**Sent:** Friday, January 22, 2021 5:26 PM  
**To:** Naik, Ramachandra <[Ramachandra.Naik@fda.hhs.gov](mailto:Ramachandra.Naik@fda.hhs.gov)>  
**Subject:** RE: BLA for the Pfizer-BioNTech Covid Vaccine

Dear Ram,

We are planning on submitting the Nonclinical package mid-February (as described below). We would also submit the clinical assay validation documents at that time as well. For the Clinical and CMC packages for the BLA we are currently working to submit a request for feedback on the proposed contents by no later than Feb 1<sup>st</sup> and we will be asking for feedback within 2 weeks from when we submit. Based on current timelines and assumptions for what will be required, we are targeting submission of the rest of the BLA the first week of April. These timings will be adjusted based on CBER pre-BLA feedback.

Best regards,  
Elisa

---

**From:** Naik, Ramachandra <[Ramachandra.Naik@fda.hhs.gov](mailto:Ramachandra.Naik@fda.hhs.gov)>  
**Sent:** Friday, January 22, 2021 2:20 PM  
**To:** Harkins Tull, Elisa <[Elisa.HarkinsTull@pfizer.com](mailto:Elisa.HarkinsTull@pfizer.com)>  
**Subject:** [EXTERNAL] RE: BLA for the Pfizer-BioNTech Covid Vaccine

Dear Ms. Harkins,

We are having internal discussion on this topic. As it would be very helpful if we know a timeline regarding what information will be submitted when, please provide a timeline regarding your plan to submit the CMC, Nonclinical and Clinical information to your future rolling BLA for the Pfizer-BioNTech COVID-19 Vaccine.

Please confirm receipt of this message.

Regards,  
Ram

---

**From:** Harkins Tull, Elisa <[Elisa.HarkinsTull@pfizer.com](mailto:Elisa.HarkinsTull@pfizer.com)>  
**Sent:** Friday, January 22, 2021 9:00 AM  
**To:** Naik, Ramachandra <[Ramachandra.Naik@fda.hhs.gov](mailto:Ramachandra.Naik@fda.hhs.gov)>; Smith, Michael (CBER) <[Michael.Smith2@fda.hhs.gov](mailto:Michael.Smith2@fda.hhs.gov)>  
**Subject:** RE: BLA for the Pfizer-BioNTech Covid Vaccine

Dear Ram,

I am writing to follow up on below as we are working to complete the non-clinical package to file. Also, to verify/confirm the non-clinical package we are planning to include in the BLA are all data thus far submitted for the IND 19736 & EUA 27034. CBER has the same understanding and expectation, correct? Please advise.

Best regards,  
Elisa

---

**From:** Naik, Ramachandra <[Ramachandra.Naik@fda.hhs.gov](mailto:Ramachandra.Naik@fda.hhs.gov)>  
**Sent:** Wednesday, January 13, 2021 11:50 AM  
**To:** Harkins Tull, Elisa <[Elisa.HarkinsTull@pfizer.com](mailto:Elisa.HarkinsTull@pfizer.com)>  
**Subject:** [EXTERNAL] RE: BLA for the Pfizer-BioNTech Covid Vaccine

Dear Elisa,

Confirming receipt of the below message.

Regards,  
Ram

---

**From:** Harkins Tull, Elisa <[Elisa.HarkinsTull@pfizer.com](mailto:Elisa.HarkinsTull@pfizer.com)>  
**Sent:** Wednesday, January 13, 2021 11:26 AM

**To:** Naik, Ramachandra <[Ramachandra.Naik@fda.hhs.gov](mailto:Ramachandra.Naik@fda.hhs.gov)>

**Subject:** BLA for the Pfizer-BioNTech Covid Vaccine

Hi Ram,

Can you believe it has only been just over a month since the EUA was authorized? That actually just hit me as I started to write this correspondence to you. It definitely feels a lot longer than that!

So here we are, BLA planning and preparation time. In the near future we are going to be sending CBER a proposal for what clinical data would be included in the BLA. We are going to submit this as a Module 1.12.4 Request for Comments and Advice rather than a pre-BLA Meeting Request.

We are still planning on a rolling BLA as we had discussed previously. We are currently planning for the first roll to be Module 4 with a submission date of mid- to end- February. Is this still acceptable to CBER?

Please advise.

Best regards,  
Elisa

*Elisa Harkins*

Senior Director  
Global Regulatory Affairs - Vaccines  
Pfizer, Inc.  
500 Arcola Road  
Collegeville, PA 19426

Mobile – 215-280-5503  
Fax – 845-474-3500



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

**DATE:** February 1, 2021                      **PAGES:** 2

**TO:**                      **BioNTech RNA Pharmaceuticals GmbH/Pfizer. Inc.**  
**Attention: Elisa Harkins**  
500 Arcola Road  
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E-mail: [elisa.harkinstull@pfizer.com](mailto:elisa.harkinstull@pfizer.com)

**FROM:**                      **Ramachandra Naik, 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:** IND 19736

**IND Title:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:**                      CBER comments regarding content of nonclinical package and timelines of rolling BLA

Dear Ms. Harkins:

References are made to the question and additional information provided in emails sent on January 13, 2021 and January 22, 2021 by Pfizer's Elisa Harkins to CBER's Ramachandra Naik regarding the nonclinical package to include in the BLA and the timelines regarding submission of nonclinical, CMC and clinical information to the rolling BLA for Pfizer-BioNTech COVID-19 Vaccine. We have the following comments:

**Sponsor Question 1:**

To verify/confirm the non-clinical package we are planning to include in the BLA are all data thus far submitted for the IND 19736 & EUA 27034. CBER has the same understanding and expectation, correct?

**FDA Response to Sponsor Question 1:**

Yes. We have the same understanding and expectation regarding the content of the nonclinical package, i.e., inclusion in the BLA of all data/information submitted thus far to IND 19736 and EUA 27034.

**Sponsor Question 2:**

- We are planning on submitting the Nonclinical package mid-February.
- We would also submit the clinical assay validation documents at that time as well.
- For the Clinical and CMC packages for the BLA we are currently working to submit a request for feedback on the proposed contents by no later than Feb 1st and we will be asking for feedback within 2 weeks from when we submit.
- Based on current timelines and assumptions for what will be required, we are targeting submission of the rest of the BLA the first week of April.
- These timings will be adjusted based on CBER pre-BLA feedback.

We are currently planning for the first roll to be Module 4 with a submission date of mid-to end- February. Is this still acceptable to CBER?

**FDA Response to Sponsor Question 2:**

No. We request that you submit the nonclinical package at a time that is more synchronous with the timing of the proposed submission of Clinical and CMC packages. We don't see any added value for early submission of the nonclinical package as these data have already been submitted for review under IND 19736 and EUA 27034.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.



**Request for Comments and Advice**

**COVID-19 Vaccine (BNT162, PF-07302048)  
Proposal for Clinical and Post-Authorization Safety Data Package  
for Biologics License Application**

**03 February 2021**

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## 1. INTRODUCTION

Reference is made to the Investigational New Drug Application (BB-IND 19736) for the COVID-19 vaccine (BNT162; PF-07302048) Pfizer and BioNTech have been developing for the prevention of COVID-19 in individuals 12 years of age and older. The IND was effective on 29 April 2020. Fast Track Designation was granted on 07 July 2020 for individuals 18 years of age and older. Reference is also made to the Emergency Use Authorization (EUA 27034) for active immunization to prevent COVID-19 in individuals 16 years of age and older that was issued for this vaccine on 11 December 2020 (EUA product identified as Pfizer-BioNTech COVID-19 Vaccine). The purpose of this communication is to request feedback from the United States (US) Food and Drug Administration (FDA) on the proposed clinical and post-authorization safety data package to support the initial Biologics License Application (BLA) for this product. The proposed indication sought in the initial BLA is active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

The COVID-19 vaccine in clinical development by Pfizer and BioNTech, and currently supplied to the US market under EUA 27034, is administered at 30 µg via intramuscular (IM) injection following a dosing regimen of two 0.3-mL doses given 3 weeks apart. BNT162b2 is intended for active immunization to prevent COVID-19 caused by the virus SARS-CoV-2. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 formulated in lipid nanoparticles (LNPs). Clinical studies include >46,000 participants, and the most recent (13 January 2021) monthly post-EUA safety review accounted for >26 million BNT162b2 doses shipped globally under EUA, Temporary Use Authorization, or Conditional Marketing Authorization.

EUA application 27034 presented safety, efficacy, and immunogenicity data available as of 14 November 2020 from the pivotal Phase 1/2/3 Study C4591001 and supporting Phase 1/2 Study BNT162-01. Data included in the EUA are summarized in [Section 1.1](#).

[Section 1.2](#) summarizes the clinical data to be included in the initial BLA to support the proposed indication. Briefly, we propose the BLA to include the data previously provided in the EUA application, plus Study C4591001 safety data consisting of follow-up to 6 months after Dose 2 (with at least 3000 BNT162b2-vaccinated Phase 2/3 participants ≥16 years of age), and safety and immunogenicity data to 1 month after Dose 2 for adolescents 12 to 15 years of age. We also propose to utilize the Summary Monthly Safety Report (SMSR) that we submit monthly to BB-IND 19736 as a condition of EUA 27034 to support the safety profile of the product and proposed prescribing information for the BLA (see [Section 1.4](#)).

An additional efficacy analysis is currently being considered to evaluate efficacy against asymptomatic SARS-CoV-2 infection based on the N-binding (N-Ig) immunoassay to detect seroconversion occurring post-vaccination in accordance with protocol C4591001 Amendment 11. FDA guidance on this proposed analysis is requested.

Pfizer and BioNTech anticipate submitting the BLA in April 2021. The draft Table of Contents (TOC) for the BLA is provided in the [Appendix](#). In lieu of a pre-BLA meeting, we

respectfully ask for Agency written feedback to the questions in [Section 2](#), within 2 weeks of receipt of this Request for Comments and Advice.

Please note that a separate request for Agency advice is being submitted for BLA contents related to chemistry, manufacturing, and controls (CMC).

### **1.1. Clinical Data Previously Submitted to FDA for Emergency Use Authorization**

The EUA application was based on data from randomized, placebo-controlled Phase 1/2/3 Study C4591001 and open-label, first-in-human (FIH) Phase 1/2 Study BNT162-01. For both studies, full clinical study reports (CSRs) containing the data outlined below were filed to the IND to support the EUA application. Briefly, these data showed overwhelming evidence of efficacy against COVID-19, robust immunogenicity including neutralizing and binding antibodies and T cell immunity directed against SARS-CoV-2 antigens; a well-characterized safety and tolerability profile; and evidence of comparable efficacy and safety across demographic, SARS-CoV-2 serostatus, and/or at-risk comorbidity subgroups.

The pivotal data in the EUA were from the Phase 2/3 portion of Study C4591001 (last data cutoff date: 14 November 2020), which included the protocol pre-specified final analysis of efficacy. Additionally, immunogenicity, reactogenicity, and safety analysis of participants with a median  $\geq 2$  months follow-up after Dose 2 was also included.

Clinical data previously provided to the FDA in the EUA application included the following:

#### ***Safety in the EUA***

Safety data were included for Study C4591001 Phase 2/3 participants  $\geq 16$  years of age (randomized 1:1 BNT162b2 vs placebo) consisting of analyses for  $\sim 44,000$  enrolled participants up to the EUA data cutoff date, and for  $\sim 38,000$  with median  $\geq 2$  months follow-up after Dose 2. Reactogenicity data recorded in electronic diaries (e-diaries) for 7 days after each dose was included for the reactogenicity subset ( $N \sim 8000$ )  $\geq 16$  years of age and for  $N=100$  participants 12 to 15 years of age. Subgroups analyses were included for Phase 2/3 reactogenicity ( $N \sim 8000$ ) by age and baseline SARS-CoV-2 serostatus and for Phase 2/3 adverse events (AEs) ( $N \sim 38,000$ ) by age, race, ethnicity, and baseline SARS-CoV-2 serostatus.

Safety data were included for Study C4591001 Phase 1 participants in the 18 to 55 years of age and 65 to 85 years of age cohorts ( $N=15$  per age group, randomized 4:1 BNT162b2 vs placebo), which consisted of reactogenicity and AEs for up to 1 month post-Dose 2 with additional AE follow-up for up to 4 months after Dose 2 (ie, up to the EUA data cutoff date). Clinical laboratory evaluations up to 1 month post-Dose 2 were also provided (per protocol, conducted for Phase 1 only).

Phase 1 safety data from Study BNT162-01 were included and consisted of reactogenicity, AEs, and clinical laboratory evaluations of participants in the 18 to 55 years of age cohort.

### ***Efficacy in the EUA***

Efficacy data were included for Study C4591001 Phase 2/3 participants  $\geq 12$  years of age in the efficacy populations and consisted of the protocol pre-specified interim analysis of first primary efficacy endpoint data (based on accrual of at least 62 cases of COVID-19) and final analyses of primary and secondary efficacy endpoint data (based on accrual of at least 164 cases of COVID-19).

The interim analysis of efficacy was conducted on an accrued 94 COVID-19 cases and included subgroup analyses by age, race, ethnicity, country, and baseline SARS-CoV-2 serostatus. The final analysis of efficacy was conducted on an accrued 170 COVID-19 cases and included subgroup analyses by age, race, ethnicity, country, baseline SARS-CoV-2 serostatus, and risk factors (age, obesity, and/or Charlson comorbidity index).

Post hoc analyses were provided to CBER in response to post-EUA queries that summarized participants in the efficacy populations who had a potential COVID-19 illness that was not confirmed to be COVID-19, or clinical COVID cases that met the case definition but were not confirmed by PCR. Additionally, post hoc analyses were provided in response to a post-EUA query from CBER with detailed subgroup analyses of the primary efficacy endpoints for at-risk participants  $\geq 65$  years of age or with specific comorbidities (hypertension, obesity, diabetes, malignancy, cardiovascular disease, or chronic pulmonary disease). Additionally, a post hoc analysis was included using the CDC definition of severe COVID-19.

### ***Immunogenicity in the EUA***

Immunogenicity data for Study C4591001 Phase 2 participants  $\geq 18$  years of age (N~360) included Phase 2 participants  $\geq 18$  years of age and consisted of SARS-CoV-2 neutralizing titers and IgG-antigen binding levels to 1 month after Dose 2.

Immunogenicity data were included for Study C4591001 Phase 1 participants in the 18 to 55 years of age and 65 to 85 years of age cohorts, which consisted of SARS-CoV-2 neutralizing titers and IgG-antigen binding levels to 1 month after Dose 2.

Phase 1 immunogenicity data from Study BNT162-01 were included and consisted of SARS-CoV-2 neutralizing titers, IgG-antigen binding levels, and T cell response data for participants in the 18 to 55 years of age cohort.

## **1.2. Clinical Data Proposed for the Initial Biologics License Application Submission**

The initial BLA will be based on the single pivotal registration study, Phase 1/2/3 Study C4591001, with supporting data from Phase 1/2 Study BNT162-01.

The BLA is planned to include the following data from Study C4591001:

- (1) data previously submitted in the EUA (see [Section 1.1](#))
- (2) follow-up safety for up to 6 months after Dose 2

(3) safety and immunogenicity for 12 to 15 years of age group up to 1 month post-Dose 2

(4) results of the efficacy analysis against asymptomatic infection.

Supportive safety and immunogenicity (including T cell response) data from Study BNT162-01 will also be included in the BLA.

C4591001 and BNT162-01 clinical data will be presented in clinical summary documents and CSRs in BLA Modules 2 and 5.

Specifically, the proposed initial BLA clinical data package would include the following:

### ***Safety in the BLA***

Safety data in the BLA will include follow-up for up to 6 months after Dose 2 in all phases of Study C4591001. For Phase 1 participants, safety follow-up to 6 months post-Dose 2 for the younger (18 to 55 years of age) and older (65 to 85 years of age) BNT162b2 30- $\mu$ g groups (N=15 per age group) will be provided. Phase 2/3 safety follow-up to 6 months post-Dose 2 will be provided for N~46,000 participants as described below.

Since the issuance of the EUA in the US, C4591001 study participants  $\geq$ 16 years of age have had the option per protocol to be unblinded to learn if they were randomized to BNT162b2 or placebo, and if randomized to placebo to be vaccinated with BNT162b2, when they become eligible per national and state/local guidance under the EUA. This process began on 14 December 2020, and in the US the process is expected to be largely completed by 01 March 2021. Operationally, this means that each participant will have been unblinded to treatment assignment on different days. AEs will have occurred in 2 different periods for each participant: the time period each participant remained blinded to treatment assignment and the time following unblinding until the data cutoff for the analysis. Hence, Pfizer proposes to summarize Phase 2/3 safety data as 3 separate analyses (see below). Available safety data will be included from all enrolled participants (N~46,000) up to the BLA data cutoff date. Specifically:

#### **(1) Blinded, placebo-controlled analysis for the duration of blinded follow-up.**

Blinded safety analyses will provide data comparing participants randomized to BNT162b2 versus placebo through 1 month post-Dose 2 and through the duration of blinded follow-up in the study (with each participant's data censored at the time of unblinding). AE rates through the end of the blinded follow-up will be adjusted for exposure time (ie, based on a denominator of person-years of exposure). These data will provide blinded, controlled safety follow-up for the maximum duration prior to participants' unblinding. Due to the post-EUA protocol provision for unblinding and crossover of placebo recipients to be vaccinated with BNT162b2, it is expected that these blinded, controlled analyses will not cover a full 6-month period of blinded safety follow-up, but should cover up to approximately 5 months.

