CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Two-Part Study (Open-Label [Part 1] Followed by Observer-Blind/Randomized [Part 2]) to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273.214 SARS-CoV-2 Vaccine in Participants Aged 12 Weeks to < 6 Months
Protocol Number:	mRNA-1273-P206 (BabyCOVE)
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	PPD PPD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: PPD E-mail: PPD
Regulatory Agency Identifier Number:	IND: 019745
Date of Original Protocol:	17 Jun 2022

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title: A Phase 2, Two-Part Study (Open-Label [Part 1] Followed by Observer-Blind/Randomized [Part 2]) to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273.214 SARS-CoV-2 Vaccine in Participants Aged 12 Weeks to < 6 Months

Protocol Number: mRNA-1273-P206 (BabyCOVE)

Date of Original Protocol: 17 Jun 2022

Protocol accepted and approved by:

See eSignature and date signed on last page of the document

PPD

Date

ModernaTX, Inc.
200 Technology Square
Cambridge, MA 02139
Telephone: PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2, Two-Part Study (Open-Label [Part 1] Followed by Observer-Blind/Randomized [Part 2]) to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273.214 SARS-CoV-2 Vaccine in Participants Aged 12 Weeks to < 6 Months," and the most recent version of the investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without institutional review board (IRB) approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or to the best of my knowledge threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, US Federal Regulations, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

The following abbreviations and terms are used in this study protocol.

Abbreviation	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
bAb	binding antibody
CDC	Centers for Disease Control and Prevention
CEAC	cardiac event adjudication committee
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DSMB	data safety monitoring board
DTaP	diphtheria, tetanus, and pertussis
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EoS	end of study
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLSM	geometric least square mean
GM	geometric mean
GMR	geometric mean titer ratio
GMT	geometric mean titer
HCP	healthcare practitioner

Abbreviation	Definition
Hib	Haemophilus influenzae type b
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IST	internal safety team
IM	intramuscular
IP	investigational product
IPV	inactivated poliovirus vaccine
IRB	institutional review board
IRT	interactive response technology
LAR	legally authorized representative
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent to treat
MMR	measles, mumps, and rubella
mRNA	messenger ribonucleic acid
NAAT	Nucleic Acid Amplification Test
nAb	neutralizing antibody
PCV13	pneumococcal conjugate vaccine
PEG	polyethylene glycol
PP	per protocol
PPIS-Neg	Per-Protocol Immunogenicity Set – SARS-CoV-2 Negative
QA	quality assurance
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM-102	heptadecan-9-yl 8-{(2hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate
SoA	schedule of assessments
SRR	seroresponse rate
S-2P	spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
US	United States
VOC	variants of concern
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1273.214 for injection

Name of Active Ingredient: mRNA-1273.214

Protocol Title: A Phase 2, Two-Part Study (Open-Label [Part 1] Followed by Observer-Blind/Randomized [Part 2]) to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273.214 SARS-CoV-2 Vaccine in Participants Aged 12 Weeks to < 6 Months

Protocol Number: mRNA-1273-P206 (BabyCOVE)

Study Duration: Approximately 27 months

Phase of Development: Phase 2

Estimated Date First Participant Enrolled: 30 Sep 2022

Estimated Date Last Participant Completed: 31 Mar 2025

Proposed Countries: United States (US)

Objectives and Endpoints

Objectives and Endpoints for Part 1	
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 2 dose levels[1] of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs throughout the entire study period • SAEs throughout the entire study period • AESIs throughout the entire study period

	• AEs leading to discontinuation from study participation postdose throughout the entire study period
Secondary Objectives	**Secondary Endpoints**
• To evaluate the immunogenicity of 2 dose levels[1] of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• GMT of antibodies against SARS-CoV-2 VOC (Omicron) at 28 days after second dose

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; GMT = geometric mean titer; MAAE = medically attended adverse event; mRNA = messenger RNA; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VOC = variants of concern.
[1.] Dose levels of mRNA-1273.214 vaccine administered to participants will be 5 µg and 10 µg.

Objectives and Endpoints for Part 2	
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of selected dose level (from Part 1) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs throughout the entire study period • SAEs throughout the entire study period • AESIs throughout the entire study period • AEs leading to discontinuation from study participation postdose throughout the entire study period
• To infer the effectiveness of selected dose level (from Part 1) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• Co-primary Endpoint: GMT of antibodies against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 compared with that of the adult participants at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 (100 µg, 2 doses 28 days apart) primary series • Co-primary Endpoint: SRR[1] against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 compared with that of the adult

	participants at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 (100 µg, 2 doses 28 days apart) primary series
Secondary Objectives	**Secondary Endpoints**
• To evaluate the immune response against SARS-CoV-2 VOC (Omicron) elicited by mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months, compared with the immune responses against original strain induced by mRNA-1273 primary series (100 µg, 2 doses 28 days apart)	• GMT of antibodies and SRR against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 primary series, compared with GMT and SRR against original strain at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 primary series
• To evaluate the immune response against SARS-CoV-2 original strain elicited by mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months, compared with the immune responses against original strain induced by mRNA-1273 primary series (100 µg, 2 doses 28 days apart)	• GMT of antibodies and SRR against SARS-CoV-2 original strain at 28 days after the second dose of mRNA-1273.214 primary series, compared with GMT and SRR against original strain at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 primary series

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; GMT = geometric mean titer; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; mRNA = messenger RNA; SAE = serious adverse event; SRR = seroresponse rate; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VOC = variants of concern.

[1.] Seroresponse is defined as a titer change from baseline (pre-Dose 1) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

Refer to Section 3 for a complete listing of primary, secondary, and exploratory endpoints related to Part 1 and/or Part 2 of the study.

Overall Study Design

This is a Phase 2, two-part, open-label in Part 1 and observer-blind, randomized, placebo-controlled in Part 2 study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273.214 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in infants aged 12 weeks to < 6 months.

The study will be conducted in 2 parts. Part 1 will consist of Arm 1 and Arm 2 that will enroll sequentially, ie, Arm 1 will begin enrollment and the periodic safety review will determine whether Arm 2 can begin enrollment. In Part 1, participants will receive 5 µg of mRNA-1273.214 in Arm 1 and 10 µg of mRNA-1273.214 in Arm 2. Arm 1 will start with 2 doses of 5 µg (sentinel dosing) administered 8 weeks apart of up to 4 participants. An internal safety team (IST) will review safety data after Dose 1 (1 week after Dose 1 of mRNA-1273.214) and provide a recommendation to further dose participants. Once safety and tolerability after Dose 1 have been reviewed by the IST, Arm 1 will continue enrollment for a total of 50 participants.

The IST will reconvene once 25 participants in Arm 1 reach Day 64 (1 week after Dose 2 of 5 µg administered 8 weeks apart). If no safety concerns are identified after IST review in Arm 1, Arm 2 will begin enrollment and participants will receive 2 doses of 10 µg of mRNA-1273.214 administered 8 weeks apart. Similar to Arm 1, safety and tolerability will be reviewed by the IST after 4 participants have received Dose 1 (1 week after Dose 1 of mRNA-1273.214) and again when 25 participants reach Day 64, and provide a recommendation for continuing dosing and enrollment at each review. Arm 2 will enroll a total of 50 participants. The immunogenicity and safety analysis will be conducted after all treated participants in both Arms 1 and 2 reach Day 85 (28 days from second dose). The results from Part 1 will determine the dose level for Part 2, which will be blinded and randomized.

Part 2 of the study will consist of 2 groups (Arm 3 and Arm 4). In Part 2, study participants will be randomly assigned to receive mRNA-1273.214 (Arm 3), at the dose level selected from Part 1, or placebo (Arm 4). The immunogenicity and safety analysis will be conducted after all treated participants reach Day 85 (28 days from second dose). Participants will be followed for approximately 12 months after completion of the primary series.

Number of Participants: A total of 100 participants (50 participants each in Arm 1 and Arm 2) will be enrolled in Part 1. In Part 2, a total of approximately 600 participants will be randomly assigned to receive mRNA-1273.214 (Arm 3) or placebo (Arm 4) in a 1:1 ratio (n = 300 per arm).

Target Population: Healthy infants aged 12 weeks to < 6 months at the time of consent, in both Part 1 and Part 2.

Study Eligibility Criteria

Inclusion Criteria:

Participants are eligible to be included in the study only if all the following criteria apply:

1. The participant is male or female, between 2 and < 6 months of age at the time of consent (Screening Visit), who is in good general health, in the opinion of the investigator, based on review of medical history and screening physical examination.
    a) Participant must be at least 12 weeks completed age and must not have completed 6 months at the time of administration of first dose.
    b) If the participant has a chronic, stable disease, they may be eligible to enroll in Part 2, but ineligible for Part 1. The chronic condition (eg, gastroesophageal reflux disease) should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion in Part 2. Note: a change in medication for dose optimization, change within class of medication, reduction in dose or increase in dose due to expected weight gain are not considered signs of instability.
2. The participant was born at ≥ 37 weeks gestation (Part 1) or ≥ 34 weeks gestation (Part 2), with a minimum birth weight of 2.5 kg, without fetal growth restriction, and the participant's height and weight are both at or above the second percentile for age according to the Centers for Disease Control and Prevention (CDC)/World Health Organization Child Growth Standard at the Screening Visit.
3. In the investigator's opinion, the parent(s)/legally authorized representatives (LARs) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures, and provide written informed consent. This includes inability to collect minimum amount of sample volume at baseline blood draw.

Exclusion Criteria:

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

1. The participant has a known history of symptomatic SARS-CoV-2 infection within 2 weeks prior to administration of investigational product (IP) or has a known close

contact (as defined in Section 8.10.2) in the past 2 weeks to someone diagnosed with SARS-CoV-2 infection or coronavirus disease 2019 (COVID-19). Participants may be rescreened after 14 days provided that they remain asymptomatic.

2. The participant is acutely ill or febrile 72 hours prior to or at the Screening Visit. Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
3. The participant has previously been administered an investigational or approved coronavirus (CoV) (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome-CoV) vaccine.
4. The participant has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (eg, receipt of SARS-CoV-2 monoclonal antibodies) within 90 days prior to enrollment.
5. The participant has a known hypersensitivity to a component of the vaccine or its excipients. Hypersensitivity includes, but is not limited to, anaphylaxis or immediate allergic reaction of any severity to any of the components of messenger RNA (mRNA) COVID-19 vaccines (including polyethylene glycol or immediate allergic reaction of any severity to polysorbate).
6. The participant has a medical, psychiatric, or occupational condition, including reported history of substance abuse, in the infant or in the parent(s)/LAR(s) that, according to the investigator's judgment, may pose additional risk as a result of participation, interfere with safety assessments, or interfere with interpretation of results.
7. The participant has a history of diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically the following:
    a) Congenital or acquired immunodeficiency
    b) Chronic hepatitis or suspected active hepatitis
    c) A bleeding disorder that is considered a contraindication to intramuscular (IM) injection or phlebotomy, or non-receipt of vitamin K at birth
    d) Dermatologic conditions that could affect local solicited adverse reaction (AR) assessments

e) Any prior diagnosis of malignancy

f) Febrile seizures

8. The participant has received the following:

   a) Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to first or second vaccination or plans to receive such a vaccine within 14 days of any study vaccination.

   b) Systemic immunosuppressants or immune-modifying drugs (including maternal use during pregnancy or lactation) for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 1 mg/kg/day or, if participant weighs > 10 kg: ≥ 10 mg/day prednisone equivalent). Participants may have visits rescheduled for enrollment if they no longer meet this criterion within the Screening Visit window. Inhaled, nasal, and topical steroids are allowed.

   c) Intravenous or subcutaneous blood products (red blood cells, platelets, immunoglobulins) within 3 months prior to enrollment.

9. The participant has participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to do so while participating in this study, or maternal participation in an interventional clinical study during pregnancy.

10. The participant is an immediate family member, or household contact, of an employee of the study site or Sponsor or someone otherwise directly involved with the conduct of the study. As applicable, family members/household contacts of employees of the larger institution or affiliated private practice not part of the study site may be enrolled.

11. The participant is a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government, or a government body, acting in accordance with powers conferred on them by laws and regulation. Does not include a child who is adopted or has an appointed legal guardian.

Study Treatment

Study Intervention Dose/Route/Schedule

The mRNA-1273.214 IP contains CX-024414, the mRNA that encodes for the prefusion stabilized spike glycoprotein (S-2P) of the Wuhan-Hu-1 isolate of SARS-CoV-2 and CX-031302, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 variant.

The IP will be administered as an IM injection into the anterolateral thigh. In Part 1, this will be a 5 µg or 10 µg dose level on a 2-dose schedule on Days 1 and 57, while in Part 2, the chosen dose from Part 1 will be administered on a 2-dose schedule on Days 1 and 57.

Placebo (as applicable) Route/Schedule

Placebo (0.9% sodium chloride) IM injection.

Study Assessments and Procedures

Immunogenicity Assessments:

The following analytes will be measured in blood samples for immunogenicity assessments and biomarker samples:

- Serum neutralizing antibody (nAb) titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays, including variants of concern (VOC; Omicron).
- Serum binding antibody (bAb) titer as measured by a multiplex ligand-binding assay specific to the SARS-CoV-2 S protein.
- Serum bAb titer as measured by a multiplex ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein.
- Testing for serologic markers for SARS-CoV-2 infection as measured by anti-nucleocapsid antibodies detected by immunoassay.

Effectiveness Assessments:

In this study, vaccine effectiveness for infants 12 weeks to < 6 months of age will be inferred based on serum antibody (Ab) responses obtained on Day 85 (28 days after the second injection of mRNA-1273.214 primary series) as compared against serum Ab responses obtained in adult participants at Day 57 in Study mRNA-1273-P301, based on geometric mean titer (GMT) and seroresponse.

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using electronic diaries.

- Unsolicited adverse events (AEs) observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days).
- AEs leading to discontinuation from Day 1 through end of study (EoS).
- Medically attended AEs (MAAEs) from Day 1 through EoS.
- Serious AEs (SAEs) from Day 1 through EoS.
- AEs of special interest (AESIs) from Day 1 through EoS.
- Assessments for SARS-CoV-2 infection from Day 1 through EoS.

Safety Oversight

The contract research organization's medical monitor, the Sponsor's medical monitor, and the individual study site investigators will monitor safety throughout the study.

Internal Safety Team:

An IST will review safety data throughout the study and provide a recommendation to further dose participants. In addition, the IST will escalate any safety concerns to the data safety monitoring board (DSMB). The frequency of IST meetings will be described in more detail in the IST charter.

Data Safety Monitoring Board:

Safety oversight will be under the direction of a DSMB composed of external, independent consultants with relevant expertise. Members of the DSMB will be independent from study conduct and free of conflict of interest. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. Details regarding the DSMB composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

Cardiac Event Adjudication Committee:

An independent cardiac event adjudication committee (CEAC) that includes pediatric cardiologists will review suspected cases of myocarditis and/or pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, assess severity, and make recommendations in consultation with the DSMB, if necessary, to the Sponsor. The CEAC will operate under the rules of an approved charter. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

Statistical Analysis Plan

Hypothesis Testing:

Part 1:

There is no statistical hypothesis to be tested in Part 1.

Part 2:

Primary Hypotheses:

1) H_A^1: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on geometric mean titer ratio (GMR) against the VOC (Omicron) with a noninferiority margin of 1.5-fold (lower bound of confidence interval [CI] for GMR > 0.67).
2) H_A^2: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on difference in seroresponse rate (SRR) against the VOC (Omicron) with a noninferiority margin of < 5% (lower bound of CI for SRR > –5%).

Secondary Hypotheses:

3) H_A^3: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is superior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a superiority margin of > 1-fold (lower bound of CI for GMR > 1).
4) H_A^4: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is superior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a superiority margin of > 0% (lower bound of CI for SRR > 0%).
5) H_A^5: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is “super” superior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a “super” superiority margin of > 1.5-fold (lower bound of CI for GMR > 1.5).
6) H_A^6: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is “super” superior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a “super” superiority margin of > 10% (lower bound of CI for SRR > 10%).

7) H_A^7: The immune response of mRNA-1273.214 against the VOC (Omicron) in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 against the SARS-CoV-2 original strain in adults, based on GMR with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.67).

8) H_A^8: The immune response of mRNA-1273.214 against the VOC (Omicron) in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 against the SARS-CoV-2 original strain in adults, based on difference in SRR with a noninferiority margin of < 5% (lower bound of CI for SRR > –5%).

9) H_A^9: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the SARS-CoV-2 original strain with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.67).

10) H_A^{10}: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 against the original strain in adults based on difference in SRR against the SARS-CoV-2 original strain with a noninferiority margin of < 5% (lower bound of CI for SRR > –5%).

Sample Size and Power Calculation:

In Part 2, approximately 600 infant participants of 12 weeks to < 6 months age will be enrolled at the dose level selected for Part 2, with an mRNA-1273.214 to placebo ratio of 1:1. Assuming 10% to 15% participants are not negative SARS-CoV-2 status at baseline, it is estimated that there will be a minimum of approximately 250 evaluable participants in the mRNA-1273.214 arm eligible for immunogenicity analyses.

The sample size of approximately 300 infant participants in the mRNA-1273.214 arm in Part 2 is considered to be sufficient to support a safety assessment. There is at least 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% in this group.

The sample size calculation for each of the 2 primary noninferiority hypothesis tests (H_A^1 and H_A^2) was performed, and the larger sample size was chosen for the study.

