BNT162b2 (COMIRNATY)

BLA STN 125742/0

Response to CBER 10 August 2021 Information Request Regarding Post-marketing Safety Studies

August 2021

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AESI	Adverse events of special interest
CI	Confidence interval
DSMB	Data Safety Monitoring Board
IRB	Institutional Review Board
IRR	Incidence rate ratio
PHN	Pediatric Heart Network
RR	Relative risk
SAP	Statistical Analysis Plan
SCCS	Self-controlled case series
SCRI	Self-controlled risk interval

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 10 August 2021.

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

2. CBER REQUESTS AND SPONSOR RESPONSES

Our review of your pharmacovigilance plan for COMIRNATY (COVID-19 Vaccine, mRNA) under BLA 125742 is ongoing. We are reviewing your response (submitted in amendment 30 dated August 3, 2021) to our July 28, 2021 information request regarding postmarketing safety studies, and have the following comments:

2.1. CBER Request 1

1. ***The primary analysis in the post-authorization safety study C4591009 protocol synopsis uses a concurrent unexposed cohort. People without vaccination codes could receive their COVID vaccinations outside of the system, and exposure misclassification could bias the results. The self-controlled methods such as self-controlled risk interval (SCRI) are less susceptible to bias due to exposure misclassification. SCRI with a post-vaccination control window was proposed as a sensitivity analysis.***

   Please clarify how you plan to assess the magnitude of exposure misclassification for the concurrent unexposed cohort and quantify the bias. If the magnitude of the exposure misclassification is large, please consider using the SCRI as the primary analysis. The proposed SCRI control window has the same length as the risk interval, which may decrease the risk of time-varying confounding bias but could result in more limited person time for some AESIs thus impacting the power of the SCRI analysis. Since SCRI allows the control window to have a different length than the risk window, please consider using a longer control window (e.g., multiples of the risk window) in the primary analysis, while maintaining the shorter control window for a sensitivity analysis. Please provide length of risk interval for each AESI.

Sponsor Response

Exposure misclassification is an important consideration for the study and this risk will be addressed in the pre-specified feasibility assessment, which is described in the full protocol (to be submitted to the agency by August 31, 2021). In Section 9.3.1 of the protocol, we state: "The completeness of exposure data will be assessed in monitoring analyses before the end of the study by comparing with publicly available estimates of vaccine coverage and/or estimates based on immunization registry data from select states (if available); if the coverage estimates differ meaningfully from the "benchmarking" estimates (meaningful difference to be defined in the Statistical Analysis Plan [SAP]), then modifications to the study approach may be considered. If this happens, the SCRI and the cohort design with

historical unexposed comparators may be designated as the primary study designs and/or linkage to immunization registries may be considered if feasible."

The length of the control window in the SCRI analyses will be assessed separately for each outcome. As per Section 9.7.3.1.1, "The control interval will be outcome specific, with the duration and timing relative to vaccination specified in more detail in the SAP. Control intervals will be defined during specific periods following vaccination (up to a maximum of 183 days); pre-vaccination periods will not be used to avoid bias due to healthy vaccinee effects."

The risk intervals for each safety event of interest will be provided in Section 9.3.2.1 of the full protocol (to be submitted to the agency by August 31, 2021). For convenience, Table A below provides the risk intervals that are described in the protocol.

Table A. General Safety Events to be Assessed in the General Population, Immunocompromised Individuals, Individuals with a History of COVID-19, and Pregnant Women