#### **(2) Six months of follow-up after Dose 2 for at least 3000 participants who were randomized to BNT162b2 at the start of the study.**

Data will be presented separately for participants randomized to BNT162b2 for up to 6 months after Dose 2, inclusive of data

obtained during blinded follow-up and after participants' unblinding. These data will provide continuous follow-up of at least 3000 BNT162b2-vaccinated individuals to 6 months after completing the two-dose regimen.

**(3) Observational data for participants randomized to BNT162b2 and placebo from the time of unblinding to the BLA cutoff date.** Observational safety data will be presented separately for participants after they were unblinded. These data will be summarized independently for two groups: the participants randomized to placebo to cover the period of time starting when they were unblinded for crossover vaccination with BNT162b2 until the BLA data cutoff date, and the participants randomized to BNT162b2 from the time starting when they were unblinded up to the BLA data cutoff date. These data, in conjunction with the blinded, placebo-controlled analysis, will provide all of the safety data reported in the study as of the data cutoff for the analysis.

Safety data will also be included for N~2200 Phase 2/3 participants 12 to 15 years of age and will consist of reactogenicity up to 7 days after each dose and AEs with follow-up to 1 month after Dose 2. These data will support the proposed indication for individuals  $\geq 12$  years of age. These data are considered sufficient to support use in this age group because the safety profile of BNT162b2 among older adolescents 16 to 17 years of age was comparable for the periods from vaccination to 1 month after Dose 2, and from 1 to 2 months after Dose 2. The safety profile of older adolescents 16 to 17 years of age was also similar to the young adult age group up to 55 years of age.

Subgroup analyses of safety to be submitted in the BLA will consist of those previously provided in the EUA submission, which included N~38,000 Phase 2/3 participants up to 1 month after Dose 2. Based on the substantial amount of subgroup data already provided in the EUA application, no new subgroup analyses are proposed for the BLA.

Supportive safety data from Study BNT162-01 will be included in the BLA, consisting of reactogenicity, AEs, and clinical laboratory evaluations of participants in the 18 to 55 years of age and 56 to 85 years of age cohorts (N=12 per group), in which the majority of BNT162b2-vaccinated participants have now completed the study (ie, followed to 1 month after Dose 2 and completed the end of study visit).

### ***Efficacy in the BLA***

Efficacy data in the BLA will include what was provided in the EUA, which serves as the basis for US licensure.

Additionally, a new analysis is currently being considered for inclusion in the BLA:

**(1) Efficacy against asymptomatic SARS-CoV-2 infection, based on the N-binding (N-Ig) immunoassay to detect seroconversion occurring post-vaccination.** This is a secondary endpoint per protocol C4591001 (Amendment 11), with efficacy analysis planned to be conducted on Phase 2/3 participants with N-Ig data at 1-month post Dose 2. This analysis will present vaccine efficacy (VE) against asymptomatic SARS-CoV-2 infection, based on N binding antibody seroconversion in participants with no serological or virological

evidence of infection or confirmed COVID-19 prior to 1-month post Dose 2. VE will be declared if the lower bound of the 2-sided 95% CI for VE is >20%.

We propose to reflect the results of this analysis in Section 14 (Clinical Studies) of the product labeling, as they provide important information regarding vaccine effectiveness.

### ***Immunogenicity in the BLA***

The BLA will include immunogenicity results (SARS-CoV-2 neutralizing titers) from Study C4591001. SARS-CoV-2 neutralizing antibody titers will be assessed using a validated assay (the validation report and data package will be provided in the BLA).

Immunogenicity results from Study C4591001 will include:

(1) **Phase 1 participants up to 6 months after Dose 2.** These data include BNT162b2 younger (18 to 55 years of age) and older (65 to 85 years of age) groups (N=15 per group).

(2) **Phase 2 participants 18 to 85 years of age (N~360) up to 1 month after Dose 2.** These data were included in the EUA submission.

(3) **Phase 2/3 participants 12 to 15 years of age (N~2200) compared participants 16 to 25 years of age (N~2200) up to 1 month after Dose 2.** A noninferiority analysis of neutralizing titers in participants 12 to 15 years of age versus neutralizing titers of participants 16 to 25 years of age at 1-month post-Dose 2 will provide immunobridging, infer effectiveness of the candidate vaccine for the younger adolescents, and support the proposed indication for individuals  $\geq 12$  years of age. The geometric mean ratio (GMR) of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

Supportive data from Study BNT162-01 immunogenicity data will be included in the BLA, consisting of SARS-CoV-2 neutralizing titers and T cell response data for participants in the 18 to 55 years of age and 56 to 85 years of age cohorts (N=12 per group).

### **1.3. eSUB/CDISC Data**

Pfizer/BNT proposes the following eSUB/CDISC data for the BLA submission. Specifically:

#### ***Study C4591001***

Similar to the EUA eSUB filing, Pfizer/BioNTech proposes to have separate eSUB packages based on the C4591001 safety and efficacy data cuts, as follows:

- eSUB package (including all Phase 2/3 participants) for safety and immunogenicity based on the safety data cut for Phase 3 3000+ vaccine/active participants with 6-month post-Dose 2 follow-up

- eSUB package (including all Phase 2/3 participants) for efficacy based on the efficacy data cut for Phase 3 N-binding asymptomatic infection analysis
- eSUB package (including only Phase 1 participants) for safety and immunogenicity with 6-month post-Dose 2 follow up can also be available upon request.

Pfizer will carry forward agreements implemented in the EUA filing and SDSP:

- Reference BB-IND 19736
- eg, SDTM mapping rules will be applied to provide flat model solely for reactogenicity data collected via e-diary per study design and data collection.

### ***Study BNT162-01***

Similar to the EUA filing, a separate eSUB package will be provided to support the BNT162-01 CSR to be included in the BLA.

## **1.4. Post-Authorization Safety Data**

The BLA will also include post-authorization safety data collected after the issuance of the EUA in the US. These post-authorization safety data are continuously reviewed by Pfizer and BioNTech and submitted to the FDA in a monthly cumulative report. Please refer to the current Summary Monthly Safety Report (SMSR) located in Module 1.13.15 as an example. The most current SMSR available at the time the BLA will be included in Module 5 and summarized in Module 2 clinical summary documents. These data will provide additional safety information reported for individuals vaccinated outside of the clinical studies and represent the safety experience from millions of doses of BNT162b2 administered globally.

## **2. QUESTIONS FOR THE AGENCY**

### **2.1. Question 1: Clinical Safety**

Does CBER agree with the proposed clinical contents of the planned BLA to support the proposed indication? Specifically:

- a. Does CBER agree with the proposed updated safety data package to support use in individuals >16 years of age?
  - i. The package will include a safety subset (>16 years of age) in at least 3000 vaccinated individuals at 6 months post-Dose 2. Please note, crossover of placebo participants has been initiated and is expected to be largely completed by 01 March 2021. Therefore, a placebo-controlled analysis will be available for up to approximately 5 months after Dose 2 but will never be available for all 3000 individuals for the 6-month period.
- b. Does CBER agree that the data package is acceptable to support the proposed indication in individuals 12 to 15 years of age?

- i. The proposed safety package includes 1 month post-Dose 2 for participants 12 to 15 years of age. Given that the clinical experience in participants >16 years of age does not indicate a difference in safety profile between 1 month post-Dose 2 and 2 months post-Dose 2, does the Agency agree that the proposed 1 month post-Dose 2 safety data in participants 12 to 15 years of age are adequate to support licensure in this age group?
- c. Does CBER agree that safety narratives submitted with the BLA can be based upon the same conditions used for the EUA submission: hybrid (programmed and prose) narratives for deaths, related serious adverse events, and safety-related withdrawals; and programmed narratives for all other serious adverse events?
- d. Does CBER agree that no new safety subgroup analyses from Study C4591001 are required beyond what was conducted for N~38,000 Phase 2/3 participants up to 1 month post-Dose 2 (and as reported in the EUA)?

## 2.2. Question 2: Clinical Efficacy, Immunogenicity, and Effectiveness

Does CBER agree that the proposed efficacy, immunogenicity, and effectiveness data package is acceptable to support the proposed indication? Specifically:

- a. Does CBER agree that the previously completed primary endpoint analysis is adequate and acceptable to support the proposed indication?
- b. Does CBER agree with Pfizer/BioNTech's plans for the evaluation of efficacy against asymptomatic infection (N-Ig; in accordance with C4591001 Protocol Amendments 11 and 13)? Assuming these endpoints are met, does CBER agree that the results may be reflected in Section 14 (Clinical Studies) of the future product labeling?
- c. Does CBER agree with the proposed analysis to infer effectiveness of the candidate vaccine in individuals 12 to 15 years of age based on demonstration of non-inferior neutralizing antibody response as compared to individuals 16 to 25 years of age in Study C4591001?
  - i. Does CBER agree that if study endpoints are met, the immunogenicity data in the 12 to 15 years of age group will support licensure of the candidate vaccine in individuals 12 to 15 years of age?

## 2.3. Question 3: eSUB/CDISC Data

Pfizer/BioNTech proposes the eSUB/CDISC data for the BLA submission in [Section 1.3](#). Does CBER agree?

## 2.4. Question 4: Post-Authorization Safety

Does CBER agree the most current cumulative aggregate monthly safety report can be provided in the BLA to support the safety profile of the product and proposed prescribing

information? This document will be provided in Module 5 with relevant information extracted from it for inclusion in the Clinical Overview and Summary of Clinical Safety.

## 2.5. Question 5: Table of Contents

Does CBER have any comments regarding the proposed Table of Contents for the BLA?

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R-20-0112 - Characterizing the Immunophenotype in Spleen and Lymph Node of Mice Treated with SARS-COV-2 Vaccine Candidates
R-20-0211 - In vitro Expression of BNT162b2 Drug Substance and Drug Product
VR-VTR-10671 - BNT162b2 (V9) Immunogenicity and Evaluation of Protection against SARS-CoV-2 Challenge in Rhesus Macaques
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None.

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## Document Approval Record

<b>Document Name:</b>	COVID-19 Vaccine_preBLA_Clinical_1.12.4 Request for Comments and Advice_03Feb2021
<b>Document Title:</b>	COVID-19 Vaccine_preBLA_Clinical_1.12.4 Request for Comments and Advice_03Feb2021

<b>Signed By:</b>	<b>Date(GMT)</b>	<b>Signing Capacity</b>
Boyce, Donna	03-Feb-2021 22:12:16	Regulatory Affairs Approval



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

**DATE:** March 9, 2021 **PAGES:** 8

**TO:** **BioNTech SE/Pfizer. Inc.**  
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**CBER Reference:** IND 19736.201

**IND Title:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:** CBER comments regarding the proposal for clinical and post-EUA safety data package for BLA

Dear Ms. Aghajani Memar:

Reference is made to the amendment 201 (dated February 4, 2021) to your IND 19736 that contained your Request for Comment and Advice (in lieu of a Pre-BLA meeting) regarding your proposal for the clinical and post-EUA safety data package for a BLA. We have the following comments regarding your proposal:

**Clinical Safety:****Sponsor Question 1.a:**

Does CBER agree with the proposed clinical contents of the planned BLA to support the proposed indication? Specifically:

- i. Does CBER agree with the proposed updated safety data package to support use in individuals >16 years of age?

The package will include a safety subset (>16 years of age) in at least 3,000 vaccinated individuals at 6 months post-Dose 2. Please note, crossover of placebo participants has been initiated and is expected to be largely completed by 01 March 2021. Therefore, a placebo-controlled analysis will be available for up to approximately 5 months after Dose 2 but will never be available for all 3,000 individuals for the 6-month period.

**FDA Response to Sponsor Question 1.a:**

A. As described in the FDA Guidance, "[Development and Licensure of Vaccines to Prevent COVID-19](#)" (June 2020), the pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure, and we expect that adequately powered COVID-19 vaccine efficacy clinical trials would be of sufficient size to provide an acceptable safety database for *each study age cohort* (e.g., 16 through 55 years and >55 years). To allow for timely licensure of the Pfizer COVID-19 vaccine while ensuring adequate safety data to support licensure, we would consider an acceptable pre-licensure safety database to include a median of 6 months of follow-up post-Dose 2 for all subjects included in the EUA safety population (as defined in your EUA request submission) who were initially randomized to BNT162b2, and also including subjects from Germany and Turkey (enrolled after cutoff date for EUA). We acknowledge the stated limitation regarding the placebo-controlled analysis. Please provide an estimate of the number of participants who will have 6 months of blinded follow up after Dose 2.

- B. We request that the BLA contents be limited to participants 16 years of age and older, for reasons stated in our response to Question 1.b.

**Sponsor Question 1.b:**

Does CBER agree that the data package is acceptable to support the proposed indication in individuals 12 to 15 years of age?

The proposed safety package includes 1 month post-Dose 2 for participants 12 to 15 years of age. Given that the clinical experience in participants >16 years of age does not indicate a difference in safety profile between 1 month post-Dose 2 and 2 months post-Dose 2, does the Agency agree that the proposed 1 month post-Dose 2 safety

data in participants 12 to 15 years of age are adequate to support licensure in this age group?

**FDA Response to Sponsor Question 1.b:**

We do not agree that the proposed data package would support an indication for use in individuals 12 to 15 years of age because the proposed 1-month duration of follow-up is not adequate to support licensure. Data to support licensure for use in individuals 12 to 15 years of age could therefore be considered in a post-approval BLA supplement following adequate follow-up (i.e., 6 months post-Dose 2) for all study subjects in this age group. Please also refer to our response to Question 1.e. regarding submission of an amendment to the EUA to support use in individuals 12 to 15 years of age before data are available to support submission of a sBLA for this age group.

**Sponsor Question 1.c:**

Does CBER agree that safety narratives submitted with the BLA can be based upon the same conditions used for the EUA submission: hybrid (programmed and prose) narratives for deaths, related serious adverse events, and safety-related withdrawals; and programmed narratives for all other serious adverse events?

**FDA Response to Sponsor Question 1.c:**

We agree that the safety narratives submitted with the BLA can be based upon the same conditions used for the EUA submission. We may request additional narratives during the course of our review.

Additionally, please provide narratives and available follow-up information for any reports of anaphylaxis and each of the following adverse events (AEs): Bell's Palsy, lymphadenopathy, appendicitis, pregnancy exposures and outcomes, and any additional AEs for which there is a numerical imbalance observed between the treatment arms.

**Sponsor Question 1.d:**

Does CBER agree that no new safety subgroup analyses from Study C4591001 are required beyond what was conducted for N~38,000 Phase 2/3 participants up to 1 month post-Dose 2 (and as reported in the EUA)?

**FDA Response to Sponsor Question 1.d:**

We request that the same subgroup analyses of safety data that were performed for the EUA submission also be conducted on the longer-term safety data (including a median of 6-months follow-up post-Dose 2 as described in our response to Question 1.a) intended to support your BLA submission. We also request the following in your BLA submission:

- i. Subgroup analyses of safety (solicited local reactions and systemic events, unsolicited AEs and SAEs) in participants with prior symptomatic COVID-19 to complement subgroup analyses of safety in participants with and without

- baseline evidence of prior SARS-CoV-2 infection. We acknowledge that these subgroup analyses will be limited to participants who were initially randomized to placebo and subsequently received BNT162b2 and will represent unblinded follow-up. We are requesting these analyses because they are of public health interest and may inform labeling.
- ii. Safety data in the subgroup who were vaccinated after receiving placebo, as part of the crossover study design, if available, by baseline SARS CoV-2 status as defined in the protocol.
  - iii. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol.

**Sponsor Question 1.e (Additional Question for CBER Regarding the EUA - sent in an email on February 18, 2021):**

In Question 1.b, we requested CBER feedback regarding the clinical data package (safety and immunogenicity) to support licensure of the 12 – 15 year-old indication. These data are expected to be available by the end of March/early April.

At this time, we seek CBER guidance on whether the same data package proposed for inclusion in the BLA would support use of the vaccine in this age group (12 -15 years) under the EUA. We would like to submit these data as an amendment to the current EUA in mid-April.

Does CBER agree that these data would support use of the vaccine in the 12 – 15 year-old age group under the EUA?

Does CBER agree that extending the indication of the vaccine down to 12 years of age may be pursued as an amendment to the current EUA?

**FDA Response to Sponsor Question 1.e:**

We agree that the proposed data package that includes safety and immunogenicity through 1-month post-Dose 2 for individuals 12 through 15 years of age could be submitted as an amendment to the current EUA to support use of your product in this age group. Additionally, please submit available longer-term safety data from participants 16 through 55 years of age to complement the 1-month safety data cutoff proposed for participants 12 through 15 years of age. We would discuss these data at a VRBPAC meeting during review of the EUA amendment. In addition to immunogenicity data, we recommend that VE data for this age group, from the time of the EUA data cutoff, be provided with the submission.

Please provide an estimate of the number of participants 12 through 15 years of age with safety data through 1-month post-Dose 2 that will be included with the EUA amendment and clarify if this number includes all participants in this age group, or a subset.

