NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Interim Analysis of Myocarditis/Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age Enrolled in the C4591036 Study
Protocol number	C4591079
Protocol version identifier	Version 1.0
Date	July 31, 2025
EU Post Authorization Study (PAS) register number	TBD
Active substance	BNT162b2
Medicinal product	COVID-19 messenger ribonucleic acid (mRNA) vaccine is a nucleoside-modified ribonucleic acid (modRNA) encoding the viral spike glycoprotein S of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Product reference	EMEA/H/C/005735
Procedure number	N/A
Marketing Authorization Holder(s)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	What are the acute and long term sequalae associated with myocarditis and pericarditis following vaccination with COMIRNATY? **Primary objective**: To characterize the potential long-term sequelae associated with myocarditis/pericarditis following COMIRNATY vaccination in persons <21 years old. **Secondary objectives**: 1) To characterize the acute course (hospital admission/ER evaluation to discharge) of COMIRNATY-associated myocarditis/pericarditis in persons <21 years old. 2) To compare acute and long-term cardiac outcomes of COMIRNATY-associated myocarditis/pericarditis with those of myocarditis/pericarditis associated with COVID-19, including the multisystem inflammatory syndrome in children associated with COVID-19 in persons <21 years old (MIS-C).

	3) To identify possible sociodemographic and medical risk factors, such as age, sex assigned at birth, race, ethnicity, insurance, and zip code, for greater frequency and severity of long-term cardiac sequelae in persons <21 years old.
Country(ies) of study	United States and Canada
Author	Stephan Lanes, PhD, Carelon Research

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany
MAH contact person	Viola Hoffmann

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AV	Atrioventricular
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cMRI	Cardiac magnetic resonance image
CRF	Case report form
CRO	Clinical Research Organization
CRP	C-reactive protein
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
Echo	Echocardiogram
EMA	European Medicine Agency
EMR	Electronic medical record
ER	Emergency room
EU	European Union
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Guidelines for Good Pharmacovigilance Practices
ICMJE	International Committee of Medical Journals Editors
IRB	Institutional Review Board

Abbreviation	Definition
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
MIS-C	Multisystem inflammatory syndrome in children
PASS	Post authorization safety study
PMR	Post-marketing requirement
RMP	Risk management plan
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SDV	Source data verification
SoA	Schedule of Activities
SOP	Standard Operating Procedure
VAERS	Vaccine Adverse Event Reporting System
XML	Extensible Markup Language

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Cynthia de Luise, MPH, PhD	Safety Surveillance Research Scientist	Pfizer, Inc.	66 Hudson Blvd East New York, NY 10001
Stephan Lanes, PhD	Principal Scientist	Carelon Research	123 Justison St Suite200 Wilmington, DE 19801
Jane Newburger, MPH, MD	Commonwealth Professor of Pediatrics, Cardiology/Study Co-Principal Investigator	Boston Children's Hospital	300 Longwood Avenue Boston, MA 02115
Dongngan Truong, MD	Associate Professor of Pediatrics, Cardiology/Study Co-Principal Investigator	Emory University	1001 Johnson Ferry Rd NE, Atlanta, GA 30342

4. ABSTRACT

Title: Interim Analysis of Myocarditis/ Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age Enrolled in the C4591036 Study

Protocol: C4591079
V 1.0
JULY 31, 2025

Cynthia de Luise, PhD, MPH, Safety Surveillance Research, Pfizer, Inc.; Stephan Lanes, PhD, Carelon Research

Rationale and background:

The C4591036 study entitled “Low- interventional Study of Myocarditis and Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age” (ClinicalTrials.gov ID NCT05295290) is an ongoing post-authorization safety study (PASS), a post-marking requirement (PMR) to the Food and Drug Administration (FDA) and a category 3 commitment in the European Union (EU) risk management plan (RMP). The C4591036 study is the first to determine the spectrum and time-course of cardiac findings using standardized and centralized assessments using Core Laboratories, and to define long-term cardiovascular and non-cardiovascular health status following vaccination with COMIRNATY.

This protocol (C4591079) describes the conduct of an interim analysis of existing data from the C4591036 study. This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer-BioNTech.

Research question and objectives:

What are the acute and long term sequalae associated with myocarditis and pericarditis following vaccination with COMIRNATY?

Primary objective:
The primary objective of this study is to characterize the potential long-term sequelae associated with myocarditis/pericarditis following COMIRNATY vaccination in persons <21 years old.

Secondary objectives:

1) To characterize the acute course (hospital admission/emergency room (ER) evaluation to discharge) of COMIRNATY-associated myocarditis/pericarditis in persons <21 years old.
2) To compare acute and long-term cardiac outcomes of COMIRNATY-associated myocarditis/pericarditis with those of myocarditis/pericarditis associated with COVID-19, including the multisystem inflammatory syndrome in children associated with COVID-19 in persons <21 years old (MIS-C).
3) To identify possible sociodemographic and medical risk factors, such as age, sex assigned at birth, race, ethnicity, insurance, and zip code, for greater frequency and severity of long-term cardiac sequelae in persons <21 years old.

Study Design:
This is an interim analysis based on data from the ongoing C4591036 study, "Low-interventional Study of Myocarditis and Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age."

Population:
This study uses data from three cohorts of participants in the ongoing C4591036 study:

> **Cohort 1**: Prospectively ascertained cases of probable or confirmed myocarditis/pericarditis associated with COMIRNATY, i.e., participants enrolled under the protocol during hospitalization or ≤ 2 weeks after hospital discharge.
>
> **Cohort 2**: Retrospectively ascertained cases of probable or confirmed myocarditis / pericarditis associated with COMIRNATY, i.e., participants enrolled >2 weeks after hospital discharge (combination of retrospective data collection from electronic medical records (EMRs) and prospective data from the time that the participant signs informed consent/assent). Participants can be retrospectively or prospectively ascertained and enrolled at any time from their COMIRNATY-associated myocarditis/pericarditis.
>
> **Cohort 3**: Comparator cohort of COVID-19-related myocarditis/pericarditis, including MIS-C. Participants can be retrospectively or prospectively ascertained and enrolled at any time from their COVID-19 or MIS-C-associated myocarditis/pericarditis. Cohort 3 participants will not be separated into COVID-19-associated myocarditis/pericarditis with or without MIS-C because of the rarity of myocardial involvement in children with acute severe COVID-19.

Variables:
Variables for this interim analysis include:

- Sociodemographics
- Medical history
- Treatments for myocarditis/pericarditis or myopericarditis
- Clinical Labs: Troponin
- BNP or NT-proBNP; c-reactive protein (CRP)
- Echocardiographic variable
- Electrocardiographic variables
- Cardiac MRI variables
- Exercise stress test variables
- Ambulatory monitoring
- Patient-reported outcome measures
- Complications and noncardiac morbidities

Data sources:
In the C4591036 study, Site Investigators have ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the case report form (CRF) and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required.

