BNT162b2 (COMIRNATY)

BLA STN 125742/0

Response to CBER 28 July 2021 Information Request Regarding Post-marketing Safety Study(ies)

August 2021

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
DoD	Department of Defense
ECG	Electrocardiogram
EU	European Union
MHS	Military Health System
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
PHN	Pediatric Heart Network
PY	Person-years
RR	Relative risk
TBD	To be determined
US	United States
VSD	Vaccine Safety Datalink

1. INTRODUCTION

Reference is made to BLA STN 125742/0 for COVID-19 mRNA Vaccine (COMIRNATY), for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age and to CBER's Information Request received via email on 28 July 2021.

CBER requests are presented in ***bold italics*** followed by Pfizer-BioNTech response in plain text.

2. CBER REQUESTS AND SPONSOR RESPONSES

Please include the following information for the postmarketing study(ies) proposal: study designs, sample sizes and justification of sample sizes including number of subjects ≤30 years of age, information to be collected at baseline, frequency and methods for follow-up data collection, plan for duration of long term follow-up and information to be collected in follow-up, study timeline and milestone dates (final protocol submission date, study completion date, and final study report submission date; please provide dates in mm/dd/yyyy format).

2.1. CBER Request 1

1. ***Please propose postmarketing observational safety study(ies) to assess myo/pericarditis following administration of COMIRNATY to:***

    a. ***Quantify the magnitude of risk by age, sex, and dose***

    b. ***Include follow up cases (e.g., via a registry) for recovery status and long-term sequelae***

Sponsor Response

Response to 1A: Quantifying the magnitude of myocarditis/pericarditis risk

As previously communicated, post-authorization safety studies C4591009 (US), C4591011 (US), C4591012 (US), and C4591021(EU) use large electronic healthcare databases to assess increased risk of safety events of interest, including myocarditis/pericarditis, following vaccination with COMIRNATY during a 2-3 year study period. In these studies, the incidence of myocarditis/pericarditis will be described overall, and stratified by age group, gender, race/ethnicity (if feasible), dose, and risk interval using structured information and following case confirmation via medical record review where feasible. To assess the magnitude of risk, these studies include comparative methods (self-controlled analyses, and analyses involving a separate comparator group). Relative risk (RR) estimates from comparative analyses will be obtained overall and stratified by the same factors as described above when supported by sufficient cell counts.

Given the demographics of their source populations, studies C4591009, C4591011, and C4591021 are expected to capture data on individuals aged 30 years and younger. In C4591012, the largest sub-population of younger individuals includes veterans aged 30-39 years; therefore, individuals 12-39 years of age will be included in this analysis.

Table 1 provides a range of estimates of the numbers of COMIRNATY-exposed persons and myocarditis cases that would be required to be included in the study in order to have sufficient power to detect RRs for various magnitudes of risk of vaccine-associated myocarditis under different assumptions within a self-controlled case series analysis. These estimates are based estimates of myocarditis/pericarditis background rates used by CDC in signal evaluations, ranging from 1/100,000 (person-years) PY to 10/100,000 PY.[1]

Table 1. Required Number of Cases to Detect Myocarditis Risk Under Different Assumptions of Background Rates

80% power, alpha = 0.05			
	Required number of myocarditis cases	**Required number of COMIRNATY-exposed persons, assumed incidence (1/100,000 PY)**	**Required number of COMIRNATY-exposed persons, assumed incidence (10/100,000 PY)**
14-day risk window			
RR=2.0	469	23,008,737	2,300,874
RR=5.0	52	2,414,759	241,476
RR=10.0	18	767,524	76,753
21-day risk window			
RR=2.0	319	15,503,995	1,550,400
RR=5.0	37	1,659,091	165,910
RR=10.0	13	516,323	51,633
60% power, alpha = 0.05			
	Required number of myocarditis cases	**Required number of COMIRNATY-exposed persons, assumed incidence (1/100,000 PY)**	**Required number of COMIRNATY-exposed persons, assumed incidence (10/100,000 PY)**
14-day risk window			
RR=2.0	262	12,853,495	1,285,350
RR=5.0	28	1,300,255	130,026
RR=10.0	9	383,726	38,377
21-day risk window			
RR=2.0	179	8,699,734	869,974
RR=5.0	20	896,806	89,681
RR=10.0	7	278,020	27,802