- With approximately 250 evaluable participants receiving mRNA-1273.214 in the Per-Protocol Immunogenicity Set - SARS-CoV-2 Negative (PPIS-Neg) in Study mRNA-1273-P206 and adults (≥ 18 years of age) in Study mRNA-1273-P301, there will be at least 90% power to demonstrate noninferiority of the immune response against Omicron variant, as measured by the GMT, in infant population at a 2-sided alpha of 0.05, compared with that in adults (≥ 18 years of age) in Study mRNA-1273-P301 receiving mRNA-1273, assuming an underlying GMR (which is calculated as ratio of

GMT) value of 1 and the standard deviation of the natural log-transformed titer is assumed to be 1.0, and a noninferiority margin of > 0.67.

- With approximately 250 evaluable participants receiving mRNA-1273.214 in the PPIS-Neg in Study mRNA-1273-P206 and adults (≥ 18 years of age) in Study mRNA-1273-P301, there will be at least 90% power to demonstrate noninferiority of the immune response against Omicron variant as measured by SRR in infants at a 2-sided alpha of 0.05, compared with SRR against Omicron variant in adults ≥ 18 years of age in Study mRNA-1273-P301 receiving mRNA-1273, assuming SRR of 60% to 70% in Study mRNA-1273-P301, true SRR improvement of 10% in infants from Study mRNA-1273-P206 compared with adults from Study mRNA-1273-P301, and a noninferiority margin of 5%.

Analysis Populations:

Analysis Set	Description
Randomization Set	All participants who are randomly assigned in Part 2, regardless of the participants' treatment status in the study.
FAS	Part 1: All enrolled participants in Part 1 who receive at least 1 dose of mRNA-1273.214. Part 2: All randomized participants in Part 2 who receive at least 1 dose of IP.
mITT Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection at baseline (ie, both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid).
mITT-1 Set	All participants in the mITT Set excluding those who received wrong treatment (ie, at least 1 dose received that is not as randomized).
PP Set	All participants in the FAS who receive planned doses of IP per schedule and are SARS-CoV-2 negative at baseline (ie, both negative RT-PCR test for SARS-CoV-2 and negative serology test) and have no major protocol deviations that impact key or critical data.
Immunogenicity Set	All participants in the FAS who provide immunogenicity samples.
PPIS	Participants in the Immunogenicity Set who receive planned doses of IP per schedule, comply with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. The PPIS will be used for analyses of immunogenicity.
PPIS-Neg	Participants in the PPIS who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline (ie, both negative RT-PCR test for SARS-CoV-2 and negative serology test). The PPIS-Neg will be the primary analysis set for analyses of immunogenicity.

Safety Set	All enrolled participants in Part 1 and all randomly assigned participants in Part 2 who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for solicited ARs.
Solicited Safety Set	All participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.

Abbreviations: AR = adverse reaction; bAb = binding antibody; FAS = Full Analysis Set; IP = investigational product; mITT = modified intent-to-treat; mRNA = messenger RNA; PP = per protocol; PPIS = Per-Protocol Immunogenicity Set; PPIS-Neg = Per-Protocol Immunogenicity Set – SARS-CoV-2 Negative; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Statistical Analyses

Immunogenicity Analyses:

The primary analysis population for immunogenicity will be the PPIS-Neg, unless specified otherwise. The primary objective of Part 2 of this study is to use the immunogenicity response to infer effectiveness of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in infants aged 12 weeks to < 6 months at the dose level selected for investigation.

Immunogenicity Analyses for mRNA-1273.214 Primary Series:

Immune response as measured by GMT value and SRR in the infant group based on Ab levels will be compared to that in adult (≥ 18 years of age) participants from Study mRNA-1273-P301 using Ab data. The immunogenicity data from participants who are assigned to the same dose level in Part 1 and Part 2 of this study may be combined for the immunogenicity analyses.

To assess the difference in immune response between the infant participants in Study mRNA-1273-P206 at 28 days after the last dose of mRNA-1273 primary series compared to the adult (≥ 18 years of age) participants in Study mRNA-1273-P301 at Day 57, an analysis of covariance model will be carried out with Ab as dependent variable and a group variable (an mRNA-1273 arm/group of Study mRNA-1273-P206 versus participants in Study mRNA-1273-P301) as the fixed variable for each participant arm/group, the analysis may adjust for key characteristics such as age, sex, etc. The GMT value of mRNA-1273.214 arm at 28 days after the last dose of mRNA-1273.214 primary series and GMT value of mRNA-1273 at Day 57 (28 days after the second dose of primary series) in Study mRNA-1273-P301 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (which is calculated as ratio of GMT) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI of GMR will also be provided.

The noninferiority of GMT of mRNA-1273.214 primary series compared with mRNA-1273 primary series will be considered demonstrated if:

- The lower bound of the 95% CI of the GMR (the infant participants in Study mRNA-1273-P206 at 28 days after the last dose of mRNA-1273.214 primary series, compared with the participants in Study mRNA-1273-P301 at Day 57) > 0.67 based on the noninferiority margin of 1.5.

In addition, the GMT of antibodies with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed titer values then back transformed to the original scale. Descriptive summary statistics for GMT including median, minimum, and maximum will also be provided.

The geometric mean fold rise of specific antibodies with corresponding 95% CI at each post-baseline time point over pre-Dose 1 baseline at Day 1 will be provided. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

The number and percentage of participants with seroresponse due to vaccination will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point with Day 28 after the last dose of mRNA-1273.214 primary series being of the primary interest in the analyses, where seroresponse is defined as a titer change from baseline (pre-Dose 1) below the lower limit of quantification (LLOQ) to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

The SRR difference with 95% CI (using Miettinen-Nurminen score method) between infants receiving mRNA-1273.214 primary series in Study mRNA-1273-P206 at 28 days after the last dose of mRNA-1273.214 primary series and adult participants receiving mRNA-1273 primary series in Study mRNA-1273-P301 at Day 57 will be provided.

The noninferiority of seroresponse of mRNA-1273.214 primary series in Study mRNA-1273-P206 compared with mRNA-1273 primary series in Study mRNA-1273-P301 will be considered demonstrated if:

- The lower bound of the 95% CI of the SRR difference is > –5% based on the noninferiority margin of 5%.

Hypothesis Testing Strategy for Immunogenicity:

The hypothesis tests for noninferiority, superiority, and "super" superiority of mRNA-1273.214 against Omicron as compared to mRNA-1273 primary series against Omicron will be performed sequentially. The noninferiority hypotheses (hypotheses H_A^1 and H_A^2) will be tested first.

Once noninferiority is demonstrated based on both GMT and SRR, superiority (hypotheses H_A^3 and H_A^4) of mRNA-1273.214 as compared to mRNA-1273 primary series will be tested. If the lower bound of the 95% CI of the GMR is > 1, superiority based on GMT is demonstrated; if the lower bound of the 95% CI of the SRR difference is > 0%, superiority based on seroresponse is demonstrated.

Once superiority is demonstrated based on both GMT and SRR, "super" superiority (hypotheses H_A^5 and H_A^6) of mRNA-1273.214 as compared to mRNA-1273 primary series will be tested. If the lower bound of the 95% CI of the GMR is > 1.5, "super" superiority based on GMT is demonstrated; if the lower bound of the 95% CI of the SRR difference is > 10%, "super" superiority based on seroresponse is demonstrated.

Safety Analyses:

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by vaccination group (dose levels of mRNA-1273.214 and placebo).

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, and AEs leading to discontinuation from IP and/or study participation.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection by toxicity grade will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, severe AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be summarized. Unsolicited AEs will be presented by Medical Dictionary for Regulatory Activities preferred term and system organ class.

Solicited AR events (starting within 7 days after any injection) that are serious or lasting beyond Day 7 after any injection will also be reported as unsolicited AEs.

The number of events of solicited ARs, unsolicited AEs/SAEs, MAAEs, severe AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided in the statistical analysis plan (SAP).

Subgroup Analyses:

Subgroup analyses will be performed in select subgroups including but not limited to the following subgroups:

- Sex (male, female)
- SARS-CoV-2 status at baseline
- Maternal immunization status
- Race
- Ethnicity

Details of subgroups analyses will be provided in the SAP.

Planned Analyses:

Interim Analyses

For Part 1, interim analyses of safety and immunogenicity will be performed after all treated participants in one or both arms have completed 28 days after the last dose of the primary series of mRNA-1273.214.

For Part 2, an interim analysis of safety and immunogenicity will be performed after all participants have completed 28 days after the last dose of the primary series of mRNA-1273.214. This interim analysis will be considered the primary analysis for immunogenicity.

Final Analyses

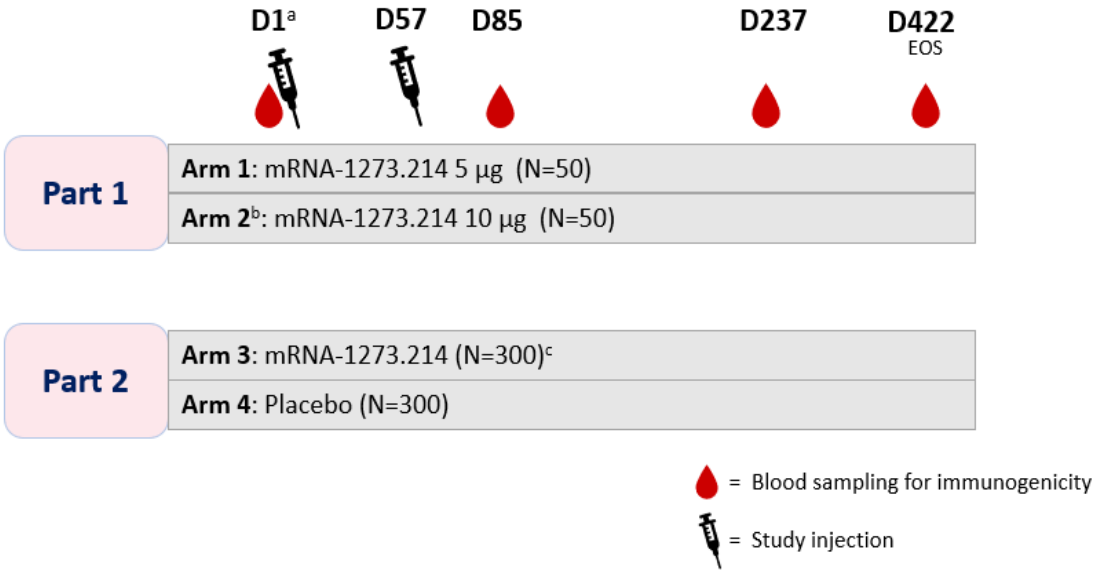
The final analysis of all endpoints will be performed after participants have completed all planned study procedures. Results of this analysis will be presented in a final clinical study report, including individual listings.

Additional information about all study analyses may be provided in the SAP.

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: D = Day; EOS = end of study; IST = internal safety team; mRNA = messenger RNA; N = number of participants.

a. Participant must be 12 weeks old at Day 1.
b. Arm 2 will begin enrollment after IST review of safety data collected from 25 participants in Arm 1 who have reached Day 64 (1 week after second dose of 5 µg).
c. At selected dose level from Part 1.

1.3. Schedule of Assessments

Table 1: Schedule of Assessments (Part 1 and Part 2)

Visit Number	0	1	2	3		4	5	6	7			8			9	USV
Type of Visit	C	C	C	TM	SFU	C	C	TM	C	SFU		C	SFU		C	C
Month Time Point		M0	M0		SC	M2	M2		M3	eDiary	SC	M8	eDiary	SC	M14	Up to M14
Study Visit Day	D-28 to D1 (Screening)[1]	D1 (Baseline)	D4[2]	D8	D29[3]	D57[4]	D60[2]	D64[4]	D85[4, 5]	Every 4 weeks D99 – D211[4, 6]	Every 4 weeks D113– D225[3, 4]	D237	Every 8 weeks D265– D377[4, 6]	Every 8 weeks D293– D405[3, 4]	D422 365 days after D57[3, 4]	Unscheduled Visit[7, 8]
Window Allowance (Days)	–	–	±1	+ 3		–14/+ 7	±1	+ 3	–14/+ 7	± 7	± 7	± 14	± 7	± 7	± 14	N/A
Days Since Most Recent Injection	–	0	3	7	28	57	3	7	28	–	–	180	–	–	365	
ICF, demographics, concomitant medications, medical history[9]	X															
Review of inclusion and exclusion criteria	X	X														
Physical examination and vital signs including length/height, weight and body temperature[10]	X	X	X			X	X		X			X			X	X
Randomization		X														
Study injection[11]		X				X										
Blood sample for vaccine immunogenicity[12]		X							X			X			X[7]	
Blood sample for SARS-CoV-2 surveillance[13]		X							X							
Nasal swab sample for SARS-CoV-2[13]		X				X			X			X			X	X

Visit Number	0	1	2	3		4	5	6	7			8			9	USV
Type of Visit	C	C	C	TM	SFU	C	C	TM	C	SFU		C	SFU		C	C
Month Time Point		M0	M0		SC	M2	M2		M3	eDiary	SC	M8	eDiary	SC	M14	Up to M14
Study Visit Day	D-28 to D1 (Screening)[1]	D1 (Baseline)	D4[2]	D8	D29[3]	D57[4]	D60[2]	D64[4]	D85[4, 5]	Every 4 weeks D99 – D211[4, 6]	Every 4 weeks D113– D225[3, 4]	D237	Every 8 weeks D265– D377[4, 6]	Every 8 weeks D293– D405[3, 4]	D422 365 days after D57[3, 4]	Unscheduled Visit[7, 8]
Window Allowance (Days)	–	–	±1	+ 3		–14/+ 7	±1	+ 3	–14/+ 7	± 7	± 7	± 14	± 7	± 7	± 14	N/A
Days Since Most Recent Injection	–	0	3	7	28	57	3	7	28	–	–	180	–	–	365	
Surveillance for COVID-19/illness visit[7]				X	X	X		X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[8]		X				X										
Review of eDiary data			X	X			X	X								
Follow-up safety telephone calls[14]					X						X			X		
Recording of unsolicited AEs		X	X	X	X	X	X	X	X							
Recording of MAAEs, SAEs, and AESIs and concomitant medications and procedures relevant to or for the treatment of the MAAE and SAE[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and procedures and nonstudy vaccinations[16]		X	X	X	X	X	X	X	X		X	X		X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eCRF = electronic case report form; EDC = electronic data capture; eDiary = electronic diary; FDA = Food and Drug Administration; ICF = informed consent form; IRB = institutional review board; LAR = legally acceptable representative; M = month; MAAE = medically attended adverse event; N/A = not applicable; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (telephone) call; SFU = safety follow-up; TM = telemedicine visit or call; USV= unscheduled visit.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency (FDA March 2020), investigators may convert study site visits to home visits or telemedicine visits (with the exception of Screening, Day 1, Day 57, Day 85, Day 237, and Day 422) with the approval of the Sponsor (home visits also require site IRB approval).

1. Screening Visit and Day 1 may be combined on the same day. Additionally, the Screening Visit may be performed over multiple visits if performed within the 28-day screening window.
2. Day 4 and Day 60 clinic visits will only be performed in Part 1 of study.
3. Safety follow-up via a safety telephone call will be performed on Day 29, every 4 weeks from Day 113 to Day 225, and every 8 weeks from Day 293 to Day 405.
4. If the visit for the second dose (Day 57) is disrupted and cannot be completed at Day 57 (–14/+7 days) as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the visit window may be extended to Day 57 + 14 days. When the extended visit window is used, the remaining study visits should be rescheduled to follow the intervisit interval from the actual date of the second dose.
5. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), a remote evaluation via a telemedicine visit or call should be conducted in place of the study site visit (except for dosing visits and visits that require a blood draw). The remote evaluation should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Home visits will be permitted for all nondosing visits, with the exception of screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the study site IRB and the participant's parent(s)/LAR(s) via informed consent and have prior approval from the Sponsor (or its designee).
6. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 99 to Day 211 and every 8 weeks from Day 265 to Day 377.
7. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. If a participant meets the pre-specified criteria of suspicion for COVID-19, the participant will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit to include a nasal swab sample (for RT-PCR testing to evaluate for the presence of SARS-CoV-2 infection) and other clinical evaluations. If a study site visit is not possible, a home visit may be arranged to collect the nasal swab sample and conduct clinical evaluations. The study site may collect an additional nasal swab sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
8. At each injection visit, participants' parent(s)/LAR(s) will record data into the eDiary starting approximately 30 minutes after injection under the supervision of the study site staff to ensure successful entry of assessment. Participants' parent(s)/LAR(s) will continue to record entries in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection. Capturing details of ARs in the eDiary should not exceed 7 days after each vaccination. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the event should be reviewed by the study site staff either via a telephone call or at an unscheduled study site visit.
9. Verbal medical history is acceptable.
10. A full physical examination and vital signs assessments, including length/height, weight, and body temperature, will be performed at the Screening Visit (and on Day 1, if Day 1 and Screening Visit occur on separate days). Symptom-directed physical examinations and vital signs assessments will be performed on Day 1, Day 4 (in Part 1), Day 57, Day 60 (in Part 1), Day 85, Day 237, Day 422, and USV, and may be performed at other time points at the discretion of the investigator. Body temperature should be measured on each injection day prior to injection. Body temperature must be measured via the axillary route and any axillary reading of ≥ 37.8°C/≥ 100°F may be confirmed by a rectal measurement. On each injection day before injection and again 7 days after injection, the injection site should be examined. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Participants who are febrile (≥ 38.0°C/≥ 100.4°F) before injection on Day 1 or Day 57 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

11. Study injection postdose observation will be 60 minutes for Part 1 and 30 minutes for Part 2.
12. On Day 1, sample must be collected prior to randomization and dosing. If a Day 1 (baseline) blood sample cannot be obtained, the participant could be rescheduled within the allowable screening period one time. If a blood sample still cannot be obtained at the rescheduled visit, then the participant will be considered a screen failure due to inability to satisfy inclusion criterion 3.
13. The nasal swab and blood sample (collected before dosing on each injection day and on other scheduled days per the SoA) will be used to ascertain the presence or history of SARS-CoV-2 infection via RT-PCR and serum binding antibody specific to SARS-CoV-2 nucleocapsid, respectively.
14. Medically qualified and trained study site personnel will call all participants to collect information relating to any MAAEs, SAEs, AEs leading to study withdrawal and information on concomitant medications associated with those events and any nonstudy vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on any COVID-19 symptoms the participant may experience.
15. A list of AESIs pertinent to this study is maintained by the Sponsor and provided to each investigator. All SAEs and AESIs will be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new SAE or AESI from a study participant or receives updated data on a previously reported SAE or AESI and the eCRF has been taken offline, then the site can report this information on a paper SAE or AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line.
16. All concomitant medications and procedures will be recorded through 28 days after each injection (through the completion of the Day 85 visit). All nonstudy vaccines given at any time during the study period should be recorded. All concomitant medications relevant to or for the treatment of an SAE, MAAE, or AESI will be recorded from Day 1 through the final visit (Day 422).