Organ System	Safety Event of Interest	Risk window (days following receipt of Pfizer-BioNTech COVID-19 Vaccine)[a]
Neurologic	Acute disseminated encephalomyelitis	1-42
	Bell's palsy	1-42
	Convulsions	1-42
	Encephalomyelitis/encephalitis	1-42
	Guillain- Barré syndrome	1-42
	Narcolepsy	1-180
	Transverse myelitis	1-42
Cardiac	Acute myocardial infarction	1-28
	Myocarditis/pericarditis	1-21[b]
Hematologic	Deep vein thrombosis	1-28
	Disseminated intravascular coagulation	1-28
	Immune hemolytic anemia	1-42
	Immune thrombocytopenia	1-42
	Pulmonary embolism	1-28
	Thromboembolic events associated with thrombocytopenia	1-28
	Thrombotic thrombocytopenic purpura	1-28
	Venous thromboembolism	1-28
	Hemorrhagic stroke	1-28
	Ischemic stroke	1-28
Respiratory	Acute respiratory distress syndrome	1-28
	Vaccine-associated enhanced respiratory disease	1-365
Other system	Anaphylaxis	0-1
	Appendicitis	1-42
	Kawasaki Disease	1-42
	Multisystem inflammatory syndrome	1-42

a. Time interval following vaccination when patients will be followed for safety events of interest. Day 0 refers to the day of vaccination.
b. Sensitivity analysis will assess alternative risk interval definitions of 1-7 days and 1-14 days.

2.2. CBER Request 2

2. Table 1 on Page 5 of the Response to Information Request provided the required number of cases to detect myocarditis under different assumptions with a self-controlled case series (SCCS) analysis. The study C4591009 protocol synopsis proposed a SCRI analysis. SCCS samples cases only, SCRI samples vaccinated individuals only, and the control interval could differ between these two study designs even with the same length of risk interval. Please clarify the length and definition of control interval in the Table 1 sample size calculation. The choice of risk window is critical for SCRI. Because the onset of myocarditis was typically within several days after mRNA COVID-19 vaccination, please add a 7-day risk window to the SCRI analysis in addition to the proposed 14-day and 21-day risk window. Please also provide the sample size calculation for a 7-day risk window for myocarditis.

For study C4591009 protocol synopsis, the sample size calculation on Page 14 was based on a true RR=1. Please recalculate the sample size under alternative RRs.

Sponsor Response

We agree that the choice of risk window is critical and plan to conduct sensitivity analyses for the myocarditis/pericarditis endpoint. The length of the control window in Table 1 in the Response to Information Request (submitted on 03 August 2021) was assumed to be 2 years (730 day follow up period) minus the risk window; 709 days for the 21-day risk window and 706 days for the 14-day risk window. The required sample size for this SCRI-based study is similar to that predicted in Table 1, which is based on the SCCS model, because the control window used in the model to determine sample size requirements includes the entire study period outside of the risk window rather than a shorter interval, e.g., matched to the duration of the risk window as is often the case for SCRI-based studies.[1] It is estimated that using a 7-day risk window, will increase sample size requirements compared to the 14-day and 21-day risk window respectively by approximately 96% to 1.9 fold, given 80% power and RR=2, for example. This reflects the fact that reducing the at-risk period results in the expectation of an increased number of cases required for the SCCS design. As requested, a 7-day risk period will be incorporated into the protocols.

For study C4591009, the sample size calculation in the synopsis was based on a true RR=1 and 1:2 matching. Within the full protocol (to be submitted to the agency by August 31, 2021), the matching ratio is presented as 1:1 matching. Study size estimates for 1:1 matching for true RR=1, 1.2 and 1.4 (estimated by the incidence rate ratio [IRR]) are provided in Appendix 1.

2.3. CBER Request 3

3. Please clarify when patient accrual will be completed for study C4591009.

Sponsor Response

Patient accrual for study C4591009 will be completed by June 30, 2024.

Given C451009 is a study of secondary data, at the time of data query for the final analysis, all available patients meeting study inclusion criteria will be included. The planned date for the data query is anticipated to occur during the 3rd quarter of 2024 (August or September 2024, contingent on data partner data refresh schedule and data quality review approval).

2.4. CBER Request 4

4. Please provide the study completion date (in mm/dd/yyyy format) for the following studies:

a. C4591009

b. C4591022

c. C4591012

d. C4591015

e. C4591021 and C4591021 substudy

f. Registry study with Pediatric Heart Network (PHN)

Sponsor Response

The planned study completion date (date of end of data collection) for each post-marketing safety study is listed below. The sponsor assumes that the agency's reference to "C4591015" in item d. was intended to refer to study "C4591011", as C4591015 is the phase 3 study in pregnant women and not a post-marketing safety study.