Abbreviations: PY=Person-years; RR=Relative risk

In general, studies C4591009, C4591011, C4591012 and C4591021 will include as many individuals as possible who meet the eligibility criteria during the relevant period of study without an upper limit (Table 2). As COMIRNATY is authorized or approved for use without significant contraindications, the number of persons enrolled in the studies depends on the following:

- The number of persons in the source population eligible for the vaccine under current authorization

- The number in eligible source population who get vaccinated with COMIRNATY vaccine

- The proportion of vaccinated, eligible individuals within the source population whose vaccination is documented in the structured data; this assumes 50% of vaccines administered are COMIRNATY and 60% of eligible persons are vaccinated, so 30% of the source population would be included in the COMIRNATY-exposed sample.

Table 2. Source Populations for Safety Surveillance Studies

Protocol ID	Title	Data Source	Source Population (size and type)	Estimated Number of Individuals ≤30 years[a]	Estimated Proportion ≤30 years of Source Population Administered Pfizer Vaccine[a]
C4591009	A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech COVID-19 Vaccine in the United States	Five Data Research Partners in US Sentinel System	Pfizer-BioNTech vaccine recipients among 100+ million individuals in general population captured in Sentinel system data sources; includes individuals <18 years of age	~ 47 million[b]	~14.1 million
C4591011	Active Safety Surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense Population Following Emergency Use Authorization	US Department of Defense (DoD) Military Health System (MHS) database	Pfizer-BioNTech vaccine recipients among about 10 million active military personnel and families in DoD MHS; includes individuals <18 years of age	~ 3.5 million	~1.1 million[b]

Table 2. Source Populations for Safety Surveillance Studies

Protocol ID	Title	Data Source	Source Population (size and type)	Estimated Number of Individuals ≤30 years[a]	Estimated Proportion ≤30 years of Source Population Administered Pfizer Vaccine[a]
C4591012	Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine	US Veterans Health Administration system	Pfizer-BioNTech vaccine recipients among about 9 million patients in Veterans' Health Administration system	≤30 years: ~ 350,000 ≤39 years: ~ 1.2 million[c]	≤30 years: ~105,000 ≤39 years: ~ 360,000[c]
C4591021	Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine	Electronic healthcare databases in Netherlands, Norway, UK, Italy, Spain	Pfizer-BioNTech vaccine recipients among about 39 million individuals in general population; includes individuals <18 years of age	~ 13.5 million	~4.1 million[b]

[a]Estimates represent the numbers of individuals in the population before study protocol eligibility criteria are applied.
[b]Estimates based on assumption that 50% vaccines administered are COMIRNATY and 60% of eligible persons are vaccinated
[c]Estimates based on number of actual Pfizer/BioNTech vaccinations as of July 1, 2021.

Given the anticipated number of persons aged ≤30 years vaccinated with the Pfizer/BioNTech vaccine expected to be captured in the studies, the studies that are expected to have 60% and 80% power to detect risks of different magnitudes assuming a range of rates of myocarditis temporally unrelated to vaccine and risk windows are summarized in Table 3.