2. INTRODUCTION

2.1. Study Rationale

There is currently no approved vaccine against SARS-CoV-2 for young infants. Although another mRNA vaccine is available to older children under EUA, the youngest pediatric population remains unprotected because the duration of protection conferred on infants by transplacentally transferred antibodies is not currently known (Halasa et al 2022). In addition, due to the shift in the disease burden to younger children over the course of the COVID-19 pandemic, there is an urgent need for pediatric vaccination strategies that induce broader protection against SARS-CoV-2 VOC, including the Omicron variant, to decrease childhood morbidity and mortality. Based on the experience of mRNA-1273 in adults and leveraging the flexible nature of the mRNA technology, ModernaTX, Inc (the Sponsor) is evaluating mRNA vaccines to address the Omicron variant in infants.

2.2. Background and Overview

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS and SARS. An outbreak of a novel coronavirus (later designated SARS-CoV-2) initially emerged in Wuhan, Hubei Province, China in December 2019, then spread internationally. The WHO declared COVID-19 a Public Health Emergency of International Concern (its highest category of public health threat) on 30 Jan 2020 (WHO 2020a), and as a global pandemic on 11 Mar 2020 (WHO 2020b). As of 15 Apr 2022, confirmed COVID-19 mortality surpassed 6.1 million worldwide and over 988,000 in the US, with COVID-19 cases numbered nearly 502.9 million worldwide and over 80 million in the US (Dong et al 2020).

Since the beginning of the COVID-19 pandemic, cases of severe disease and deaths associated with COVID-19 have occurred more frequently in adults (Hay et al 2020; Ayoub et al 2020; CDC 2022b); however, COVID-19 can also lead to severe outcomes in children (Kim et al 2020; Havers et al 2021). By March 2022, over 7.7 million cases of COVID-19 had been reported among ages 0 to 4 years in 104 countries (UNICEF 2022). In the US, there have been over 2.2 million cases of COVID-19 and over 465 deaths due to COVID-19 reported among children 0 to 4 years of age (CDC 2022a), and an excess of 3578 hospitalizations among children 0 to 4 years of age have been observed in the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) system through 09 Apr 2022 due to COVID-19, with 24.1% requiring ICU interventions and more than 21 related in-hospital deaths (CDC 2022b).

Of particular concern is the phenomenon known as MIS-C, a hyperinflammatory syndrome with features of Kawasaki disease in children and adolescents infected with SARS-CoV-2

(PICS 2020; Belhadjer et al 2020; Dufort et al 2020; Verdoni et al 2020). The condition affects a variety of organ systems, including the gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory systems. Through 28 Mar 2022, there were a total of 7880 cases of MIS-C reported in the US with approximately 3.2% reported among the less than 1-year-old age group and 20.8% reported among the 1- to 4 year-old age group (CDC 2022c).

Over the course of the pandemic, SARS-CoV-2 variants have emerged and have raised concern, due to reports of increased infectivity or reduction in the neutralization ability of convalescent sera or sera from vaccinated participants (Pajon et al 2022). The emergence of these variants indicates that SARS-CoV-2 evolution may lead to immune escape and allow the pathogen to develop more efficient transmission between human hosts (Martin et al 2021). Hence, vaccination strategies to control the virus need to be responsive to this evolution.

In November 2021, the SARS-CoV-2 Omicron variant (B.1.1.529) was detected in South Africa and was found to contain potential Ab escape site mutations (such as K417N, T478K, E484A, and N501Y). The ability of the Omicron variant to escape prior immunity led to an unprecedented rise in COVID-19 infections and related hospitalizations, in adults as well as children, between December 2021 and February 2022. Clinical studies in adults conducted during the Omicron wave found lowered efficacy of the prototype vaccine against this new variant (Ferdinands et al 2022; Tseng et al 2022). Similar to the findings in adults in Study mRNA-1273-P204, which enrolled children under 12 years of age, efficacy of the mRNA-1273 vaccine was observed against symptomatic COVID-19 during the Omicron variant wave, but less than during previous variant waves (Tseng et al 2022).

An evaluation of COVID-19 incidence over time indicates marked increases in the ages 0 to 4 years with the Omicron variant wave. Prior to the Omicron wave, peak incidence among 0 to 4 years was 187.0 incident cases per 100,000 population in August 2021, increasing to 894.6 cases per 100,000 population during the Omicron wave in January 2022 (CDC 2022c).

Data also suggests that the demographics of hospitalized patients with COVID-19 shifted to younger age groups after the onset of the Omicron wave (Goga et al 2021; UKHSA 2021; Abdullah et al 2022). The cumulative incidence of COVID-19-associated hospitalizations was 49.7 per 100,000 children and adolescents from 01 Mar 2020 through 14 Aug 2021 (Delahoy et al 2021). During the Omicron wave, hospitalizations among those aged 0 to 17 years rose to 46.2% when comparing the week of 01 to 07 Jan 2022 to the last week in December 2021. Children aged 0 to 4 years had a dramatic 5-fold increase in hospitalization from 2.9 to 15.6 per 100,000 children (Marks et al 2022). The proportion of emergency room visits diagnosed with COVID-19 increased from a peak of 4% prior to the Omicron wave to a peak of 13.8% among those 11 years and younger (CDC 2022d). These trends support the need

for pediatric vaccination strategies that induce broader protection against VOC in addition to the ancestral SARS-CoV-2 strain. To address this need, the Sponsor has developed mRNA-1273.214, a bivalent vaccine which contains CX-024414, the mRNA that encodes for the prefusion stabilized spike glycoprotein (S-2P) of the Wuhan-Hu-1 isolate of SARS-CoV-2 and CX-031302, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 variant.

In December 2020, following review of safety and efficacy data observed to date, the FDA granted EUA to 2 mRNA-based SARS-CoV-2 vaccines, including mRNA-1273 for adults. In October 2021, the FDA granted EUA to an mRNA-based SARS-CoV-2 vaccine in children aged 5 to 11 years old. To address prevention of pediatric COVID-19 as well as to potentially help curb SARS-CoV-2 transmission, there is an urgent public health need for rapid development of SARS-CoV-2 vaccines in children. Finally, there are currently no clinical trials evaluating the safety and effectiveness of COVID-19 vaccines in children under 6 months of age.

Emerging evidence suggests that although maternal antibodies are transferred to infants transplacentally after maternal vaccination, titers wane over the course of the first 6 months of life and are undetectable in up to 43% of infants at 6 months of age, supporting the need for early vaccination in this age group (Shook et al 2022). While observational data (Halasa et al 2022) demonstrate that maternal vaccination during pregnancy can be 61% effective (95% CI = 31%-78%) in preventing hospitalization of infants aged < 6 months, there are no systematic studies of the need and risk-benefit of infant immunization against COVID-19. Additionally, it remains unknown if transferred passive immunity after maternal immunization with vaccines targeting prototype SARS-CoV-2 confer benefit of protection against emerging variants to the infants. Hence, there remains a need for active immunization strategies in this age group.

In the ongoing Study mRNA-1273-P204 (data snapshot on 21 Feb 2022), the safety profile of the 2 dose primary series in children and toddlers/infants (6 months to < 6 years of age) was generally consistent with the known safety profile observed in other studies of mRNA-1273. In addition, the events commonly seen in this pediatric population consisted primarily of grade 1 and grade 2 reactogenicity occurring within 2 days after either dose lasting 2 to 3 days. Solicited local and systemic ARs in children 6 months to < 6 years of age were generally consistent with the AE profile of mRNA-1273 in older age groups with the exception of fever. Fever was most commonly reported on Day 1 or Day 2 after any vaccination and lasted for a median duration of 1 day. Beyond Day 2 (after any dose) fever rates were similar between the mRNA-1273 group and the placebo group. Although no studies to date have evaluated mRNA-1273.214 in young children, ongoing trials in adults have not raised any safety concerns. Based on experience to date, the risk-benefit profile of evaluating mRNA-1273.214 in younger children is favorable.

The objective for this Phase 2 study is to evaluate the safety, tolerability, reactogenicity, and effectiveness of 2 dose levels (5 and 10 µg) of mRNA-1273.214 vaccine or another modified vaccine (both referred to as 1273.214 in the document) administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months.

2.2.1. Nonclinical Studies

mRNA-1273.214 was studied as a primary vaccination series in BALB/c mice. Mice were vaccinated with 2 doses of monovalent mRNA-1273, BA.1-matched monovalent mRNA-1273.529, or bivalent mRNA-1273.214, with the 2 doses administered 3 weeks apart. The mRNA-1273, mRNA-1273.529, and mRNA-1273.214 IPs administered are described in Section 6.1.

At Day 36 (2 weeks after the second dose), robust serum nAb responses, determined via a research-grade vesicular stomatitis virus-based SARS-CoV-2 pseudovirus neutralization assay, were measured against Wuhan-1 D614G after a 2-dose primary series of 1 µg mRNA-1273, with slightly lower nAb titers observed against B.1.351 or B.1.617.2. Serum neutralizing activity, however, was significantly reduced against the BA.1 and BA.2 compared with Wuhan-1 D614G. Mice immunized mRNA-1273.529 had high neutralization Ab titers against BA.1 and BA.2, but low levels of neutralization against Wuhan-1 D614G, B.1.351, and B.1.617.2. In mice vaccinated with the bivalent mRNA-1273.214, significant neutralization against both the prototype strain (Wuhan-1 D614G) and against BA.1 and BA.2 was measured, indicating that the bivalent affords broader neutralization across variants.

Overall, these data suggest that a primary series with a monovalent vaccine induces robust neutralization against the matched and closely related variants but does not induce significant neutralization against highly divergent SARS-CoV-2 lineages. A bivalent vaccine, however, induces broader neutralization across divergent lineages.

In these studies, no significant differences were measured in CD4 or CD8 cytokine production in mice that received mRNA-1273, mRNA-1273.529, or mRNA-1273.214.

Nonclinical study data for mRNA-1273 is available in the IB.

2.2.2. Clinical Studies

No finalized clinical study data is available for mRNA-1273.214. mRNA-1273.214 is being evaluated in the Sponsor's trial, mRNA-1273-P205, a phase 2/3, open-label study to evaluate the immunogenicity and safety of mRNA vaccine boosters for SARS-CoV-2 variants, and mRNA-1273-P305, a phase 2/3, randomized, observer-blind, active-controlled study to evaluate the immunogenicity and safety of Omicron variant vaccines in comparison with mRNA-1273 (prototype) booster vaccine. Preliminary data from the Sponsor's Phase 2 trial

Study mRNA-1273-P205 suggest that mRNA-1273.211, a bivalent vaccine that contains mRNA encoding for the S-2P of Wuhan-Hu-1 and mRNA encoding for the S-2P of B.1.351 at a 1:1 ratio, induced numerically similar or higher and more durable neutralizing responses against both vaccine matched and unmatched strains compared to the monovalent mRNA-1273 and mRNA-1273.351 (encodes for S-2P of B.1.351) vaccine. This supports the hypothesis that the bivalent mRNA-1273.214 vaccine to be tested in this study may generate more durable neutralizing responses against the Omicron variant strain and the prototype strain compared to mRNA-1273.

Clinical study data for mRNA-1273, including in the pediatric age group, is available in the IB.

2.3. Benefit/Risk Assessment

2.3.1. Known Potential Benefits

The following benefits may accrue to participants:

- The mRNA-1273.214 vaccine may be an effective vaccine against COVID-19 in the study population, including diseases caused by VOC.
- The mRNA-1273.214 vaccine may be effective in preventing the rare but serious complication of MIS-C (Zambrano et al 2022).
- Participants will have a baseline (Day 1) evaluation for SARS-CoV-2 infection and ongoing surveillance for COVID-19 throughout the study.
- The study will contribute to the development of a bivalent vaccine against COVID-19 for participants aged 12 weeks to < 6 months.

2.3.2. Risks From Study Participation and Their Mitigation

The safety profile of mRNA-1273 is largely based on data from the pivotal Phase 3 study conducted in > 30,000 adults aged 18 years and older (Study mRNA-1273-P301). In addition, the safety of mRNA-1273 in > 10,000 children aged 6 months to < 6 years of age has been studied in Study mRNA-1273-P204. It is expected that the safety profile of mRNA-1273.214 will be similar to mRNA-1273. In the studies mRNA-1273-P205 and mRNA-1273-P305, 443 (enrollment completed) and approximately 1250 (as of 24 May 2022) adults have received mRNA-1273.214, respectively.

Intramuscular injection with other mRNA vaccines manufactured by the Sponsor containing the SM-102 LNP commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection. Solicited ARs

were reported more frequently among vaccine participants than among placebo participants in both Study mRNA-1273-P301 and Study mRNA-1273-P204 (data cutoff 21 Feb 2022).

In Study mRNA-1273-P301, the most frequently reported ARs after any dose in the vaccine group were pain at the injection site, fatigue, headache, myalgia, and chills. The most common solicited local AR was pain. Solicited systemic ARs were reported more frequently by vaccine participants after Dose 2 (fatigue [65.3%], headache [58.6%], myalgia [58%], and arthralgia [42.8%]) than after Dose 1 (fatigue [37.2%], headache [32.7%], myalgia [22.7%], and arthralgia [16.6%]). Grade 3 systemic ARs were also reported more frequently after Dose 2 than after Dose 1. The majority of local and systemic ARs had a median duration of 1 to 3 days. Several participants reported injection site reactions after Day 7 that were characterized by erythema, induration, and often pruritus. Consultation with a dermatopathologist suggested that these were most likely dermal hypersensitivity and were unlikely to represent a long-term safety concern. Overall, there was a higher reported rate of some ARs in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Grade 3 solicited local ARs were more frequently reported after Dose 2 than after Dose 1.

In Study mRNA-1273-P204 (6 months to < 2 years), pain was the most commonly reported local solicited AR. In the infants, irritability/crying were the most commonly systemic solicited ARs, and in the older age group headache and fatigue were the most common systemic solicited ARs.

Unsolicited AEs that occurred within 28 days following each vaccination were collected in both mRNA-1273-P301 and mRNA-1273-P204. In Study mRNA-1273-P301, these were reported by 23.9% of participants who received mRNA-1273 and 21.6% of participants who received placebo. Unsolicited AEs that occurred in ≥ 1% of study participants who received mRNA-1273 and at a rate at least 1.5-fold higher rate than placebo were lymphadenopathy-related events (1.1% vs. 0.6%). All of the lymphadenopathy events were similar to the axillary swelling/tenderness in the injected arm reported as solicited ARs.

Hypersensitivity AEs in Study mRNA-1273-P301 were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. There have been no cases of severe hypersensitivity or anaphylactic reactions reported immediately after vaccination in the trial to date.

In the placebo-controlled part of Study mRNA-1273-P204, overall incidence of unsolicited AEs was similar in participants who received mRNA-1273 and the placebo group (40% and 37.5%, respectively, in participants aged 2 to < 6 years of age; 49.3% and 48.2% in participants aged 6 months to < 2 years, respectively). Unsolicited AEs that were higher in the mRNA-1273 group

compared with the placebo group by at least > 1% were as follows: in participants aged 2 years to < 6 years – injection site erythema (1.3% vs. 0.2%); and in participants aged 6 months to < 2 years – croup infections (1.3% vs. 0.3%), diarrhea (3.2% vs. 2.2%), and injection site lymphadenopathy (1.4% vs. 0.2%). Hypersensitivity AEs related to study vaccination were reported in 1.1% of vaccine recipients and 0.7% of placebo recipients in the 2- to < 6-year-old age group. In the 6 months to < 2-year age group, hypersensitivity AEs related to study vaccination were rare (< 0.1%).

In Study mRNA-1273-P301 that included adults > 18 years of age, SAEs were reported at the same rates in participants who received mRNA-1273 and placebo from the first dose until the last observation. There were 2 SAEs of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination and was likely related to vaccination. There was 1 SAE of intractable nausea and vomiting in a participant with prior history of severe headache and nausea requiring hospitalization. This event occurred 1 day after vaccination and was likely related to vaccination.

There were no other notable patterns or numerical imbalances between study arms in Study mRNA-1273-P301 for specific categories of AEs (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

During the placebo-controlled part of Study mRNA-1273-P204 (data cutoff 21 Feb 2022), there were no SAEs related to the study vaccination within 28 days of any dose in participants aged 2 to < 6 years of age, while in participants aged 6 months to < 2 years, < 0.1% of participants in the treatment group experienced a related SAE (1 participant experienced an event of fever associated with a febrile seizure). No related SAEs were reported in the placebo group.

In the post-authorization period, there have been very rare reports of anaphylaxis following mRNA-1273 administration. In addition, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in male adolescents and young male adults shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Investigators and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021).

