COVID-19 Vaccine (BNT162, PF-07302048)

IND 19736

Response to 30 June 2021 Information Request Regarding Updating Informed Consent Documents and Investigator's Brochure with Information Related to Myocarditis and Pericarditis

July 2021

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LIST OF ABBREVIATIONS

Abbreviation	Term
20vPnC	20-valent pneumococcal conjugate vaccine
BB-IND	Biological Investigational New Drug
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
EC	Ethics Committee
ECG/EKG	electrocardiogram
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
ICD	Informed consent document
IRB	Institutional Review Board
mRNA	messenger ribonucleic acid
PCR	Polymerase chain reaction
RNA	ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction

1. INTRODUCTION

Reference is made to BB-IND 19736 for the COVID-19 vaccine (BNT162; PF-07302048), which Pfizer and BioNTech are developing for the indication of active immunization to prevent COVID-19 caused by SARS-CoV-2. The IND was effective on 29 April 2020.

Further reference is made to CBER's 30 June 2021 Information Request regarding updating Informed Consent Documents and Investigator's Brochure with information related to myocarditis and pericarditis.

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

2. CBER REQUEST

Available data regarding myocarditis or pericarditis reported in individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine strongly support a plausible causal relationship to the vaccine and have warranted revision of the EUA Fact Sheets to include a warning statement and other information about these events. We also consider it necessary to adequately inform investigators and study participants in ongoing clinical trials with the Pfizer-BioNTech COVID-19 Vaccine, and modified formulations thereof (e.g., for different presentations or to address SARS-CoV-2 variants), about the risk of myocarditis or pericarditis associated with the vaccine.

2.1. CBER Comment 1

Please update informed consent documents to include information about the risk of myocarditis and pericarditis. This information should include that:

- ***a. Myocarditis or pericarditis have been reported in greatest numbers in males under the age of 30 years following the second dose, but cases have been reported in older males and in females as well, and also following the first dose.***

- ***b. Symptoms of myocarditis or pericarditis include chest pain, shortness of breath, or feelings of having a fast-beating, fluttering, or pounding heart, with onset of symptoms most commonly reported within a few days following vaccination. Study participants should seek medical attention and also notify study site staff if any of these symptoms occur following vaccination.***

- ***c. While some severe cases have been reported, most cases have been associated with full resolution of symptoms in the short term. However, long-term follow-up is limited.***

- ***d. It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of the vaccine (e.g., following a booster dose).***

2.1.1. Response to CBER Comment 1

Pfizer-BioNTech acknowledges CBER's comments regarding the need to inform investigators and study participants in ongoing clinical trials with the Pfizer-BioNTech COVID-19 Vaccine, and modified formulations thereof (e.g., for different presentations or to address SARS-CoV-2 variants), about the risk of myocarditis or pericarditis associated with the vaccine. Pfizer-BioNTech agrees to add the requested information to ICDs as follows:

> Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received BNT162b2. Cases have mainly been reported in males under 30 years of age and following the second vaccination; however, there have been some cases reported in older males and females as well as following the first vaccination. The chance of having this occur is very low and, in most of these people, symptoms began within a few days to a week following vaccination. As a precaution, you should seek medical attention right away if you have any of the following symptoms after receiving the vaccine:
>
> - Chest pain
> - Shortness of breath
> - Feelings of having a fast-beating, fluttering, or pounding heart
>
> Please also notify study staff, when appropriate, if you have any of these symptoms.
>
> Whilst some severe cases have been reported, most cases have been associated with full resolution of symptoms in the short term; however, long-term follow-up is limited. It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of the vaccine, e.g. following a booster dose.
>
> If you have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart) previously, please tell your study doctor.

2.2. CBER Comment 2

We note that you have submitted revised informed consent documents for several ongoing studies addressing myocarditis and pericarditis, and that these revisions state, "…it is not clear that it is due to the vaccine." We do not agree with this statement, as there is a substantial basis to believe there is a causal relationship to vaccination. Please further revise your informed consent documents for all ongoing clinical trials to remove this statement and according to items 1a-1d above.

2.2.1. Response to CBER Comment 2

Pfizer-BioNTech acknowledges CBER's comment and has revised this part of the ICD as indicated in response to Comment 1 above. Updated ICDs for all studies will be submitted in parallel to BB-IND 19736 on 06 July 2021.

2.3. CBER Comment 3

While we would agree that the balance of benefits vs. risks remains favorable for completion of the 2-dose vaccination regimen in most individuals (excepting, for example, individuals who are recovering from myocarditis or pericarditis following the first dose), study participants who are awaiting their second dose should be re-consented after being provided information about myocarditis and pericarditis as described above.