**Clinical Efficacy, Immunogenicity, and Effectiveness:****Sponsor Question 2.a:**

Does CBER agree that the proposed efficacy, immunogenicity, and effectiveness data package is acceptable to support the proposed indication? Specifically:

- a. Does CBER agree that the previously completed primary endpoint analysis is adequate and acceptable to support the proposed indication?

**FDA Response to Sponsor Question 2.a:**

We disagree with your proposed efficacy, immunogenicity and effectiveness data package, which includes only primary endpoint efficacy data provided in the EUA, immunogenicity data from 360 Phase 2/3 participants from 1-month post-Dose 2 that was provided in the EUA, and 6-month neutralization titer results from 30 Phase 1 participants.

- i. Given the increased circulation of variants and the variable incidence rates of COVID-19 disease as compared to the time of the EUA submission review, we request the following components for the effectiveness data package for your BLA submission:
  - A. Supplemental efficacy results for the primary and secondary efficacy endpoints based on the blinded phase. All potential COVID-19 and severe COVID-19 cases as of the data cutoff date for the BLA should be adjudicated and included in the BLA.
  - B. Reference is made to the telephone conversation dated March 3, 2021 between Donna Boyce of Pfizer and Dr. Marion Gruber of this office during which you informed us that you have accrued around 1,000 total COVID-19 cases but that you are not planning to conduct further analyses. On March 4, 2021, we advised (via email from Dr. Marion Gruber to Donna Boyce) that you should conduct these additional analyses. On March 5, 2021, you stated (email from Donna Boyce to Dr. Marion Gruber) that Pfizer would conduct these additional analyses but that the results would be submitted to the IND. However, in the event that these results would warrant labeling, you would submit the data as an amendment to the BLA. On March 5, 2021, we advised (via email from Dr. Marion Gruber to Donna Boyce) that the data from these additional analyses should be included at the time of the original BLA submission as these data may provide important additional information regarding VE against severe COVID-19 disease, duration of protection and potentially efficacy against VOCs.
  - C. Sequencing analysis on breakthrough cases to assess the prevalence of variant strains among cases (all cases in vaccine recipients and a

corresponding random sampling of cases in placebo recipients, by geographic region/site).

D. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol.

- ii. In addition to phase 1 participants, please provide immunogenicity data through 6-months post-Dose 2 from all phase 2 participants and from phase 3 participants, if available.

**Sponsor Question 2.b:**

Does CBER agree with Pfizer/BioNTech's plans for the evaluation of efficacy against asymptomatic infection (N-Ig; in accordance with C4591001 Protocol Amendments 11 and 13)? Assuming these endpoints are met, does CBER agree that the results may be reflected in Section 14 (Clinical Studies) of the future product labeling?

**FDA Response to Sponsor Question 2.b:**

While we agree that data to inform VE against asymptomatic infection might be of interest for inclusion in product labeling, considerations for whether and how such data from analyses of the objectives described above are presented in labeling will depend upon our review of the data, including data to support fitness for purpose of the N-Ig serology assay to determine asymptomatic infection.

**Sponsor Question 2.c:**

Does CBER agree with the proposed analysis to infer effectiveness of the candidate vaccine in individuals 12 to 15 years of age based on demonstration of non-inferior neutralizing antibody response as compared to individuals 16 to 25 years of age in Study C4591001?

- i. Does CBER agree that if study endpoints are met, the immunogenicity data in the 12 to 15 years of age group will support licensure of the candidate vaccine in individuals 12 to 15 years of age?

**FDA Response to Sponsor Question 2.c:**

We defer final comment, as discussions with you about the seroresponse definition and statistical success criteria for immunobridging based on seroresponse rates are ongoing. Additionally, we request that you adjust the sample size calculation for the immunobridging analysis in individuals 12 through 15 years of age based on an assumption of a true GMR of 1, as your assumption of a true GMR of ~0.8 does not reflect non-inferiority.

**eSUB/CDISC Data:****Sponsor Question 3:**

Pfizer/BioNTech proposes the eSUB/CDISC data for the BLA submission as described in Section 1.3.

Does CBER agree?

**FDA Response to Sponsor Question 3:**

We generally agree with your proposal. Please refer to our responses to Questions 1.d and 2.a and adjust the planned data sets for the BLA submission based on those requests.

**Post-Authorization Safety:****Sponsor Question 4:**

Does CBER agree that the most current cumulative aggregate monthly safety report can be provided in the BLA to support the safety profile of the product and proposed prescribing information? This document will be provided in Module 5 with relevant information extracted from it for inclusion in the Clinical Overview and Summary of Clinical Safety.

**FDA Response to Sponsor Question 4:**

Monthly safety reports primarily focus on events that occurred during the reporting interval and include information not relevant to a BLA submission such as line lists of adverse events by country. We are most interested in a cumulative analysis of post-authorization safety data to support your future BLA submission. Please submit an integrated analysis of your cumulative post-authorization safety data, including U.S. and foreign post-authorization experience, in your upcoming BLA submission. Please include a cumulative analysis of the Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in your Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). Please also include distribution data and an analysis of the most common adverse events. In addition, please submit your updated Pharmacovigilance Plan with your BLA submission.

**Table of Contents:****Sponsor Question 5:**

Does CBER have any comments regarding the proposed Table of Contents for the BLA?

**FDA Response to Sponsor Question 5:**

We agree with the proposed overall table of contents (regarding the nonclinical and clinical information) for the planned BLA.

**Additional FDA Comments:**

1. Please plan to submit specified BLA data analyses in 508-compliant word format tables, as previously submitted with Amendment 3 to the EUA 27034, identified as responses to the FDA's November 17, 2020 and November 19, 2020 Requests; we will provide a revised request for the BLA submission.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.



**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH  
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**DATE:** March 31, 2021 **PAGES:** 7

**TO:** **BioNTech SE/Pfizer. Inc.**  
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**CBER Reference:** IND 19736.230

**IND Title:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:** CBER comments regarding the strategy for submitting the CMC contents of the BLA for COVID-19 vaccine

Dear Ms. Aghajani Memar:

Reference is made to amendment 230 (dated March 1, 2021) to your IND 19736 that contained your Request for Comments and Advice (in lieu of a Pre-BLA meeting) regarding your strategy for submitting the CMC contents of the BLA for COVID-19 vaccine.

Reference is also made to the following:

- Pfizer's Request for Comments and Advice regarding proposal for clinical and post-EUA safety data package for BLA (IND 19736.201 submission dated February 4, 2021)
- Pfizer's Request for Comments and Advice regarding plans for CMC portions of the BLA (IND 19736.230 submission dated March 1, 2021)
- CBER comments on IND 19736.201 submission were sent on March 9, 2021.
- CBER's communication dated September 28, 2020 regarding the practical aspects of the planned BLA submission (IND 19736.84 submission). As per May 2014 FDA Guidance: Expedited Programs for Serious Conditions -Drugs and Biologics <https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf>, for preliminary agreement on your rolling BLA approach, we requested that you provide: (1) the schedule for submission of each portion of the BLA, and (2) a description of portions of the application to be submitted separately (late components). We noted that the cited guidance recommends submissions of complete BLA sections such as the entire CMC section, toxicology section or clinical section. Although we may have indicated that we would accept rolling sub-sections within these main sections, to reach preliminary agreement, we requested that the number of rolling sub-sections be limited and that you describe the timeline and the information to be included in each.

In addition, please note that the review clock will not begin until you inform us that a complete BLA was submitted. After you have notified us that your application is complete, we will make a filing determination within the usual time.

In this communication, we are providing additional comments on and requests for clinical/statistical and CMC/facilities information that should be included in the BLA for your COVID-19 vaccine. Please note that our comments are not all inclusive, and we may have additional comments or questions after we receive the requested information.

In addition to responding to our comments and questions, please provide a detailed timeline for your planned submissions and indicate what type of submission each would be:

1. an amendment to the EUA
2. a section of the original rolling BLA
3. an amendment to the original BLA
4. a post-approval BLA supplement

We recommend that after you submit your responses to our comments (including a detailed timeline for your planned submissions), a teleconference be scheduled for additional discussion and clarifications.

**FDA comments on your questions included in amendment 230:**

**Sponsor Question 1:**

Does CBER agree with the proposed Table of Contents of the CMC modules of the BLA?

**FDA Response to Sponsor Question 1:**

We generally agree with the proposed Table of Contents of the CMC modules of the BLA. However, the Table of Contents does not appear to contain references to the information listed below that is required in your BLA submission. In addition, please refer to the Preliminary Meeting Responses (Type C meeting; CRMTS-12822; IND 19736.67) sent on September 18, 2020 and the September 23, 2020 Meeting Summary sent on October 14, 2020 for additional list of items to be included in the BLA.

(b) (4)

A large grey rectangular box containing the text "(b) (4)" in a large, bold, black font, indicating a redacted section of the document.

**Sponsor Question 2:**

Does CBER agree that the proposed CMC modules contain all changes introduced under the EUA/IND through March 31, 2021 and that additional changes implemented under the EUA may be submitted as post approval BLA supplements?

**FDA Response to Sponsor Question 2:**

We defer our response until we have reviewed your timeline for your planned submissions for CMC information. This issue will be further discussed in the recommended teleconference.

**Sponsor Question 3:**

Does CBER agree that the EUA may remain in place following approval of the BLA to enable manufacture and distribution of vaccine through the remainder of 2021 and to allow time to update the BLA with changes implemented between April 2021 and BLA approval?

**FDA Response to Sponsor Question 3:**

As stated in the Guidance for Industry “Emergency use authorization of medical products and related authorities” <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>, the HHS Secretary’s EUA declaration will terminate on the earlier of: (1) a determination by the HHS Secretary that the circumstances that precipitated the declaration have ceased (after consultation as appropriate with the Secretary of Homeland Security or the Secretary of Defense), or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved (section 564(b)(2)). For example, an EUA issued to allow an unapproved use of an approved product may no longer be needed if that product is later approved by FDA for the use permitted by the EUA. Thus, while it may be possible for your EUA to remain in place following approval of the BLA through the remainder of 2021, a final determination cannot be made at this time. It is our expectation that the majority of vaccine distribution occurs under the BLA rather than the EUA. Please note that after BLA approval, all manufacturing changes must be done under the BLA as post-approval supplements. All the CMC information for the vaccine lots intended for distribution under the BLA and the information on all the facilities used for production of these lots should be included in the original BLA. Please note that changes in manufacture or addition of facilities during the BLA review may result in a major amendment. Alternatively, if you were to submit these proposed manufacturing changes as a rolling BLA, the review clock would not begin

until you inform us that the final piece containing complete manufacturing information has been submitted.

As stated in our response to Question 2, we will provide additional guidance after we have reviewed the timeline for your planned submissions regarding the CMC and facilities information. This issue will be further discussed in the recommended teleconference.

**Additional FDA Comments regarding information included in amendment 230:**

1. Please explain what changes are being made for (b) (4) " referred to in Table 1.
2. Please note that Table 2 states that (b) (4)  
Please make the appropriate corrections to the Table.

**Additional FDA comments on the clinical/statistical and CMC/facilities information that should be included in the BLA for your COVID-19 vaccine:**

**Clinical/Statistical:**

1. The safety database should include a median follow-up duration of 6 months post Dose 2 for Phase 2/3 participants 16 years of age and older who were included in the EUA Safety Population and initially randomized to BNT162b2.
2. Safety Data:
  - a. Safety narratives as outlined in our response to amendment 201.
  - b. Subgroup analyses of safety (solicited local reactions and systemic events, unsolicited AEs and SAEs) in participants with prior symptomatic COVID-19 to complement subgroup analyses of safety in participants with and without baseline evidence of prior SARS-CoV-2 infection. We acknowledge that these subgroup analyses will be limited to participants who were initially randomized to placebo and subsequently received BNT162b2 and will represent unblinded follow-up. We are requesting these analyses because they are of public health interest and may inform labeling.
  - c. Safety data in the subgroup who were vaccinated after receiving placebo, as part of the crossover study design, if available, by baseline SARS CoV-2 status as defined in the protocol.
  - d. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol.

### 3. Effectiveness Data:

- a. Supplemental efficacy results for the primary and secondary efficacy endpoints based on the blinded phase. All potential COVID-19 and severe COVID-19 cases as of the data cutoff date for the BLA should be adjudicated and included in the BLA.
- b. Sequencing analysis on breakthrough cases to assess the prevalence of variant strains among cases (all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site).
- c. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol.

### Product (CMC):



### Product (Assays/Methods):

5. In your BLA submission, please include methods and method validations for analytical tests used for drug substance (DS) and DP release:
  - a. Method descriptions should be of sufficient detail to show they are being performed within validation limits. The descriptions of compendial methods should be sufficient to confirm they are being performed as specified in USP or European Pharmacopeia.
  - b. Full validation reports should be provided for non-compendial release tests and the qualification/verification reports for compendial assays should demonstrate that they are suitable (lack of matrix effect) for their intended purpose. Examples include the following:
6. Please provide a complete qualification report for bioburden testing using drug substance including the type of media, conformance lot numbers, incubation conditions and duration, to ensure the method is suitable under the actual conditions of use.

7. Please provide detailed bacterial endotoxin test qualification reports for the drug substance and BNT162b2 drug product to ensure the method is suitable under the actual conditions of use. The reports should include MVD, lot numbers of product tested, positive product control percent recoveries and an optimal selected product testing dilution.
8. At the time of submission, please be prepared to provide CBER with three lots of DP samples that are representative of material to be distributed under the approved license. In addition, be prepared to send any in-house generated standards/references and/or reagents used in the testing of the DP. CBER will provide information on when and where to send the samples, standards/references and reagents after submission of the BLA.
9. In your BLA submission, please include a lot release protocol template which includes quality control data for the DS and DP. Do not submit lot release protocols for specific lots until after CBER has reviewed and found the lot release protocol template acceptable.

**Facilities:**

10. Referring to Table 2, *Planned US EUA and BLA Supply Chain Manufacturing Nodes* (in IND 19736.230 submission dated March 1, 2021), please provide the following information:

- (b) (4)

[Redacted]

11. (b) (4)

[Redacted]

12. (b) (4)

[Redacted]

13. Please provide a table in the BLA submission detailing new and/or additional information from the information submitted for EUA authorization.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.



**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH  
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**DATE:** April 1, 2021 **PAGES:** 5

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**CBER Reference:** IND 19736.201

**IND Title:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:** CBER clarification to a few of the comments sent on March 9, 2021 regarding the proposal for clinical and post-EUA safety data package for BLA

Dear Ms. Aghajani Memar:

Reference is made to the amendment 201 (dated February 4, 2021) to your IND 19736 that contained your Request for Comment and Advice (in lieu of a Pre-BLA meeting)

regarding your proposal for the clinical and post-EUA safety data package for a BLA, and CBER's comments regarding Pfizer's proposal sent on March 9, 2021.

Reference is also made to Pfizer's clarification questions sent in emails to CBER's Ramachandra Naik by Pfizer's Neda Aghajani Memar (on March 12, 2021) and Elisa Harkins (on March 17, 2021) regarding few of CBER's March 9, 2021 comments. We have the following responses to your clarification questions:

***FDA Response to Sponsor Question 1.c (sent on March 9, 2021):***

*We agree that the safety narratives submitted with the BLA can be based upon the same conditions used for the EUA submission. We may request additional narratives during the course of our review.*

*Additionally, please provide narratives and available follow-up information for any reports of anaphylaxis and each of the following adverse events (AEs): Bell's Palsy, lymphadenopathy, appendicitis, pregnancy exposures and outcomes, and any additional AEs for which there is a numerical imbalance observed between the treatment arms.*

**Sponsor's clarification Question to item 1.c:**

In response to CBER's request for narratives and follow up information for "... any additional AEs for which there is a numerical imbalance observed between treatment arms" Pfizer anticipates there will be many numerical differences in any large study. We therefore plan to screen AESIs identified by the CDC using the statistical criterion and clinical assessment summarized below, to determine which events warrant narratives:

- AESIs with lower bound of 2-sided 95% CI for between-group difference that excludes 0
- Among screened AESIs identified by the statistical criterion above, we will prepare narratives for the set of events for which the difference is clinically meaningful.

Does CBER agree?

**FDA Response to item 1.c.:**

We disagree with your proposal. Please plan to provide narratives and line listings for AESIs as identified by the CDC, without the application of your proposed statistical criterion or assignment of clinical significance. Please provide narratives for the AESIs (that were not already categorized as a SAE) that occur at higher frequency in the vaccine group than the control group, which led to study withdrawal, considered at least possibly related to vaccination, or biologically plausible.

***FDA Response to Sponsor Question 2.a.i.C (sent on March 9, 2021):***

- i. Given the increased circulation of variants and the variable incidence rates of COVID-19 disease as compared to the time of the EUA submission review, we*

*request the following components for the effectiveness data package for your BLA submission:*

- C. Sequencing analysis on breakthrough cases to assess the prevalence of variant strains among cases (all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site).*

**Sponsor's clarification Question to item 2.a.i.C:**

Please note Pfizer/BioNTech will include an efficacy analysis by country in the BLA submission. However, sequencing analysis of breakthrough cases will not be available to be included at the time of the BLA submission. As these data are not required for initial licensure, Pfizer/BioNTech will provide these data as a post-approval supplement, once available. Does CBER agree?