Participant adherence to the C4591036 study design is required, including those activities specified in the schedule of activities (SoA) at time points after enrollment. Relevant data will be collected from testing obtained as part of routine care prior to enrollment.

Study size:
This study (C4591079) will analyze interim data collected for the first 300[1] participants enrolled in C4591036 between 21 Nov 2022 and 16 Apr 2025 who meet study inclusion/exclusion criteria, from acute presentation through the 1-year post-discharge study visit. Enrollment per participant cohort is as follows:

- 200 prospectively and retrospectively ascertained cases of children, adolescents, and young adults <21 years of age who receive care at participating medical centers for myocarditis/pericarditis associated with COMIRNATY, and
- 100 persons <21 years of age with COVID-associated myocarditis/pericarditis, including MIS-C.

The statistical analysis is descriptive in nature and study sample size is not based on any statistical hypothesis testing.

The study cohort may be updated, and planned analyses repeated to allow for the evaluation of additional annual study visits as those milestones are met.

Data analysis:
Study participants' medical history, clinical course, long-term sequelae (see Table 1), risk factors for long term sequelae, time to resolution, and quality of life impact of myocarditis/pericarditis associated with COMIRNATY will be characterized and summarized using descriptive statistics (see Section 9.7) at the study time points, namely during the hospitalization, at 2 weeks, 6 weeks, and 6 months, and annually up to the 1-year post-discharge study visit. Similar summaries will be produced for a comparator cohort of children and young adults <21 years of age with COVID-19–associated myocarditis/pericarditis, including MIS-C.

Detailed methodology for the statistical analysis of the study data, in alignment with the objectives outlined in Section 8, will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor.

Milestones: Data will be accessed for this study after institutional review board approval is received, and data cleaning activities have been completed. The following planned milestones are shown below.

Start of data collection: 01 Sep 2025
End of data collection: 31 Dec 2025
Submission of interim study report to FDA: 31 Mar 2026

[1] 200 prospectively ascertained or retrospective ascertained cases of COMIRNATY associated myocarditis or pericarditis and 100 cases of COVID-19 associated myocarditis or pericarditis are the minimum enrollment targets in the C4591036 study.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Registration in the HMA-EMA Catalogues of Real-world Data Sources and Studies	TBD
Start of data collection	01 Sep 2025
End of data collection	31 Dec 2025
Final study report	31 Mar 2026

7. RATIONALE AND BACKGROUND

Rare cases of myocarditis/pericarditis have been reported in adults following COVID-19 vaccination with most cases occurring in males <30 years old.[1-5] Post-marketing data for mRNA COVID-19 vaccines suggest increased risks of myocarditis/pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 30 years of age than among females and older males.[2] Although some cases have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management.[2-7] However, there are limited data on possible long-term sequelae associated with post-vaccine myocarditis/pericarditis.

The Food and Drug Administration (FDA) requested that Pfizer-BioNTech conduct follow-up of cases of myocarditis/pericarditis after vaccination with COMIRNATY for recovery status and long- term sequelae. The European Medicines Agency (EMA) also requested similar follow-up of cases of myocarditis/pericarditis, specifically to capture long-term outcomes, risk factors, and impact of myocarditis/pericarditis on quality of life. The ongoing Study C4591036, entitled “Low- interventional Study of Myocarditis and Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age” (ClinicalTrials.gov ID NCT05295290), was undertaken to fulfil this request from both agencies. C4591036 is the first study to determine the spectrum and time-course of cardiac findings using standardized and centralized assessments using Core Laboratories, and to define long-term cardiovascular and non-cardiovascular health status following vaccination with COMIRNATY.

C4591036 is a PASS, a PMR to the FDA, and a Category 3 commitment in the EU RMP. C4591036 will continue enrollment through November 21, 2025, and will follow participants for up to 5 years from illness onset, or until an end of study status has been reached (i.e., early termination, lost to follow-up).

This protocol (C4591079) describes the conduct of an interim analysis of existing data from the C4591036 study. This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer-BioNTech.

8. RESEARCH QUESTION AND OBJECTIVES

What are the acute and long term sequalae associated with myocarditis/pericarditis following vaccination with COMIRNATY?

Primary objective: The primary objective of this study is to characterize the potential long-term sequelae associated with myocarditis/pericarditis following COMIRNATY vaccination in persons <21 years old.

Secondary objectives:

1) To characterize the acute course (hospital admission/ER evaluation to discharge) of COMIRNATY-associated myocarditis/pericarditis in persons <21 years old.
2) To compare acute and long-term cardiac outcomes of COMIRNATY-associated myocarditis/pericarditis with those of myocarditis/pericarditis associated with COVID-19, including the multisystem inflammatory syndrome in children associated with COVID-19 in persons <21 years old (MIS-C).

3) To identify possible sociodemographic and medical risk factors, such as age, sex assigned at birth, race, ethnicity, insurance, and zip code, for greater frequency and severity of long-term cardiac sequelae in persons <21 years old.

Study endpoints tied to each objective are listed below in Table 1.

Table 1. Objectives and Endpoints

Objectives	Endpoints	Measurement Schedule[c]
Primary:	**Primary:**	
To characterize the potential long-term sequelae associated with myocarditis/pericarditis following vaccination with COMIRNATY in persons <21 years old.	Primary study endpoint: Composite of left ventricular dysfunction (LVEF by < 55% by echocardiogram), findings of myocarditis by original or revised Lake Louise criteria on cMRI, or high-grade arrhythmia or conduction system disturbance at 6 months[a]	6 months after illness onset
	LVEF by echocardiography	2 weeks, 6 weeks, 6 months[b], and 1-5 years[b]
	Findings of myocarditis by original or revised Lake Louise criteria on cMRI[14]	If ordered for routine clinical care, 6 months; annually at 1-5 years if previous study was abnormal
	Arrhythmias and conduction system disturbances[a]	ECG: 2 weeks, 6 weeks, 6 months. Ambulatory monitoring and exercise stress testing by 6 months; annually at 1-5 years if previous study was abnormal
	Complications and non-cardiac morbidities	Assessed throughout study duration; captured on CRFs at 2 weeks, 6 weeks, 6 months, and 1-5 years or during hospital admissions
	Patient-reported outcomes of global health, functional status, and quality of life	2 weeks, 6 weeks, 6 months, and 1-5 years
	Secondary:	
	Time to recovery (return to normal) from the presence of the primary study endpoint	Echocardiography: 2 weeks, 6 weeks, 6 months[b], and 1-5 years[b] cMRI: If ordered for routine clinical care, 6 months; annually at 1-5 years if previous study was abnormal ECG: 2 weeks, 6 weeks, 6 months. Ambulatory monitoring and exercise stress testing by 6 months; annually at 1-5 years if previous study was abnormal