2.3.3. Overall Benefit/Risk Conclusion

The proposed study is designed to evaluate the safety and immunogenicity of the mRNA-1273.214 vaccine for SARS-CoV-2 VOCs in participants aged 12 weeks to < 6 months administered as a 2-dose primary series.

Part 1 will enroll participants aged 12 weeks to < 6 months and assess 2 dose levels (5 and 10 µg). Based on the safety and immunogenicity observed in Part 1, dose level for Part 2 will be selected.

Part 2 will enroll participants aged 12 weeks to < 6 months in a placebo-controlled observer-blind evaluation of the selected dose level.

Immunogenicity data from participants who receive the mRNA-1273.214 vaccine at the selected dose level will be used to infer vaccine effectiveness of the primary series. All participants will be followed up for 12 months after receipt of the second injection.

Safety will be monitored throughout the study (Section 8.12).

Although Phase 2/3 studies of mRNA-1273.214 are currently ongoing, the safety profile is expected to be similar to that of mRNA-1273 and other bivalent vaccines studied to date. Based on prior evidence of immunogenicity of bivalent vaccines (Chalkias et al 2022), mRNA-1273.214 may be used to address the current COVID-19 outbreak as a result of its uniquely rapid and scalable manufacturing process. In particular, a safe and effective vaccine against SARS-CoV-2 and the Omicron VOC in young infants will help facilitate a return towards normalization of daily activities, including safe in-person attendance at childcare centers.

Considering the lack of approved vaccines for SARS-CoV-2 and VOCs, the participants' risk of COVID-19 outside the study during a pandemic, the continued emergence of new variants, and the nonclinical and clinical data to date, the Sponsor considers the potential benefits of participation in this study to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

The objectives that will be evaluated in this study and endpoints associated with each objective are provided in Table 2 (Part 1) and Table 3 (Part 2).

Table 2: Objectives and Endpoints for Part 1

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 2 dose levels[1] of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs throughout the entire study period • SAEs throughout the entire study period • AESIs throughout the entire study period • AEs leading to discontinuation from study participation postdose throughout the entire study period
Secondary Objectives	**Secondary Endpoints**
• To evaluate the immunogenicity of 2 dose levels[1] of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• GMT of antibodies against SARS-CoV-2 VOC (Omicron) at 28 days after second dose

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; GMT = geometric mean titer; MAAE = medically attended adverse event; mRNA = messenger RNA; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VOC = variants of concern.
[1.] Dose levels of mRNA-1273.214 vaccine administered to participants will be 5 µg and 10 µg.

Table 3: Objectives and Endpoints for Part 2

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of selected dose level (from Part 1) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs throughout the entire study period • SAEs throughout the entire study period • AESIs throughout the entire study period • AEs leading to discontinuation from study participation postdose throughout the entire study period
• To infer the effectiveness of selected dose level (from Part 1) of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months	• Co-primary Endpoint: GMT of antibodies against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 compared with that of the adult participants at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 (100 µg, 2 doses 28 days apart) primary series • Co-primary Endpoint: SRR[1] against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 compared with that of the adult participants at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 (100 µg, 2 doses 28 days apart) primary series
Secondary Objectives	**Secondary Endpoints**
• To evaluate the immune response against SARS-CoV-2 VOC (Omicron) elicited by mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months, compared with the immune responses against original strain induced by mRNA-1273	• GMT of antibodies and SRR against SARS-CoV-2 VOC (Omicron) at 28 days after the second dose of mRNA-1273.214 primary series, compared with GMT and SRR against original strain at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 primary series

primary series (100 µg, 2 doses 28 days apart)	
• To evaluate the immune response against SARS-CoV-2 original strain elicited by mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in participants aged 12 weeks to < 6 months, compared with the immune responses against original strain induced by mRNA-1273 primary series (100 µg, 2 doses 28 days apart)	• GMT of antibodies and SRR against SARS-CoV-2 original strain at 28 days after the second dose of mRNA-1273.214 primary series, compared with GMT and SRR against original strain at Day 57 (28 days after the second dose) in Study mRNA-1273-P301 dosed with mRNA-1273 primary series
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the incidence of COVID-19 after mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart	• The incidence of the first occurrence of COVID-19 postbaseline, where COVID-19 is defined as symptomatic disease based on CDC case definition[2]
• To evaluate the incidence of SARS-CoV-2 infection after mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart	• The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or RT-PCR) postbaseline SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline: o bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1, that becomes positive (as measured by ligand-binding assay) postbaseline, OR o Positive RT-PCR postbaseline
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart	• The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by ligand-binding assay) postbaseline in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)

• To evaluate immune response elicited by the primary series of mRNA-1273.214 against variant(s) of interest	• GMT, SRR, and GMFR of Ab against variant(s) of interest

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; mRNA = messenger RNA; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; VOC = variants of concern.

1. Seroresponse is defined as a titer change from baseline (pre-Dose 1) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.
2. The case definition of COVID-19 includes at least one of the following systemic symptoms: fever (temperature > 38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours); cough (of any duration, including ≤ 48 hours); shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours); fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea or vomiting, poor appetite or poor feeding; AND a positive test for SARS-CoV-2 by RT-PCR.

4. STUDY DESIGN

4.1. General Design

This is a Phase 2, two-part, open-label in Part 1 and observer-blind, randomized, placebo-controlled in Part 2 study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273.214 SARS-CoV-2 vaccine in infants aged 12 weeks to < 6 months. The study will be conducted at multiple sites in the US enrolling approximately 700 participants. Participants who withdraw or are withdrawn from the study will not be replaced.

The study will be conducted in 2 parts. Part 1 will consist of Arm 1 and Arm 2 that will enroll sequentially, ie, Arm 1 will begin enrollment and the periodic safety review will determine whether Arm 2 can begin enrollment. A total of 100 participants (50 participants in each arm) will be enrolled in Part 1 and will receive 5 µg of mRNA-1273.214 in Arm 1 and 10 µg of mRNA-1273.214 in Arm 2. While participants may be screened up to 1 month prior to dosing, they must be 12 weeks completed age at the time of receipt of first dose. Arm 1 will start with 2 doses of 5 µg (sentinel dosing) administered 8 weeks apart of up to 4 participants. An IST will review safety data after Dose 1 (1 week after Dose 1 of mRNA-1273.214) and provide a recommendation to further dose participants. Once safety and tolerability after Dose 1 have been reviewed by the IST, Arm 1 will continue enrollment for a total of 50 participants.

The IST will reconvene once 25 participants in Arm 1 reach Day 64 (1 week after Dose 2 of 5 µg administered 8 weeks apart). If no safety concerns are identified after IST review in Arm 1, Arm 2 will begin enrollment and participants will receive 2 doses of 10 µg of mRNA-1273.214 administered 8 weeks apart. Similar to Arm 1, safety and tolerability will be reviewed by the IST after 4 participants have received Dose 1 (1 week after Dose 1 of mRNA-1273.214), and again when 25 participants reach Day 64, and provide a recommendation for continuing dosing and enrollment at each review. Arm 2 will enroll a total of 50 participants. The immunogenicity and safety analysis will be conducted after all treated participants in both Arms 1 and 2 reach Day 85 (28 days from second dose). The results from Part 1 will determine the dose level for Part 2, which will be blinded and randomized.

Part 2 of the study will consist of 2 groups (Arm 3 and Arm 4). In Part 2, a total of approximately 600 participants will be randomly assigned to receive mRNA-1273.214 (Arm 3) or placebo (Arm 4) in a 1:1 ratio (n = 300 per arm). Part 2 will utilize the mRNA-1273.214 dose selected in Part 1. Study vaccine will be administered nonconcomitantly to routine pediatric vaccinations. Participants will be followed for approximately 12 months after completion of the primary series.

All participants will participate in a Screening Period, Treatment Period, and Follow-up Period. The study schema is illustrated in Figure 1 and the SoA is provided in Table 1.

4.1.1. Study Periods

This study involves up to 10 scheduled visits in Part 1 and 8 scheduled visits in Part 2. In both Part 1 and Part 2, there will be up to 6 in-person visits (if screening and baseline are done separately) and 2 remote visits (Visit 3 and Visit 6; remote evaluation by means of telecommunication technology or phone call). Two additional clinic visits on Day 4 and Day 60 will be performed only in Part 1 (Table 1).

The study duration for each participant will be approximately 15 months, which includes 1 month for screening (Day –28 to Day –1), 2 months for dosing (on Day 1 and Day 57), and 12 months of follow-up after the second dose.

All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), a remote evaluation via a telemedicine visit or call should be conducted in place of the study site visit (except for dosing visits and visits that require a blood draw). The remote evaluation should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Home visits will be permitted for all nondosing visits, with the exception of screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the study site IRB and the participant’s parent(s)/LAR(s) via informed consent and have prior approval from the Sponsor (or its designee).

This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements (Section 11.1.1).

4.1.1.1. Screening Period

Participants will undergo screening assessments to determine study eligibility. Screening assessments (Table 1) must be completed after the participant’s parent(s)/LAR(s) signs the ICF. The investigator will review study entry criteria to determine participant eligibility during the screening period.

Screening Visit and Day 1 may be combined on the same day. Additionally, the Screening Visit may be performed over multiple visits if performed within the 28-day screening window (Table 1).

Eligible participants will enter the Treatment Period.

4.1.1.2. Treatment and Follow-up Period

In both Parts 1 and 2, on Day 1, after the completion of the scheduled assessments (Table 1), participants will be administered a single IM dose of the IP mRNA-1273.214 (at the applicable dose based on study part and arm) or placebo. Placebo will be administered only to those who are randomized to the placebo arm in Part 2 of the study. The procedures for IP administration will be detailed in the mRNA-1273-P206 Pharmacy Manual.

Participants will be closely monitored for safety and will remain at the study site for observation for at least 60 minutes after dosing in Part 1 and 30 minutes after dosing in Part 2. On Day 57, the second dose of IP will be administered. If the visit for the second dose (Day 57) is disrupted and cannot be completed at Day 57 (–14/+7 days) as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place") or due to extenuating circumstances (to be evaluated by the Sponsor on a case-by-case basis), the visit window may be extended to Day 57 + 14 days. When the extended visit window is used, the remaining study visits should be rescheduled to follow the intervisit interval from the actual date of the second dose.

Participants will be followed for 12 months after the second dose of IP. To test for the presence of SARS-CoV-2 by RT-PCR, nasal swab samples will be collected on each day of injection prior to dosing (Day 1 and Day 57), and on Day 85 (28 days after Dose 2), Day 237 (6 months after Dose 2), and Day 422 (12 months after Dose 2) according to the SoA (Table 1).

During the course of the study, participants who meet prespecified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment, including a nasal swab sample to be tested for the presence of SARS-CoV-2 by RT-PCR. Confirmed, symptomatic cases of SARS-CoV-2 infection will be captured as MAAEs and, if severe, reported in an expedited time frame to the Sponsor (Section 8.11.4).

All participants will be monitored for safety and reactogenicity. All participants in the study will provide blood specimens for immunogenicity assessments on Day 1 (prior to the first dose), Day 85 (28 days after Dose 2), Day 237 (6 months after Dose 2), and Day 422 (12 months after Dose 2).

4.2. Scientific Rationale for Study Design

This Phase 2 study is designed as a two-part, dose-finding and open-label (Part 1), and randomized, observer-blinded, and placebo-controlled study (Part 2) to demonstrate the

immunogenicity and safety of the mRNA-1273.214 vaccine in participants aged 12 weeks to < 6 months. This pediatric study is intended to confirm safety in infants between 12 weeks to < 6 months of age and bridge immunogenicity between infants and adults (> 18 years of age) enrolled in the pivotal adult Phase 3 study (Study mRNA-1273-P301). It is necessary to demonstrate noninferiority of the induced immune response in infants compared with that in adults to infer vaccine effectiveness in this age group.

Part 1 of the study is designed to dose escalate starting with a low dose level in Arm 1. Arm 2 will test the next higher dose level if there are no safety concerns (after IST review of 25 participants in Arm 1 who have reached Day 64). Safety and immunogenicity analysis after both Arm 1 and Arm 2 have completed enrollment and participants have reached Day 85 will determine the dose level for Part 2. Part 2 of the study is designed to assess safety and immunogenicity of the selected dose level from Part 1 in a randomized, placebo-controlled design. This randomization and placebo arm is necessary to assess safety since no trials have assessed an mRNA vaccine in this age group.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre- and post-injection blood samples for analysis of antibodies to non-vaccine antigens as described in the SoA (Table 1). In addition, participants will have nasal swab samples collected before vaccination according to the SoA. Furthermore, in case of any signs or symptoms or MAAEs suggesting SARS-CoV-2 infection in a participant, an additional nasal swab sample will be collected to confirm the diagnosis of SARS-CoV-2 via RT-PCR. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

Since it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the nasal swab samples collected before study injection and the serologic assays performed for Ab responses to non-vaccine antigen(s), may help to discriminate between natural infection and vaccine-induced Ab responses, should such discrimination be needed.

4.3. Justification for Dose, Control Product, and Choice of Study Population

In Study mRNA-1273-P204, a 50 and a 25 µg, 2-dose primary series of mRNA-1273 given to children aged 6 to 12 years of age and 6 months to 6 years of age, respectively, elicited a robust nAb response with a favorable safety profile. Based on these results, the dose for children aged 12 weeks to < 6 months is anticipated to be 10 µg. Hence in this study, Part 1 will be conducted for dose selection of mRNA-1273.214 for participants aged 12 weeks to < 6 months given as a 2-dose primary series starting with a lower dose of 5 µg, which will serve as a sentinel dose for

safety evaluation and to support determination of end-of-shelf life limits for the target 10 µg dose.

A normal saline formulation was chosen as the control product in Part 2 in order to ascertain the safety of mRNA-1273.214 in this age group.

As participants aged 12 weeks to < 6 months are anticipated to be new vaccine recipients over time and with this period of life coinciding with waning of maternal antibodies, this age group was chosen for this study evaluating pediatric bivalent primary and booster vaccination for COVID-19.

4.4. End of Study Definition

The end of the study for the full study is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the SoA (Table 1) for the last participant in this study.

5. STUDY POPULATION

Prospective approval of protocol deviation(s) to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. The participant is male or female, between 2 and < 6 months of age at the time of consent (Screening Visit), who is in good general health, in the opinion of the investigator, based on review of medical history and screening physical examination.
    a) Participant must be at least 12 weeks completed age and must not have completed 6 months at the time of administration of first dose.
    b) If the participant has a chronic, stable disease, they may be eligible to enroll in Part 2, but ineligible for Part 1. The chronic condition (eg, gastroesophageal reflux disease) should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion in Part 2. Note: a change in medication for dose optimization, change within class of medication, reduction in dose or increase in dose due to expected weight gain are not considered signs of instability.
2. The participant was born at ≥ 37 weeks gestation (Part 1) or ≥ 34 weeks gestation (Part 2), with a minimum birth weight of 2.5 kg, without fetal growth restriction, and the participant's height and weight are both at or above the second percentile for age according to the CDC/WHO Child Growth Standard (Section 11.1.18) at the Screening Visit.
3. In the investigator's opinion, the parent(s)/LAR(s) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures, and provide written informed consent. This includes inability to collect minimum amount of sample volume at baseline blood draw.

5.2. Exclusion Criteria

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

1. The participant has a known history of symptomatic SARS-CoV-2 infection within 2 weeks prior to administration of IP or has a known close contact (as defined in Section 8.10.2) in the past 2 weeks to someone diagnosed with SARS-CoV-2 infection or

COVID-19. Participants may be rescreened after 14 days provided that they remain asymptomatic.

2. The participant is acutely ill or febrile 72 hours prior to or at the Screening Visit. Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
3. The participant has previously been administered an investigational or approved CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.
4. The participant has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (eg, receipt of SARS-CoV-2 monoclonal antibodies) within 90 days prior to enrollment.
5. The participant has a known hypersensitivity to a component of the vaccine or its excipients. Hypersensitivity includes, but is not limited to, anaphylaxis or immediate allergic reaction of any severity to any of the components of mRNA COVID-19 vaccines (including PEG or immediate allergic reaction of any severity to polysorbate).
6. The participant has a medical, psychiatric, or occupational condition, including reported history of substance abuse, in the infant or in the parent(s)/LAR(s) that, according to the investigator's judgment, may pose additional risk as a result of participation, interfere with safety assessments, or interfere with interpretation of results.
7. The participant has a history of diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically the following:
    a) Congenital or acquired immunodeficiency
    b) Chronic hepatitis or suspected active hepatitis
    c) A bleeding disorder that is considered a contraindication to IM injection or phlebotomy, or non-receipt of vitamin K at birth
    d) Dermatologic conditions that could affect local solicited AR assessments
    e) Any prior diagnosis of malignancy
    f) Febrile seizures

8. The participant has received the following:
    a) Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to first or second vaccination or plans to receive such a vaccine within 14 days of any study vaccination.
    b) Systemic immunosuppressants or immune-modifying drugs (including maternal use during pregnancy or lactation) for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 1 mg/kg/day or, if participant weighs > 10 kg: ≥ 10 mg/day prednisone equivalent). Participants may have visits rescheduled for enrollment if they no longer meet this criterion within the Screening Visit window. Inhaled, nasal, and topical steroids are allowed.
    c) Intravenous or subcutaneous blood products (red blood cells, platelets, immunoglobulins) within 3 months prior to enrollment.
9. The participant has participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to do so while participating in this study, or maternal participation in an interventional clinical study during pregnancy.
10. The participant is an immediate family member, or household contact, of an employee of the study site or Sponsor or someone otherwise directly involved with the conduct of the study. As applicable, family members/household contacts of employees of the larger institution or affiliated private practice not part of the study site may be enrolled.
11. The participant is a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government, or a government body, acting in accordance with powers conferred on them by laws and regulation. Does not include a child who is adopted or has an appointed legal guardian.