**FDA Response to item 2.a.i.C.:**

Because of the increased circulation of variants and increasing incidence rates of COVID-19 disease, we request the sequence analysis data of all COVID-19 cases that will be provided with the BLA submission (all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site). Please acknowledge and update your timeline for expected BLA submission based on our data requests provided on March 9, 2021.

**FDA Response to Sponsor Question 2.a.ii (sent on March 9, 2021):**

- ii. In addition to phase 1 participants, please provide immunogenicity data through 6-months post-Dose 2 from all phase 2 participants and from phase 3 participants, if available.*

**Sponsor's clarification Question to item 2.a.ii:**

Please note that 6 month immunogenicity data for phase 2 and Phase 3 participants will not be available for the BLA. The Phase 2 data are anticipated by no later than end of 2Q 2021 and will be submitted to IND 19736 when available, the Phase 3 data will be completed subsequently. Does CBER agree with this plan?

**FDA Response to item 2.a.ii:**

We agree with your plan.

**FDA Response to Sponsor Question 2.b (sent on March 9, 2021):**

*While we agree that data to inform VE against asymptomatic infection might be of interest for inclusion in product labeling, considerations for whether and how such data from analyses of the objectives described above are presented in labeling will depend upon our review of the data, including data to support fitness for purpose of the N-Ig serology assay to determine asymptomatic infection.*

**Sponsor's clarification Question to item 2.b:**

Please note that the VE against asymptomatic infection based on the N-binding serology will not be available for the BLA. Pfizer/BioNTech will submit these data in a future labeling supplement. Does CBER agree with this plan?

**FDA Response to item 2.b:**

We agree with your change in plans to include analyses of VE against asymptomatic infection in a BLA supplement rather than in the original BLA.

**FDA Response to Sponsor Question 3 (sent on March 9, 2021):**

*We generally agree with your proposal. Please refer to our responses to Questions 1.d and 2.a and adjust the planned data sets for the BLA submission based on those requests.*

**Sponsor's clarification Question to item 3:**

Pfizer/BioNTech acknowledge CBER's comment and agree, that we will adjust the planned data sets (eSUB) for the BLA and EUA amendment submissions as appropriate.

Pfizer/BioNTech would like to make a further clarification on the SDTM mapping for reactogenicity data for C4591001. Specifically, Pfizer/BioNTech will provide the same mapping logic as in the EUA and also stated in the pre-BLA briefing document Section 1.3 whereby the SDTM mapping rules will be applied to provide a flat model (FACE, CE, VS, etc.) solely for reactogenicity data collected via e-diary per study design and data collection (e.g., not from an AE form). Pfizer/BioNTech will not be submitting a supplemental format schema as part of the BLA as most recently described in the [Response to CBER Comment #1 of the 08 January 2021 Information Request regarding Trumenba \(Meningococcal Group B Vaccine\) submitted on 12 March 2021 \(STN 125549/737\)](#). If required, Pfizer/BioNTech can submit tables using the new mapping if required. Does CBER agree?

**FDA Response to item 3:**

Your reference to a supplemental format schema as described under STN 125549/737 is unclear. We recommend standardizing the CE dataset format, as previously communicated in correspondences under IND 19736 and IND 15150, and summarized below:

- Reactogenicity events that begin within the prespecified assessment period, but are currently reported in the AE dataset should be transferred from AE to FACE, or be flagged in AE so that we know that it is being included in the CE dataset.
- Records covering the entire event duration (which could go beyond the protocol-defined assessment period) be created in the ADaM3 ADCEVD dataset with start/end dates and durations (based on first and last days the symptom was present as recorded in the e-diary and/or Symptom

Resolved Dates CRF, ignoring any gaps) derived from both the e-diary and CRF data.

- Include all individual supporting assessments (daily e-diary and any unplanned assessments) in the FACE domain and the assessor for each finding can be identified using FAEVAL (STUDY SUBJECT or INVESTIGATOR).
- Maintain one row per subject/vaccination/symptom in the CE domain, with CE summarizing the duration of the event and maximum severity. Maximum severity (CESEV) should be based on the highest-level severity reported by the subject (via e-diary) or investigator (in the unplanned assessment CRF).
- Use SUPPCE CESEV1 and CEDIFFRS to show assessment of severity by study subject and reason investigator's assessment of severity differed from study subject as needed for events reported in CE.

***Additional FDA Comment 1 (sent on March 9, 2021):***

*Please plan to submit specified BLA data analyses in 508-compliant word format tables, as previously submitted with Amendment 3 to the EUA 27034, identified as responses to the FDA's November 17, 2020 and November 19, 2020 Requests; we will provide a revised request for the BLA submission.*

**Sponsor's clarification Question to Additional FDA Comment 1:**

- a. We are looking to start working on programming for these. Do you have an estimate on when the request will be sent?
- b. Also, the Agency's note regarding the request for 508 tables coming was specific to the BLA. Please confirm that the Agency will not be issuing a request for specific 508 tables for the EUA Amendment to include the 12 to 15 year olds, or if this is not accurate, please let us know. We are actively working on both the EUA Amendment for the 12 to 15 years olds as well as the BLA (for 16 and above as requested) while we are waiting for CBER feedback.

**FDA Response to Additional Comment 1:**

Our request for 508-compliant tables in word format for the EUA Amendment for adolescents 12 through 15 years of age was sent to you on March 31, 2021. The request for 508-compliant tables for the BLA submission will be sent as soon as possible.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.

**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 19736**

**Response to CBER Comments received on 09 March 2021, 31 March 2021, and 01 April 2021, Regarding the Proposal for Clinical and Post-EUA Safety Data Package for BLA**

**07 April 2021**

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## INTRODUCTION

Reference is made to BB-IND 19736 for the Pfizer/BioNTech COVID-19 Vaccine (BNT162; PF07302048) and to IND amendment 201 (dated 04 February 2021), which contained a Request for Comments and Advice seeking Center for Biologics Research and Evaluation (CBER) feedback regarding the proposal for the clinical and post-EUA safety data package to support the initial Biologics License Application (BLA). CBER responded on 09 March 2021 and the Sponsor (hereafter referred to as Pfizer/BioNTech) requested clarification in our 12 March 2021 and 17 March 2021 submissions. CBER provided a response to Pfizer/BioNTech's clarification questions on 01 April 2021. Responses to CBER's comments are provided herein.

Reference is also made to the 31 March 2021 CBER communication regarding Pfizer/BioNTech's strategy for submitting the CMC contents of the BLA and additional CBER requirements for clinical/statistical information to be included in the planned BLA. In this correspondence, CBER requested that Pfizer/BioNTech provide a detailed timeline for the planned submissions and indicate what type of submission each would be:

1. an amendment to the EUA
2. a section of the original rolling BLA
3. an amendment to the original BLA
4. a post-approval BLA supplement

Provided herein are responses to CBER's correspondence of 09 March 2021, 31 March 2021, and 01 April 2021. Specific information can be found in the following sections:

- Clinical safety (Section 1)
- Clinical efficacy, immunogenicity, and effectiveness (Section 2)
- eSUB/CDISC Data (Section 3)
- Post-authorization safety (Section 4)
- Table of contents (Section 5)
- Additional FDA comments (Section 6)
- Timeline for Planned Submissions and Type of Submission (Section 7)

CBER's comments/requests in ***bold italics*** are followed by Pfizer/BioNTech's responses below. Pfizer/BioNTech respectfully requests a teleconference (as offered by CBER on 31 March 2021) the week of April 12, 2021 to discuss and align on the responses provided herein, including the timing of the planned BLA.

## CBER COMMENTS

### 1. CLINICAL SAFETY

#### 1.1. Sponsor's Question 1.a (sent on 04 February 2021)

Does CBER agree with the proposed clinical contents of the planned BLA to support the proposed indication? Specifically:

- i. Does CBER agree with the proposed updated safety data package to support use in individuals >16 years of age? The package will include a safety subset (>16 years of age) in at least 3,000 vaccinated individuals at 6 months post-Dose 2. Please note, crossover of placebo participants has been initiated and is expected to be largely completed by 01 March 2021. Therefore, a placebo-controlled analysis will be available for up to approximately 5 months after Dose 2 but will never be available for all 3,000 individuals for the 6-month period.

#### 1.1.1. CBER Response to Sponsor Question 1.a (received 09 March 2021)

- A. *As described in the FDA Guidance, "Development and Licensure of Vaccines to Prevent COVID-19" (June 2020), the pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure, and we expect that adequately powered COVID-19 vaccine efficacy clinical trials would be of sufficient size to provide an acceptable safety database for each study age cohort (e.g., 16 through 55 years and >55 years). To allow for timely licensure of the Pfizer COVID-19 vaccine while ensuring adequate safety data to support licensure, we would consider an acceptable pre-licensure safety database to include a median of 6 months of follow-up post-Dose 2 for all subjects included in the EUA safety population (as defined in your EUA request submission) who were initially randomized to BNT162b2, and also including subjects from Germany and Turkey (enrolled after cutoff date for EUA). We acknowledge the stated limitation regarding the placebo-controlled analysis. Please provide an estimate of the number of participants who will have 6 months of blinded follow up after Dose 2.*
- B. *We request that the BLA contents be limited to participants 16 years of age and older, for reasons stated in our response to Question 1.b.*

#### 1.1.2. Additional CBER Comments (received 31 March 2021)

1. *The safety database should include a median follow-up duration of 6 months post Dose 2 for Phase 2/3 participants 16 years of age and older who were included in the EUA Safety Population and initially randomized to BNT162b2.*

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### 1.1.3. Sponsor Response

- A. Pfizer/BioNTech plan to provide safety data in the BLA representing the entire safety population (N~44,000) through the data analysis cutoff date of 13 March 2021. Approximately 12,000 participants originally randomized to BNT162b2 will have follow-up of at least 6 months after Dose 2. Of these, 1778 will have blinded follow-up for  $\geq 6$  months after Dose 2.
  
- B. Pfizer/BioNTech acknowledge CBER's request. The BLA contents will be limited *to data from participants 16 years of age and older* and the initial proposed indication will be for use in individuals 16 years of age and older.

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## **1.2. Sponsor's Question 1.b. (sent on 04 February 2021)**

Does CBER agree that the data package is acceptable to support the proposed indication in individuals 12 to 15 years of age?

The proposed safety package includes 1 month post-Dose 2 for participants 12 to 15 years of age. Given that the clinical experience in participants >16 years of age does not indicate a difference in safety profile between 1 month post-Dose 2 and 2 months post-Dose 2, does the Agency agree that the proposed 1 month post-Dose 2 safety data in participants 12 to 15 years of age are adequate to support licensure in this age group?

### **1.2.1. CBER Response to Sponsor Question 1.b (received 09 March 2021)**

*We do not agree that the proposed data package would support an indication for use in individuals 12 to 15 years of age because the proposed 1-month duration of follow-up is not adequate to support licensure. Data to support licensure for use in individuals 12 to 15 years of age could therefore be considered in a post-approval BLA supplement following adequate follow-up (i.e., 6 months post-Dose 2) for all study subjects in this age group. Please also refer to our response to Question 1.e. regarding submission of an amendment to the EUA to support use in individuals 12 to 15 years of age before data are available to support submission of a sBLA for this age group.*

### **1.2.2. Sponsor Response**

Per CBER feedback, Pfizer/BioNTech will not include data from individuals 12-15 years of age in the initial BLA. Data to support use in this age group will be submitted at a later time as a supplemental BLA when further safety follow-up data are available.

As agreed with CBER, we plan to submit data for all participants in the 12-15 years of age group up to at least 1 month after Dose 2 in an EUA amendment planned for mid-April 2021 (see below, response to CBER Comment 1.e, [Section 1.5](#)). Additionally, Pfizer will submit all safety data through the data cutoff date of 13 March 2021.

### **1.3. Sponsor's Question 1.c (sent on 04 February 2021)**

Does CBER agree that safety narratives submitted with the BLA can be based upon the same conditions used for the EUA submission: hybrid (programmed and prose) narratives for deaths, related serious adverse events, and safety-related withdrawals; and programmed narratives for all other serious adverse events?

#### **1.3.1. CBER Response to Sponsor Question 1.c (received 09 March 2021)**

*We agree that the safety narratives submitted with the BLA can be based upon the same conditions used for the EUA submission. We may request additional narratives during the course of our review.*

*Additionally, please provide narratives and available follow-up information for any reports of anaphylaxis and each of the following adverse events (AEs): Bell's Palsy, lymphadenopathy, appendicitis, pregnancy exposures and outcomes, and any additional AEs for which there is a numerical imbalance observed between the treatment arms.*

#### **1.3.2. Sponsor's Clarification Question to 1.c (sent on 17 March 2021)**

In response to CBER's request for narratives and follow up information for "... any additional AEs for which there is a numerical imbalance observed between treatment arms" Pfizer anticipates there will be many numerical differences in any large study. We therefore plan to screen AESIs identified by the CDC using the statistical criterion and clinical assessment summarized below, to determine which events warrant narratives:

- AESIs with lower bound of 2-sided 95% CI for between-group difference that excludes 0
- Among screened AESIs identified by the statistical criterion above, we will prepare narratives for the set of events for which the difference is clinically meaningful.

Does CBER agree?

#### **1.3.3. CBER Response to Item 1.c (sent on 01 April 2021)**

*We disagree with your proposal. Please plan to provide narratives and line listings for AESIs as identified by the CDC, without the application of your proposed statistical criterion or assignment of clinical significance. Please provide narratives for the AESIs (that were not already categorized as a SAE) that occur at higher frequency in the vaccine group than the control group, which led to study withdrawal, considered at least possibly related to vaccination, or biologically plausible.*

#### **1.3.4. Sponsor Response**

Pfizer/BioNTech acknowledge CBER's comment regarding acceptable use of hybrid (programmed and prose) narratives based on the same conditions used for EUA submission.

Regarding CBER's request for narratives and available follow-up information for specified events, Pfizer agrees with CBER's request with clarifications. We will provide narratives (Hybrid, programmed, or prose) for the following categories:

- Deaths, Vaccine-Related Serious Adverse Events, Safety-Related Withdrawals
- Adverse Events of Interest Requested by CBER: anaphylaxis, Bell's Palsy, lymphadenopathy, appendicitis, and pregnancy exposures and outcomes
- All Other Serious Adverse Events
- AESIs with a Numerical Imbalance that occur at a higher frequency in the vaccine group than the control group as described below\*
- COVID-19 Cases (Severe and/or Multiple),

\*Pfizer acknowledges CBER's request to provide narratives for the AESIs (that were not already categorized as a SAE) that occur at higher frequency in the vaccine group than the control group, which led to study withdrawal, considered at least possibly related to vaccination, or biologically plausible. For non-AESI, Pfizer/BioNTech will submit narratives where there is a numerical imbalance that occurs at a higher frequency in the vaccine group than the control group and has biological plausibility.

The greatest imbalances between vaccine and placebo are reactogenicity terms (i.e. pain at injection site, headache). These events will be discussed in the e-diary and the AE section of the BLA and thus narratives will not be generated for those AEs. If CBER determines that additional narratives are required, Pfizer/BioNTech will be prepared to promptly respond.

#### **1.4. Sponsor's Question 1.d (sent on 04 February 2021)**

Does CBER agree that no new safety subgroup analyses from Study C4591001 are required beyond what was conducted for N~38,000 Phase 2/3 participants up to 1 month post-Dose 2 (and as reported in the EUA)?

##### **1.4.1. CBER Response to Sponsor Question 1.d (sent on 09 March 2021)**

*We request that the same subgroup analyses of safety data that were performed for the EUA submission also be conducted on the longer-term safety data (including a median of 6-months follow-up post-Dose 2 as described in our response to Question 1.a) intended to support your BLA submission. We also request the following in your BLA submission:*

- i. Subgroup analyses of safety (solicited local reactions and systemic events, unsolicited AEs and SAEs) in participants with prior symptomatic COVID-19 to complement subgroup analyses of safety in participants with and without baseline evidence of prior SARS-CoV-2 infection. We acknowledge that these subgroup analyses will be limited to participants who were initially randomized to placebo and subsequently received BNT162b2 and will represent unblinded follow-up. We are requesting these analyses because they are of public health interest and may inform labeling.*
- ii. Safety data in the subgroup who were vaccinated after receiving placebo, as part of the crossover study design, if available, by baseline SARS CoV-2 status as defined in the protocol.*
- iii. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol.*

##### **1.4.2. Sponsor Response**

Pfizer/BioNTech acknowledge CBER's requests regarding safety subgroup analyses in the BLA. We plan to conduct subgroup analyses in the BLA based on the N~44,000 safety population up to the unblinding date (to provide blinded placebo-controlled subgroup data through the end of blinded follow-up).

We will provide analyses of the same subgroups that were included in the EUA (ie, age, sex, race, ethnicity, and baseline SARS-CoV-2 status), and others requested by CBER. Specifically:

- i. Subgroup analyses of safety for original placebo participants who had COVID-19 occurrence after Dose 1 and then were unblinded to receive BNT162b2, and continue in open-label follow-up. Please note that solicited events cannot be reported for this group, as they did not complete e-diaries for reactogenicity after receiving BNT162b2 (Dose 3/Dose 4); however, unsolicited AEs and SAEs will be analyzed and reported.*

- ii. Subgroup analyses of safety for participants originally randomized to placebo who then received BNT162b2 by baseline SARS-CoV-2 status (where baseline refers to positive or negative per NAAT or N-binding assay at the time of randomization).
- iii. Given the small number of participants with 2 separate episodes of COVID-19 (up to 5), Pfizer/BioNTech proposes to submit detailed narratives as opposed to descriptive summary data.