Table 1. Objectives and Endpoints

Objectives	Endpoints	Measurement Schedule[c]
	Time to recovery (return to normal) from the presence of LV strain on echocardiography	Echocardiography: 2 weeks, 6 weeks, 6 months[b], and 1-5 years[b]
Secondary:	**Secondary:**	
To characterize the acute course of COMIRNATY-associated myocarditis/pericarditis in persons <21 years old.	Left ventricular ejection fraction (LVEF) by echocardiogram as a measure of myocardial performance	Admission and discharge
	Myocardial inflammation and injury by the original or revised Lake Louise criteria on cMRI[14]	During hospitalization or within 2 weeks of discharge
	Arrhythmias or conduction system disturbances[a]	Admission and discharge ECG and during hospital telemetry
	Complications and non-cardiac morbidities	Throughout hospital course
To compare acute and long-term cardiac outcomes of COMIRNATY-associated myocarditis/pericarditis with those of myocarditis/pericarditis associated with COVID-19, including multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) in persons <21 years old.	Point estimates and trends over time in:	
	Echocardiographic LVEF	2 weeks, 6 weeks, 6 months[b], and 1-5 years[b]
	Myocardial inflammation and scarring (cMRI), including late gadolinium enhancement (LGE)	If ordered for routine clinical care, 6 months; annually at 1-5 years if the preceding study was abnormal
	Arrhythmias and conduction system disturbances[a]	ECG: 2 weeks, 6 weeks, 6 months. Ambulatory monitoring and exercise stress testing at 6 months; annually at 1-5 years if the preceding study was abnormal
	Complications and non-cardiac morbidities	2 weeks, 6 weeks, 6 months, and 1-5 years
To identify possible sociodemographic and medical risk factors, such as age, sex assigned at birth, race, ethnicity, insurance, and zip code, for greater frequency and severity of long-term cardiac sequelae in persons <21 years old.	Primary study endpoint: Composite of left ventricular dysfunction (LVEF by < 55% by echocardiogram), findings of myocarditis by original or revised Lake Louise criteria on cMRI, or high-grade arrhythmia or conduction system disturbance at 6 months[a]	Assessed throughout study duration; sociodemographic and medical risk factors: captured on CRFs at baseline/Visit 1: echocardiography: 2 weeks, 6 weeks, 6 months[b], and 1-5 years[b] cMRI: If ordered for routine clinical care, 6 months; annually at 1-5 years if previous study was abnormal ECG: 2 weeks, 6 weeks, 6 months. Ambulatory monitoring and exercise stress testing by 6 months; annually at 1-5 years

Table 1. Objectives and Endpoints

Objectives	Endpoints	Measurement Schedule[c]
		if previous study was abnormal

a Arrythmias and conduction system disturbances can be documented by 12 or 15-lead ECG, ambulatory monitor, other studies obtained at time of symptoms (e.g., Kardia, rhythm strip, events monitors, Apple watch), or exercise stress testing.
b For patients with LVEF ≥55% at 2 and 6 weeks, then LVEF will be presumed to be ≥55% at 6 months and annually, and thus echocardiograms are not required at those time points. However, data from subsequent echocardiograms will be collected if conducted as part of clinical care.
c From day of discharge from first myocarditis/pericarditis hospitalization.

9. RESEARCH METHODS

9.1. Study Design

This is an interim analysis of data collected in the ongoing C4591036 study, "Low-interventional Study of Myocarditis and Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age."

C4591036 is a low-interventional cohort study to determine cardiac and non-cardiac long-term outcomes of persons <21 years of age with myocarditis/pericarditis after the administration of COMIRNATY, compared with similarly aged persons with myocarditis/pericarditis associated with COVID-19, including MIS-C.

9.2. Setting

This study analyzes data from the ongoing C4591036 study, "Low- interventional Study of Myocarditis and Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age."

Three cohorts of participants are included in this study:

> **Cohort 1**: Prospectively ascertained cases of probable or confirmed myocarditis/pericarditis associated with COMIRNATY, i.e., participants enrolled under the protocol during hospitalization or ≤2 weeks after hospital discharge.
>
> **Cohort 2**: Retrospectively ascertained cases of probable or confirmed myocarditis/pericarditis associated with COMIRNATY, i.e., participants enrolled >2 weeks after hospital discharge (combination of retrospective data collection from EMRs and prospective data from the time that the participant signs informed consent/assent). Participants can be retrospectively or prospectively ascertained and enrolled at any time from their COMIRNATY-associated myocarditis/pericarditis.
>
> **Cohort 3**: Comparator cohort of COVID-19-related myocarditis/pericarditis, including MIS-C. Participants can be retrospectively or prospectively ascertained and enrolled at any time from their COVID-19 or MIS-C-associated myocarditis/pericarditis. Cohort 3 participants will not be separated into COVID-19-associated myocarditis/pericarditis with or without MIS-C because of the rarity of myocardial involvement in children with acute severe COVID-19.

Among Cohorts 2 and 3, a waiver of consent can be requested for collection of information related to clinical care when participants with a history of vaccine myocarditis/pericarditis or COVID-19-related myocarditis/pericarditis, including MIS-C, are unreachable after 5 documented contact attempts. Patients who are enrolled under a waiver will not undergo

any studies for research purposes. In such patients, data collection will be limited to "retrospective" medical records review, including images obtained in the course of clinical care. No activities that are solely research-related are obtained or required in waiver of consent participants.

Study participants' medical history, clinical course, long-term sequelae, risk factors, time to resolution, and quality of life impact of myocarditis/pericarditis associated with COMIRNATY will be characterized and summarized using descriptive statistics at the study time points, namely during the hospitalization, at 2 weeks, 6 weeks, and 6 months, and annually up to 5 years of follow-up after illness onset. Similar summaries will be produced for a comparator cohort of children and young adults <21 years of age with COVID-19–associated myocarditis/pericarditis, including MIS-C.

Participant adherence to the C4591036 study design is required, including those activities specified in the SoA, at time points after enrollment. Relevant data will be collected from testing obtained as part of routine care prior to enrollment. The Schedule of Activities for C4591036 is in Table 2 below.