Table 3. Post-Authorization Safety Studies With 60% and 80% Power to Detect Myocarditis in Persons ≤30 Years[a] , Under Different Assumptions of Background Rates

80% power, alpha = 0.05		
	Assumed incidence (1/100,000 PY)	**Assumed incidence (10/100,000 PY)**
14-day risk window		
RR=2.0	None	1009, 1021
RR=5.0	1009, 1021	1009, 1011, 1012 1021
RR=10.0	1009, 1011, 1021	1009, 1011, 1012, 1021
21-day risk window		
RR=2.0	None	1009, 1021
RR=5.0	1009, 1021	1009, 1011, 1012, 1021
RR=10.0	1009, 1011, 1021	1009, 1011, 1012, 1021
60% power, alpha = 0.05		
	Assumed incidence (1/100,000 PY)	**Assumed incidence (10/100,000 PY)**
14-day risk window		
RR=2.0	1009	1009, 1021
RR=5.0	1009, 1021	1009, 1011, 1012 1021
RR=10.0	1009, 1011, 1021	1009, 1011, 1012, 1021
21-day risk window		
RR=2.0	1009	1009, 1011, 1021
RR=5.0	1009, 1011, 1021	1009, 1011, 1012, 1021
RR=10.0	1009, 1011, 1012, 1021	1009, 1011, 1012, 1021

a. Note: for study 1012 sample size estimates for persons 39 and under were used.
Abbreviations: PY=Person-years; RR=Relative risk

Given that governments are making vaccine available at no cost and administration often occurs outside of typical health care delivery systems, capture of vaccination within secondary structured data such as electronic health care records and insurance claims may be incomplete. Capture is expected to vary by data source and methods to address this potential limitation will be discussed in each protocol as applicable.

Response to 1b: Follow-up of myocarditis/pericarditis cases

Pfizer and BioNTech have been exploring the feasibility of conducting studies using real-world data sources within the US and EU to identify risk factors for and characterize long-term outcomes of myocarditis/pericarditis following vaccination with COMIRNATY.

Within the US, we are conducting a broad feasibility assessment of healthcare data systems and external partnerships that permit the evaluation of long-term prognosis of patients with myocarditis/pericarditis temporally associated with COMIRNATY vaccination. As discussed with CDC and FDA, including Drs. Sara Oliver, Tom Shimabukuro, and Narayan Nair as well as other colleagues, in an informal meeting on July 19th, we understand that the CDC is conducting enhanced surveillance within the Vaccine Safety Datalink (VSD) to follow vaccine-associated myocarditis/pericarditis cases for 3-6 months for symptomatic recovery. CDC is also exploring methods to follow cases reported to VAERs.

To complement the CDC's efforts, we propose the following:

1. Incorporate myo-/pericarditis-specific analytic endpoints in currently planned or ongoing studies C4591009, C4591011, C4591012, and C4591021 to assess the natural history of post-vaccination myo-/pericarditis, e.g., recovery status (medical record review) and/or identification of serious cardiovascular outcomes (structured data) within 1 year of myo-/pericarditis diagnosis among individuals vaccinated with COMIRNATY as well as individuals not vaccinated with a COVID-19 vaccine.

2. An additional US study to be conducted within the Pediatric Heart Network (PHN), in collaboration with the National Institutes of Health (NIH)/National Heart, Lung and Blood Institute (NHLBI).

    - This study is proposed in partnership with the PHN, funded by the NHLBI /NIH. The PHN is a multi-center consortium of major pediatric cardiovascular academic centers in the US and Toronto, Canada that has been conducting studies of cardiovascular disease in children since 2001. The PHN has significant experience with both clinical trials and observational studies and has done several studies in collaboration with pharmaceutical companies and under FDA regulation. To date, a convenience sample of ~130 patients <21 years old with COVID-19 vaccine-associated myocarditis has been collected under waiver of consent. In response to CBER's urgent request, below is a proposal based on an initial discussion between Pfizer and PHN/NIH scientists. Details of study design and research agreement are under discussion. We will promptly notify the Agency if there are any challenges encountered with this proposal.

      Specific Aims

      AIM 1: To characterize the clinical course of acute post-vaccine myocarditis in children and young adults <21 years old

      AIM 2: To characterize potential long-term sequelae of post-vaccine myocarditis, and quality of life in children and young adults <21 years old

      AIM 3: To compare long-term effects of post-vaccine myocarditis with those of non-vaccine myocarditis, including myocarditis arising in COVID-infected children and young adults <21 years old

      AIM 4: To identify possible risk factors for post-vaccine myocarditis in children and young adults <21 years old including age, sex, race, ethnicity, obesity, and other factors.