## 1.5. Sponsor's Question 1.e

### **Additional Question for CBER Regarding the EUA – sent in an email on February 18, 2021**

In Question 1.b, we requested CBER feedback regarding the clinical data package (safety and immunogenicity) to support licensure of the 12-15 year-old indication. These data are expected to be available by the end of March/early April.

At this time, we seek CBER guidance on whether the same data package proposed for inclusion in the BLA would support use of the vaccine in this age group (12-15 years) under the EUA. We would like to submit these data as an amendment to the current EUA in mid-April.

Does CBER agree that these data would support use of the vaccine in the 12-15 year-old age group under the EUA?

Does CBER agree that extending the indication of the vaccine down to 12 years of age may be pursued as an amendment to the current EUA??

#### **1.5.1. CBER Response to Sponsor Question 1.e (sent on March 9, 2021)**

*We agree that the proposed data package that includes safety and immunogenicity through 1-month post-Dose 2 for individuals 12 through 15 years of age could be submitted as an amendment to the current EUA to support use of your product in this age group. Additionally, please submit available longer-term safety data from participants 16 through 55 years of age to complement the 1-month safety data cutoff proposed for participants 12 through 15 years of age. We would discuss these data at a VRBPAC meeting during review of the EUA amendment. In addition to immunogenicity data, we recommend that VE data for this age group, from the time of the EUA data cutoff, be provided with the submission.*

*Please provide an estimate of the number of participants 12 through 15 years of age with safety data through 1-month post-Dose 2 that will be included with the EUA amendment and clarify if this number includes all participants in this age group, or a subset.*

### 1.5.2. Sponsor Response

In accordance with CBER's recommendation/request, Pfizer/BioNTech plan to submit an amendment to the EUA to support emergency use for individuals 12-15 years of age (~ 2200 individuals) that includes safety, immunogenicity, and efficacy data. This amendment is planned for submission in mid-April 2021. Specifically:

- Safety:
  - Adolescent (12-15 years of age) and young adult (16-25 years of age) safety up to 1 month after Dose 2 and up to analysis cutoff date
  - Protocol specified younger adult (16-55 years of age) safety up to unblinding date as reference data to compare with the 12-15 year old population
- Immunogenicity: Adolescent (12-15 years of age) and young adult (16-25 years of age) immunogenicity (non-inferiority analysis) up to 1 month after Dose 2

Please also see, response to CBER Comment 2.c.i ([Section 2.3](#)) regarding immunobridging (ie, non-inferiority comparison) analyses.

- Efficacy: Updated VE in the 12-15 years of age group including COVID-19 cases accrued through analysis unblinding date

(Note: same analysis cutoff date, 13 March 2021, will apply to both BLA and EUA data)

## 2. CLINICAL EFFICACY, IMMUNOGENICITY, AND EFFECTIVENESS

### 2.1. Sponsor's Question 2.a

Does CBER agree that the proposed efficacy, immunogenicity, and effectiveness data package is acceptable to support the proposed indication? Specifically:

- a. Does CBER agree that the previously completed primary endpoint analysis is adequate and acceptable to support the proposed indication?

#### 2.1.1. CBER Response to Sponsor Question 2.a sent on March 9, 2021

*We disagree with your proposed efficacy, immunogenicity and effectiveness data package, which includes only primary endpoint efficacy data provided in the EUA, immunogenicity data from 360 Phase 2/3 participants from 1-month post-Dose 2 that was provided in the EUA, and 6-month neutralization titer results from 30 Phase 1 participants.*

- i. *Given the increased circulation of variants and the variable incidence rates of COVID-19 disease as compared to the time of the EUA submission review, we request the following components for the effectiveness data package for your BLA submission:*
  - A. *Supplemental efficacy results for the primary and secondary efficacy endpoints based on the blinded phase. All potential COVID-19 and severe COVID-19 cases as of the data cutoff date for the BLA should be adjudicated and included in the BLA.*
  - B. *Reference is made to the telephone conversation dated March 3, 2021 between Donna Boyce of Pfizer and Dr. Marion Gruber of this office during which you informed us that you have accrued around 1,000 total COVID-19 cases but that you are not planning to conduct further analyses. On March 4, 2021, we advised (via email from Dr. Marion Gruber to Donna Boyce) that you should conduct these additional analyses. On March 5, 2021, you stated (email from Donna Boyce to Dr. Marion Gruber) that Pfizer would conduct these additional analyses but that the results would be submitted to the IND. However, in the event that these results would warrant labeling, you would submit the data as an amendment to the BLA. On March 5, 2021, we advised (via email from Dr. Marion Gruber to Donna Boyce) that the data from these additional analyses should be included at the time of the original BLA submission as these data may provide important additional information regarding VE against severe COVID-19 disease, duration of protection and potentially efficacy against VOCs.*
  - C. *Sequencing analysis on breakthrough cases to assess the prevalence of variant strains among cases (all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site).*

- D. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol .***
- ii. In addition to phase 1 participants, please provide immunogenicity data through 6-months post-Dose 2 from all phase 2 participants and from phase 3 participants, if available.***

#### **2.1.2. Sponsor's Clarification Question to Item 2.a.i.C sent to CBER on 12 March 2021**

Please note Pfizer/BioNTech will include an efficacy analysis by country in the BLA submission. However, sequencing analysis of breakthrough cases will not be available to be included at the time of the BLA submission. As these data are not required for initial licensure, Pfizer/BioNTech will provide these data as a post-approval supplement, once available. Does CBER agree?

#### **2.1.3. CBER Response to item 2.a.i.C sent on 01 April 2021**

***Because of the increased circulation of variants and increasing incidence rates of COVID-19 disease, we request the sequence analysis data of all COVID-19 cases that will be provided with the BLA submission (all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site). Please acknowledge and update your timeline for expected BLA submission based on our data requests provided on March 9, 2021.***

#### **2.1.4. Sponsor Response (2.a.i)**

Pfizer/BioNTech acknowledge CBER's comments regarding the proposed efficacy, immunogenicity, and effectiveness data package in the BLA. Accordingly, we will provide the following in the BLA:

- i. We will provide updated efficacy analyses in the BLA based on accrued COVID-19 cases through the analysis cutoff date as follows:
  - A. Updated analysis of primary efficacy endpoints and the secondary efficacy endpoint of severe disease, counting cases confirmed from at least 7 days after Dose 2 in blinded follow-up through the analysis cutoff date. Please note that COVID-19 cases are not adjudicated, but instead are programmatically confirmed with an algorithm. Severe cases undergo blinded medical review under circumstances specified in the protocol.
  - B. As noted above (A), we will provide updated efficacy analyses based on cases accrued through the analysis unblinding date, to include all confirmed COVID-19 cases in the evaluable and all-available efficacy populations and those meeting prespecified criteria as severe.

- C. Data from the sequence analysis of all COVID-19 cases, including all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site, will be provided as an amendment to the BLA (within 30 days of the BLA submission)? Does CBER agree with this proposal?
- D. As noted in the response to CBER Comment 1.d.iii above ([Section 1.4](#)), given the small number of participants with 2 separate episodes of COVID-19 (up to 5), Pfizer/BioNTech propose to submit detailed narratives as opposed to descriptive summary data. Does CBER agree?

#### **2.1.5. Sponsor's Clarification Question to Item 2.a.ii sent on 12 March 2021**

Please note that 6 month immunogenicity data for Phase 2 and Phase 3 participants will not be available for the BLA. The Phase 2 data are anticipated by no later than end of 2Q 2021 and will be submitted to IND 19736 when available, the Phase 3 data will be completed subsequently. Does CBER agree with this plan?

#### **2.1.6. CBER Response to item 2.a.ii sent on 01 April 2021**

*We agree with your plan.*

#### **2.1.7. Sponsor Response (2.a.ii)**

In addition to the above clarification sent by Pfizer/BioNTech on 12 March 2021, we would like to note that we will provide Phase 1 data through 6 months after Dose 2 and Phase 2 data through 1 month after Dose 2 in the BLA.

## **2.2. Sponsor's Question 2.b (sent on 04 February 2021)**

Does CBER agree with Pfizer/BioNTech's plans for the evaluation of efficacy against asymptomatic infection (N-Ig; in accordance with C4591001 Protocol Amendments 11 and 13)? Assuming these endpoints are met, does CBER agree that the results may be reflected in Section 14 (Clinical Studies) of the future product labeling?

### **2.2.1. CBER Response to Sponsor Question 2.b (sent on 09 March 2021)**

*While we agree that data to inform VE against asymptomatic infection might be of interest for inclusion in product labeling, considerations for whether and how such data from analyses of the objectives described above are presented in labeling will depend upon our review of the data, including data to support fitness for purpose of the N-Ig serology assay to determine asymptomatic infection.*

### **2.2.2. Sponsor's clarifying question to Item 2.b (sent on 12 March 2021)**

Please note that the VE against asymptomatic infection based on the N-binding serology will not be available for the BLA. Pfizer/BioNTech will submit these data in a future labeling supplement. Does CBER agree with this plan?

### **2.2.3. CBER Response to item 2.b (sent on 01 April 2021)**

*We agree with your change in plans to include analyses of VE against asymptomatic infection in a BLA supplement rather than in the original BLA.*

## **Sponsor Response**

Pfizer/BioNTech acknowledge CBER's comment, that consideration of data on asymptomatic infection in the product labeling would depend on CBER review.

As stated in Pfizer/BioNTech's clarifying question to Item 2.b sent on 12 March 2021, the VE against asymptomatic infection based on the N-binding serology will not be available for the BLA. Pfizer/BioNTech will submit these data in a future labeling supplement.

### **2.3. Sponsor's Question 2.c (sent on 04 February 2021)**

Does CBER agree with the proposed analysis to infer effectiveness of the candidate vaccine in individuals 12 to 15 years of age based on demonstration of non-inferior neutralizing antibody response as compared to individuals 16 to 25 years of age in Study C4591001?

- i. Does CBER agree that if study endpoints are met, the immunogenicity data in the 12 to 15 years of age group will support licensure of the candidate vaccine in individuals 12 to 15 years of age?

#### **2.3.1. CBER Response to Sponsor Question 2.c (sent on 09 March 2021)**

*We defer final comment, as discussions with you about the seroresponse definition and statistical success criteria for immunobridging based on seroresponse rates are ongoing. Additionally, we request that you adjust the sample size calculation for the immunobridging analysis in individuals 12 through 15 years of age based on an assumption of a true GMR of 1, as your assumption of a true GMR of ~0.8 does not reflect non-inferiority.*

#### **2.3.2. Sponsor Response**

A separate request for comments and advice (SN 0241) was sent to CBER on 15 March 2021 to solicit feedback on the planned immunobridging analyses for participants 12-15 years of age, specifically related to immunogenicity testing and the non-inferiority comparison. CBER feedback and additional comments were received on 29 March 2021 and a response from Pfizer/BioNTech is forthcoming.

### 3. ESUB/CDISC DATA

#### 3.1. Sponsor's Question 3 (sent on 04 February 2021)

Pfizer/BioNTech proposes the eSUB/CDISC data for the BLA submission as described in Section 1.3. Does CBER agree?

##### 3.1.1. CBER Response to Sponsor Question 3 (sent on 09 March 2021)

*We generally agree with your proposal. Please refer to our responses to Questions 1.d and 2.a and adjust the planned data sets for the BLA submission based on those requests.*

##### 3.1.2. Sponsor's clarifying question to Item 3 (sent on 12 March 2021)

Pfizer/BioNTech acknowledge CBER's comment and agree, that we will adjust the planned data sets (eSUB) for the BLA and EUA amendment submissions as appropriate.

Pfizer/BioNTech would like to make a further clarification on the SDTM mapping for reactogenicity data for C4591001. Specifically, Pfizer/BioNTech will provide the same mapping logic as in the EUA and also stated in the pre-BLA briefing document Section 1.3 whereby the SDTM mapping rules will be applied to provide a flat model (FACE, CE, VS, etc.) solely for reactogenicity data collected via e-diary per study design and data collection (e.g., not from an AE form). Pfizer/BioNTech will not be submitting a supplemental format schema as part of the BLA as most recently described in the Response to CBER Comment #1 of the 08 January 2021 Information Request regarding Trumenba (Meningococcal Group B Vaccine) submitted on 12 March 2021 (STN 125549/737). If required, Pfizer/BioNTech can submit tables using the new mapping if required. Does CBER agree?

##### *CBER Response to item 3 (sent on 01 April 2021)*

*Your reference to a supplemental format schema as described under STN 125549/737 is unclear. We recommend standardizing the CE dataset format, as previously communicated in correspondences under IND 19736 and IND 15150, and summarized below:*

- *Reactogenicity events that begin within the prespecified assessment period, but are currently reported in the AE dataset should be transferred from AE to FACE, or be flagged in AE so that we know that it is being included in the CE dataset.*
- *Records covering the entire event duration (which could go beyond the protocol-defined assessment period) be created in the ADaM3 ADCEVD dataset with start/end dates and durations (based on first and last days the symptom was present as recorded in the e-diary and/or Symptom*
- *Resolved Dates CRF, ignoring any gaps) derived from both the e-diary and CRF data.*

- ***Include all individual supporting assessments (daily e-diary and any unplanned assessments) in the FACE domain and the assessor for each finding can be identified using FAEVAL (STUDY SUBJECT or INVESTIGATOR).***
- ***Maintain one row per subject/vaccination/symptom in the CE domain, with CE summarizing the duration of the event and maximum severity. Maximum severity (CESEV) should be based on the highest-level severity reported by the subject (via e-diary) or investigator (in the unplanned assessment CRF).***
- ***Use SUPPCE CESEV1 and CEDIFFRS to show assessment of severity by study subject and reason investigator's assessment of severity differed from study subject as needed for events reported in CE.***

### **3.1.3. Sponsor Response**

A response from Pfizer/BioNTech is pending discussion with CBER during a teleconference that is scheduled for 8 April.

## 4. POST-AUTHORIZATION SAFETY

### 4.1. Sponsor's Question 4 (sent on 04 February 2021)

Does CBER agree that the most current cumulative aggregate monthly safety report can be provided in the BLA to support the safety profile of the product and proposed prescribing information? This document will be provided in Module 5 with relevant information extracted from it for inclusion in the Clinical Overview and Summary of Clinical Safety?

#### 4.1.1. CBER Response to Sponsor Question 4 (sent on 09 March 2021)

*Monthly safety reports primarily focus on events that occurred during the reporting interval and include information not relevant to a BLA submission such as line lists of adverse events by country. We are most interested in a cumulative analysis of post-authorization safety data to support your future BLA submission. Please submit an integrated analysis of your cumulative post-authorization safety data, including U.S. and foreign post-authorization experience, in your upcoming BLA submission. Please include a cumulative analysis of the Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in your Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). Please also include distribution data and an analysis of the most common adverse events. In addition, please submit your updated Pharmacovigilance Plan with your BLA submission.*

#### 4.1.2. Sponsor Response

Pfizer/BioNTech will submit a post-authorization safety data cumulative analysis in the BLA submission. The cumulative analysis of the Important Identified Risks, Important Potential Risks, and areas of Important Missing Information will be provided in the Pharmacovigilance Plan in the related sections. The analysis of the cumulative post-authorization safety data will include adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event), distribution data and an analysis of the most common adverse events. It will be provided as a standalone document in the BLA submission.

In accordance with CBER's request, Pfizer/BioNTech will submit an updated Pharmacovigilance Plan with the BLA.

In addition, at the time of the BLA submission, Pfizer/BioNTech propose to submit a single PVP for both the BLA and EUA for the time period during which the BLA and EUA co-exist. The EUA PVP, containing information to support the use in individuals 12 years and older, will be updated for the BLA submission to include information to support the use in individual greater than 16 years of age. Does CBER agree?

## 5. TABLE OF CONTENTS

### 5.1. Sponsor's Question 5

Does CBER have any comments regarding the proposed Table of Contents for the BLA?

#### 5.1.1. CBER Response to Sponsor Question 5

*We agree with the proposed overall table of contents (regarding the nonclinical and clinical information) for the planned BLA.*

#### 5.1.2. Sponsor Response

Pfizer/BioNTech acknowledge CBER's comment regarding the planned BLA table of contents for clinical and nonclinical information.

## 6. ADDITIONAL FDA COMMENTS (SENT ON 09 MARCH 2021)

*1. Please plan to submit specified BLA data analyses in 508-compliant word format tables, as previously submitted with Amendment 3 to the EUA 27034, identified as responses to the FDA's November 17, 2020 and November 19, 2020 Requests; we will provide a revised request for the BLA submission.*

### 6.1. Sponsor's clarification Question to Additional CBER Comment 1 sent on 19 March 2021

- a. We are looking to start working on programming for these. Do you have an estimate on when the request will be sent?
- b. Also, the Agency's note regarding the request for 508 tables coming was specific to the BLA. Please confirm that the Agency will not be issuing a request for specific 508 tables for the EUA Amendment to include the 12 to 15 year olds, or if this is not accurate, please let us know. We are actively working on both the EUA Amendment for the 12 to 15 years olds as well as the BLA (for 16 and above as requested) while we are waiting for CBER feedback.