C4591009: 06/30/2025 (this date could be extended based on the extent of validation activities and/or the need for immunization registry linkages)

C4591022: 08/01/2025

C4591012: 06/10/2023

C4591011: 06/10/2023

C4591021 and C4591021 substudy: 9/30/2024

Registry study with Pediatric Heart Network (PHN): 12/01/2026

2.5. CBER Request 5

5. For the registry study with PHN, you have stated that you have identified approximately 130 patients and plan to enroll additional patients. Please provide a proposed sample size for this study, and the basis for the sample size calculation. You have also proposed 1-year prospective follow-up. We request 5 years of follow-up to capture potential long-term sequelae of myocarditis after vaccination.

Sponsor Response

This study will enroll patients <21 years of age who are diagnosed with vaccine-associated myocarditis within the PHN during the study period and who fulfill study inclusion criteria (yet to be determined, will include informed consent). A full IRB and DSMB approved protocol will be shared with the agency by November 30, 2021 and will include sample size estimates. The estimation of study size in the study protocol will require assumptions about future approvals of vaccines, numbers of people vaccinated by age, gender, type of vaccine and dose, effects of each vaccine by dose, number of participating PHN sites, etc. These scenarios will be elaborated in a study protocol under preparation with our PHN collaborators. We will plan for a 5-year follow-up period. Feasibility discussions with our PHN collaborators are ongoing; should any issues or unexpected challenges emerge, we will inform the agency promptly.

2.6. CBER Request 6

6. Please provide the protocol synopses and current status for the study C4591021 and C4591021 substudy.

Sponsor Response

Study protocol C4591021, Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine, was approved by the European Medicines Agency on 24 June 2021, in collaboration with the VAC4EU Consortium Team. The protocol is provided as requested (Appendix 2).

A substudy of C4591021 is planned to assess the natural history of post-vaccination myo-/pericarditis, eg, recovery status (medical record review), risk factors, 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. A synopsis of the study is provided in Table B. This substudy is still under development and subject to change based on data availability and feedback from EMA. The study milestones are listed in Table B below. We will share the final protocol with FDA following EMA endorsement.

Table B. C4591021 Substudy Synopsis

Study title	Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine (Myo-/pericarditis Substudy)
Research question	What are the incidence rates/prevalence of myocarditis and pericarditis outcomes among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine within selected European data sources compared to people who have not received the vaccine?
Objectives	Primary objective: • To describe the clinical course, for at least one year of follow-up, of Myocarditis and/or Pericarditis following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine and in individuals with no COVID-19 vaccination. Secondary objective: • To explore risk factors for myocarditis and pericarditis.
Background	The Pfizer-BioNTech COVID-19 vaccine, tozinameran (Comirnaty®) has been associated with the occurrence of myocarditis and/or pericarditis. Description of occurrence and the natural course of these events is needed.
Study design	This post-authorization active surveillance study of safety events of interest associated with the Pfizer-BioNTech COVID-19 vaccine will use a retrospective cohort design involving multiple databases. Within a retrospective cohort design on the safety of the Pfizer Vaccine, a cohort study of the natural history of Myocarditis / Pericarditis will be performed distinguishing between vaccinated and non-vaccinated subjects
Population	The source population will comprise all individuals registered in each of the health care data sources from the parent study C4591021 who meet the myo/peri carditis case definition. Inclusion criteria: subjects must meet Brighton Collaboration case (https://brightoncollaboration.us/myocarditis-case-definition-update/). This will create levels of certainty of the diagnosis. Data availability for each institution might be affected by third parties or external circumstances that are independent from the institution involved in the study as described below in Section 9.9 of the attached approved C4591021 protocol.
Data sources	The study will be performed within the following selected data sources: • PHARMO (PHARMO Institute for Drug Outcomes Research) (NL) • ARS Toscana (Agenzia Regionale di Sanita' della Toscana) (IT) • Pedianet/Health Search Database (HSD) (IT) • EpiChron (EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute) (ES) • CPRD (Clinical Practice Research Datalink) (UK), the Norwegian health registers (NO) • SIDIAP (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària) [Information System for the Improvement of Research in Primary Care] (ES)