Table 2. Schedule of Activities

Visit Identifier[a]	Acute Presentation[b] Baseline/Visit 1	Hospital Discharge Visit 2	Week 2 Visit 3[c]	Week 6 Visit 4[c]	Month 6 Visit 5	Years 1-5 Visits 6, 7, 8, 9, 10
Visit Window	Day 1	± 2 days	3 days to < 3 weeks	3 to < 9 weeks	9 weeks to < 1 year[d]	± 6 months around the 1 year mark[e]
Obtain Informed Consent/Assent	X					
Confirm eligibility and assign participant number	X					
Collect demographics, past medical history, prior COVID-19 infection	X					
Medical History[f]	X	X	X	X	X	X
Echocardiogram[g]	X	X[h]	X	X	X[i]	X[i]
ECG	X	X	X	X	X	X[j]
Record cMRI results in CRF, if performed as part of routine medical care, during particular time windows[k]	X	X	X	X	X	X
Exercise stress test[l]			X[m]	X[m]	X	X[m]
Ambulatory monitoring (3-7 days)[l]		X[n]	X[n]	X[n]	X	X[n]
Patient reported outcome measures[o,p]			X	X	X	X

Table 2. Schedule of Activities

Visit Identifier[a]	Acute Presentation[b] Baseline/Visit 1	Hospital Discharge Visit 2	Week 2 Visit 3[c]	Week 6 Visit 4[c]	Month 6 Visit 5	Years 1-5 Visits 6, 7, 8, 9, 10
Visit Window	Day 1	± 2 days	3 days to < 3 weeks	3 to < 9 weeks	9 weeks to < 1 year[d]	± 6 months around the 1 year mark[e]
Troponin[l]	X[q]	X[q]	X[r]	X[r]		
Serious and nonserious AE monitoring[s]						

ECG = Electrocardiogram; cMRI = cardiac Magnetic Resonance Imaging; PROMIS = Patient Reported Outcomes Measurement Information System

a. Relevant for patients who meet criteria for myocarditis/pericarditis. The 2-week, 6-week, 6-month, and annual visits date from day of discharge from first myocarditis/pericarditis hospitalization. In those rare patients who are not hospitalized, the follow-up visits date from the date of evaluation in an emergency room or equivalent acute care setting.
b. This ambidirectional (combined retrospective and prospective study) will extract retrospective data prior to the time of enrollment from medical records and will prospectively follow the study protocol after participant enrollment.
c. The protocol will require a research visit in either the 2- or 6-week visit windows, which occur after hospital discharge by definition. However, we will collect research data in both windows when feasible.
d. Because the primary study endpoint occurs at the 6-month visit, the 6-month window extends up to 1 year to maximize data capture. A single visit occurring within the 6-month window will always be analyzed with the 6- month endpoint. If there is more than 1 visit in the 6-month window, choose the visit closest to 6 months. However, for patients who have a 6-month visit, an additional visit between 9 months to up to 1 year can qualify for the 1-year visit window.
e. The annual visits will have a window of 6 months before and after the year begins, with the exception of the 1-year visit. If there is more than 1 visit within an annual window, choose the visit closest to the year mark. For the 1-year visit, the window can begin at 9 months (39 weeks) from illness in patients who have a 6-month visit.
f. Medical history will include complete cardiac and non-cardiac systems review. Medical history in the interim since the latest research evaluation will be obtained at each study visit.
g. For patients with isolated pericarditis, echocardiograms will no longer be required as part of the research protocol once there is ≤ small pericardial effusion by echo and symptoms have resolved off medication.
h. Echocardiogram at discharge is not required for the research protocol in participants who had LVEF ≥55% at baseline/Visit 1. However, we will collect data on echocardiograms obtained at the time of, or near, discharge in those participants who had them performed for clinical reasons.
i. Echocardiograms at 6 months and annually between years 1 and 5 are not required for the research protocol in participants who have previously had 2 consecutive normal echocardiograms. However, data from such echocardiograms will be collected if conducted as part of clinical care.
j. ECGs are not needed beyond the 6-month visit if there are no ECG abnormalities other than sinus bradycardia, sinus tachycardia, ectopic atrial rhythm, incomplete right bundle branch block and borderline right axis deviation (QRS axis less 100°) on two consecutive ECGs. As with other tests, if ECG is done for clinical purposes, it should be transmitted to the Core Lab.
k. CMRI will be obtained only as part of routine clinical care, based on the clinical judgment of the local care team. Results of the cMRI at acute presentation may include elements of the CDC criteria for possible or confirmed myocarditis. Core laboratory will review each cMRI that the treating physician decides to perform during study participation, even if there are multiple studies within a time window (from 0 to a maximum of 7 results).
l. Patients with isolated pericarditis will not be required to have ambulatory monitors, exercise tests, or troponin at any time after enrollment.
m. Exercise stress tests between years 1 and 5 are not required for the research protocol in participants who had previously normal studies. However, data will be collected from any exercise stress tests that are obtained as part of routine clinical care at any time point. If a participant did not have an exercise

Table 2. Schedule of Activities

Visit Identifier[a]	Acute Presentation[b] Baseline/Visit 1	Hospital Discharge Visit 2	Week 2 Visit 3[c]	Week 6 Visit 4[c]	Month 6 Visit 5	Years 1-5 Visits 6, 7, 8, 9, 10
Visit Window	Day 1	± 2 days	3 days to < 3 weeks	3 to < 9 weeks	9 weeks to < 1 year[d]	± 6 months around the 1 year mark[e]

stress test performed during the 6-month study window, then exercise stress testing may be performed as an optional research test at an annual visit after enrollment.

n. Ambulatory monitoring is only required at the 6-month time point. Ambulatory monitoring at discharge, 2-weeks, 6-weeks, or beyond 6-months may be performed as part of routine clinical care. If so, data will be collected at these time points. If a participant did not have any ambulatory monitoring during the 6-month study window, then ambulatory rhythm monitoring may be performed as an optional research test at an annual visit after enrollment.

o. Patient reported outcome measures include 1) PROMIS Global Health; 2) functional status questionnaires: BASC-3 (<8 y) or PROMIS Short Forms (≥8 y), including Pain Interference and Functional Disability Inventory; 3) quality of life: PEDS QL in participants who are 2 to <18 years old, and Quality of Life Scale (QOLS) if ≥ 18 years old.

p. Patient reported outcome measures will not be required beyond end of study for isolated pericarditis, defined as freedom from 1) symptoms/signs of pericarditis; 2) typical ECG findings of pericarditis; 3) greater than small pericardial effusion; 4) therapy with anti-inflammatory medications.

q. Daily troponins will be obtained while the participant is hospitalized or until levels have decreased for 2 successive measurements. More frequent troponin monitoring may be obtained as part of routine clinical care. Centers will measure the type of troponin standard to their clinical practice (e.g., troponin T, troponin I) and record the units of measurement. Less than 1 ml of blood is needed for measurement of troponin levels.

r. If 2 consecutive troponin values have been normal in patients with no symptoms, further troponins are not mandatory per protocol. For additional troponin values obtained for clinical purposes and not mandated by protocol, we will record the worst troponin value and first documented normal troponin value. Data will also be collected for other selected laboratory tests that are obtained as part of routine clinical care.

s. See C4591036 Protocol Section 8.3

9.2.1. Inclusion Criteria

Data for this interim analysis are derived from the ongoing C4591036 study, “Low-interventional Study of Myocarditis and Pericarditis Associated with COMIRNATY in Persons Less Than 21 Years of Age.” The following inclusion criteria are used for eligibility in the C4591036 study:

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

Cohort 1 (prospectively ascertained) and Cohort 2 (retrospectively ascertained): Cases of probable or confirmed myocarditis/pericarditis associated with COMIRNATY

1. Age <21 years
2. Presentation to a participating medical center with evaluation in Emergency Room and/or hospitalization
3. Received either the 1st, 2nd, 3rd, or booster dose(s) of COMIRNATY ≤21 days of symptom onset, even if a different brand of COVID-19 vaccine had been administered in earlier vaccinations. Participants can be retrospectively

ascertained and enrolled at any time from their COMIRNATY-associated myocarditis/pericarditis.