2.3.1. Response to CBER Comment 3

Pfizer-BioNTech agrees that study participants who are awaiting their second dose should be re-consented after being provided with information about myocarditis and pericarditis. On the same day that Pfizer-BioNTech received the request from CBER to include language in the EUA factsheet, Pfizer-BioNTech already updated ICDs for all ongoing BNT162b2 studies to include reference to cases of myocarditis and pericarditis after vaccination. Given the time needed to obtain the required IRB/EC approvals for the updated ICDs across countries and sites, so as not to delay second doses (which could result in partial protection, particularly in the context of emerging variants), and in accordance with Pfizer SOPs, any participants due for their second dose were provided this information verbally, informed of the right to withdraw from the clinical study at any time, and asked if they are agreeable to continue with the study following receipt of the new information. This interaction is to be documented in a Pfizer Provision of Critical Safety Form, as well as in the participant source documents at the site. The status of informed consent for ongoing studies is presented in Table 1. This verbal process is only utilized during the time period in which the ICD is being updated and approved. Once the updated ICD is approved, these participants will also be required to sign the updated ICD.

In light of CBER comments and our commitment to re-update the ICD (per response to Comment 1), once approved by IRB/ECs, we will utilize the updated ICD with CBER-requested text for re-consenting.

Table 1. Status of Informed Consent for Ongoing Studies

Study Number	Brief Title	Interim Verbal Provision of Safety Information Used for Second or Subsequent Doses (Yes/No)[a]	Date for Updated ICD[b]
C4591001	A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals	Yes	Week commencing 05 July 2021

Table 1. Status of Informed Consent for Ongoing Studies

Study Number	Brief Title	Interim Verbal Provision of Safety Information Used for Second or Subsequent Doses (Yes/No)[a]	Date for Updated ICD[b]
C4591007	A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children <12 Years of Age	Yes	Week commencing 05 July 2021
C4591015	A Phase 2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of a SARS-CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older	Yes	Week commencing 05 July 2021
C4591017	A Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Production Lots and Dose Levels of BNT162b2 RNA-Based COVID-19 Vaccines Against COVID-19 in Healthy Participants	No	Week commencing 05 July 2021
C4591020	A Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Formulation of BNT162b2 Against COVID-19 in Healthy Adults	No	Week commencing 05 July 2021
C4591024	Phase 2b, Open-Label Study to Evaluate Safety, Tolerability, and Immunogenicity of Vaccine Candidate BNT162b2 in Immunocompromised Participants ≥2 Years of Age	No	Week commencing 05 July 2021

Table 1. Status of Informed Consent for Ongoing Studies

Study Number	Brief Title	Interim Verbal Provision of Safety Information Used for Second or Subsequent Doses (Yes/No)[a]	Date for Updated ICD[b]
C4591031	A Study to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2	No	Week commencing 05 July 2021
B7471026[c]	A Phase 3 Safety and Immunogenicity Study of 20vPnC When Coadministered With a Booster Dose of BNT162b2	No	Week commencing 05 July 2021

a. Based on wording in the updated EUA fact sheet.
b. 3 subjects in Study C4591007 and 16 subjects in Study C4591031 were consented and dosed on the updated ICD that CBER asked us to modify. These subjects will be re-consented using the new and approved ICD.
c. ICD for Study B7471026 will be filed under PCV20 IND 17039.

2.4. CBER Comment 4

Please describe how study materials (including the Investigator's Brochure) and procedures for ongoing clinical trials will ensure adequate detection and reporting, as well as appropriate diagnosis and management, of cases of myocarditis or pericarditis that occur in study participants. Please also describe what circumstances would represent a significant and unreasonable risk related to myocarditis or pericarditis and result in halting of study vaccinations in participants for whom the vaccine is not yet authorized for use.

2.4.1. Response to CBER Comment 4

The Investigator's Brochure is in the process of being updated and will include information regarding the occurrence of cases of myocarditis and pericarditis. The updated final document is planned to be available by 14 July 2021 and will be submitted to BB-IND 19736 in parallel with distribution to Investigators and IRBs and/or ECs.

In a Dear Investigator letter sent to sites (24 June 2021), the following guidance was already provided to investigators:

> If any study participants report symptoms that could represent myocarditis or pericarditis, please follow the CDC Clinical Considerations for myocarditis and pericarditis following COVID-19 vaccination published on 28 May 2021:

- For initial evaluation, consider an ECG, troponin level, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. In the setting of normal ECG, troponin, and inflammatory markers, myocarditis or pericarditis is unlikely.
- Consider consultation with:
    - Cardiology for assistance with cardiac evaluation and management.
    - Infectious disease and/or rheumatology to assist in this evaluation.
- Where available, evaluate for potential etiologies of myocarditis and pericarditis, particularly acute COVID-19 infection (e.g., PCR testing), prior SARS-CoV-2 infection (e.g., detection of SARS-CoV-2 nucleocapsid-binding antibodies), and other viral etiologies (e.g., enterovirus PCR and comprehensive respiratory viral pathogen testing).