Table B. C4591021 Substudy Synopsis

Information to be collected at baseline	Demographics and clinical characteristics including comorbidities, comedications, and concurrent vaccinations, risk factors for myocarditis and pericarditis including: COVID-19 history, other vaccines, infectious disease comorbidities; immunocompromising conditions and systemic immune- mediated diseases, comedication use during the year before time zero (prescriptions or dispensing, no over-the-counter medication use).
Method of data collection	Structured data and medical record review.
Study period	The study period will start on the date of launch of the Pfizer-BioNTech COVID-19 vaccine and will end on the date of the latest data availability or 31 Dec 2023. It is expected that follow-up will last for 1 year. Cohort entry: day of myocarditis/pericarditis diagnosis (time zero)
Information collected at follow up	Treatments for myocarditis include: symptomatic treatment for viral myocarditis based on clinical presentation, immunosuppression treatment for autoimmune myocarditis, heart failure therapy (i.e., beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs), aldosterone agonists, cardiac glycosides or calcium-channel blockers); procedural treatment (i.e., pacemaker, implantable cardiac defibrillator, mechanical circulatory support and heart transplantation. Treatments for pericarditis include: Antimicrobial treatment, anti-inflammatory treatment (Non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine (for recurrent pericarditis); procedural treatment (i.e., intrapericardial administration of steroids, pericardioscopy for direct instillation of treatments into the pericardial space, pericardial drainage. Subdiaphragmatic laparoscopic technique, video-assisted thoracoscopic technique, and pericardioscopy to easy drainage of effusion, pericardiocentesis, cardiac catheterisation during pericardiocentesis, balloon pericardial window formation, instillation of sclerosing agents. Instillation of fibrinolytic agents, pericardiectomy. Outcomes for myocarditis include: recovery, sudden cardiac death, heart failure; cardiogenic shock, fulminant myocarditis, inflammatory cardiomyopathy, heart transplant, arrhythmia Outcomes for pericarditis include: recovery, chronic, restrictive and recurrent pericarditis
Study timelines and milestone dates	Protocol submission to EMA: 01/31/2022 Final report: 09/30/2024

2.7. CBER Request 7

7. You have proposed to analyze troponin I levels at a central laboratory in 3,000 samples of stored sera (drawn <1 year ago) in 12-30-year-old individuals participating in BNT162b2 studies, prior to receipt of BNT162b2. We acknowledge that the results of this analysis will help determine what sample size might be required for a prospective study to assess the incidence of subclinical myocarditis following vaccination. Please provide projected dates for the Final Protocol Submission, Study Completion, and Final Report Submission for a prospective study to assess the incidence of subclinical myocarditis following vaccination.

Sponsor Response

Reference is made to Pfizer-BioNTech's response to the Agency regarding the risk of myocarditis and pericarditis associated with the Pfizer BioNTech Vaccine submitted to BB-IND 19,736 on 23 July 2021 (SN 0422).

Specifically, we proposed 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 (ie, 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% and amongst each age stratum if the background rate is 0.3%. This was to 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.

The current status of this work is as follows. A central laboratory that can perform the work has been identified; contracting and logistical aspects are being prepared: 3000 appropriate samples need to be identified, retrieved from frozen storage, aliquoted and shipped to the central laboratory. The samples then need to be analyzed and the data analyzed and interpreted. This work is anticipated to be completed by the end of December 2021.