4. Probable or confirmed myocarditis/pericarditis as per the contemporaneous CDC case definition (Table 3)*[11-12] at the time of diagnosis.
5. Capable of giving signed informed consent/assent (by parents/legal guardians of minors and/or patients) as described in (see protocol), which includes compliance with the requirements and restrictions listed in the Informed Consent/Assent Document and in this protocol OR meets criteria for waiver of consent.

Table 3. CDC Working Case Definitions

Centers for Disease Control and Prevention Working Case Definitions for Acute Myocarditis, Pericarditis, & MIS-C

Acute Myocarditis

Probable Case

- Presence of ≥ 1 new or worsening of the following clinical symptoms:
  - chest pain/pressure/ discomfort
  - dyspnea/shortness of breath
  - palpitations
  - syncope

  OR
- Infants and children aged <12 years might instead have ≥2 of the following symptoms:
  - irritability
  - vomiting
  - poor feeding
  - tachypnea
  - lethargy
- AND ≥ 1 new finding of
  - elevated troponin above upper limit of normal
  - abnormal ECG or rhythm monitoring finding consistent with myocarditis
  - abnormal cardiac function or wall motion abnormalities on echocardiogram
  - cMRI findings consistent with myocarditis
- AND no other identifiable cause of the symptoms and findings

Confirmed Case

- Presence of ≥ 1 new or worsening of the following clinical symptoms:
  - chest pain/pressure/ discomfort
  - dyspnea/shortness of breath
  - palpitations
  - syncope

  OR
- Infants and children aged <12 years might instead have ≥2 of the following symptoms:
  - irritability
  - vomiting
  - poor feeding
  - tachypnea
  - lethargy
- AND
  - histopathologic confirmation of myocarditis

  OR
  - Elevated troponin above upper limit of normal AND cMRI findings consistent with myocarditis
- AND no other identifiable cause of the symptoms and findings

Acute Pericarditis

Probable Case

- Presence of ≥ 2 new or worsening of the following clinical features:
  - acute chest pain
  - pericarditis rub on exam
  - new ST-elevation or PR-depression on ECG
  - new or worsening pericardial effusion on echocardiogram or MRI
- Autopsy cases may be classified as pericarditis on basis of meeting histopathologic criteria of the pericardium

MIS-C

Definition prior to January 2023

- Age <21 years
- Fever ≥38°C for ≥24 hours
- Laboratory evidence of inflammation
- Evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement based on clinical judgment from record review, discharge dx, lab or diagnostic tests.
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms
- No plausible alternative explanation.

Definition as of January 2023

Clinical Criteria	Lab Criteria	Epidemiologic Link

• Fever >38 **AND**
• Clinical severity requiring hospitalization (or death) **AND**
• Evidence of systemic inflammation with CRP >3 **AND**
• New manifestations in **at least two** of the following categories:
  • Cardiac involvement
  • LV EF <55 OR coronary dilation OR troponin elevation
  • Mucocutaneous involvement
  • Rash, mucositis, conjunctivitis, extremity findings
  • Shock (clinician documented)
  • GI involvement
  • Abdominal pain OR vomiting OR diarrhea
  • Hematologic involvement
  • Plt <150,000 OR ALC <1,000
	• +COVID RNA in a clinical specimen up to 60 days prior to or during hospitalization **OR**
	• Detection of COVID specific antigen **OR**
	• Detection of COVID antibodies
		Close contact (within 6 feet for >15 minutes) with confirmed or probably case of COVID in 60 days prior to hospitalization

***Need to meet clinical criteria + lab criteria or epidemiologic link**

Clinical criteria + lab criteria = confirmed case
Clinical criteria + epidemiologic link = probable case

Council of State and Territorial Epidemiologists, CDC, 2022.

Adapted from Centers for Disease Control and Prevention. Copyright ©2021, Centers for Disease Control and Prevention.
Abbreviations: cMRI = cardiac magnetic resonance imaging; ECG = electrocardiogram.
* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
† Using the Dallas criteria. Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects, excluding first degree AV block, Mobitz Type I (Wenkebach), and incomplete right bundle branch block.
¶ Using either the original or the revised Lake Louise criteria.
†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

**This table is adapted from Bozkurt et al (2021) and the Centers for Disease Control and Prevention.*[11-14]

Cohort 3: Comparator cohort of COVID-19-related myocarditis/pericarditis, including MIS-C

1. Age <21 years
2. Presentation to a participating medical center with evaluation in an Emergency Room and/or hospitalization
3. COVID-19-related disease
    a. Acute COVID-19 infection based on characteristic signs and symptoms, together with a positive microbial test (either a positive nucleic acid amplification test (NAAT), most commonly with a reverse-transcription polymerase chain reaction (RT-PCR) assay, or an antigen test on an upper respiratory sample)[15-17]

    OR

    b. Multi-system Inflammatory Syndrome in Children Associated with COVID- 19 (MIS-C) as per the contemporaneous CDC case definition at the time of diagnosis[13,18], i.e. participants diagnosed with MIS-C prior to 01 Jan 2023 should follow the original (May 2020) CDC case definition, and those diagnosed with MIS-C on or after 01 Jan 2023 should follow the new case definition.[14,18]

    AND

4. Probable or confirmed myocarditis/pericarditis as per the contemporaneous CDC case definition (See Table 3)[*11-12] at the time of diagnosis.
    a. Probable myocarditis/pericarditis as defined by ≥1 new finding of:
        a. Elevated troponin above upper limit of normal
        b. Abnormal ECG or rhythm monitoring finding consistent with myocarditis, excluding those in whom the sole abnormality was first degree atrioventricular (AV) block
        c. Abnormal cardiac function or wall motion abnormalities on echocardiogram
        d. cMRI findings consistent with myocarditis

    OR

    b. Confirmed myocarditis/pericarditis as defined by:
        a. Histopathologic confirmation of myocarditis

    OR

        b. Elevated troponin above upper limit of normal AND cMRI findings consistent with myocarditis
5. Capable of giving signed informed consent/assent (by parents/legal guardians of minors and/or patients), which includes compliance with the requirements and restrictions listed in the Informed Consent/Assent Document and in this protocol OR meets criteria for waiver of consent.