#### 6.1.1. CBER Response to Additional Comment 1 sent on 01 April 2021:

*Our request for 508-compliant tables in word format for the EUA Amendment for adolescents 12 through 15 years of age was sent to you on March 31, 2021. The request for 508-compliant tables for the BLA submission will be sent as soon as possible.*

#### 6.1.2. Sponsor Response

Contingent on a revised request from FDA to submit 508-compliant Word formatted tables, Pfizer/BioNTech will submit these for specified analyses in the BLA.

## 7. TIMELINE FOR THE PLANNED SUBMISSIONS AND TYPE OF SUBMISSION

### 1. an amendment to the EUA

The following Amendments are planned to the EUA in 2021:

- Safety, immunogenicity, and efficacy data to support emergency use in individuals 12-15-years of age - no later than 12 April 2021
- EUA Label Update to reflect updated post-hoc efficacy analyses and 6-month safety update in individuals 16 years and above - by early May 2021
- Safety and immunogenicity data to support use of a third/booster dose of BNT162b2 following two previous doses of the BNT162b2 by end of June 2021
- Safety and immunogenicity data to support use of a booster dose of the variant BNT162b2 (B.1.351) following two doses of BNT162b2 - no later than end of June 2021
- Safety and immunogenicity data to support use of two primary doses of the variant BNT162b2 (B.1.351) - no later than end of July 2021
- Safety and immunogenicity data to support emergency use in individuals 5-11-years of age – no later than mid-September 2021
- Safety and immunogenicity data to support emergency use in individuals 2-5-years of age – no later than end of September 2021
- (b) (4) 
- (b) (4) 
- CMC and Label update to reflect new storage conditions for the current frozen formulation to allow up to 4 weeks at 2-8°C – end of April 2021
- EUA Label Update to reflect results of study C4591028 entitled, “A Phase 2 Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and

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*Immunogenicity of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 When Administered After Prior Receipt of Adenovirus-Based COVID-19 Vaccine in Healthy Individuals”.*

**2. a section of the original rolling BLA**

- A rolling BLA is planned for submission starting early May 2021. A proposed TOC for the BLA roll is presented in Table 1 and Table 2:

**Table 1. Proposed Table of Contents for the COVID-19 Vaccine BLA – ROLL 1**

<b>MODULE 1</b>
<b>1.1 Forms</b>
Form FDA 356h
Form FDA 3397
Form FDA 3674
<b>1.2 Cover Letter</b>
Cover Letter
<b>MODULE 2</b>
<b>2.2 Introduction Summary</b>
<b>2.4 Nonclinical Overview</b>
<b>2.5 Clinical Overview</b>
<b>2.6 Nonclinical Written &amp; Tabulated Summaries</b>
2.6.1 Introduction
2.6.2 Pharmacology Written Summary
2.6.3 Pharmacology Tabulated Summary
2.6.4 Pharmacokinetics Written Summary
2.6.5 Pharmacokinetics Tabulated Summary
2.6.6 Toxicology Written Summary
2.6.7 Toxicology Tabulated Summary
<b>2.7 Clinical Summary</b>
2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods
2.7.3 Summary of Clinical Efficacy
2.7.4 Summary of Clinical Safety
2.7.5 References
2.7.6 Synopses of Individual Studies
<b>MODULE 4</b>
<b>4.2 Nonclinical Study Reports</b>
<b>4.2.1 Pharmacology</b>
<b>4.2.1.1 Primary Pharmacology</b>
R-20-0085 - COVID-19: Immunogenicity Study of the LNP-Formulated ModRNA Encoding the Viral S Protein-V9
R-20-0112 - Characterizing the Immunophenotype in Spleen and Lymph Node of Mice Treated with SARS-COV-2 Vaccine Candidates
R-20-0211 - In vitro Expression of BNT162b2 Drug Substance and Drug Product
VR-VTR-10671 - BNT162b2 (V9) Immunogenicity and Evaluation of Protection against SARS-CoV-2 Challenge in Rhesus Macaques
VR-VTR-10741 - Structural and Biophysical Characterization of SARS-CoV-2 Spike Glycoprotein (P2 S) as a Vaccine Antigen
<b>4.2.2 Pharmacokinetics</b>
<b>4.2.2.2 Absorption</b>
PF-07302048_06Jul20_072424 - A Single Dose Rat Pharmacokinetic Study of ALC-0315 and ALC-0159 Following Intravenous Bolus Injection of PF-07302048 Nanoparticle Formulation in Wistar Han Rats
<b>4.2.2.3 Distribution</b>
R-20-0072 - Expression of Luciferase-Encoding ModRNA After I.M. Application of GMP-Ready

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**Table 1. Proposed Table of Contents for the COVID-19 Vaccine BLA – ROLL 1**

Acuitas LNP Formulation
185350 - A Tissue Distribution Study of a [3H]-Labelled Lipid Nanoparticle-mRNA Formulation Containing ALC-0315 and ALC-0159 Following Intramuscular Administration in Wistar Han Rats
<b>4.2.2.4 Metabolism</b>
01049-20008 - In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Liver Microsomes
01049-20009 - In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Cynomolgus Monkey, and Human Liver S9 Fractions
01049-20010 - In Vitro Metabolic Stability of ALC-0315 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Hepatocytes
01049-20020 - In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Liver Microsomes
01049-20021 - In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Cynomolgus Monkey, and Human Liver S9 Fractions
01049-20022 - In Vitro Metabolic Stability of ALC-0159 in CD-1/ICR Mouse, Sprague Dawley Rat, Wistar Han Rat, Cynomolgus Monkey, and Human Hepatocytes
PF-07302048_05Aug20_043725 - Investigation of the Biotransformation of ALC-0159 and ALC-0315 In Vitro and In Vivo in Rats
<b>4.2.3 Toxicology</b>
<b>4.2.3.2 Repeat-Dose Toxicity</b>
Study 38166 - Repeat-Dose Toxicity Study of Three LNP-Formulated RNA Platforms Encoding for Viral Proteins by Repeated Intramuscular Administration to Wistar Han Rats
SEND Data Package
Study 20GR142 - 17-Day, 3 Intramuscular Toxicity Study of BNT162b2 (V9) and BNT162b3c in Wistar Han Rats With a 3-week Recovery
SEND Data Package
<b>4.2.3.5 Reproductive and Developmental Toxicity</b>
<b>4.2.3.5.1 Fertility and Early Embryonic Development</b>
Study 20256434 (RN9391R58) - Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat
<b>4.3 Literature References</b>
Literature References
<b>MODULE 5</b>
<b>5.2 Tabular Listing of All Clinical Studies</b>
Tabular Listing of All Clinical Studies
Listing of Clinical Sites and CVs
<b>5.3 Clinical Study Reports and Related Information</b>
<b>5.3.1 Reports of Biopharmaceutic Studies</b>
<b>5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies</b>
SARS-CoV-2 Neutralization Assay
SARS-CoV-2 S1-Binding and RBD-Binding IgG Level Assays
SARS-CoV-2 N-Binding Antibody Assay
<b>5.3.5 Reports of Efficacy and Safety Studies</b>
<b>5.3.5.1 Study Reports and Related Information of Controlled Clinical Studies Pertinent to the Claimed Indication</b>
<b>C4591001</b>
Clinical Study Report
Case Report Forms (for subjects with narratives)
Dataset eSUB Packages
<b>BNT162-01</b>
Clinical Study Report
Case Report Forms (for subjects with narratives)
Dataset eSUB Packages
<b>5.3.6 Reports of Postmarketing Experience</b>
Cumulative Analysis of Post-Authorization Adverse Event Reports

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**Table 1. Proposed Table of Contents for the COVID-19 Vaccine BLA – ROLL 1**

<b>5.4 Literature References</b>
Literature References

**Table 2. Proposed Table of Contents for the COVID-19 Vaccine BLA – ROLL 2**

<b>MODULE 1</b>
<b>1.1 Forms</b>
Form FDA 356h
<b>1.2 Cover Letter</b>
Cover Letter
Priority Review Request
<b>1.3 Administrative Information</b>
<b>1.3.1 Contact/sponsor/applicant information</b>
<b>1.3.1.4 Transfer of obligation</b>
Transfer of Obligation
<b>1.3.3 Debarment Certification</b>
Debarment Certification
<b>1.3.4 Financial Certification and Disclosure</b>
Financial Certification and Disclosure
<b>1.3.5 Patent and exclusivity</b>
<b>1.3.5.3 Exclusivity Claim</b>
Exclusivity Claim
<b>1.4 References</b>
<b>1.4.2 Statement of Right to Reference</b>
DMF Letters of Authorization
<b>1.4.3 List of Authorized Persons to Incorporate by Reference</b>
Letter of Authorization to Appoint US Agent
<b>1.6 Meetings</b>
<b>1.6.3 Correspondence Regarding Meetings</b>
Relevant meeting minutes/written feedback to be included
<b>1.7 Fast Track</b>
<b>1.7.4 Correspondence Regarding Fast Track/Rolling Review</b>
Grant Fast Track Designation Letter
<b>1.9 Pediatric Administrative Information</b>
<b>1.9.2 Request for Deferral of Pediatric Studies</b>
Request for Deferral of Pediatric Studies
<b>1.9.4 Proposed Pediatric Study Request and amendments</b>
initial Pediatric Study Plan (iPSP)
<b>1.9.6 Other Correspondence Regarding Pediatric Exclusivity or Study Plans</b>
Letter of FDA Agreement with iPSP
<b>1.12 Other Correspondence</b>
<b>1.12.5 Request for Waiver</b>
Waiver Request for FDA-Designated Suffix for Biologics
<b>1.12.14 Environmental Analysis</b>
Environmental Analysis
<b>1.14 Labeling</b>
<b>1.14.1 Draft Labeling</b>
<b>1.14.1.1 Draft Carton and Container Labels</b>
Draft Carton and Container Labels
<b>1.14.1.2 Annotated Draft Labeling Text</b>
Draft Annotated USPI
<b>1.14.1.3 Draft Labeling Text</b>
Draft USPI - PDF and Word format
Structured Product Labeling (SPL) - XML format

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**Table 2. Proposed Table of Contents for the COVID-19 Vaccine BLA – ROLL 2**

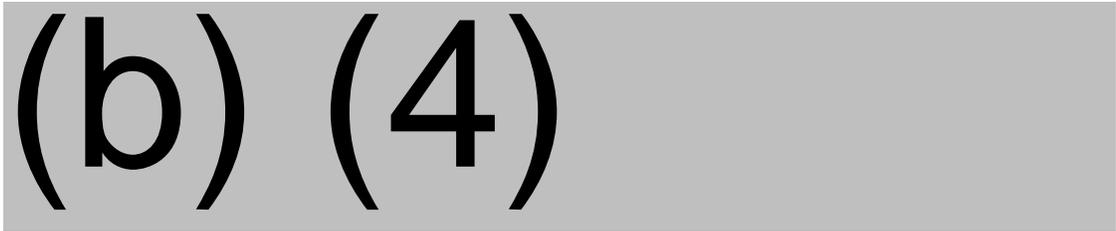
<b>1.14.1.5 Labeling History</b>
Summary of Literature Search on Pregnancy, Lactation and Fertility
Pregnancy and Lactation Cumulative Review
Waiver Request for Summary of Drug Utilization Rates
Waiver Request for Pregnancy Registry Report
<b>1.16 Risk Management Plans</b>
Pharmacovigilance Plan
<b>MODULE 2</b>
<b>2.3 Quality Overall Summary</b>
<b>MODULE 3</b>
<b>3.2. Body of Data</b>
3.2.S Drug Substance
3.2.P Drug Product
3.2.A Appendices
3.2.R Regional Information
<b>3.3 Literature References</b>

BLA Amendment

- (b) (4) 
  - Data from the requested sequence analysis of all COVID-19 cases - to be submitted within 30 days of the BLA submission
3. The following will be submitted as a **post-approval BLA supplement** (or major amendment to pending BLA, depending on timing of BLA approval)

**Chemistry, Manufacturing, and Controls (CMC)**

(b) (4) 

(b) (4) 

**Clinical**

- VE against Asymptomatic Infections, including that defined by N-binding serology

- Pediatric indications will be added via post approval BLA supplements as the required data become available

## **REFERENCES**

None

## Document Approval Record

**Document Name:**

COVID-19 Response to FDA Feedback Received 09March2021 Regarding Clinical and Post-EUA Safety Data Package

**Document Title:**

COVID-19 Response to FDA Feedback Received 09March2021 Regarding Clinical and Post-EUA Safety Data Package

**Signed By:**

**Date(GMT)**

**Signing Capacity**

Boyce, Donna

07-Apr-2021 16:28:57

Regulatory Affairs Approval

**Pfizer-BioNTech COVID-19 Vaccine**

**Additional Response to CBER Comments Received on 09 March 2021, 31 March 2021,  
and 01 April 2021, Regarding eSUB/CDISC data**

**BB-IND 19736**

**14 April 2021**

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*CBER Response to Item 3 (sent on 01 April 2021)*.....4

*CBER Discussion with Pfizer/BioNTech on 08 April 2021* .....4

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## 1. INTRODUCTION

Reference is made to BB-IND 19736 for the Pfizer/BioNTech COVID-19 Vaccine (BNT162; PF-07302048) and to IND amendment 201 (dated 04 February 2021), which contained a Request for Comments and Advice seeking Center for Biologics Research and Evaluation (CBER) feedback regarding the proposal for the clinical and post-EUA safety data package to support the initial Biologics License Application (BLA). CBER responded on 09 March 2021 on Pfizer's proposal for eSUB/CDISC data for the BLA submission and the Sponsor (hereafter referred to as Pfizer/BioNTech) requested clarification in our 12 March 2021 submission. CBER provided a response to Pfizer/BioNTech's clarification questions on 01 April 2021. A teleconference was held with CBER on 08 April 2021. Pfizer's response to discussions with CBER are provided herein.

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

## 2. CBER COMMENTS

### 2.1. Sponsor's Question 3 (sent on 04 February 2021)

Pfizer/BioNTech proposes the eSUB/CDISC data for the BLA submission as described in Section 1.3. Does CBER agree?

#### CBER Response to Sponsor Question 3 (sent on 09 March 2021)

***We generally agree with your proposal. Please refer to our responses to Questions 1.d and 2.a and adjust the planned data sets for the BLA submission based on those requests.***

#### Sponsor's clarifying question to Item 3 (sent on 12 March 2021)

Pfizer/BioNTech acknowledge CBER's comment and agree, that we will adjust the planned data sets (eSUB) for the BLA and EUA amendment submissions as appropriate.

Pfizer/BioNTech would like to make a further clarification on the SDTM mapping for reactogenicity data for C4591001. Specifically, Pfizer/BioNTech will provide the same mapping logic as in the EUA and also stated in the pre-BLA briefing document Section 1.3 whereby the SDTM mapping rules will be applied to provide a flat model (FACE, CE, VS, etc.) solely for reactogenicity data collected via e-diary per study design and data collection (e.g., not from an AE form). Pfizer/BioNTech will not be submitting a supplemental format schema as part of the BLA as most recently described in the Response to CBER Comment #1 of the 08 January 2021 Information Request regarding Trumenba (Meningococcal Group B Vaccine) submitted on 12 March 2021 (STN 125549/737). If required, Pfizer/BioNTech can submit tables using the new mapping if required. Does CBER agree?

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### **CBER Response to Item 3 (sent on 01 April 2021)**

*Your reference to a supplemental format schema as described under STN 125549/737 is unclear. We recommend standardizing the CE dataset format, as previously communicated in correspondences under IND 19736 and IND 15150, and summarized below:*

- *Reactogenicity events that begin within the prespecified assessment period, but are currently reported in the AE dataset should be transferred from AE to FACE, or be flagged in AE so that we know that it is being included in the CE dataset.*
- *Records covering the entire event duration (which could go beyond the protocol-defined assessment period) be created in the ADaM3 ADCEVD dataset with start/end dates and durations (based on first and last days the symptom was present as recorded in the e-diary and/or Symptom*
- *Resolved Dates CRF, ignoring any gaps) derived from both the e-diary and CRF data.*
- *Include all individual supporting assessments (daily e-diary and any unplanned assessments) in the FACE domain and the assessor for each finding can be identified using FAEVAL (STUDY SUBJECT or INVESTIGATOR).*
- *Maintain one row per subject/vaccination/symptom in the CE domain, with CE summarizing the duration of the event and maximum severity. Maximum severity (CESEV) should be based on the highest-level severity reported by the subject (via e-diary) or investigator (in the unplanned assessment CRF).*
- *Use SUPPCE CESEV1 and CEDIFFRS to show assessment of severity by study subject and reason investigator's assessment of severity differed from study subject as needed for events reported in CE.*

### **Sponsor Response**

A response from Pfizer/BioNTech is pending discussion with CBER during a teleconference that is scheduled for 8 April.