      Study Population and Testing

      AIM 1: ~130 patients, already identified, who presented to PHN main and auxiliary sites after receiving a first or second dose of a COVID-19 vaccine and were diagnosed with myocarditis. Additional patients continue to present and could be

enrolled. In patients presenting with clinical symptoms suggesting myocarditis, all had elevated troponin levels, which led to additional investigations including ECG, echocardiography, and cardiac MRI.

AIM 2: Myocarditis patients identified in AIM 1 will be followed prospectively for one year to collect data from assessments, such as lab testing, ECG, Holter or Zio patch, echocardiogram, cardiac MRI with gadolinium, and exercise stress tests. Standard, age-appropriate tools to assess quality of life and psychosocial functioning will also be administered.

AIM 3: Unvaccinated myocarditis comparator group: Identify through EHR search of approximately previous 3 years about 100 patients with confirmed non-vaccine myocarditis and obtain clinical course and long-term sequelae. Parameters for comparison (descriptive) will include age at diagnosis, sex, co-morbidities, clinical features of acute event (need for pressors, days in ICU, presence and character of dysrhythmias, time to discharge, discharge cardiac meds), long-term sequelae and time to recovery.

COVID Myocarditis sub-group: Identify through EHR search of previous year available patients with confirmed SARS-CoV-2 infection and confirmed myocarditis (but not MIS-C)

AIM 4: Prospective patients aged 12-21 years who were vaccinated but did not have myocarditis.

Summary of Current and Proposed Studies

Table 4 summarizes the study design of the current and proposed studies. Pfizer/BioNTech believe these studies provide a comprehensive plan to satisfy the above CBER requests. Formal protocols will be submitted to FDA when available.

Table 4. Current and Proposed Post-marketing Safety Surveillance Studies

	C4591009	C4591011	C4591012	C4591021	C4591021 substudy	Pediatric Heart Network Study
Study title	A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech COVID-19 Vaccine in the United States	Active Safety Surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense Population Following Emergency Use Authorization	Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine	Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine	Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine (Substudy)	TBD
Study design	Retrospective cohort study	Rapid-cycle, longitudinal, observational cohort study	Rapid-cycle, longitudinal, observational cohort study	Retrospective cohort study	Natural history cohort study within a retrospective cohort study	Prospective cohort study
Comparator group	Risk: unvaccinated comparator Follow up: myocarditis in unvaccinated comparator	Risk: Self-controls, unvaccinated comparator and influenza vaccine comparator Follow up: myocarditis /pericarditis cases	Risk: Self-controls, unvaccinated comparator and influenza vaccine comparator Follow up: myocarditis /pericarditis cases	Risk: unvaccinated comparator Follow up: myocarditis in unvaccinated comparator	Risk: unvaccinated comparator Follow up: myocarditis in unvaccinated comparator	Risk: unvaccinated comparator Follow up: myocarditis in unvaccinated comparator
Suitability for identifying risk factors (Y/N)	Y	TBD	TBD	N	Y	Y
Suitability to assess change in risk over time (Y/N)	Y	Y	Y	Y	Y	Y
Information to be collected at baseline	Demographics and clinical characteristics including health care utilization, comorbidities, comedications, and concurrent vaccinations	Demographics and clinical characteristics including health care utilization, comorbidities, and concurrent vaccinations	Demographics and clinical characteristics including health care utilization, comorbidities, and concurrent vaccinations	Demographics and clinical characteristics including health care utilization, comorbidities, comedications, and concurrent vaccinations	Demographics and clinical characteristics including comorbidities, comedications, and concurrent vaccinations	Demographics and clinical characteristics including comorbidities, comedications, and concurrent vaccinations