9.2.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A plausible alternative etiology for myocarditis/pericarditis, as determined by the site based upon their routine clinical practice for evaluation of potential causes for myocarditis/pericarditis.
2. Pre-existing cardiac conditions that could impact the primary endpoint, including but not limited to, documented history of left ventricular dysfunction (e.g., cardiomyopathy or myocardial infarction), pacemaker, or congenital heart disease, with the exceptions of:
    a. Bicommissural aortic valve with ≤ trivial stenosis and/or insufficiency
    b. Mitral valve prolapse with ≤ trivial insufficiency
    c. Hemodynamically insignificant atrial septal or ventricular septal defects
3. Previous administration with an investigational drug or vaccine within 30 days of enrollment (or as determined by the local requirement)

Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened. For example, if a patient is considered for enrollment after first vaccination but fails to meet admission criteria, he or she could still be rescreened if symptoms occur after the second vaccine or booster.

9.3. Variables

Variables collected in this study including their role, data source, and operational definition are summarized in Table 4.

Table 4. Study Variables

Variable	Role	Data source(s)	Operational definition
Sociodemographic: Age, sex assigned at birth, gender identity (defined as one's self- identification as male, female, or other), race, ethnicity, insurance, zip code, census tract/dissemination area.	Predictors	Medical records; participant report	All study participants: post-vaccine* (Cohorts 1 and 2) and control participants (Cohort 3)
Dates and brand of 1st, 2nd, 3rd, or booster dose(s) of COVID-19 vaccine; type/name and Lot # of all COMIRNATY doses.	Exposure of interest	Medical records; participant report	All study participants: post-vaccine* (Cohorts 1 and 2) and control participants (Cohort 3)
Prior SARS-CoV-2 infection (symptomatic COVID-19 or asymptomatic): Yes/No. If yes, approximate date and method of ascertainment (e.g., positive RT-PCR, antigen, antibody, and/or exposure).	Predictors	Medical records; participant report	All study participants: post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants

Table 4. Study Variables

Variable	Role	Data source(s)	Operational definition
Medical history: Date of admission, intensive care unit (ICU) stay, co-morbid conditions including overweight and obesity by BMI (age-and sex-adjusted z scores using CDC [primary] and World Health Organization [WHO] [secondary] norms), prior doses and brands of COVID-19 vaccine administered before the COMIRNATY vaccine given within 7 days of myocarditis/pericarditis onset, prior history of myocarditis/pericarditis, clinical features at the time of presentation (e.g., chest pain, fever); type of shock if present (hypovolemic, distributive, cardiogenic); individual organ dysfunction at presentation; mechanical ventilation (date of intubation and first extubation, total days of intubation); ECMO, other serious medical events, death, discharge date.	Predictors	Medical records; participant report	All study participants: post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants
Treatments for myocarditis/pericarditis or myopericarditis: Anti-inflammatory agents [e.g., intravenous immunoglobulins (IVIG), steroids, colchicine]; symptomatic treatments and analgesics [e.g., non-steroidal anti- inflammatory drugs (NSAIDs)]; antithrombotic (anticoagulants, antiplatelet agents), pressors, vasoactive agents, heart failure therapies [digoxin, diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and procedural treatments (i.e., pacemaker, implantable cardiac defibrillator, mechanical circulatory support and heart transplantation].	Predictors	Medical records	All study participants: post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants
Clinical Labs: **Troponin**	Predictors	Medical records	Per protocol, in post-vaccine* myocarditis/pericarditis (Cohorts 1 and 2): daily troponins (I or T in accordance with routine center clinical practice) while participants are

Table 4. Study Variables

Variable	Role	Data source(s)	Operational definition
			hospitalized or until levels have decreased for 2 successive measurements. If 2 consecutive troponin values have been normal in patients with no symptoms, further troponins are not mandatory per protocol. All study participants (Cohorts 1, 2, and 3): any troponin values that are obtained as part of routine clinical care.
Clinical Labs: **BNP or NT-proBNP; c-reactive protein (CRP)**	Predictors	Medical records	All study participants (Cohorts 1, 2, and 3): clinical labs obtained as part of routine clinical care
Electrocardiographic variables	Outcomes	Core laboratory	All study participants: post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants
Echocardiographic variables	Outcomes	Core laboratory	All study participants: post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants
Cardiac MRI variables	Outcomes	Core laboratory	Study participants for whom cMRI is performed as part of routine clinical care: post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants
Exercise stress test variables	Outcomes	Medical records	Post-vaccine* (Cohorts 1 and 2); some control (Cohort 3) participants
Ambulatory monitoring	Outcomes	Medical records	Post-vaccine* (Cohorts 1 and 2); some control (Cohort 3) participants
Patient-reported outcome measures	Outcomes	Participant report	Post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants
Complications and noncardiac morbidities	Outcomes	Medical records	Post-vaccine* (Cohorts 1 and 2) and control (Cohort 3) participants

*Post-vaccine refers to cohorts receiving a dose of COMIRNATY ≤21 days from onset of myocarditis symptoms.

9.4. Data Sources

In the C4591036 study, the Site Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original,

attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry. In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts. In rare cases, the CRF may also serve as the source document.

All data derived from the medical records will be de-identified and coded. Pfizer will only receive de-identified and aggregated data results.

9.5. Study Size

The study cohort for this interim analysis will be comprised of the interim study data collected for the first 300[2] participants enrolled in C4591036 between 21 Nov 2022 and 15 Apr 2025 who meet study inclusion/exclusion criteria, from acute presentation to the 1-year post-discharge study visit. Enrollment per participant cohort is as follows:

- 200 prospectively and retrospectively ascertained cases of children, adolescents, and young adults <21 years of age who receive care at participating medical centers for myocarditis/pericarditis associated with COMIRNATY, and
- 100 persons <21 years of age with COVID-associated myocarditis/pericarditis, including MIS-C.

As the statistical analysis is descriptive in nature, the study sample size is not based on any statistical hypothesis testing.

Study participants' medical history, clinical course, long-term sequelae, risk factors, time to resolution and impact on quality of life associated with myocarditis/pericarditis associated with COMIRNATY will be characterized and summarized using descriptive statistics. These summaries will encompass the safety measurements and assessments, as well as the primary composite study endpoint. Similar summaries will be produced for the comparator cohort of children and young adults <21 years old with myocarditis/pericarditis associated with COVID-19, including MIS-C.

The study cohort may be updated and planned analyses repeated to allow for the evaluation of additional annual study visits as those milestones are met.

9.6. Data Management

An Electronic Data Capture (EDC) system is currently being used for ongoing collection of clinical, safety, and laboratory data under C4591036. The system is designed to support reliable and secure data entry for clinical research purposes and provides seamless integration of electronic case report forms (eCRFs), implementation of protocol amendments and Statistical Analysis System (SAS) and Extensible Markup Language (XML) study data exports. Data is entered directly from multiple study sites via a fully validated and 21 Code of Federal Regulations (CFR) Part 11 compliant, secure Web application and stored centrally. In addition, three central core laboratories are processing imaging data from echocardiography, cardiac MRI, and electrocardiography assessments performed on study participants.