5.3. Screen Failures

Screen failures are defined as participants whose parent(s)/LAR(s) provide consent to participate in the study but are not subsequently assigned (Part 1) or randomly assigned (Part 2) to treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent, demography, reason(s) for screen failure, eligibility criteria, and information on any SAE that may have occurred after dosing to the time of withdrawal.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time if they will be eligible upon rescreening.

On Day 1, blood sample for immunogenicity assessment must be collected prior to randomization and dosing. In both Part 1 and Part 2 of study, if a Day 1 (baseline) blood sample cannot be obtained, the participant could be rescheduled within the allowable screening period one time. If a blood sample still cannot be obtained at the rescheduled visit, then the participant will be considered a screen failure due to inability to satisfy inclusion criterion 3.

6. STUDY TREATMENT

6.1. Investigational Products Administered

The term IP refers to both the mRNA-1273.214 vaccine and placebo (0.9% sodium chloride) administered in this study.

mRNA-1273.214 is a bivalent vaccine containing mRNA-1273 and mRNA-1273.529, co-formulated at a 1:1 ratio. mRNA-1273 is an LNP dispersion containing the mRNA encoding for the prefusion stabilized S protein (S-2P) of SARS-CoV-2 of Wuhan-Hu-1. mRNA-1273.529 is an LNP dispersion containing the mRNA encoding for the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529). Each mRNA is formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG). mRNA-1273.214 injection is provided as a sterile liquid for injection and is a white to off-white dispersion at a concentration of CCI mg/mL in 20 mM Tris buffer with sucrose and at pH 7.5.

6.2. Randomization and Blinding

Random assignment of participants in Part 2 of the study will use a centralized IRT, in accordance with pregenerated randomization schedules. Approximately 600 participants will be randomized in a 1:1 ratio to the mRNA-1273.214 arm or placebo arm (n = ~300 participants in each group).

As the appearance of the study treatments differs, enrollment will be observer blinded as to treatment assignment.

No set of individual treatment codes will be held at the study sites.

Neither the participant nor participant's parent(s)/LAR(s), nor the investigator nor clinical staff responsible for study assessments/safety will have access to the treatment assignment during the conduct of the study.

Dose preparation, administration, and accountability will be performed by designated unblinded site personnel who will not participate in any of the clinical study evaluations. The unblinded site personnel will prepare the dose out of view of the participant's parent(s)/LAR(s) and the blinded site personnel, and will administer the vaccine in a separate room, or at minimum, using a curtain to shield view of the injected arm/leg. The unblinded site personnel will not be involved in participant evaluations and will not reveal the identity of the IP to either the participant's parent(s)/LAR(s) or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency. Once the injection is completed, only the

blinded clinic staff will perform further assessments and interact with the participant's parent(s)/LAR(s). Access to the randomization code will be strictly controlled at the pharmacy.

The laboratory personnel in charge of immunogenicity testing will be blinded to the treatment assignment of the samples tested throughout the course of the study.

Except in the case of medical necessity, a participant's treatment should not be unblinded without the approval of the Sponsor. The treatment code should be broken only if the investigator in charge of the participant feels that the case cannot be treated without knowing the identity of the study vaccine. Instructions regarding emergency unblinding will be provided to the investigator and are discussed in Section 6.3.8.

The investigator, clinic staff, study participant's parent(s)/LAR(s), site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded for the final analysis. At the planned analyses (see Section 9.6), pre-identified Sponsor team members and selected CRO team members will be unblinded to conduct the analyses. Study participant's parent(s)/LAR(s), investigators, and blinded site personnel will remain blinded.

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Clinical Study Material Preparation

Each dose of IP will be prepared for each participant based on the assigned treatment, as detailed in the mRNA-1273-P206 Pharmacy Manual.

6.3.2. Clinical Study Material Administration

Each participant will receive 2 doses of IP by IM injection approximately 8 weeks apart (Day 1 and Day 57) in Part 1 and Part 2 of study. The IM injections will be administered into the anterolateral thigh, according to their assigned regimen and according to the procedures specified in the mRNA-1273-P206 Pharmacy Manual.

At each visit when IP is administered, participants will be monitored for a minimum of 60 minutes after administration in Part 1 and 30 minutes after administration in Part 2. Assessments will include body temperature measurements (must be measured via the axillary route and any axillary reading of ≥ 37.8°C/≥ 100°F may be confirmed by a rectal measurement) and monitoring for local or systemic reactions.

Eligibility for the subsequent dose of IP will be determined by the criteria outlined in Section 7.

The study sites will be appropriately staffed with individuals with basic pediatric cardiopulmonary resuscitation training/certification. Either on-site resuscitation equipment and

personnel or appropriate protocols for the rapid transport of participants to a resuscitation area or facility are required.

6.3.3. Clinical Study Material Delivery and Receipt

The description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IP are described in the mRNA-1273-P206 Pharmacy Manual.

6.3.4. Clinical Study Material Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of IP. The sterile IP is packaged in 2R borosilicate glass vials. The IP will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

The IP will be packaged and labeled in accordance with the standard operating procedures of the Sponsor or its designee, CFR Title 21, Good Manufacturing Practice guidelines, ICH GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

6.3.5. Clinical Study Material Storage

The IP must be stored as per the temperature conditions printed on the IP label in a secure area with limited access and be protected from moisture and light until it is prepared for administration (Section 6.3.1). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of freezer malfunction. There must be an available back-up freezer. The freezer must be connected to a back-up generator, or an alternate plan must be in place in the event of a power failure. In addition, IP accountability study staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The study site is responsible for reporting any IP that was not temperature controlled during shipment or during storage. Such IP will be retained for inspection by the monitor and disposed of according to approved methods.

6.3.6. Clinical Study Material Accountability

It is the investigator's responsibility that the IP accountability study staff maintain accurate records in an IP accountability log of receipt of all IP, study site IP inventory, IP dispensing, IP injections, and return to the Sponsor or alternative disposition of used and unused IP vials.

A study site monitor will review the inventory and accountability log during study site visits and at the completion of each part of the study. Additional details are found in the mRNA-1273-P206 Pharmacy Manual.

6.3.7. Clinical Study Material Handling and Disposal

A study site monitor will reconcile the IP inventory during the conduct and at the end of each part of the study for compliance. Once fully reconciled after each monitoring visit at the study site, the IP can be destroyed at the investigational site or by a Sponsor-selected third party, as appropriate.

Vaccine may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A certificate of destruction must be completed and sent to the Sponsor or designee. For further direction, refer to mRNA-1273-P206 Pharmacy Manual.

6.3.8. Unblinding

Except in the case of medical necessity, a participant's treatment assignment in Part 2 should not be unblinded without the approval of the Sponsor. If a participant becomes seriously ill during the study, the blind will be broken only if knowledge of the treatment assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual treatment assignment, the investigator will make every attempt to contact the CRO clinical research associate (who must inform the Sponsor medical lead) to explain the need for unblinding within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for unblinding, and the names of the personnel involved. The investigator (or designee) will have access to unblind participants within IRT. All unblindings will be tracked via an audit trail in IRT and documented in the final study report.

If a COVID-19 vaccine (mRNA-1273 or other) is authorized or licensed for infants, parent(s)/LAR(s) of eligible study participants (by virtue of their age) will be offered the opportunity to unblind via a phone call and learn what treatment the participant received, ideally after they have reached at least Day 85 in the study. Participants who have received mRNA-1273.214 will continue in the study and will be followed per protocol. If a participant previously received placebo, then their parent(s)/LAR(s) will be advised to discuss with the participant's primary care physician and follow current CDC recommendations regarding COVID-19 immunization. If a participant who received placebo in the study chooses to receive a nonstudy COVID-19 vaccine, they will be withdrawn from the study.

6.4. Study Treatment Compliance

All doses of IP will be administered at the study site under direct observation of medically qualified study staff and appropriately recorded (date and time) in the eCRF. Qualified study site staff will confirm that the participant has received the entire dose of IP. If a participant does not receive IP or does not receive all of the planned doses, the reason for the missed dose will be recorded. Data will be reconciled with study site accountability records to assess compliance.

Participants who miss the second dose due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol and their regimen schedule. Unless consent is withdrawn, a participant whose parent(s)/LAR(s) withdraws or if the participant is withheld from receiving the second dose will remain in the study and complete all safety and immunogenicity assessments required through the participant's last scheduled study visit.

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window. If a participant does not complete a visit within the time window, that visit may be performed out of window or may be classified as a missed visit per investigator discretion. If classified as a missed visit, the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

6.5. Prior and Concomitant Medications

6.5.1. Maternal Medications and Therapies

Information about the participant's mother's COVID-19 vaccine(s) and COVID-19 infection(s) before conceiving the participant, while pregnant with the participant, and while breastfeeding the participant will be recorded in the participant's eCRF.

6.5.2. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before their parent(s)/LAR(s) provided informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

6.5.3. Concomitant Medications and Therapies

At each study visit, study site staff must question the participant's parent(s)/LAR(s) regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the first dose of IP and throughout the study period, including:
    - Any authorized or investigational COVID-19 vaccine
    - Routine pediatric vaccines including but not limited to hepatitis B, rotavirus, Hib, DTaP, PCV13, IPV, MMR, varicella, hepatitis A

  - Seasonal influenza vaccine administered for the current influenza season (typically October through April in the Northern Hemisphere).

- All concomitant medications taken through 28 days after each dose of IP (through the completion of the Day 85 visit). Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- All concomitant immunosuppressants or immune-modifying drugs potentially transferred through breastmilk throughout the study period.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Any concomitant medications relevant to or for the treatment of an AESI, SAE, or an MAAE throughout the study period.
- Participant's parent(s)/LAR(s) will be asked in the eDiary if the participant has taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each IP injection, including on the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the clinic visits after vaccination or via other interactions with participant's parent(s)/LAR(s) (eg, telephone calls).

Data regarding nutritional supplements, eg, vitamins, probiotics, and herbal supplements, will not be collected unless relevant to an AE.

Concomitant medications (including vaccinations) will be coded using the WHODrug Dictionary.

If a participant takes a prohibited drug therapy, the investigator and the CRO's medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding concomitant medications are adequately recorded in the eCRF.

6.5.4. Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant from Per-protocol Analyses

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study, but may determine a participant's eligibility to receive a second dose or be included in the PP analysis. Analysis sets are described in Section 9.4.

- Any investigational or nonregistered product (drug or vaccine) other than the IP used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, > 14 days in total), including through breastmilk, during the study period. For corticosteroids, receipt of prednisone or the equivalent at a dose of ≥ 1 mg/kg/day (or ≥ 10 mg/day if participant weighs > 10 kg) is not permitted. Inhaled, nasal, and topical steroids are allowed.
- Long-acting, immune-modifying drugs administered at any time during the study period (eg, infliximab).
- Immunoglobulins and/or any Ab-containing blood products (eg, packed red blood cells) administered during the study period.

7. DELAY OR DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Criteria for Delay of Vaccine Administration

7.1.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature must be measured on dosing visits before vaccine administration (body temperature must be measured via the axillary route and any axillary reading of ≥ 37.8°C/≥ 100°F may be confirmed by a rectal measurement). The following events constitute criteria for delay of injection, and if any of these events occur at the time scheduled for dosing, the participant may receive the study injection at a later date within the time window specified in the SoA (Table 1), or the participant may be discontinued from dosing at the discretion of the investigator (Section 7.2):

- Acute moderate or severe infection with or without fever at the time of dosing
- Fever, defined as body temperature ≥ 38.0°C/≥ 100.4°F at the time of dosing

Participants with a minor illness without fever, as assessed by the investigator, can be vaccinated.

Participants with a fever of ≥ 38.0°C/≥ 100.4°F will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the investigator determines that the participant's health on the day of dosing temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

If a participant was exposed to a household contact (excluding school or other exposures) who tested positive for SARS-CoV-2 after the participant received the first dose, the administration of the second dose may be delayed to allow for at least 14 days between the positive test or the last day of symptoms (if present) of the household contact and Dose 2 as long as the participant remains asymptomatic.

If a participant tests positive for SARS-CoV-2 after having received Dose 1 but remains asymptomatic and the second dose is due before 14 days after the positive test, administration of the second dose may be delayed to allow for at least 14 days between the participant's positive test and Dose 2 as long as participant remains asymptomatic.

If a participant tests positive for SARS-CoV-2 after having received Dose 1 and develops symptoms of COVID-19, the participant may still receive a second dose, but the second dose should be delayed until approximately 90 days after diagnosis with COVID-19.

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the investigator and the CRO's medical monitor (Section 6.5.3).

7.2. Discontinuation of Study Vaccination

Participant's parent(s)/LAR(s) can choose to discontinue study injection (ie, refuse the second dose) for any reason, without prejudice to further treatment the participant may need to receive.

The investigator, in consultation with the Sponsor's medical monitor, may withhold or delay a participant from further injection under the following circumstances:

- The participant's parent(s)/LAR(s) withdraw consent.
- The participant develops, during the course of the study, symptoms or conditions listed in the exclusion criteria (Section 5.2).
- The participant experiences an AE (other than solicited reactogenicity) after injection that is considered by the investigator to be related to IP (Section 8.11.8) and is assessed as severe (Section 8.11.7).
- The participant experiences an AE or SAE that, in the judgment of the investigator, requires IP withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine.
- The participant experiences an AESI (Section 11.2).
- The participant experiences a clinically significant change in general condition that, in the judgment of the investigator, requires vaccine withdrawal.
- The participant experiences anaphylaxis (described in Section 8.11.4) clearly related to IP.
- The participant experiences a hypersensitivity reaction related to IP.

The reason(s) for withdrawal from further injection must be recorded in the eCRF.

If a participant takes a prohibited drug therapy, the investigator could withhold the second dose based on a joint decision of the investigator and the CRO's medical monitor (Section 6.5.3).

Every reasonable attempt should be made to follow up with participants for safety throughout the entire scheduled study period according to the SoA (Table 1), even if the participant does not receive the second dose or misses 1 or more visits. Unless the participant's parent(s)/LAR(s) withdraw consent, the participant is expected to remain in the study and complete all scheduled visits and assessments.

7.3. Participant Discontinuation/Withdrawal From the Study

Participants who withdraw or are withdrawn from the study will not be replaced. A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

The participant's parent(s)/LAR(s) can withdraw consent and withdraw the participant from the study at any time during the study, for any reason, without prejudice to further treatment the participant may need to receive. The investigator will request that the participant complete all study procedures pending at the time of withdrawal.

If participant's parent(s)/LAR(s) desires to withdraw the participant from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant's parent(s)/LAR(s) until the event is considered resolved or stable and will then complete the end of the study eCRF.

Information related to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a participant from the study was made by the participant's parent(s)/LAR(s) or by the investigator, as well as which of the following possible reasons was the cause for withdrawal:

- AE (specify)
- SAE (specify)
- Death
- LTFU
- Physician decision (specify)
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant's parent(s)/LAR(s)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including AESIs and SAEs) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow up with parent(s)/LAR(s) of the participants who are withdrawn from the study as result of an SAE or AE until resolution of the event.

Any parent(s)/LAR(s) who withdraws the participant from the study may request destruction of any samples taken and not tested. The investigator must document this in the study site study records and inform the Sponsor.

If the participant's parent(s)/LAR(s) withdraw consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (Section 11.1.10).

The Sponsor will continue to retain and use all research data that have already been collected for the study evaluation, unless the participant's parent(s)/LAR(s) have requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

Unblinding of still blinded participants based only on parental/LAR request and not related to a safety event or health concern will not be permitted, in order to protect the data integrity of the blinded portion of the study. If a parent/LAR wishes to withdraw their child from the study, they may withdraw at any time but will only be able to learn the treatment group assignment once an unblinding trigger is reached as described in Section 6.3.8. If an unblinding trigger is reached and a participant who received placebo in the study chooses to receive a nonstudy COVID-19 vaccine, they will be withdrawn from the study (Section 6.3.8).

7.3.1. End-of-study Visit (Prior to Day 422)

Once the parent(s)/LAR(s) withdraw the participant from the study, the investigator (or delegate) should confirm all ongoing AEs have been addressed and answer any additional questions the participant's parent(s)/LAR(s) may have; this may be done via a telephone call. The communication should be documented in the source. The End-of-Study/Study Discontinuation eCRF page must be completed.

7.4. Study Pause Rules

The investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause. Study pause rule criteria, events, and thresholds are described in Table 4.

Table 4: Pause Rule Criteria, Events, and Thresholds

Pause Rule Criterion	Event	Participant Threshold for Triggering Study Pause
Pause Rule Assessed by Investigator		
1	Any SAE that cannot be reasonably attributed to a cause other than the study vaccination	≥ 1
Pause Rules to be Assessed by Medical Monitoring Team (Sponsor/CRO)		
2[a]	Individual Grade 3 or higher solicited local AR lasting ≥ 24 hours in duration and occurring within 7 days of injection (Days 1 to 7)[b]	At least 2 participants and ≥ 5% of the dosed participants in each arm
3[a]	Individual Grade 3 or higher solicited systemic AR lasting ≥ 24 hours in duration that cannot be reasonably attributed to a cause other than the study vaccination, within 7 days of injection (Days 1 to 7)[b]	At least 2 participants and ≥ 5% of the enrolled participants in each arm
4	Any severe unsolicited AE that cannot be reasonably attributed to a cause other than the study vaccination, within the 7-day (Days 1 to 7) post-vaccination period	At least 2 participants and ≥ 5% of the enrolled participants in each arm

Abbreviations: AE = adverse event; AR = adverse reaction; CRO = contract research organization; eDiary = electronic diary; SAE = serious adverse event.

a. "Individual AR" is defined as 1 AR type, eg, pain, erythema, or headache could each be an "individual AR."

b. This will be tracked in the following manner: if a participant reports a Grade 3 or higher AR in 2 consecutive eDiary entries within 22 to ≥ 24 hours apart, the participant will be contacted and asked whether the AR lasted ≥ 24 hours in duration. If an eDiary entry is not entered the day after a Grade 3 or higher AR was reported, the participant will also be contacted and asked whether the AR lasted ≥ 24 hours in duration.