Table 4. Current and Proposed Post-marketing Safety Surveillance Studies

	C4591009	C4591011	C4591012	C4591021	C4591021 substudy	Pediatric Heart Network Study
Frequency of data collection	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	3, 6, and 12 months after diagnosis of myocarditis
Method of data collection	Risk: structured data Follow up: structured data	Risk: structured data Follow up: medical records	Risk: structured data Follow up: medical records	Risk: structured data Follow up: medical records	Risk: structured data Follow up: medical records	Primary data collection
Length of follow up	Up to 1 year	Up to 30 months	Up to 30 months	Up to 2 years	1 year	1 year
Information collected at follow up	Clinical outcomes	Clinical outcomes, labs, imaging	Clinical outcomes, labs, imaging	Clinical outcomes, labs, imaging	Treatment for myocarditis and pericarditis, clinical outcomes, recovery	Clinical outcomes (eg, resolution, long term sequelae), labs, imaging, quality of life parameters
Assessment of impact on daily life (Y/N)	N	N	N	N	TBD	Y
Study timelines and milestone dates	Protocol: 08/31/2021 Monitoring report: 10/31/2022 Interim report: 10/31/2023 Final study report: 10/31/2025	Protocol: 01/29/2021 Interim report 1: 12/31/2021 Interim report 2: 06/30/2022 Interim report 3: 12/31/2022 Final study report: 12/31/2023	Protocol: 01/29/2021 Interim report 1: 06/30/2021 Interim report 2: 12/31/2021 Interim report 3: 06/30/2022 Interim report 4: 12/31/2022 Final study report: 12/31/2023	Protocol: 05/20/2021 Progress report: 09/30/2021 Interim report 1: 03/31/2022 Interim report 2: 09/30/2022 Interim report 3: 03/31/2023 Interim report 4: 09/30/2023 Interim report 5: 03/31/2024 Final study report: 09/30/2024	Protocol: 12/31/2021 Final report: 09/30/2024	Protocol: 11/30/2021 Final report: 10/31/2025

Abbreviations: TBD=To be determined; Y=Yes; N=No.

2.2. CBER Request 2

3. Please also provide your plans to characterize subclinical cases of myocarditis.

Sponsor Response

Myocarditis and pericarditis are inflammatory conditions of the myocardium and the pericardium respectively. A definitive diagnosis of myocarditis requires histological or immunohistological confirmation of an endomyocardial biopsy or other tissue specimen (e.g. from an autopsy). Due to their invasive nature, biopsies are rarely obtained, and therefore a diagnosis of myocarditis is often based upon a compatible clinical scenario associated with noninvasive biomarker and imaging features.[2] This results in case definitions that are very complex, potentially based on multiple parameters (e.g. Brighton Collaboration definitions).[3]

Abnormal ECG, echocardiogram, or troponin findings consistent with myocarditis with no cardiac symptoms have been reported in association with SARS-CoV-2 infection[4] but are not well characterized phenomena, and there is no widely accepted definition of subclinical myocarditis.

Many different ECG abnormalities can occur in symptomatic myocarditis, none of which are pathognomonic for the condition.[5] Similarly, troponin levels can be elevated in a number of cardiac and non-cardiac conditions, as well as spuriously.[6] One study, in 1993 patients 0 to 21 years of age without history of cardiac disease, evaluated troponin T levels in those with both cardiac and noncardiac presentations. Troponin was elevated in 9% of patients overall, only 60% of whom had a cardiac diagnosis; furthermore, a cardiac diagnosis was made in 12% of those with a normal troponin level.[7] Hence neither is specific to symptomatic myocarditis, and certainly not subclinical myocarditis, which makes them unsuitable to serve as screening tests for a rare entity like myocarditis. The background incidence of troponin abnormalities in vaccine recipients is unknown and likely heterogeneous.