With respect to halting of study vaccinations in participants for whom the vaccine is not yet authorized for use (interpreted as individuals <12 years of age or pregnant women), we believe that is not possible to identify *a priori* what circumstances would represent a significant and unreasonable risk related to myocarditis or pericarditis. Rather, we propose to carefully review the details of each new case identified in clinical studies (including frequency, severity and outcome/symptoms resolution), as well as cumulatively, to identify whether to halt study vaccinations. Additionally, our external Data Monitoring Committee will be alerted about all suspected myocarditis/pericarditis cases in real time.

2.5. CBER Comment 5

We expect that cases of myocarditis or pericarditis occurring in temporal association with vaccination of study participants, if occurring at greater frequency or severity than as described in the Investigator's Brochure, would be reported as SUSARs as required by 21 CFR 312.32. Please confirm.

2.5.1. Response to CBER Comment 5

Pfizer-BioNTech acknowledges CBER's comment. Pfizer-BioNTech will carefully review the details of each new case of myocarditis or pericarditis identified in clinical studies and will report cases of myocarditis or pericarditis as a SUSAR per 21 CFR 312.32.

2.6. CBER Comment 6

Please describe your plans to further understand the risk of myocarditis or pericarditis associated with the Pfizer-BioNTech Vaccine, including but not necessarily limited to:

a. The frequency of these events attributable to vaccination in various demographic subgroups classified by age, gender, race, and ethnicity;

b. The biological mechanism responsible for these events;

c. The long-term prognosis for post-vaccination myocarditis and pericarditis;

d. Whether initially subclinical cases occur (e.g., as detected through routine baseline and post-vaccination cardiac enzymes and/or EKGs in relevant populations), and if so at what frequency and with what long-term prognosis; and

e. Whether myocarditis or pericarditis, including initially subclinical cases, are associated with other mRNA vaccines manufactured using the same platform and in clinical development for non-COVID indications.

2.6.1. Response to CBER Comment 6

Pfizer-BioNTech is actively working to understand the risk of myocarditis and pericarditis associated with the Pfizer-BioNTech vaccine and will provide a thorough response with regards to parts b, d, and e, by 02 August 2021.

At this time, several hypotheses for the biological mechanism of vaccine-associated myocarditis and pericarditis are under discussion, including secondary to vaccine-elicited non-specific immune stimulation (e.g., exacerbation of subclinical autoimmune myocarditis), antigen-specific immune-mediated myocarditis (e.g., antigen mimicry), and hypersensitivity. There is no nonclinical evidence of direct cardiotoxicity, and there was no vaccine-related myocardial or pericardial inflammation identified in nonclinical toxicity studies in rats or in vaccine efficacy studies in rhesus macaques. Although there are animal models of myocarditis, without further clarity around the underlying cause of the myocarditis observed clinically in vaccine recipients, the translatability of animal study results to the mechanism of putative vaccine-related myocarditis in humans would be quite opaque. Therefore, no animal model studies are proposed at this time.

Response to CBER Comment 6a

Our planned post-authorization safety studies involving large-scale electronic health care databases (protocols C4591009, C4591011, and C4591012) are designed to measure the incidence of myocarditis and pericarditis events occurring within 42 days of a vaccination dose. Incidence estimates will be based on structured data, stratified by dose, age group, gender, and race/ethnicity. In addition, these stratified incidence estimates will be calculated for shorter risk intervals, e.g., 7 days post-vaccination. Results will be available within the first interim reports (due in October 2023 for C4591009, and in December 2021 for C4591011 and C4591012).

Response to CBER Comment 6c

Post-authorization safety studies C4591011 and C4591012 follow vaccinated individuals for up to approximately 2 years. These studies are designed to use structured information to identify signals and use information from individual medical records to further evaluate events that exhibit a signal. Given that myocarditis and pericarditis have generated a signal outside of these studies, any myocarditis or pericarditis events identified, i.e., by presence of corresponding ICD codes in electronic medical records, will be prioritized for review to confirm diagnosis and to obtain information on prognosis (e.g., time to resolution).

Further plans to evaluate long term prognosis of myocarditis or pericarditis in other real-world secondary data sources, such as the Sentinel Data Research partners included within the planned post-authorization safety study C4591009, and in clinical trial participants will be included in the 02 August 2021 proposal.

Document Approval Record

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