Furthermore, in a response to the Agency's recommendation to collect and store blood samples during the time period when symptomatic myocarditis cases have most frequently been reported (ie, within the first 4 days post-vaccination), submitted on 4 August 2021 (SN 0436), we made the following proposal.

In each case, we proposed to schedule a blood draw to obtain a serum sample for storage, and potential future troponin testing, at baseline and 2-5 days after the second or third dose of BNT162b2 in two studies.

C4591007: Pfizer/BioNTech propose to add 750 participants 5 to <12 years of age (randomized 2:1 to receive BNT162b2 10 µg or placebo) and 500 participants 12-15 years of age (open label receipt of BNT162b2 30 µg). These participants would be introduced through a protocol amendment.

C4591031: Pfizer/BioNTech propose to add a new substudy of 1000 participants with documented receipt of 2 prior 30 µg doses of BNT162b2 (the second dose received at least 6 months ago), 16 to 30 years of age (randomized 1:1 in a crossover design to receive 30 µg BNT162b2 or placebo at baseline and the alternate 4 weeks later).

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 the 3000 existing study participants (as described above) and expert advice.

Once those results are available, proper consideration can be given to the design, size and feasibility of a potential prospective study. Therefore, at this point in time, we are not able to provide projected dates for the Final Protocol Submission, Study Completion, and Final Report Submission for a prospective study to assess the incidence of subclinical myocarditis following vaccination. Once we have data to inform these decisions, we will share them and our plans to move forward with the Agency.

3. APPENDICES

3.1. Appendix 1

In response to Request 2 (Section 2.2) above, three different Study Size scenarios for Study C4591009 are provided below; (original incidence rate ratio [IRR]=1.0, alternatives IRR =1.2 and 1.4) with matching ratio 1:1.

Table 1 presents the probability that the upper limit of the 95% confidence interval (CI) for the observed relative risk will be below 1.5, 2.0, 2.5, and 3.0 for study sizes ranging from 500,000 to 20,000,000 vaccinated individuals (1,000,000 doses to 40,000,000 doses, under the assumption that each person will receive 2 doses), assuming that the true relative risk is 1.0 and a matching ratio of 1:1. These estimates are presented to cover a range of safety events of interest with respect to rareness, based on background rates in the general population.

Table 2 presents the probability that the upper limit of the 95% CI for the observed relative risk will be below 1.5, 2.0, 2.5, and 3.0 for study sizes ranging from 500,000 to 20,000,000 vaccinated individuals (1,000,000 doses to 40,000,000 doses, under the assumption that each person will receive 2 doses), assuming that the true relative risk is 1.2 and a matching ratio of 1:1. These estimates are presented to cover a range of safety events of interest with respect to rareness, based on background rates in the general population.

Table 3 presents the probability that the upper limit of the 95% CI for the observed relative risk will be below 1.5, 2.0, 2.5, and 3.0 for study sizes ranging from 500,000 to 20,000,000 vaccinated individuals (1,000,000 doses to 40,000,000 doses, under the assumption that each person will receive 2 doses), assuming that the true relative risk is 1.4 and a matching ratio of 1:1. These estimates are presented to cover a range of safety events of interest with respect to rareness, based on background rates in the general population.

Table 1. Study Size Calculations - IRR=1.0, Matching Ratio 1:1

Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021)	Number of individuals vaccinated	Probability that the upper confidence limit of RR will be below the following thresholds[a]			
			1.5	2.0	2.5	3.0
Guillain-Barré syndrome	1.68	500,000	0.06	0.10	0.14	0.19
		1,000,000	0.08	0.16	0.25	0.33
		2,500,000	0.14	0.33	0.52	0.68
		5,000,000	0.24	0.58	0.81	0.93
		10,000,000	0.43	0.86	0.98	1.00
		20,000,000	0.71	0.99	1.00	1.00
Bell's palsy	25.2	500,000	0.24	0.58	0.81	0.93
		1,000,000	0.43	0.86	0.98	1.00
		2,500,000	0.80	1.00	1.00	1.00
		5,000,000	0.98	1.00	1.00	1.00
		10,000,000	1.00	1.00	1.00	1.00
		20,000,000	1.00	1.00	1.00	1.00
Myocardial infarction	208	500,000	0.95	1.00	1.00	1.00
		1,000,000	1.00	1.00	1.00	1.00
		2,500,000	1.00	1.00	1.00	1.00
		5,000,000	1.00	1.00	1.00	1.00
		10,000,000	1.00	1.00	1.00	1.00
		20,000,000	1.00	1.00	1.00	1.00