If any of the thresholds for a study pause are met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators and the DSMB will convene on an ad hoc basis. The DSMB will review all available unblinded study data (as applicable) to help adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

The investigator or designee is responsible for reporting each event that potentially meets any pause rule criterion within 24 hours of observation to the Sponsor. The Sponsor will inform the DSMB of any event that potentially meets the pause rule criterion. The DSMB will review all

available study data to help adjudicate such events in accordance with the DSMB charter (Section 8.12.2).

The Sponsor will notify the Center for Biologics and Evaluation Research within 48 hours in the event of a study pause. In the event of a study pause, all safety and immunogenicity assessments will continue per protocol. The window allowance for injection visits may be extended by an additional 7 days (ie, + 21 days) for affected participants at the discretion of the Sponsor.

7.5. Lost to Follow-up

A participant will be considered LTFU if the participant's parent(s)/LAR(s) repeatedly fail to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site staff must attempt to contact the participant's parent(s)/LAR(s) and reschedule the missed visit as soon as possible, counsel the participant's parent(s)/LAR(s) on the importance of maintaining the assigned visit schedule and ascertain whether they wish the participant to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant's parent(s)/LAR(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's medical record.
- A participant whose parent(s)/LAR(s) continue to be unreachable or continue to be noncompliant with study visits or procedures will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will undergo study procedures at the time points specified in the SoA (Table 1).

A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. The study site also has the discretion to make reminder telephone calls or send text messages to inform the participant's parent(s)/LAR(s) about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

In accordance with FDA guidance on "Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits (with the exception of Screening, Day 1, Day 57, Day 85, Day 237, and Day 422) with the approval of the Sponsor (home visits also require site IRB approval). Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

8.1. Screening

Before performing any study procedures, parent(s)/LAR(s) of all potential participants will sign an ICF (as detailed in Section 11.1.6).

At the Screening Visit (up to 28 days for the Day 1 visit), all screening requirements, including reason for screen failure if a participant is not randomized, must be completed. The Enrollment Page in the eCRF must also be completed.

The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window. Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline assessments provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

8.2. Confirm Inclusion and Exclusion Criteria

All inclusion and exclusion criteria described in Section 5.1 and Section 5.2 must be met before randomization (Day 1 visit).

8.3. Demographic and Baseline Data

Demographic information relating to the participant's sex, age, race, ethnicity, height, and weight will be recorded at the Screening Visit on the appropriate eCRF page. Maternal history of SARS-CoV-2 infection, COVID-19 immunization, as well as pregnancy, labor, and delivery details will also be recorded at the Screening Visit on the appropriate eCRF page.

8.4. Medical History

Medical history will be collected and recorded for each participant and the participant's mother on the appropriate eCRF page. Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page.

8.5. Randomization

Vaccination group allocation in Part 2 will be performed at the Day 1 visit as described in Section 6.2. The confirmation for study vaccine administration must be recorded on the Exposure page of the eCRF.

8.6. Physical Examination and Vital Signs

A full physical examination will be performed at the Screening Visit. The full examination will include length/height and weight measurements and assessment of skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, lymph nodes, and musculoskeletal system/extremities. Symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the investigator. Any clinically significant finding identified by an HCP during clinic visits should be reported as an MAAE (Section 8.11.4).

Vital sign measurements will be assessed at the Screening visit. Vital signs will include the assessment of systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Body temperature must be measured via the axillary route and any axillary reading of ≥ 37.8°C/≥ 100°F may be confirmed by a rectal measurement. On the day of vaccination, vital signs will be collected prior to vaccination and only if clinically indicated after vaccination per the discretion of the investigator. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.

The information collected will be recorded in the eCRF.

8.7. Study Vaccine Administration

A single injection (mRNA-1273.214 or placebo) will be administered to all participants on dosing visits as described in the SoA (Table 1).

After completing all prerequisite procedures prior to vaccination, the study vaccine will be administered via IM injection into the anterolateral thigh. Additional details regarding vaccine administration procedure are provided in Section 6.3.2.

The participants will be observed closely (via clinical assessment including measurement of vital signs if clinically indicated based on discretion of the investigator) for at least 60 minutes (Part 1) or 30 minutes (Part 2) following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis or other hypersensitivity reactions.

8.8. Immunogenicity Assessments

Blood samples for immunogenicity assessments and biomarker samples will be collected at the time points indicated in in the SoA (Table 1). The following analytes will be measured:

- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays, including VOC (Omicron).
- Serum bAb titer as measured by a multiplex ligand-binding assay specific to the SARS-CoV-2 S protein.
- Serum bAb titer as measured by a multiplex ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein.
- Testing for serologic markers for SARS-CoV-2 infection as measured by anti-nucleocapsid antibodies detected by immunoassay.

Sample aliquots will be designed to have back-up samples, if possible; vial volumes will likely be adequate for future testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study laboratory manual.

Measurement of bAb and nAb levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 11.1.6), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize

the immune response to SARS-CoV-2, additional assay development, and the immune response across SARS-CoV-2 viruses.

8.9. Vaccine Effectiveness Assessments and Surveillance for COVID-19 Symptoms

8.9.1. Vaccine Effectiveness Assessments

Vaccine effectiveness for participants will be inferred based on serum Ab responses obtained on Day 85 (28 days after the second injection of mRNA-1273.214 primary series). Inference will be based on assessing the Ab responses against the geometric mean (GM) value of serum Ab and SRR after mRNA-1273 primary series in adults (Study mRNA-1273-P301). The statistical parameters to infer effectiveness are described in Section 3.

8.9.2. COVID-19 Case Definitions

The incidence of COVID-19 will be assessed as an exploratory objective in Part 2 of this study. Active surveillance for COVID-19 and SARS-CoV-2 infection will be performed in both parts of the study (see Table 5 and Table 6).

To be considered as a case of COVID-19, the following case definition must be met:

- The participant must have at least 1 nasal swab (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR AND
- ONE of the following:
  - Fever (temperature ≥ 38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 4 hours)
  - Shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours)
  - Cough (of any duration, including ≤ 48 hours)
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Abdominal pain
  - Nausea or vomiting

- Diarrhea
- Poor appetite/poor feeding

Severe COVID-19:

To be considered severe COVID-19, the following criteria must be met:

- Confirmed COVID-19 as per the COVID-19 case definition, plus any of the following:
  - Meeting criteria for systemic inflammatory response syndrome based on age-specific variables (Table 5) OR
  - Respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation), medical intervention for shock (intravenous fluids, vasopressors, etc), OR
  - Significant acute renal, hepatic, or neurologic dysfunction (Table 6), OR
  - Admission to an ICU or death.

Table 5: Age-specific Cutoffs for Vital Signs and Laboratory Variables

Age Group	Heart Rate, Beats/Min		Respiratory Rate, Breaths/Min	Leukocyte Count, Leukocytes × 10^3/mm^3	Systolic Blood Pressure, mm Hg
	Tachycardia	Bradycardia			
1 month to 1 year	> 180	< 90	> 34	> 17.5 or < 5	< 70
> 1 year to 5 years	> 140	NA	> 22	> 15.5 or < 6	< 70 + (age in years × 2)

Abbreviations: AHA = American Heart Association; NA = not applicable.
Note: Lower values for heart rate or leukocyte count are for the fifth percentile and upper values for heart rate, respiratory rate, or leukocyte count are for the 95th percentile for the age group. Systolic blood pressure values are based on AHA definitions of hypotensive shock for pediatric population.
Source: Goldstein et al 2005 and Topjian et al 2020.

Table 6: Definition of Renal, Liver, and Neurological Dysfunction for Pediatric Population (< 12 years of age)

Acute Renal Dysfunction	• Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours OR • Increase in serum creatinine to ≥ 1.5 × baseline, known or presumed to have occurred within prior 7 days OR • Urine volume ≤ 0.5 mL/kg/hour for 6 hours
Acute Liver Dysfunction	• > 3-fold elevation above the upper normal limit for ALT or AST OR • > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Acute Neurological Dysfunction[a]	ANY of the following: • Loss of sense of smell or taste • Seizures or status epilepticus • Severe headache (preventing normal daily activities) • Persistent difficulty walking or crawling (if crawling/walking before) • Persistent altered awareness or confusion (preventing normal daily activities) • Persistent severe fatigue or weakness (preventing normal daily activities)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase.
Source: [a] LaRovere et al 2021.

Death attributed to COVID-19 is defined as any participant who dies during the study with a cause directly attributed to a complication of COVID-19.

SARS-CoV-2 Infection:

- SARS-CoV-2 infection is defined in participants with SARS-CoV-2 negative at baseline as follows:
  - bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive postbaseline, OR
  - Positive RT-PCR postbaseline.

8.9.3. Surveillance for COVID-19 Symptoms

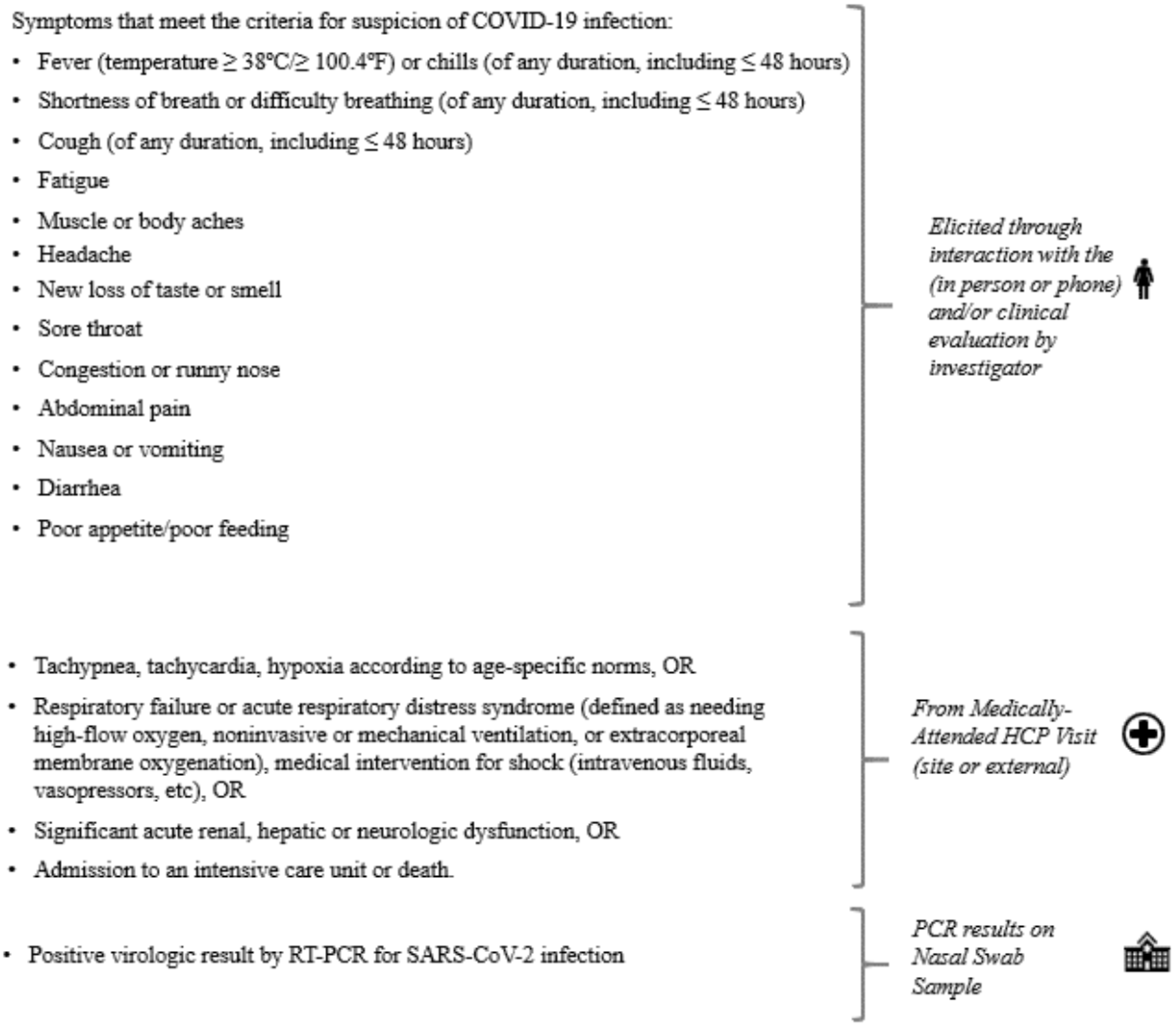
Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary prompts as specified in Section 8.10.2 and Figure 2; starting after participant enrollment and continuing throughout the study.

If there is no response to an eDiary prompt for 2 days, the study site staff will contact the study participant by telephone.

According to the CDC, as of 22 Dec 2020 (CDC 2020a), patients with COVID-19 have reported a wide range of symptoms ranging from mild symptoms to severe illness. Throughout the study, to survey for COVID-19, the following pre-specified symptoms that meet the criteria for suspicion of COVID-19 will be elicited periodically (Section 8.10.2 and Section 8.9.4) from the participant, and the presence of any one of these symptoms (in the absence of an alternative diagnosis) lasting at least 48 hours (except for fever and/or respiratory symptoms) will result in the study site staff arranging an illness visit to collect a nasal swab for SARS-CoV-2 within 72 hours, or as soon as possible thereafter.

- Fever (temperature ≥ 38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours)
- Shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours)
- Cough (of any duration, including ≤ 48 hours)
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Abdominal pain
- Nausea or vomiting
- Diarrhea
- Poor appetite/poor feeding

Figure 2: Surveillance for COVID-19 Symptoms and the Corresponding Clinical Data Pathways



Abbreviations: COVID-19 = coronavirus disease 2019; HCP = healthcare practitioner; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Blood sample for SARS-CoV-2 surveillance not shown in figure.

It is important to note that some of the symptoms of COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1273.214 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common, investigators should use their clinical judgment to decide if a nasal swab should be collected. The collection of a nasal swab prior to the first dose on Day 1, prior to the second dose on Day 57, and then at all subsequent study visits (Day 85, Day 237, and Day 422) can help ensure that cases of COVID-19 are not overlooked. Any study participant who reports respiratory symptoms

during the 7-day period after vaccination without an alternative diagnosis should be evaluated for COVID-19.

For children with febrile illnesses, if an alternative diagnosis is identified (eg, positive urine culture, streptococcal pharyngitis, cellulitis), the investigator may decide to omit the illness visit. Identification of an alternative viral agent (such as respiratory syncytial virus or influenza by rapid testing) does not satisfy this requirement, as co-infections with SARS-CoV-2 may occur.

An investigator may elect to omit the illness visit if standard-of-care testing prior to the illness visit reveals a negative COVID-19 NAAT performed at a CLIA-certified or CLIA-waived laboratory (or a laboratory of equivalent accreditation if the test was done outside the US) and the principal investigator can obtain a copy of the negative test. Home testing kits cannot be used to satisfy this testing requirement. Standard-of-care evaluation of household contacts that reveals a negative COVID-19 is not sufficient to omit an illness visit in the study participant.

During the course of the study, participants with symptoms of COVID-19 will be asked to return within 72 hours or as soon as possible to the study site or trained staff from the study site will conduct a home visit as soon as possible to collect a nasal swab sample (for RT-PCR) for evaluation of COVID-19. Both study site visits and home visits are referred to as illness visits (Section 8.9.3.1).

Cases are defined as participants meeting clinical criteria based both on symptoms for COVID-19 and on RT-PCR detection of SARS-CoV-2 from samples collected within 72 hours of the study participant reporting symptoms meeting the definition of COVID-19. Participants who are hospitalized for COVID-19 without the opportunity for a clinic or home visit will also be considered cases, assuming that the symptomology criteria for COVID-19 are met and a respiratory sample is positive for SARS-CoV-2 by RT-PCR at a certified laboratory.

Investigators are encouraged to try to obtain a respiratory sample during the course of hospitalization or immediately after hospital discharge as an unscheduled visit for submission to the study central laboratory, if feasible. The investigator should determine if the criteria for severe COVID-19 have been met.

Severe COVID-19 is defined in Section 8.9.2.

All clinical findings will be recorded in the eCRF. All confirmed cases of symptomatic COVID-19 will be captured as MAAEs if an illness visit was conducted at the site or if they were evaluated by a healthcare provider, along with relevant concomitant medications and details about severity, seriousness, and outcome, and will be collected throughout the study period (Section 8.11.4).

8.9.3.1. Assessment for SARS-CoV-2 Infection

Study participants will have nasal swab and blood samples collected for SARS-CoV-2 testing at the time points specified in in the SoA (Table 1).

A study illness visit (study site visit or home visit) will be arranged within 72 hours of qualifying symptoms or as soon as possible thereafter if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2022c)
- MAAE suggesting a SARS-CoV-2 infection

At each study illness visit, an initial assessment will be performed to determine general appearance. This initial assessment may be performed by physicians, advanced practice nurses, physician assistants, or registered nurses. If indicated, a physical examination by a study clinician (MD, DO, NP, or PA experienced in pediatric examination) may occur.

The study illness visit (study site visit or home visit) may collect additional clinical information, including assessments such as updated medical history, physical examination, blood sampling for clinical laboratory testing, and nasal swab sampling for viral RT-PCR to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. The study site may also collect an additional nasal swab sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. All findings will be recorded in the eCRF.

Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

If a participant experiences an exposure to an individual in the household confirmed to be infected with SARS-CoV-2 (ie, close contact as defined in Section 8.10.2), an exposure visit (study site visit or home visit) will be arranged approximately 7 days after the contact tests positive. This exposure will be captured in the COVID-19 exposure form. A negative local diagnostic test (NAAT) may be used to satisfy the study visit, provided that the participant remains asymptomatic for COVID-19 and the test is collected at least 5 days after the index case in a household. In accordance with CDC guidance on COVID-19 testing, exposure visits are not required for participants who are within 90 days of a COVID-19 illness (from the date of positive COVID-19 test). Illness visits should still be performed, even if within 90 days of a previous SARS-COV-2 infection, for participants with signs/symptoms consistent with COVID-19.

If participants are confirmed to have SARS-CoV-2 infection by study clinical laboratory testing, the investigator will notify the participant's parent(s)/LAR(s) and the participant's primary care physician of the diagnosis via fax or other Health Information Portability and Accountability Act compliant electronic data transfer (eg, e-mail if applicable). If the study participant does not have

a primary care physician, the investigator will assist them to obtain one. The participant and participant's parent(s)/LAR(s) will also be instructed on infection prevention measures consistent with local public health guidance. Laboratory test results for SARS-CoV-2 infection in study participants should be submitted to state or local public health departments according to local policy. The investigator must either directly report to state or local public health department or obtain confirmation from the participant's primary care physician that the positive test was reported.

Any confirmed symptomatic SARS-CoV-2 infection that occurs in participants assessed at a site visit or by another healthcare provider will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome.

If a participant tests positive at baseline but remains asymptomatic, the second dose may still be administered as long as the participant remains asymptomatic and no other concerns arise.

The following alternative process may be used for assessment of SARS-CoV-2 infection:

- If an illness visit is not feasible due to COVID-19-related restrictions at the site or in the wider community, a telehealth visit or phone call combined with a local diagnostic test (or home visit by site personnel if permitted [Section 4.1.1]) can substitute for a clinic visit.
- There are currently no rapid antigen tests approved for children < 2 years of age.
    - A negative home rapid antigen test must not be taken as a reason to forgo the illness visit.
    - If the participant reports symptoms, or is asymptomatic after a household exposure, and the home rapid antigen test was positive, the investigator should encourage the family to seek confirmatory polymerase chain reaction-based testing at a local testing center or return to the site for an illness visit.
- If a rapid antigen test becomes authorized/approved for children of the participant's age, the participant's parent(s)/LAR(s) may perform a home test rather than obtaining a test performed by an HCP that may be inaccessible due to COVID-19-related restrictions in the community. In such a scenario, the following process should apply:
    - If the participant is asymptomatic but was exposed to a positive household member, and the home test obtained within the appropriate window (at least 5 days post-positive test of household contact) was negative, the investigator may accept this result and forego the illness visit.

- If the participant reports symptoms but the home test was negative, the investigator may forego the illness visit but report the AE as appropriate (eg, upper respiratory infection).
- If the participant reports symptoms, or is asymptomatic after a household exposure, and the home test was positive, the investigator should encourage the family to seek confirmatory polymerase chain reaction-based testing at a local testing center or return to the site for an illness visit.

8.9.4. Follow-up Period After Diagnosis With COVID-19

Any confirmed symptomatic COVID-19 occurring in a participant assessed at a site visit will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. The investigator should determine if the criteria for severe COVID-19 have been met. If the participant is hospitalized, study site personnel will try to obtain medical records and SARS-CoV-2 diagnostic results. If the participant is later discharged from the hospital during the 28-day period following diagnosis of COVID-19, the study site personnel will arrange for a resumption of the protocol schedule.

8.10. Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant, according to the SoA (Table 1):

- Solicited local and systemic ARs (Section 8.11.3) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 8.10.2).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 8.11.1.
- AEs leading to discontinuation from Day 1 through EoS.
- MAAEs (Section 8.11.4) from Day 1 through EoS.
- SAEs (Section 8.11.2) from Day 1 through EoS.
- AESIs (Section 8.11.5) from Day 1 through EoS.
- Assessments for SARS-CoV-2 infection from Day 1 through EoS (Section 8.9.3.1).

8.10.1. Safety Telephone Calls

A safety telephone call is a telephone call made to the participants' parent(s)/LAR(s) by trained study site personnel. This call will follow a script, which will facilitate the collection of relevant

safety information. Safety telephone calls follow a schedule for each participant as indicated in the SoA (Table 1). The participants' parent(s)/LAR(s) will be interviewed according to the script and SoA about the occurrence of AEs, MAAEs, SAEs, AESIs, AEs leading to study withdrawal, concomitant medications associated with those events, and any nonstudy vaccinations (Section 8.11.6). In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. All safety information collected from the telephone contact must be documented in source documents as described by the participant's parent(s)/LAR(s) and not documented on the script used for the safety telephone contact. As noted in Section 8.10.2, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

8.10.2. Use of Electronic Diaries

At the time of consent, participants' parent(s)/LAR(s) must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, participants' parent(s)/LAR(s) will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 8.11.3) on Day 1. Based on availability, smartphone devices may be provided to those participants' parent(s)/LAR(s) who do not have their own device to use for eDiary activities.

At each injection visit, participants' parent(s)/LAR(s) will be instructed (Day 1) or reminded (Day 57) on thermometer (axillary and rectal) usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and assessment for localized axillary swelling or tenderness on the same side as the injection arm/thigh.

At each injection visit, participants' parent(s)/LAR(s) will record data into the eDiary starting approximately 30 minutes after injection under the supervision of the study site staff to ensure successful entry of assessments. The study site staff will perform any retraining as necessary. Participants' parent(s)/LAR(s) will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants' parent(s)/LAR(s) will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 8.11.3, that occur on the day of each vaccine administration and during the 7 days after vaccine administration (ie, the day of injection and 6 subsequent days). Capturing details of ARs in the eDiary should not exceed 7 days after each vaccination. If a solicited local or

systemic AR continues beyond Day 7 after vaccination, the event should be reviewed by the study site staff either via a telemedicine visit/call or at an unscheduled study site visit.

- Body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded. Body temperature must be measured via the axillary route and any axillary reading of ≥ 37.8°C/≥ 100°F may be confirmed by a rectal measurement.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Any medications taken to treat or prevent pain or fever on a day of injection or for the next 6 days.

The eDiary will be the only source document allowed for solicited systemic or local ARs (including body temperature measurements). Participants' parent(s)/LAR(s) will be instructed to complete eDiary entries daily. Quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

Study site staff will review eDiary data with participants' parent(s)/LAR(s) at telemedicine visits 7 days after each injection in both Part 1 and Part 2. eDiary data will also be reviewed during the additional visits 3 days after each injection (ie, on Day 4 and Day 60) in Part 1 only.

The eDiary will be used every 4 weeks, starting at Day 99 through Day 211 and every 8 weeks, starting at Day 265 through Day 377, to capture the occurrence of AEs, MAAEs, SAEs, AESIs, or AEs leading to withdrawal. As specified in the SoA (Table 1), the eDiary will prompt the participant's parent(s)/LAR(s) to complete an eDiary questionnaire that collects the following data:

- Changes in health since last completing the questionnaire or since in contact with the study site
- Any MAAEs, AESIs, or SAEs
- Known close contact with someone in the household who has known COVID-19 or SARS-CoV-2 infection. An infected person can spread SARS-CoV-2 starting 2 days before they have any symptoms (or, for asymptomatic people, 2 days before the positive specimen collection date) through 10 days after symptom onset (or, for asymptomatic

people, 10 days after positive test). Per the CDC, "close contact" to someone with COVID-19 is defined as follows:

  - Being within 6 feet for a total of 15 minutes or more
  - Providing care at home
  - Having direct physical contact (hugged or kissed them)
  - Sharing eating or drinking utensils
  - Being sneezed or coughed upon or getting respiratory droplets on the participant

- Any experience of symptoms of COVID-19

If an eDiary record results in identification of relevant safety events according to the study period or of symptoms of COVID-19, a follow-up telemedicine visit or telephone call will be triggered which may in turn lead to an unscheduled clinic visit for an assessment as per the discretion of the investigator.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 8.10.1) as the procedure for safety follow-up. These safety telephone calls will take place every 4 weeks from Day 113 through Day 225, and every 8 weeks from Day 293 through Day 405 (Table 1).

8.10.3. Blood Sampling Volumes

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed blood limits specified by local regulations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further details are provided in both the ICF and Laboratory Reference Manual.

8.10.4. Safety Laboratory Assessments

No scheduled laboratory assessments for safety are planned. This is based on the absence of clinically significant abnormal laboratory findings in the Phase 1 and Phase 2 studies of mRNA-1273 in adults.

8.10.5. Ancillary Supplies for Participant Use

Study sites will distribute Sponsor-provided axillary and rectal thermometers and rulers for use by participants' parent(s)/LAR(s) in assessing body temperature and injection site reactions for recording solicited ARs in eDiaries. Based on availability, smartphone devices may be provided to those participants' parent(s)/LAR(s) who do not have their own device to use for eDiary activities.

8.11. Safety Definitions and Related Procedures

8.11.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Events Meeting the Adverse Event Definition

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after the first dose of IP even though they may have been present before the start of the study.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Planned procedures (eg, tonsillectomy or pressure-equalization tubes) that occur during the study period but were planned prior to enrollment will not be considered AEs unless complications arise.

An AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 8.11.8). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the vaccine and the AE.

An unsolicited AE is any AE reported by the participant' parent(s)/LAR(s) that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (ie, the day of each injection and 6 subsequent days after injection).

8.11.2. Serious Adverse Events

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- **Death**
  A death that occurs during the study or that comes to the attention of the investigator

during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to the IP.

- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least 1 overnight stay for treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as AEs; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE. Note: 24-hour observation admissions, typically used to extend the period of observation from an emergency department or urgent care visit, will not be considered inpatient hospitalization unless they are converted to hospital admission after the 24 hours of observation have expired.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but that jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.11.3. Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) that occur after IP injection. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 8.10.2). Participant's parent(s)/LAR(s) will record such occurrences in an eDiary on the day of each dose of injection and for the 6 days after the day of dosing.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 7, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Capturing details of ARs in the eDiary should not exceed 7 days after each vaccination. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the event should be reviewed by the study site staff either via a telephone call or an unscheduled study site visit. All solicited ARs (local and systemic) will be considered related to the IP. If a participant's parent(s)/LAR(s) reported a solicited AR during the solicited period and did not record the event in the eDiary, the event should be recorded on the Reactogenicity page of the eCRF. If the event starts during the solicited period, but continues beyond 7 days after dosing, the participant's parent(s)/LAR(s) should notify the site to provide an end date to close out the event on the Reactogenicity page of the eCRF. If the participant's parent(s)/LAR(s) reported an event after the solicited period (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF.

Table 7: Solicited Adverse Reactions and Grades: Age 12 Weeks to < 6 Months

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[1]
Local Reaction					
Injection site pain/tenderness	None	Mild discomfort to touch or some pain but no interference with normal daily activities	Cries when limb is moved/refuses to move limb or pain interferes with normal daily activities	Significant pain at rest or pain prevents normal daily activities	Requires emergency room visit[2] or hospitalization
Injection site erythema (redness)	< 5 mm/ < 0.5 cm	5-20 mm/ 0.5-2.0 cm	> 20-50 mm > 2.0-5.0 cm	> 50 mm/ > 5 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 5 mm/ < 0.5 cm	5-20 mm/ 0.5-2.0 cm	> 20-50 mm > 2.0-5.0 cm	> 50 mm/ > 5 cm	Necrosis

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[1]
Groin or underarm swelling or tenderness ipsilateral to the side of injection	None	Some swelling or tenderness but no interference with normal daily activities	Swelling or tenderness that interferes with normal daily activities	Swelling or tenderness that prevents normal daily activities	Emergency room visit[2] or hospitalization
Systemic Reaction					
Fever	< 38.0°C	38.0-38.4°C 100.4-101.1°F	38.5-39.5°C 101.2-103.1°F	39.6-40.0°C 103.2-104.0°F	> 40.0°C > 104.0°F
Irritability/crying	None	Lasting < 1 hour or easily consolable	Lasting 1 to 3 hours or requiring increased attention	Lasting > 3 hours or inconsolable	Requires emergency room visit[2] or hospitalization
Sleepiness	None	Sleepier than usual or less interested in surroundings	Not interested in surroundings or sleeps through meals	Sleeps most of the time, hard to arouse	Inability to arouse
Loss of appetite	None	Eating less than normal for 1-2 feeds/meals	Missed 1-2 feeds/ meals completely	Missed > 2 feeds/meals completely or refuses most feeds/meals	Requires emergency room visit[2] or hospitalization

Abbreviations: AE = adverse event; eCRF = electronic case report form.
Note: Events listed above but starting > 7 days post-study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the investigator.
1. Grading for Grade 4 events per investigator assessment (with exception of fever).
2. Emergency room visit includes urgent care visit.
Source: Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the study site staff on the solicited AR page of the participant's eCRF:

- Solicited local or systemic AR that results in a visit to an HCP (otherwise meets the definition of an MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days after injection

- Solicited local or systemic AR that leads to participant withdrawal from IP
- Solicited local or systemic AR that otherwise meets the definition of an SAE

8.11.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, abnormal laboratory test result follow-up, COVID-19 [Section 8.9.2]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAE. Unsolicited AEs will be captured on the AE page of the eCRF.

All confirmed symptomatic COVID-19 cases (Section 8.9.2) will be recorded as MAAEs. Any severe COVID-19 cases will be reported to the Sponsor or designee immediately and in all circumstances within 24 hours, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 8.11.10). The investigator will submit any updated COVID-19 case data to the Sponsor within 24 hours of it being available.

All suspected cases of anaphylaxis associated with study drug administration should be recorded as MAAEs and reported as an AESI and SAE, based on criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours as per Section 8.11.10. The investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as described below should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources.

Anaphylaxis is a clinical syndrome characterized by:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involves 2 or more organ systems, as follows:
  - **Skin/mucosal:** urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes

- **Cardiovascular:** measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation
- **Respiratory:** bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea
- **Gastrointestinal:** diarrhea, abdominal pain, nausea, vomiting

8.11.5. Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the investigator to the Sponsor is required and documentation is in the form of a case narrative. Such events may require further investigation to characterize and understand them. Refer to Section 11.2, Appendix 2 for a list of AESIs pertinent to this study. All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI and the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 8.11.10).

8.11.5.1. Acute Myocarditis and/or Pericarditis

The CDC have established diagnostic criteria for probable or confirmed myocarditis, pericarditis, or myopericarditis. The CDC Working Case Definitions are provided in Section 11.3 as guidance. In addition to probable or confirmed cases, cases of suspected myocarditis, pericarditis, or myopericarditis should be reported as AESIs, even if all of the criteria per the CDC Working Case Definitions are not met. Events should also be reported as SAEs if seriousness criteria are met (Section 8.11.10).

An independent CEAC will be utilized and is described in Section 8.12.3.

8.11.5.2. MISC-C

MIS-C Case Definition

Investigators will also be asked to report, as an AESI, clinical signs/symptoms consistent with the CDC case definition of MIS-C (CDC 2020b):

- An individual aged < 21 years presenting with fever (fever ≥ 38.0°C/≥ 100.4ºF for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6; elevated neutrophils; reduced lymphocytes; or low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology (non-S protein-based), or antigen test or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Some participants may fulfill full or partial criteria for Kawasaki disease but it should be reported if they meet the case definition for MIS-C. Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

8.11.6. Recording and Follow-up of an AE and/or SAE

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor.

Solicited ARs will be collected during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Other (unsolicited) AEs will be collected during the 28 days following each injection (ie, the day of injection and 27 subsequent days).

Both MAAEs and SAEs will be collected from participants as specified in the SoA (Table 1) until the end of their participation in the study. Any AEs that occur before administration of IP will be analyzed separately from AEs that occur after vaccine administration.

At every study site visit or telephone contact, participant's parent(s)/LAR(s) will be asked a standard question to elicit any medically-related changes in the participant's well-being (including COVID-19 symptoms). Participant's parent(s)/LAR(s) will also be asked if the participant has been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any nonstudy vaccinations.

In addition to participant observations, physical examination findings or data relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.5).

8.11.7. Assessment of Intensity

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 8.11.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007), modified for use in infants 12 weeks to < 6 months of age (Table 7), will be used to categorize local and systemic reactogenicity events (solicited ARs) and body temperature measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 8.11.3.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity, as follows:

- Mild: These events do not interfere with the participant's daily activities.
- Moderate: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Study staff should elicit from the participant's parent(s)/LAR(s) the impact of AEs on the participant's activities of daily living to assess severity and document it appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and the duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

8.11.8. Assessment of Causality

The investigator's assessment of an AE's relationship to IP is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the IP caused the event) for all AEs and SAEs. The relationship will be characterized using the following classifications:

Not related: There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP OR the temporal sequence of AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by a cause other than the IP.

Related: There is a reasonable possibility of a relationship to the IP. There is evidence of exposure to the IP. The temporal sequence of AE onset relative to the administration of the IP is reasonable. The AE is more likely explained by the IP than by another cause.

8.11.9. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported at the times specified in the SoA (Table 1), regardless of their relationship to IP or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes type of event, time of onset, investigator-specified assessment of severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, any required treatments or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant, including ongoing SAEs after study completion. The MedDRA will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

8.11.10. Reporting SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Any AE considered serious by the investigator or that meets SAE criteria (Section 8.11.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE) via the EDC system. The investigator will assess whether there is a reasonable possibility that the IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities

of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the IRB directly.