[2] 200 prospectively ascertained or retrospective ascertained cases of COMIRNATY associated myocarditis or pericarditis and 100 cases of COVID-19 associated myocarditis or pericarditis are the minimum enrollment targets in the C4591036 study.

eCRFs are required for each included participant under C4591036. The completed original eCRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

For this study, EDC study data will be extracted and combined with imaging data for the study population defined in Section 9.5. All study data will be securely stored in a centralized repository, with adequate backup systems and access controls in place to protect against data loss and unauthorized access. Proper documentation and metadata will accompany the stored data to facilitate future retrieval and analysis in accordance with Carelon Research Standard Operating Procedures (SOPs).

9.7. Data Analysis

Detailed methodology for the summary and statistical analysis of the study data, in alignment with the objectives outlined in Section 8, will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. Descriptive statistics will include means, medians and standard deviations, first and third quartiles, minimum and maximum values for continuous variables, and absolute/relative frequencies for categorical data. Logistic regression will also be used to assess potential risk factors for binary outcomes. Mixed-effects linear regression models for repeated measures will be used to examine trends for continuous outcome measures. Other statistical measures will be described in the SAP.

All programming necessary for the creation of analytic datasets and the conduct and validation of statistical analyses outlined in the SAP will be performed using SAS.

9.8. Quality Control

The following quality control measures are in place for the ongoing C4591036 study, to ensure data quality and integrity:

- Integrated into the electronic data capture system: real time validations (including both inter- and intra-instrument data checks), inconsistent or questionable values flagged during entry, generation of an automatic edit report to the data entry client to provide the information necessary to investigate any data entry errors or resolved questions regarding out-of-range or questionable values, second level query tracking for real time access to unresolved queries as well as the date and time of query generation and resolution.
- Data review: ongoing data review of C4591036 data via manual listings and reports conducted by the clinical data manager and/or biostatistician; Pinnacle 21 validation of the data used in this interim analysis and any additional interim analyses in the future.
- Study-related monitoring activities: source data verification (SDV) through on-site and/or remote monitoring visits, Clinical Research Organization (CRO) and/or Sponsor audits, IRB/EC review, and regulatory agency inspections.
    - Source documents are filed at the investigator site. Investigators are required to maintain accurate and complete source documentation following the principles of ALCOA: **A**ttributable, **L**egibility, **C**ontemporaneous, **O**riginal, **A**ccuracy.

In this study, all programming necessary for the extraction of study databases and creation of analytic datasets will adhere to Carelon Research programming standards and SOPs.

Data validation will take place consistently throughout the data management and analysis phases. Data quality checks will include independent programming of primary and key secondary results by a secondary statistician to verify findings, assessments of internal dataset consistency, and compliance checks against protocol criteria. All study databases and programming will be stored and archived in accordance with Carelon Research SOPs.

9.9. Limitations of the Research Methods

As C4591079 utilizes data from C4591036, potential limitations are common to both studies and should be noted:

- Because of the decline in number of COMIRNATY-associated myocarditis cases (according to the Vaccines Adverse Events Reporting System [VAERS], cases reported in the US reached a peak in June 2021 and dropped dramatically after October 2021),[19] the myocarditis/pericarditis cohort is largely comprised of retrospectively ascertained cases.
- Patients will be excluded from participation if plausible etiologies for myocarditis other than COMIRNATY-associated myocarditis are known at enrollment. It is possible that a plausible alternative etiology will be discovered only after a participant is enrolled. If so, those participants will be followed per C4591036 but will be accounted for separately in the statistical analysis.
- Some individuals who had COMIRNATY-associated myocarditis/pericarditis prior to the start of the study period may decline consent/assent or be difficult to reach. Each clinical center enrolling under C4591036 will work closely with pediatric offices to maximize return for scheduled visits. Participants who have returned to normal health and cardiac status may also be less inclined to return for follow-up at the recommended time points.
- A waiver of consent can be requested for collection of information related to clinical care when clinical sites are unable to reach participants with a history of vaccine myocarditis/pericarditis or COVID-19-related myocarditis/pericarditis, including MIS-C. In such patients, data collection will be limited to “retrospective” medical records review, including images obtained in the course of clinical care. No activities that are solely research-related are obtained or required.
- CMRIs are performed only when ordered as part of routine clinical care, and there may be practice variation among centers/providers regarding timing and protocols for cMRI.
- The COMIRNATY myocarditis and comparison participants are symptomatic patients evaluated and diagnosed in medical centers. They will not include individuals in the community with subclinical myocarditis/pericarditis. The study population will only include those with clinical myocarditis/pericarditis. Therefore, results from this study cannot be generalized to those in a subclinical myocarditis population.
- While the comparator cohort of persons <21 years of age with COVID-19-associated myocarditis/pericarditis, including MIS-C, is the most relevant from a clinical standpoint in weighing the risks of vaccination vs. COVID-19-related myocardial injury, patients with COVID-19-associated myocarditis/pericarditis are less likely to have had a cMRI during the acute episode of

myocarditis/pericarditis due to practices in place to minimize the risks of COVID-19 exposures to hospital personnel. Compared to patients with COMIRNATY-associated myocarditis/pericarditis, they are expected to include a lower percentage of patients who are white, non-Hispanic, and male, and their age distribution will include children who are younger.

- We do not anticipate being able to separate Cohort 3 into COVID-19-associated myocarditis/pericarditis with or without MIS-C because of the rarity of myocardial involvement in children with acute severe COVID-19. The rarity of myocardial involvement in acute severe COVID-19 versus MIS-C may relate to the fact that children with myocardial involvement often meet the CDC's case definition for MIS- C.
- Although the study uses data from the US and Canada, given the expected diversity of study participants, the results of the study should be generalizable to the population in regions outside the United States. We will explore the association of race, ethnicity, and other sociodemographic factors with acute and long-term outcomes of myocarditis.
- The incidence of COVID-19 vaccine-associated myocarditis is changing over time. For example, the incidence of myocarditis associated with booster doses is much lower than that observed in the primary series. Moreover, vaccines themselves may be modified, and the background prevalence of prior COVID-19 in the population is increasing and may change susceptibility to vaccine-associated myocarditis. For these reasons, we may have limited power to determine differences in the natural history of outcomes of vaccine- associated myocarditis between different COVID-19 Pfizer-BioNTech vaccines.[20]

9.10. Other Aspects

Not Applicable

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in de-identified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