a. Estimates in this table assume a risk window duration of 42 days for Guillain-Barré syndrome, and 28 days for Bell's palsy and myocardial infarction.

Table 2. Study Size Calculations - IRR=1.2, Matching Ratio 1:1

Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021)	Number of individuals vaccinated	Probability that the upper confidence limit of RR will be below the following thresholds[a]			
			1.5	2.0	2.5	3.0
Guillain-Barré syndrome	1.68	500,000	0.04	0.08	0.11	0.15
		1,000,000	0.05	0.11	0.19	0.26
		2,500,000	0.07	0.22	0.39	0.56
		5,000,000	0.11	0.38	0.66	0.85
		10,000,000	0.17	0.65	0.92	0.99
		20,000,000	0.30	0.91	1.00	1.00
Bell's palsy	25.2	500,000	0.11	0.38	0.66	0.85
		1,000,000	0.17	0.65	0.92	0.99
		2,500,000	0.37	0.96	1.00	1.00
		5,000,000	0.63	1.00	1.00	1.00
		10,000,000	0.90	1.00	1.00	1.00
		20,000,000	1.00	1.00	1.00	1.00
Myocardial infarction	208	500,000	0.55	1.00	1.00	1.00
		1,000,000	0.84	1.00	1.00	1.00
		2,500,000	1.00	1.00	1.00	1.00
		5,000,000	1.00	1.00	1.00	1.00
		10,000,000	1.00	1.00	1.00	1.00
		20,000,000	1.00	1.00	1.00	1.00

a. Estimates in this table assume a risk window duration of 42 days for Guillain-Barré syndrome, and 28 days for Bell's palsy and myocardial infarction.

Table 3. Study Size Calculations - IRR=1.4, Matching Ratio 1:1

Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021)	Number of individuals vaccinated	Probability that the upper confidence limit of RR will be below the following thresholds[a]			
			1.5	2.0	2.5	3.0
Guillain-Barré syndrome	1.68	500,000	0.03	0.06	0.09	0.12
		1,000,000	0.03	0.08	0.14	0.21
		2,500,000	0.04	0.13	0.28	0.44
		5,000,000	0.04	0.22	0.49	0.73
		10,000,000	0.05	0.40	0.79	0.95
		20,000,000	0.07	0.67	0.97	1.00
Bell's palsy	25.2	500,000	0.04	0.22	0.49	0.73
		1,000,000	0.05	0.40	0.79	0.95
		2,500,000	0.07	0.76	0.99	1.00
		5,000,000	0.11	0.97	1.00	1.00
		10,000,000	0.18	1.00	1.00	1.00
		20,000,000	0.31	1.00	1.00	1.00
Myocardial infarction	208	500,000	0.10	0.93	1.00	1.00
		1,000,000	0.15	1.00	1.00	1.00
		2,500,000	0.32	1.00	1.00	1.00
		5,000,000	0.56	1.00	1.00	1.00
		10,000,000	0.85	1.00	1.00	1.00
		20,000,000	0.99	1.00	1.00	1.00

a. Estimates in this table assume a risk window duration of 42 days for Guillain-Barré syndrome, and 28 days for Bell's palsy and myocardial infarction.

3.2. Appendix 2

C4591021. Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. 20 May 2021.

4. REFERENCES

1 Li R, Stewart B, Weintraub E. Evaluating efficiency and statistical power of self-controlled case series and self-controlled risk interval designs in vaccine safety. J Biopharm Stat 2016;26(4):686-93.

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