In this context, a prospective study to detect subclinical myocarditis is not practically feasible at this time, as it would need to enroll a large number of participants, and if performed, would not yield clearly interpretable data. Furthermore, spurious findings from non-specific positive laboratory results could undermine vaccine uptake and cause unnecessary work ups and vaccinee anxiety.

We therefore propose to analyze troponin I levels at a central laboratory in samples of stored sera (drawn <1 year ago) in 12-30-year-old individuals participating in BNT162b2 studies, prior to receipt of BNT162b2 (i.e. either at baseline, or at any visit for placebo recipients). This is planned to include 3000 samples, stratified equally in the 12-17-, 18-24- and 25-30-years age groups. This sample size will provide 95% probability of observing one abnormal result amongst the overall sample if the background rate of abnormality is 0.1%, amongst each age stratum if the background rate is 0.3%, as follows (Table 5).

Table 5. Probability of Observing 1 Abnormal Result with Given Abnormal Result Rates (%)

Abnormal Result Rate (%)	N=1000	N=3000
0.01	9.5	25.9
0.05	39.4	77.7
0.1	63.2	**95.0**
0.2	86.5	99.8
0.3	**95.0**	100.0
0.4	98.2	100.0
0.5	99.3	100.0

Once we have ascertained timelines in which this can be performed, we will communicate them to the Agency.

This will enable us to determine the background rate of abnormality of a potential non-invasive biomarker in the relevant population. These data are critical to determining what sample size might be required for a potential future clinical study to distinguish a true signal of cardiac findings in the absence of compatible clinical signs and symptoms.

In the meantime, we are adding myocarditis and pericarditis as AESIs in all protocols with ongoing administration of study vaccines, as well as the following requirement:

> "Any study participant who reports acute chest pain, shortness of breath, palpitations, or any other symptom(s) that might be indicative of myocarditis or pericarditis within 4 weeks of a study vaccination should be specifically evaluated, preferably by a cardiologist, for possible myocarditis or pericarditis."
>
> In addition to a clinical evaluation, the following should be performed:
>
> - Electrocardiogram (ECG)
> - Troponin level
>
> If myocarditis or pericarditis are suspected based upon the initial evaluation, the following should also be performed:
>
> - Cardiac echocardiogram, and/or
> - Cardiac magnetic resonance study
>
> Results of these investigations will be recorded in the Case Report Form."

In addition, we are including routine ECGs in the Study BNT162-17 (submitted to BB-IND 19736 on 22 July 2021; SN 0416), which will start shortly, evaluating versions of BNT162b2 encoding the delta variant S protein, or the alpha and delta variants. This study consists of two parts, Part A and Part B, and will evaluate the safety and immunogenicity of a third injection of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), and the safety and immunogenicity of a third injection of the monovalent vaccine BNT162b2 (B.1.617.2), in

participants who have received two doses of the parent vaccine BNT162b2 at 30 µg, at least 6 months after the second dose of BNT162b2. In addition, it will evaluate the safety and immunogenicity of a two-dose regimen (21-days apart) of BNT162b2 (B.1.1.7 + B.1.617.2) in participants who have not received prior COVID-19 vaccination. Part A will include ~120 participants 18 to 55 years of age: 100 will have been previously vaccinated, 80 of whom will receive a 3rd dose and 20 of whom will receive a 3rd and 4th dose; 20 vaccine-naïve participants will receive 2 primary doses. Part B will include ~1125 participants: 750 will have been previously vaccinated and will receive a 3rd dose; 375 vaccine-naïve participants will receive 2 primary doses. ECGs will be obtained for all participants at screening, on the day of each vaccination and 1 week after each vaccination.

Finally, Pfizer/BioNTech is also proposing (in response to a separate CBER information request received on 30 July 2021) to include blood draws in Studies C4591007 and C4591031 to obtain serum samples for potential future troponin testing. Determination whether to test some or all of these samples for troponins would be predicated on the analysis of background rate of troponin abnormalities in study participants and expert advice.

3. REFERENCES

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