### **CBER Discussion with Pfizer/BioNTech on 08 April 2021**

#### **Sponsor's Response following 08 April teleconference discussion with FDA**

As agreed by the Agency on 8 April 2021, Pfizer/BioNTech will provide reactogenicity data as requested above for the BLA submission, with one set of analysis tables based on the original reactogenicity flat model data (without general adverse events from AE form that meet reactogenicity criteria included) plus a supplemental analysis with the revised reactogenicity data (with the addition of any events reported as general adverse events in the AE form which meet reactogenicity criteria). Adverse events from the AE domain will be flagged if determined to meet reactogenicity criteria (only for subjects participating in the

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reactogenicity subset). Flagged AE data will be copied over to the FACE domain with FAEVAL as INVESTIGATOR and used to create the global event records in the CE domain. Pfizer/BioNTech will maintain one record per subject/vaccination/symptom in the CE domain, with event start date being the earliest and event end date being the latest along with the worst reported severity during the diary period in CESEV (from any source). Any original values which are updated as a result of adding general AE data will be included in SUPPCE (CESTDTC1, CEENDTC1, CESEV1, etc.). Specific details of the mapping and additional non-standard qualifiers (SUPPQUAL) will be provided in the supplemental analysis package which will be submitted as part of the BLA.

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**Pfizer/BNT's COVID-19 Vaccine  
BB IND 019736**

**Request for Comments and Advice:**

**Plans for Submitting the CMC Portions of the BLA**

**March 2021**

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## 1. INTRODUCTION

Pfizer and BioNTech have developed an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) that is caused by the virus SARS-CoV-2 for use in individuals  $\geq 12$  years of age. The vaccine is based on SARSCoV-2 S glycoprotein antigens encoded in RNA, which is formulated in lipid nanoparticles (LNPs), and is referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF-07302048). The IND was effective on April 29, 2020. An Emergency Use Authorization (EUA 27034) for emergency use of the Pfizer-BioNTech COVID-19 Vaccine in individuals  $> 16$  years of age was issued on December 11, 2021, under section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3).

Pfizer/BioNTech intend to submit a BLA for the candidate vaccine in April 2021. CBER's feedback is requested regarding the proposed overall CMC contents of the planned BLA. The CMC content and any approved in the EUA and any commitments will serve as the basis for content in the BLA. The BLA will include all CMC changes intended for longer term commercial supply that have been submitted to the IND/EUA through March 31, 2021. Changes planned for introduction under the EUA after this date will be submitted as supplement to the BLA. See [Table 1](#).

It is anticipated that the existing EUA will remain in place through 4Q2021 in order to maintain supply continuity in accordance with the EUA and to ensure distribution commitments to government authorities are met. During FDA review of the BLA and through a transition period after BLA approval, Pfizer/BioNTech must continue introducing manufacturing and control optimizations and changes to the EUA to meet volume demands. Pfizer/BioNTech proposes submitting these relevant EUA CMC updates to the BLA immediately after approval.

(b) (4)



The BLA will describe the commercial manufacturing facilities. These facilities and those in described in the EUA are presented [Table 2](#).

In addition to the information and data provided in the EUA all PPQ data for the facilities being described in the initial BLA (see [Table 2](#)) will be provided. Also, updated specifications based on significant production data under EUA, additional method validation information and additional stability data will be provided in the BLA.

A tentative Table of Contents for the CMC modules of the BLA is provided in [Appendix 1](#).

(b) (4)

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(b) (4)

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## 2. QUESTIONS FOR FDA

1. Does CBER agree with the proposed Table of Contents of the CMC modules of the BLA?
2. Does CBER agree that the proposed CMC modules contain all changes introduced under the EUA/IND through March 31, 2021 and that additional changes implemented under the EUA may be submitted as post approval BLA supplements?
3. Does CBER agree that the EUA may remain in place following approval of the BLA to enable manufacture and distribution of vaccine through the remainder of 2021 and to allow time to update the BLA with changes implemented between April 2021 and BLA approval?

## 3. RESPONSES TO FDA REQUEST FOR ADDITIONAL INFORMATION

Reference is also made to the February 05, 2021 Request for additional information regarding changes to CMC and facilities information that addresses the ramping up of vaccine production. Specifically, responses to question 9 and additional FDA comments 1, 2 and 3 are provided below.

### 3.1. Question 9

*Please explain, in tabular format, the proposed manufacturing nodes under EUA with the addition of these facilities.*

#### 3.1.1. Response to Question 9

The current and proposed additional manufacturing nodes under EUA are depicted in [Table 2](#).

### 3.2. FDA Additional Comment 1

*Please update the “EUA and Commercial Supply Chain Manufacturing Nodes” table (as was submitted in IND 19736 Amendment 119; October 21, 2020) to include the new manufacturing facilities and nodes. Please note that, as stated previously, data from three PPQ DS lots (CBER feedback sent on November 6, 2020 in response to Pfizer’s November 4, 2020 email message) and at least three GMP commercial-scale DP lots (CBER comments sent on November 20, 2020 regarding overall CMC information) will be required prior to distribution from a new node under EUA. In addition, final reports from PPQ studies at all manufacturing facilities/nodes must be submitted in support of the BLA.*

#### 3.2.1. Response to FDA Additional Comment 1

Acknowledged.

### 3.3. FDA Additional Comment 2

*Please provide a list of the facilities that are planned to be included in the BLA submission.*

#### 3.3.1. Response to FDA Additional Comment 2

The manufacturing facilities planned to be included in the BLA submission are noted in [Table 2](#).

### **3.4. FDA Additional Comment 3**

*Please explain, in tabular format, the proposed manufacturing nodes to be included in the BLA.*

#### **3.4.1. Response to FDA Additional Comment 2**

The planned manufacturing nodes to be included in the BLA are depicted in [Table 2](#).

**Appendix 1. Tentative Table of Contents for the CMC modules of the BLA**

(b) (4)

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

**DATE:** March 31, 2021 **PAGES:** 7

**TO:** **BioNTech SE/Pfizer. Inc.**  
**Attention: Neda Aghajani Memar**  
235 East 42<sup>nd</sup> Street, 219/9/69  
New York, NY 10017  
Phone: 212-733-2613  
Fax number: 845-474-3500  
E-mail: [Neda.Aghajani.Memar@pfizer.com](mailto:Neda.Aghajani.Memar@pfizer.com)

**FROM:** **Ramachandra Naik, 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:** IND 19736.230

**IND Title:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**SUBJECT:** CBER comments regarding the strategy for submitting the CMC contents of the BLA for COVID-19 vaccine

Dear Ms. Aghajani Memar:

Reference is made to amendment 230 (dated March 1, 2021) to your IND 19736 that contained your Request for Comments and Advice (in lieu of a Pre-BLA meeting) regarding your strategy for submitting the CMC contents of the BLA for COVID-19 vaccine.

Reference is also made to the following:

- Pfizer's Request for Comments and Advice regarding proposal for clinical and post-EUA safety data package for BLA (IND 19736.201 submission dated February 4, 2021)
- Pfizer's Request for Comments and Advice regarding plans for CMC portions of the BLA (IND 19736.230 submission dated March 1, 2021)
- CBER comments on IND 19736.201 submission were sent on March 9, 2021.
- CBER's communication dated September 28, 2020 regarding the practical aspects of the planned BLA submission (IND 19736.84 submission). As per May 2014 FDA Guidance: Expedited Programs for Serious Conditions -Drugs and Biologics <https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf>, for preliminary agreement on your rolling BLA approach, we requested that you provide: (1) the schedule for submission of each portion of the BLA, and (2) a description of portions of the application to be submitted separately (late components). We noted that the cited guidance recommends submissions of complete BLA sections such as the entire CMC section, toxicology section or clinical section. Although we may have indicated that we would accept rolling sub-sections within these main sections, to reach preliminary agreement, we requested that the number of rolling sub-sections be limited and that you describe the timeline and the information to be included in each.

In addition, please note that the review clock will not begin until you inform us that a complete BLA was submitted. After you have notified us that your application is complete, we will make a filing determination within the usual time.

In this communication, we are providing additional comments on and requests for clinical/statistical and CMC/facilities information that should be included in the BLA for your COVID-19 vaccine. Please note that our comments are not all inclusive, and we may have additional comments or questions after we receive the requested information.

In addition to responding to our comments and questions, please provide a detailed timeline for your planned submissions and indicate what type of submission each would be:

1. an amendment to the EUA
2. a section of the original rolling BLA
3. an amendment to the original BLA
4. a post-approval BLA supplement

We recommend that after you submit your responses to our comments (including a detailed timeline for your planned submissions), a teleconference be scheduled for additional discussion and clarifications.

**FDA comments on your questions included in amendment 230:**

**Sponsor Question 1:**

Does CBER agree with the proposed Table of Contents of the CMC modules of the BLA?

**FDA Response to Sponsor Question 1:**

We generally agree with the proposed Table of Contents of the CMC modules of the BLA. However, the Table of Contents does not appear to contain references to the information listed below that is required in your BLA submission. In addition, please refer to the Preliminary Meeting Responses (Type C meeting; CRMTS-12822; IND 19736.67) sent on September 18, 2020 and the September 23, 2020 Meeting Summary sent on October 14, 2020 for additional list of items to be included in the BLA.

Please include the following information in your BLA:

(b) (4)

A large grey rectangular box containing the text "(b) (4)" in a large, bold, black font, indicating a redacted section of the document.

**Sponsor Question 2:**

Does CBER agree that the proposed CMC modules contain all changes introduced under the EUA/IND through March 31, 2021 and that additional changes implemented under the EUA may be submitted as post approval BLA supplements?

**FDA Response to Sponsor Question 2:**

We defer our response until we have reviewed your timeline for your planned submissions for CMC information. This issue will be further discussed in the recommended teleconference.

**Sponsor Question 3:**

Does CBER agree that the EUA may remain in place following approval of the BLA to enable manufacture and distribution of vaccine through the remainder of 2021 and to allow time to update the BLA with changes implemented between April 2021 and BLA approval?

**FDA Response to Sponsor Question 3:**

As stated in the Guidance for Industry “Emergency use authorization of medical products and related authorities” <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>, the HHS Secretary’s EUA declaration will terminate on the earlier of: (1) a determination by the HHS Secretary that the circumstances that precipitated the declaration have ceased (after consultation as appropriate with the Secretary of Homeland Security or the Secretary of Defense), or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved (section 564(b)(2)). For example, an EUA issued to allow an unapproved use of an approved product may no longer be needed if that product is later approved by FDA for the use permitted by the EUA. Thus, while it may be possible for your EUA to remain in place following approval of the BLA through the remainder of 2021, a final determination cannot be made at this time. It is our expectation that the majority of vaccine distribution occurs under the BLA rather than the EUA. Please note that after BLA approval, all manufacturing changes must be done under the BLA as post-approval supplements. All the CMC information for the vaccine lots intended for distribution under the BLA and the information on all the facilities used for production of these lots should be included in the original BLA. Please note that changes in manufacture or addition of facilities during the BLA review may result in a major amendment. Alternatively, if you were to submit these proposed manufacturing changes as a rolling BLA, the review clock would not begin

until you inform us that the final piece containing complete manufacturing information has been submitted.

As stated in our response to Question 2, we will provide additional guidance after we have reviewed the timeline for your planned submissions regarding the CMC and facilities information. This issue will be further discussed in the recommended teleconference.

**Additional FDA Comments regarding information included in amendment 230:**

1. Please explain what changes are being made for “(b) (4) [REDACTED]” referred to in Table 1.
2. Please note that Table 2 states that (b) (4) [REDACTED]  
[REDACTED] Please make the appropriate corrections to the Table.

**Additional FDA comments on the clinical/statistical and CMC/facilities information that should be included in the BLA for your COVID-19 vaccine:**

**Clinical/Statistical:**

1. The safety database should include a median follow-up duration of 6 months post Dose 2 for Phase 2/3 participants 16 years of age and older who were included in the EUA Safety Population and initially randomized to BNT162b2.
2. Safety Data:
  - a. Safety narratives as outlined in our response to amendment 201.
  - b. Subgroup analyses of safety (solicited local reactions and systemic events, unsolicited AEs and SAEs) in participants with prior symptomatic COVID-19 to complement subgroup analyses of safety in participants with and without baseline evidence of prior SARS-CoV-2 infection. We acknowledge that these subgroup analyses will be limited to participants who were initially randomized to placebo and subsequently received BNT162b2 and will represent unblinded follow-up. We are requesting these analyses because they are of public health interest and may inform labeling.
  - c. Safety data in the subgroup who were vaccinated after receiving placebo, as part of the crossover study design, if available, by baseline SARS CoV-2 status as defined in the protocol.
  - d. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol.

**3. Effectiveness Data:**

- a. Supplemental efficacy results for the primary and secondary efficacy endpoints based on the blinded phase. All potential COVID-19 and severe COVID-19 cases as of the data cutoff date for the BLA should be adjudicated and included in the BLA.
- b. Sequencing analysis on breakthrough cases to assess the prevalence of variant strains among cases (all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site).
- c. Descriptive summary data on participants who had more than one COVID-19 illness after the first episode post-vaccination, by study arm and by baseline positive COVID-19 status as defined in the protocol.

**Product (CMC):****Product (Assays/Methods):**

5. In your BLA submission, please include methods and method validations for analytical tests used for drug substance (DS) and DP release:
  - a. Method descriptions should be of sufficient detail to show they are being performed within validation limits. The descriptions of compendial methods should be sufficient to confirm they are being performed as specified in USP or European Pharmacopeia.
  - b. Full validation reports should be provided for non-compendial release tests and the qualification/verification reports for compendial assays should demonstrate that they are suitable (lack of matrix effect) for their intended purpose. Examples include the following:
6. Please provide a complete qualification report for bioburden testing using drug substance including the type of media, conformance lot numbers, incubation conditions and duration, to ensure the method is suitable under the actual conditions of use.

7. Please provide detailed bacterial endotoxin test qualification reports for the drug substance and BNT162b2 drug product to ensure the method is suitable under the actual conditions of use. The reports should include MVD, lot numbers of product tested, positive product control percent recoveries and an optimal selected product testing dilution.
8. At the time of submission, please be prepared to provide CBER with three lots of DP samples that are representative of material to be distributed under the approved license. In addition, be prepared to send any in-house generated standards/references and/or reagents used in the testing of the DP. CBER will provide information on when and where to send the samples, standards/references and reagents after submission of the BLA.
9. In your BLA submission, please include a lot release protocol template which includes quality control data for the DS and DP. Do not submit lot release protocols for specific lots until after CBER has reviewed and found the lot release protocol template acceptable.

**Facilities:**

10. Referring to Table 2, *Planned US EUA and BLA Supply Chain Manufacturing Nodes* (in IND 19736.230 submission dated March 1, 2021), please provide the following information:

- (b) (4)

[Redacted]

[Redacted] (b) (4)

12. Please explain why the following sites and associated activities will not be included in the original BLA submission for your BNT162b2 product.

- (b) (4)

[Redacted]

13. Please provide a table in the BLA submission detailing new and/or additional information from the information submitted for EUA authorization.

If you have any questions, please contact me by email: [ramachandra.naik@fda.hhs.gov](mailto:ramachandra.naik@fda.hhs.gov) or at 301-796-2640.

**COVID-19 Vaccine (BNT162, PF-07302048)**

**BB-IND 19736**

**Response to CBER Comments received on 31 March 2021 Regarding the Strategy for  
Submitting the CMC Contents of the BLA**

**06 April 2021**

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## 1. INTRODUCTION

Reference is made to BB-IND 19736 for the COVID-19 Vaccine in clinical development by Pfizer/BioNTech (BNT162; PF-07302048) and to amendment 230 (dated 01 March 2021), which contained a Request for Comments and Advice seeking Center for Biologics Research and Evaluation (CBER) feedback regarding the proposal (in lieu of a Pre-BLA meeting) regarding the strategy for submitting the CMC contents of the BLA for COVID-19 vaccine.

The following information is provided in response to CBER's CMC-related comments and questions received on 31-March-2021. Questions are shown in bold italics, followed by responses in plain text.

## 2. SPONSOR'S QUESTIONS, CBER COMMENTS AND SPONSOR'S RESPONSES

### 2.1. Sponsor Question 1

***Does CBER agree with the proposed Table of Contents of the CMC modules of the BLA?***

#### **FDA Response:**

We generally agree with the proposed Table of Contents of the CMC modules of the BLA. However, the Table of Contents does not appear to contain references to the information listed below that is required in your BLA submission. In addition, please refer to the Preliminary Meeting Responses (Type C meeting; CRMTS-12822; IND 19736.67) sent on September 18, 2020 and the September 23, 2020 Meeting Summary sent on October 14, 2020 for additional list of items to be included in the BLA.

Please include the following information in your BLA:

(b) (4)

(b) (4)

**Sponsor Response:**

Pfizer/BioNTech acknowledge CBER’s comment. These will be provided as part of the initial CMC package for the BLA or as a subsequent amendment.

**2.2. Sponsor Question 2**

***Does CBER agree that the proposed CMC modules contain all changes introduced under the EUA/IND through March 31, 2021 and that additional changes implemented under the EUA may be submitted as post approval BLA supplements?***

**FDA Response:**

We defer our response until we have reviewed your timeline for your planned submissions for CMC information. This issue will be further discussed in the recommended teleconference.