Under C4591036, a central IRB with reliance from local IRBs (or local IRB if not applicable) is responsible for the safe conduct of research at each study site. C4591036 also uses the Pediatric Heart Network Data and Safety Monitoring Board (DSMB). The DSMB is independent of the study team and includes only external members. The board is responsible for ongoing monitoring of the safety of participants in the study according to the DSMB Charter. The recommendations made by the DSMB to alter the conduct of the study are forwarded to Pfizer personnel for final decision. Pfizer will forward such decisions, which

may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

This study will also be reviewed by a central IRB. A copy of the approval will be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP).[21]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As per EMA Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 3)[22] the study and its protocol will be registered in the HMA-EMA Catalogues of real-world data sources[23] prior to the start of data collection. Any publication of the results from this study will follow The International Committee of Medical Journals Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.[24] In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if Carelon (CRO for studies C4591036 and C4591079) is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, Olsha-Castell S, Arad D, Hasin T, Levi N, Asleh R, Amir O, Meir K, Cohen D, Dichtiar R, Novick D, Hershkovitz Y, Dagan R, Leitersdorf I, Ben-Ami R, Miskin I, Saliba W, Muhsen K, Levi Y, Green MS, Keinan-Boker L and Alroy-Preis S. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. *New England Journal of Medicine*. 2021.
2. Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, Edwards K, Soslow JH, Dendy JM, Schlaudecker E, Lang SM, Barnett ED, Ruberg FL, Smith MJ, Campbell MJ, Lopes RD, Sperling LS, Baumblatt JA, Thompson DL, Marquez PL, Strid P, Woo J, Pugsley R, Reagan-Steiner S, DeStefano F and Shimabukuro TT. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. *JAMA*. 2022;327:331-340.
3. Truong DT, Dionne A, Muniz JC, McHugh KE, Portman MA, Lambert LM, Thacker D, Elias MD, Li JS, Toro-Salazar OH, Anderson BR, Atz AM, Bohun CM, Campbell MJ, Chrisant M, D'Addese L, Dummer KB, Forsha D, Frank LH, Frosch OH, Gelehrter SK, Giglia TM, Hebson C, Jain SS, Johnston P, Krishnan A, Lombardi KC, McCrindle BW, Mitchell EC, Miyata K, Mizzi T, Parker RM, Patel JK, Ronai C, Sabati AA, Schauer J, Sexson Tejtel SK, Shea JR, Shekerdemian LS, Srivastava S, Votava-Smith JK, White S and Newburger JW. Clinically Suspected Myocarditis Temporally Related to COVID-19 Vaccination in Adolescents and Young Adults: Suspected Myocarditis After COVID-19 Vaccination. *Circulation*. 2022;145:345-356.
4. Goddard K, Hanson KE, Lewis N, Weintraub E, Fireman B and Klein NP. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. *Ann Intern Med*. 2022;175:1169-1771.
5. Jain SS, Steele JM, Fonseca B, Huang S, Shah S, Maskatia SA, Buddhe S, Misra N, Ramachandran P, Gaur L, Eshtehardi P, Anwar S, Kaushik N, Han F, Chaudhuri NR, and Grosse-Wortmann L. COVID-19 Vaccination-Associated Myocarditis in Adolescents. *Pediatrics*. 2021;148.
6. Schauer J, Buddhe S, Colyer J, Sagiv E, Law Y, Mallenahalli Chikkabyrappa S and Portman MA. Myopericarditis after the Pfizer mRNA COVID-19 Vaccine in Adolescents. *J Pediatr*. 2021;238:317-320.
7. Marshall M, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, Shaughnessy R, Caron R, Fuss C, Corbin KJE, Emuren L, Faherty E, Hall EK, Di Pentima C, Oster ME, Paintsil E, Siddiqui S, Timchak DM and Guzman-Cottrill JA. Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination. *Pediatrics*. 2021;148.
8. Dove ML, Slesnick TC, Oster ME, Hashemi S, Patel T, Wilson HC. Cardiac Magnetic Resonance Findings of Coronavirus Disease 2019 (COVID-19) Vaccine-Associated Myopericarditis at Intermediate Follow-Up: A Comparison with Classic Myocarditis. *J Pediatr*. 2023 Sep;260:113462. doi: 10.1016/j.jpeds.2023.113462. Epub 2023 May 11. PMID: 37172812; PMCID: PMC10171891.
9. Hadley SM, Prakash A, Baker AL, de Ferranti SD, Newburger JW, Friedman KG, and Dionne A. Follow-up cardiac magnetic resonance in children with vaccine-associated myocarditis. *Eur J Pediatr*. 2022;181:2879-2883.

10. Schauer J, Buddhe S, Gulhane A, Sagiv E, Studer M, Colyer J, Chikkabyrappa SM, Law Y and Portman MA. Persistent Cardiac Magnetic Resonance Imaging Findings in a Cohort of Adolescents with Post-Coronavirus Disease 2019 mRNA Vaccine Myopericarditis. *J Pediatr*. 2022;245:233-237.

11. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. *Circulation.* 2021;144(6):471-484.Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19). cdc.gov/dotw/covid-19/index.html. Published 2021. Accessed November 11, 2021.

12. Centers for Disease Control and Prevention (CDC). Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Published 2021. Accessed March 1, 2022.

13. Centers for Disease Control and Prevention (CDC). Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp. Published 2020. Accessed November 11, 2021.

14. Centers for Disease Control and Prevention (CDC). Multisystem Inflammatory Syndrome (MIS). https://www.cdc.gov/mis/index.html. Published 2021. Accessed November 11, 2021.

15. Melgar M LE, Miller AD, et al. Council of State and Territorial Epidemiologists/CDC Surveillance Case Definition for Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 Infection — United States. *MMWR Recomm Rep.* 2022(No. RR-4):1–14.

16. Struyf T, Deeks JJ, Dinnes J, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database Syst Rev.* 2020;7:CD013665.

17. Altmann RA, Reynolds CR, Kamphaus RW, Vannest KJ. BASC-3. In: Kreutzer J, DeLuca J, Caplan B, eds. *Encyclopedia of Clinical Neuropsychology.* Cham: Springer International Publishing; 2017:1-7.

18. Truong DT. Truong DT, Truong DT, Trachtenberg FL, Pearson GD, et al. The NHLBI Study on Long- terM OUtcomes after the Multisystem Inflammatory Syndrome In Children (MUSIC): Design and Objectives. *Am Heart J.* 2021;243:43-53.

19. Vaccine Adverse Event Reporting System (VAERS). Available from: https://vaers.hhs.gov/index.html. Accessed on: 14 Jun 2023.

20. Gargano JW, Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(27):977-982.

21. Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891

22. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3). Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev 3)

23. European Medicines Agency. HMA-EMA Catalogues of Real-world Data Sources and Studies. HMA-EMA Catalogues of real-world data sources and studies

24. International Committee on Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals. ICMJE | Recommendations

14. LIST OF TABLES

15. LIST OF FIGURES

None

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

N/A

ANNEX 3. ADDITIONAL INFORMATION

None

Document Approval Record

Document Name:	C4591079_PROTOCOL_31JUL2025
Document Title:	C4591079_PROTOCOL_31JUL2025

Signed By:	Date(GMT)	Signing Capacity
De Bernardi, Barbara	04-Aug-2025 19:35:29	EUQPPV Approval
Younus, Muhammad	05-Aug-2025 13:24:37	Final Approval