**Sponsor Response:**

Pfizer/BioNTech response is pending discussion with CBER during a teleconference that is to be determined.

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### 2.3. Sponsor Question 3

***Does CBER agree that the EUA may remain in place following approval of the BLA to enable manufacture and distribution of vaccine through the remainder of 2021 and to allow time to update the BLA with changes implemented between April 2021 and BLA approval?***

#### **FDA Response:**

As stated in the Guidance for Industry “Emergency use authorization of medical products and related authorities” <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>, the HHS Secretary’s EUA declaration will terminate on the earlier of: (1) a determination by the HHS Secretary that the circumstances that precipitated the declaration have ceased (after consultation as appropriate with the Secretary of Homeland Security or the Secretary of Defense), or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved (section 564(b)(2)). For example, an EUA issued to allow an unapproved use of an approved product may no longer be needed if that product is later approved by FDA for the use permitted by the EUA. Thus, while it may be possible for your EUA to remain in place following approval of the BLA through the remainder of 2021, a final determination cannot be made at this time. It is our expectation that the majority of vaccine distribution occurs under the BLA rather than the EUA. Please note that after BLA approval, all manufacturing changes must be done under the BLA as post-approval supplements. All the CMC information for the vaccine lots intended for distribution under the BLA and the information on all the facilities used for production of these lots should be included in the original BLA. Please note that changes in manufacture or addition of facilities during the BLA review may result in a major amendment. Alternatively, if you were to submit these proposed manufacturing changes as a rolling BLA, the review clock would not begin until you inform us that the final piece containing complete manufacturing information has been submitted.

As stated in our response to Question 2, we will provide additional guidance after we have reviewed the timeline for your planned submissions regarding the CMC and facilities information. This issue will be further discussed in the recommended teleconference.

#### **Sponsor Response:**

Pfizer/BioNTech acknowledge CBER’s comment.

### **3. ADDITIONAL FDA COMMENTS REGARDING INFORMATION INCLUDED IN AMENDMENT 230:**

#### **3.1. FDA Question 1**

***Please explain what changes are being made for (b) (4) ” referred to in Table 1.***

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**Response:**

(b) (4)

**3.2. FDA Question 2**

(b) (4) *r the*

**Response:**

(b) (4)

**4. PRODUCT (CMC):**

**4.1. FDA Question 4**

(b) (4)

**Response:**

Pfizer/BioNTech acknowledge CBER’s comment. These will be provided as part of the initial CMC package for the BLA.

**5. PRODUCT (ASSAYS/METHODS):**

**5.1. FDA Question 5**

In your BLA submission, please include methods and method validations for analytical tests used for drug substance (DS) and DP release:

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- a. Method descriptions should be of sufficient detail to show they are being performed within validation limits. The descriptions of compendial methods should be sufficient to confirm they are being performed as specified in USP or European Pharmacopeia.
- b. Full validation reports should be provided for non-compendial release tests and the qualification/verification reports for compendial assays should demonstrate that they are suitable (lack of matrix effect) for their intended purpose. Examples include the following:

**Response:**

Pfizer/BioNTech acknowledge CBER's comment. These will be provided as part of the initial CMC package for the BLA or as a subsequent amendment.

**5.2. FDA Question 6**

Please provide a complete qualification report for bioburden testing using drug substance including the type of media, conformance lot numbers, incubation conditions and duration, to ensure the method is suitable under the actual conditions of use.

**Response:**

Pfizer/BioNTech acknowledge CBER's comment. These will be provided as part of the initial CMC package for the BLA or as a subsequent amendment.

**5.3. FDA Question 7**

Please provide detailed bacterial endotoxin test qualification reports for the drug substance and BNT162b2 drug product to ensure the method is suitable under the actual conditions of use. The reports should include MVD, lot numbers of product tested, positive product control percent recoveries and an optimal selected product testing dilution.

**Response:**

Pfizer/BioNTech acknowledge CBER's comment. These will be provided as part of the initial CMC package for the BLA or as a subsequent amendment.

**5.4. FDA Question 8**

At the time of submission, please be prepared to provide CBER with three lots of DP samples that are representative of material to be distributed under the approved license. In addition, be prepared to send any in-house generated standards/references and/or reagents used in the testing of the DP. CBER will provide information on when and where to send the samples, standards/references and reagents after submission of the BLA.

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**Response:**

Pfizer/BioNTech acknowledge CBER’s comment.

**5.5. FDA Question 9**

In your BLA submission, please include a lot release protocol template which includes quality control data for the DS and DP. Do not submit lot release protocols for specific lots until after CBER has reviewed and found the lot release protocol template acceptable.

**Response:**

Pfizer/BioNTech acknowledge CBER’s comment.

**6. FACILITIES:**

**6.1. FDA Question 10**

Referring to Table 2, Planned US EUA and BLA Supply Chain Manufacturing Nodes (in IND 19736.230 submission dated March 1, 2021), please provide the following information:

(b) (4)

**Response:**

(b) (4) e

(b) (4)

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**6.2. FDA Question 11**

(b) (4)

**Response:**

(b) (4)

**6.3. FDA Question 12**

Please explain why the following sites and associated activities will not be included in the original BLA submission for your BNT162b2 product.

(b) (4)

**Response:**

(b) (4)



## Teleconference Summary

**Meeting date & time:** April 16, 2021, 3:00 – 4:30 PM

**Submission:** IND 19736

**Product name:** Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

**Proposed indication:** Active immunization against COVID-19 in adults 18 years of age and older

**Sponsor:** BioNTech SE/Pfizer, Inc.  
Sponsor Agent: Pfizer, Inc.

**SUBJECT:** Teleconference to discuss Pfizer's submission regarding the clinical and CMC information to be included in the BLA for their COVID-19 vaccine and the timing of the planned BLA submission

### CBER Participants

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**Background:**

Reference is made to the following:

- Pfizer’s request in IND 19736 amendment 201 (dated February 4, 2021) for comments and advice regarding their proposal for the clinical and post-EUA safety data package for the BLA
- CBER’s feedback on IND 19736.201 submission, dated March 9, 2021
- CBER’s April 1, 2021 responses to Pfizer’s clarification questions (sent in emails dated March 13, 2021 and March 17, 2021) regarding a few of the items in CBER’s feedback dated March 9, 2021
- Pfizer’s request in IND 19736 amendment 230 (dated March 1, 2021) for comments and advice regarding their proposal for CMC content of the BLA
- CBER’s feedback on IND 19736.230 submission, dated March 31, 2021
- CBER’s additional comments and requests for CMC and clinical information to be included in the BLA, sent to Pfizer on March 31, 2021
- Pfizer’s submission in IND 19736 amendment 279 (dated April 7, 2021) that contained their responses to CBER’s comments sent on March 9, 2021, March 31, 2021, and April 1, 2021.

**Teleconference Summary:**

Below are the items (from the IND 19736.279 submission) that were identified by CBER and Pfizer as needing additional clarification, followed by a summary of the discussion that occurred during the meeting.

**Clinical:**

**Clinical Safety:**

**Sponsor response 1.1.3.** (page 4 of Response to 3/9/2021, 3/31/2021 and 4/1/2021 comments document; IND 19736.279 submission):

Pfizer/BioNTech plan to provide safety data in the BLA representing the entire safety population (N~44,000) through the data analysis cutoff date of 13 March 2021.

Approximately 12,000 participants originally randomized to BNT162b2 will have follow-up of at least 6 months after Dose 2. Of these, 1778 will have blinded follow-up for >6 months after Dose 2.

**Meeting Discussion:**

Pfizer asked if their response is acceptable. We stated that Pfizer’s plan is acceptable.

**Sponsor response 1.c** (page 8 of Response to 3/9/2021, 3/31/2021 and 4/1/2021 comments document; IND 19736.279 submission):

Pfizer/BioNTech acknowledge CBER’s comment regarding acceptable use of hybrid (programmed and prose) narratives based on the same conditions used for EUA submission.

Regarding CBER's request for narratives and available follow-up information for specified events, Pfizer agrees with CBER's request with clarifications. We will provide narratives (Hybrid, programmed, or prose) for the following categories:

- Deaths, Vaccine-Related Serious Adverse Events, Safety-Related Withdrawals
- Adverse Events of Interest Requested by CBER: anaphylaxis, Bell's Palsy, lymphadenopathy, appendicitis, and pregnancy exposures and outcomes
- All Other Serious Adverse Events
- AESIs with a Numerical Imbalance that occur at a higher frequency in the vaccine group than the control group as described below\*
- COVID-19 Cases (Severe and/or Multiple),

\*Pfizer acknowledges CBER's request to provide narratives for the AESIs (that were not already categorized as a SAE) that occur at higher frequency in the vaccine group than the control group, which led to study withdrawal, considered at least possibly related to vaccination, or biologically plausible. For non-AESI, Pfizer/BioNTech will submit narratives where there is a numerical imbalance that occurs at a higher frequency in the vaccine group than the control group and has biological plausibility.

The greatest imbalances between vaccine and placebo are reactogenicity terms (i.e. pain at injection site, headache). These events will be discussed in the e-diary and the AE section of the BLA and thus narratives will not be generated for those AEs. If CBER determines that additional narratives are required, Pfizer/BioNTech will be prepared to promptly respond.

**Meeting Discussion:**

Pfizer asked if their response is acceptable or if CBER has any questions. We stated that Pfizer's plan is acceptable.

**Clinical Efficacy, Immunogenicity and Effectiveness**

**Sponsor response 2.a.i.C** (page 16 of Response to 3/9/2021, 3/31/2021 and 4/1/2021 comments document; IND 19736.279 submission):

Data from the sequence analysis of all COVID-19 cases, including all cases in vaccine recipients and a corresponding random sampling of cases in placebo recipients, by geographic region/site, will be provided as an amendment to the BLA (within 30 days of the BLA submission)? **Does CBER agree with this proposal?**

**Meeting Discussion:**

We asked if the data from the sequence analysis of all COVID-19 cases will be provided within 30 days of the first roll or within 30 days of the last piece. Pfizer responded that they are planning to submit the first roll that contains clinical information on May 7, 2021, and the data from the sequence analysis of all COVID-19 cases will be submitted on June 7, 2021. Regarding CBER's question about how comprehensive the sequence analysis data package will be, Pfizer replied that it will consist of a summary paragraph plus the sequence information. We acknowledged,

and agreed with Pfizer submitting the sequence analysis data for COVID-19 cases within 30 days of submitting the first roll of the BLA.

Pfizer asked if the COVID-19 case sequence information will be included in the label. We responded that internal discussion of that question is needed, and we will get back to Pfizer in the future. Pfizer acknowledged.

**Sponsor Response to Additional FDA Comment 1** (page 16 of Response to 3/9/2021, 3/31/2021 and 4/1/2021 comments document; IND 19736.279 submission): Contingent on a revised request from FDA to submit 508-compliant Word formatted tables, Pfizer/BioNTech will submit these for specified analyses in the BLA.

**Meeting Discussion:**

Pfizer asked when CBER will be sending the recommended shell tables to present clinical data in 508-compliant Word formatted tables. We stated that we are working on them and will provide them as soon as they are available. Pfizer acknowledged.

**Timeline for the Planned Submissions and Type of Submission** (page 23 of Response to 3/9/2021, 3/31/2021 and 4/1/2021 comments document; IND 19736.279 submission):

**1. an amendment to the EUA**

The following Amendments are planned to the EUA in 2021:

- a. Safety, immunogenicity, and efficacy data to support emergency use in individuals 12-15-years of age - no later than 12 April 2021 (*submitted on April 9, 2021*)
- b. EUA Label Update to reflect updated post-hoc efficacy analyses and 6-month safety update in individuals 16 years and above - by early May 2021

**Meeting Discussion:**

We expressed concern regarding Pfizer's plan to submit an EUA amendment to update the EUA label to reflect the updated post-hoc efficacy analyses and 6-month safety update in individuals 16 years and above during the review of the BLA. Pfizer clarified that the post-hoc efficacy analyses and 6-month safety data in individuals 16 years and above is the same package that will be included in the BLA. We acknowledged and indicated that it is helpful to know Pfizer's plan.

- c. Safety and immunogenicity data to support use of a third/booster dose of BNT162b2 following two previous doses of the BNT162b2 by end of June 2021

**Meeting Discussion:**

For CBER's question regarding the time interval for waning immunity, Pfizer replied that they have waning virus neutralization titer data. Pfizer asked if the

immunogenicity and safety results (n = 300 vaccinated, 1-month post boost dose) described in study C4591001 protocol amendment 14 are adequate to support use of booster dose of BNT162b2 under EUA. We stated that we need to discuss this question internally, and we will get back to Pfizer in the future. Pfizer acknowledged.

- d. Safety and immunogenicity data to support use of a booster dose of the variant BNT162b2 (B.1.351) following two doses of BNT162b2 - no later than end of June 2021

**Meeting Discussion:**

Pfizer indicated that, at present, as there is no clear public health need for protection specifically against the South African strain and the need for a booster dose with BNT162<sub>SA</sub> is not determined yet, they are postponing submission of this information. However, Pfizer's intention regarding this submission was to pave the potential regulatory pathway for switching quickly if the need for a variant vaccine arises. We stated that while the BLA is under review, Pfizer should prioritize the submission of amendments to the EUA to address the current public health need at that time. Pfizer agreed and indicated that they will remove from their plan submission of an EUA amendment for a variant vaccine.

- e. Safety and immunogenicity data to support use of two primary doses of the variant BNT162b2 (B.1.351) - no later than end of July 2021

**Meeting Discussion:**

See Meeting Discussion under item 1.d above.

- f. Safety and immunogenicity data to support emergency use in individuals 5-11-years of age – no later than mid-September 2021
- g. Safety and immunogenicity data to support emergency use in individuals 2-5-years of age – no later than end of September 2021

- h. (b) (4)

[Redacted content for item h]

- i. (b) (4)

[Redacted content for item i]

- j. CMC and Label update to reflect new storage conditions for the current frozen formulation to allow up to 4 weeks at 2-8°C – end of April 2021

- k. EUA Label Update to reflect results of study C4591028 entitled, “A Phase 2, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidates against COVID-19 when administered after prior receipt of adenovirus-based COVID-19 vaccine in healthy individuals”.

**Meeting Discussion:**

We indicated that if all of the above-listed information is submitted at the same time or very close in time, it will be difficult to review and thus, we asked Pfizer to prioritize these items. Pfizer stated that review of the following data is priority for them:

- Data in subjects 12-15 years of age (1.a),
- Third/booster dose with BNT162b2 data (1.c),
- CMC/label update to reflect new storage conditions for the current frozen formulation (1.j),
- (b) (4)
- Label Update for efficacy and 6-month safety in subjects 16 years and above (1.b)

Pfizer indicated that they will discuss internally and send a modified list of items (EUA amendments) that has been revised based on their priority for our review. We agreed.

2. **BLA amendment** (page 27 of Response to 3/9/2021, 3/31/2021 and 4/1/2021 comments document; IND 19736.279 submission):

Depending on timing of the CBER review of the BLA, we plan to submit the following information as a supplement to the approved BLA or as a major amendment to the pending BLA (while under CBER review):

(b) (4)

**Meeting Discussion:**

(b) (4)

We acknowledged.

3. **The following will be submitted as a post-approval BLA supplement (or major amendment to pending BLA, depending on timing of BLA approval)** (page 27 of Response to 3/9/2021, 3/31/2021 and 4/1/2021 comments document; IND 19736.279 submission):

**Chemistry, Manufacturing, and Controls (CMC)**

Update the BLA with all CMC changes submitted to the EUA while the BLA is under review. For example:

- (b) (4) [Redacted]

**Meeting Discussion:**

We advised (b) (4) LA  
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(b) (4) . Pfizer also added that  
licensing the product would address the vaccine hesitancy or boost  
confidence in the vaccine.

We asked if the CMC module will be complete when Pfizer submits Roll 2 of the BLA on May 15, 2021. Pfizer stated that the modules will be complete, except for the data from the sequence analysis of COVID-19 cases.

Regarding facilities, Pfizer stated the following:

- (b) (4) [Redacted]

(b) (4)

(b) (4)

**Clinical**

- VE against Asymptomatic Infections, including that defined by N-binding Serology post-approval BLA supplement
- Pediatric indications will be added via post approval BLA supplements as the required data become available.

**Meeting Discussion:**

We advised submission of the above clinical information as post-approval BLA supplement(s). Pfizer agreed.

**In the Response to CBER Comments received on 31 March 2021 Regarding the Strategy for Submitting the CMC Contents of the BLA document (IND 19736.279 submission), Pfizer indicated that**

**The following will be provided as part of the initial CMC package for the BLA or as a subsequent amendment.**

- Assay methods and method validations for analytical tests used for drug substance (DS) and DP release (Question 5)
- Qualification report for bioburden testing using drug substance (Question 6)
- Bacterial endotoxin test qualification reports for the drug substance and BNT162b2 drug product (Question 7)

**Meeting Discussion:**

We advised submission of this information in the initial BLA or very soon after. Pfizer indicated that this information will be included in the initial BLA.

**Additional FDA Comment:**

You did not include a request for proprietary name review in the proposed table of contents for the BLA submission. As stated in the November 20, 2020 letter, please

provide a request for a re-review of your proposed proprietary name COMIRNATY within 14 days following submission of your Biologics License Application.

**END**