If the eCRF is unavailable at the time of the SAE, the paper SAE/AESI report form distributed to the study sites should be completed and sent via e-mail or fax as provided on the forms.

Regulatory reporting requirements for SAEs are described in Section 8.11.14.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs and AESIs, and remain responsible for following up AEs that are serious, considered related to IP or study procedures, or that caused the participant to discontinue the study.

8.11.11. Time Period and Frequency for Collecting AE, AESI, MAAE, and SAE Information

Medical occurrences that begin before the start of IP dosing but after obtaining informed consent/assent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

Adverse events may be collected as follows:

- Observing the participant
- Receiving an unsolicited complaint from the participant's parent(s)/LAR(s)
- Questioning the participant's parent(s)/LAR(s) in an unbiased and nonleading manner

Solicited ARs will be collected from the day of injection through 6 days after each dose. Other (unsolicited) AEs will be collected from the day of injection through 28 days after each dose.

Serious AEs, AESIs, and MAAEs will be collected from the start of IP dosing until the last day of study participation at the time points specified in the SoA (Table 1).

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new SAE or AESI from a study participant or receives updated data on a previously reported SAE or AESI and the eCRF has been taken offline, then the site can report this information on a paper SAE or AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 8.11.10).

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant (eg, leads to dose modification or study drug discontinuation, or meets any serious criteria, or is considered an AESI). If this is the

case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation (EoS). However, if an investigator learns of any SAE, including a death, at any time after a participant has completed or withdrawn from the study, and considers the event to be reasonably related to the study IP or study participation, the investigator must promptly notify the Sponsor.

8.11.12. Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

The investigator is responsible for the documentation of AEs regardless of treatment group or suspected causal relationship to IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant's parent(s)/LAR(s) is the preferred method to inquire about the occurrence of AEs.

8.11.13. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits and contacts.

All AEs, AESIs, MAAEs, and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 7.5.

8.11.14. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious ARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.12. Safety Oversight

Safety monitoring for this study will include the blinded study team members, inclusive of at a minimum, the Sponsor medical monitor and CRO's medical monitor, as well as safety reviews by an unblinded DSMB. The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the DSMB of potential safety signals.

8.12.1. Internal Safety Team

An IST will review safety data throughout the study. Further details of IST review are described in the overall study design Section 4.1. In addition, the IST will escalate any safety concerns to the DSMB. The frequency of IST meetings will be described in more detail in the IST charter.

8.12.2. Data Safety Monitoring Board

The DSMB, composed of external, independent subject matter experts, including an unblinded statistician, will conduct unblinded reviews of safety data on a periodic basis, as defined in a DSMB charter, or as otherwise requested by the study team.

Members of the DSMB will be independent from study conduct and free of conflict of interest. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. Details regarding the DSMB composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

If any of the study pause rules as described in Section 7.4 are met, the Sponsor will immediately suspend further enrollment and/or study dosing and the DSMB will convene on an ad hoc basis. The DSMB will review all available unblinded study data (as applicable) to help adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to

study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

8.12.3. Cardiac Event Adjudication Committee

An independent CEAC that includes pediatric cardiologists will review suspected cases of myocarditis and/or pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, assess severity (Gargano et al 2021), and make recommendations in consultation with the DSMB, if necessary, to the Sponsor. Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis and/or pericarditis will be referred to the Sponsor, who will then make a final decision on whether to suspend further enrollment and/or study dosing based on an assessment of the overall potential risk to study participants.

The CEAC will operate under the rules of an approved charter. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

8.13. Treatment of Overdose

As the study treatment is to be administered by an HCP, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 11.1.8).

8.14. Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.15. Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.16. Biomarkers

Immunogenicity assessments are presented in Section 8.8. Biomarkers will not be evaluated in this study.

9. STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the SAP, which will be finalized before the clinical database lock for the study. If changes are made to primary and/or key secondary objectives and hypotheses or the statistical methods related to those hypotheses after the study has begun but prior to any data unblinding, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

9.1. Blinding and Responsibility for Analyses

Part 1 of this study will be open-label, blinding procedures will not be applicable.

Part 2 of this study will be conducted in an observer-blind manner. The investigator, study staff, study participant's parent(s)/LAR(s), study site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) responsible for vaccine management, documentation, accountability, preparation, and administration (Section 6.2).
- Unblinded study site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that study sites are following all proper IP accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team who are not involved in the design and conduct of the study will perform the primary analyses in Part 2 (Section 9.6.2). Selected Sponsor team members including biostatistician and statistical programmers will be pre-specified to be unblinded to the primary analysis results and will not communicate the results of primary analysis to the blinded investigators, study site staff, clinical monitors, or participants. The details will be included in the Data Blinding Plan.
- The DSMB may review data, as appropriate, to safeguard the interests of clinical study participants and to help ensure the integrity of the study.

The planned study analyses are described in Section 9.6. Procedures for breaking the blind in the case of a medical emergency are provided in Section 6.3.8.

9.2. Statistical Hypotheses

Part 1:

There is no statistical hypothesis to be tested in Part 1.

Part 2:

Primary Hypotheses:

1) H_A^1: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.67).
2) H_A^2: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a noninferiority margin of < 5% (lower bound of CI for SRR > –5%).

Secondary Hypotheses:

3) H_A^3: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is superior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a superiority margin of > 1-fold (lower bound of CI for GMR > 1).
4) H_A^4: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is superior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a superiority margin of > 0% (lower bound of CI for SRR > 0%).
5) H_A^5: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is "super" superior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the VOC (Omicron) with a "super" superiority margin of > 1.5-fold (lower bound of CI for GMR > 1.5).
6) H_A^6: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is "super" superior to the primary series of 100 µg mRNA-1273 in adults based on difference in SRR against the VOC (Omicron) with a "super" superiority margin of > 10% (lower bound of CI for SRR > 10%).
7) H_A^7: The immune response of mRNA-1273.214 against the VOC (Omicron) in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 against the SARS-CoV-2 original strain in adults, based on GMR with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.67).

8) H_A^8: The immune response of mRNA-1273.214 against the VOC (Omicron) in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 against the SARS-CoV-2 original strain in adults, based on difference in SRR with a noninferiority margin of < 5% (lower bound of CI for SRR > –5%).
9) H_A^9: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 in adults based on GMR against the SARS-CoV-2 original strain with a noninferiority margin of 1.5-fold (lower bound of CI for GMR > 0.67).
10) H_A^{10}: The immune response of mRNA-1273.214 in participants 12 weeks to < 6 months is noninferior to the primary series of 100 µg mRNA-1273 against the original strain in adults based on difference in SRR against the SARS-CoV-2 original strain with a noninferiority margin of < 5% (lower bound of CI for SRR > –5%).

9.3. Sample Size and Power Calculation

In Part 2, approximately 600 infant participants 12 weeks to < 6 months of age will be enrolled at the dose level selected for Part 2, with an mRNA-1273.214 to placebo ratio of 1:1. Assuming 10% to 15% participants are not negative SARS-CoV-2 status at baseline, it is estimated that there will be a minimum of approximately 250 evaluable participants in the mRNA-1273.214 arm eligible for immunogenicity analyses.

The sample size of approximately 300 infant participants in the mRNA-1273.214 arm in Part 2 is considered to be sufficient to support a safety assessment. There is at least 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% in this group.

The sample size calculation for each of the 2 primary noninferiority hypothesis tests (H_A^1 and H_A^2) was performed, and the larger sample size was chosen for the study.

- With approximately 250 evaluable participants receiving mRNA-1273.214 in the PPIS-Neg in Study mRNA-1273-P206 and adults (≥ 18 years of age) in Study mRNA-1273-P301, there will be at least 90% power to demonstrate noninferiority of the immune response against Omicron variant, as measured by the GMT, in infant population at a 2-sided alpha of 0.05, compared with that in adults (≥ 18 years of age) in Study mRNA-1273-P301 receiving mRNA-1273, assuming an underlying GMR (which is calculated as ratio of GMT) value of 1 and the standard deviation of the natural log-transformed titer is assumed to be 1.0, and a noninferiority margin of > 0.67.
- With approximately 250 evaluable participants receiving mRNA-1273.214 in the PPIS-Neg in Study mRNA-1273-P206 and adults (≥ 18 years of age) in Study mRNA-1273-P301, there will be at least 90% power to demonstrate noninferiority

of the immune response against Omicron variant as measured by SRR in infants at a 2-sided alpha of 0.05, compared with SRR against Omicron variant in adults ≥ 18 years of age in Study mRNA-1273-P301 receiving mRNA-1273, assuming SRR of 60% to 70% in Study mRNA-1273-P301, true SRR improvement of 10% in infants from Study mRNA-1273-P206 compared with adults from Study mRNA-1273-P301, and a noninferiority margin of 5%.

9.4. Analysis Populations

The analysis populations are defined in Table 8.

Table 8: Populations for Analyses

Analysis Set	Description
Randomization Set	All participants who are randomly assigned in Part 2, regardless of the participants' treatment status in the study.
FAS	Part 1: All enrolled participants in Part 1 who receive at least 1 dose of mRNA-1273.214. Part 2: All randomized participants in Part 2 who receive at least 1 dose of IP.
mITT Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection at baseline (ie, both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid).
mITT-1 Set	All participants in the mITT Set excluding those who received the wrong treatment (ie, at least 1 dose received that is not as randomized).
PP Set	All participants in the FAS who receive planned doses of IP per schedule and are SARS-CoV-2 negative at baseline (ie, both negative RT-PCR test for SARS-CoV-2 and negative serology test) and have no major protocol deviations that impact key or critical data.
Immunogenicity Set	All participants in the FAS who provide immunogenicity samples.
PPIS	Participants in the Immunogenicity Set who receive planned doses of IP per schedule, comply with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. The PPIS will be used for analyses of immunogenicity.

Analysis Set	Description
PPIS-Neg	Participants in the PPIS who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline (ie, both negative RT-PCR test for SARS-CoV-2 and negative serology test). The PPIS-Neg will be the primary analysis set for analyses of immunogenicity.
Safety Set	All enrolled participants in Part 1 and all randomly assigned participants in Part 2 who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for solicited ARs.
Solicited Safety Set	All participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.

Abbreviations: AR = adverse reaction; bAb = binding antibody; FAS = full analysis set; IP = investigational product; mITT = modified intent to treat; mRNA = messenger RNA; PP = per protocol; PPIS = Per-Protocol Immunogenicity Set; PPIS-Neg = Per-Protocol Immunogenicity Set – SARS-CoV-2 Negative; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

9.5. Statistical Analyses

9.5.1. Immunogenicity Analyses

The primary analysis population for immunogenicity will be the PPIS-Neg, unless specified otherwise. The primary objective of Part 2 of this study is to use the immunogenicity response to infer effectiveness of mRNA-1273.214 vaccine administered as 2 doses 8 weeks apart in infants aged 12 weeks to < 6 months at the dose level selected for investigation.

Immunogenicity Analyses for mRNA-1273.214 Primary Series

Immune response as measured by GMT value and SRR in the infant group based on Ab levels will be compared to that in adult (≥ 18 years of age) participants from Study mRNA-1273-P301 using Ab data. The immunogenicity data from participants who are assigned to the same dose level in Part 1 and Part 2 of this study may be combined for the immunogenicity analyses.

To assess the difference in immune response between the infant participants in Study mRNA-1273-P206 at 28 days after the last dose of mRNA-1273 primary series compared to the adult (≥ 18 years of age) participants in Study mRNA-1273-P301 at Day 57, an analysis of covariance model will be carried out with Ab as dependent variable and a group variable (an mRNA-1273 arm/group of Study mRNA-1273-P206 versus participants in Study mRNA-1273-P301) as the fixed variable for each participant arm/group, the analysis may adjust for key characteristics such as age, sex, etc. The GMT value of mRNA-1273.214 arm at 28 days after the last dose of mRNA-1273.214 primary series and GMT value of mRNA-1273 at Day 57 (28 days after the second dose of primary series) in Study mRNA-1273-P301 will be

estimated by the GLSM from the model. The GMR (which is calculated as ratio of GMT) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI of GMR will also be provided.

The noninferiority of GMT of mRNA-1273.214 primary series compared with mRNA-1273 primary series will be considered demonstrated if:

- The lower bound of the 95% CI of the GMR (the infant participants in Study mRNA-1273-P206 at 28 days after the last dose of mRNA-1273.214 primary series, compared with the participants in Study mRNA-1273-P301 at Day 57) > 0.67 based on the noninferiority margin of 1.5.

In addition, the GMT of antibodies with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed titer values then back transformed to the original scale. Descriptive summary statistics for GMT including median, minimum, and maximum will also be provided.

The GM fold rise of specific antibodies with corresponding 95% CI at each post-baseline time point over pre-Dose 1 baseline at Day 1 will be provided. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

The number and percentage of participants with seroresponse due to vaccination will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point with Day 28 after the last dose of mRNA-1273.214 primary series being of the primary interest in the analyses, where seroresponse is defined as a titer change from baseline (pre-Dose 1) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

The SRR difference with 95% CI (using Miettinen-Nurminen score method) between infants receiving mRNA-1273.214 primary series in Study mRNA-1273-P206 at 28 days after the last dose of mRNA-1273.214 primary series and adult participants receiving mRNA-1273 primary series in Study mRNA-1273-P301 at Day 57 will be provided.

The noninferiority of seroresponse of mRNA-1273.214 primary series in Study mRNA-1273-P206 compared with mRNA-1273 primary series in Study mRNA-1273-P301 will be considered demonstrated if:

- The lower bound of the 95% CI of the SRR difference is > –5% based on the noninferiority margin of 5%.

Hypothesis Testing Strategy for Immunogenicity:

The hypothesis tests for noninferiority, superiority, and "super" superiority of mRNA-1273.214 against Omicron as compared to mRNA-1273 primary series against Omicron will be performed sequentially. The noninferiority hypotheses (hypotheses H_A^1 and H_A^2) will be tested first.

Once noninferiority is demonstrated based on both GMT and SRR, superiority (hypotheses H_A^3 and H_A^4) of mRNA-1273.214 as compared to mRNA-1273 primary series will be tested. If the lower bound of the 95% CI of the GMR is > 1, superiority based on GMT is demonstrated; if the lower bound of the 95% CI of the SRR difference is > 0%, superiority based on seroresponse is demonstrated.

Once superiority is demonstrated based on both GMT and SRR, "super" superiority (hypotheses H_A^5 and H_A^6) of mRNA-1273.214 as compared to mRNA-1273 primary series will be tested. If the lower bound of the 95% CI of the GMR is > 1.5, "super" superiority based on GMT is demonstrated; if the lower bound of the 95% CI of the SRR difference is > 10%, "super" superiority based on seroresponse is demonstrated.

9.5.2. Safety Analyses

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by vaccination group (dose levels of mRNA-1273.214 and placebo).

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESIs, and AEs leading to discontinuation from IP and/or study participation.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection by toxicity grade will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, severe AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be summarized. Unsolicited AEs will be presented by MedDRA preferred term and system organ class.

Solicited AR events (starting within 7 days after any injection) that are serious or lasting beyond Day 7 after any injection will also be reported as unsolicited AEs.

The number of events of solicited ARs, unsolicited AEs/SAEs, MAAEs, severe AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided, and Table 9 summarizes the analysis strategy for safety endpoints. Further details will be described in the SAP.

Table 9: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any solicited AR (overall and by local, systemic)	X	X
Any unsolicited AE	X	–
Any SAE	X	–
Any unsolicited MAAE	X	–
Any unsolicited treatment-related AE	X	–
Any treatment-related SAE	X	–
Discontinuation due to AE	X	–
Any severe AE	X	–
Any treatment-related severe AE	X	–
Any AESI	X	–

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Note: 95% CI using the Clopper-Pearson method. X = results will be provided. Solicited ARs and unsolicited AEs will be summarized by SOC and PT coded by MedDRA.

9.5.3. Exploratory Analyses

The exploratory analyses of the effectiveness of mRNA-1273.214 will evaluate the incidence of COVID-19, SARS-CoV-2 infection regardless of symptomatology or severity, severe COVID-19, etc.

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273.214 or placebo, the incidence rate will be provided by vaccination group, calculated as the number of cases divided by the total person-time.

For serologically confirmed SARS-CoV-2 infection or COVID-19, regardless of symptomatology or severity, infection rate will be provided by vaccination group. The same analysis will be performed for asymptomatic SARS-CoV-2 infection.

The exploratory analyses of the effectiveness will be performed primarily on the PP Set, unless specified otherwise. Sensitivity analyses for effectiveness will be performed on other select analysis sets, eg, mITT and/or mITT-1.

For the exploratory analyses for mRNA-1273.214 against other variants of interests, the same analyses methods described in Section 9.5.1 will be employed to analyze immunogenicity data. More details of exploratory analyses will be described in the SAP before database lock.

9.5.4. Subgroup Analyses

Subgroup analyses will be performed in select subgroups including but not limited to the following subgroups:

- Sex (male, female)
- SARS-CoV-2 status at baseline
- Maternal immunization status
- Race
- Ethnicity

Details of subgroups analyses will be provided in the SAP.

9.6. Planned Analyses

9.6.1. Interim Analyses

- For Part 1, interim analyses of safety and immunogenicity will be performed after all treated participants in one or both arms have completed 28 days after the last dose of the primary series of mRNA-1273.214.
- For Part 2, an interim analysis of safety and immunogenicity will be performed after all participants have completed 28 days after the last dose of the primary series of mRNA-1273.214. This interim analysis will be considered the primary analysis for immunogenicity.

9.6.2. Final Analysis

The final analysis of all endpoints will be performed after participants have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings.

Additional information about all study analyses may be provided in the SAP.

10. REFERENCES

Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, et al. Decreased severity of disease during the first global Omicron variant COVID-19 outbreak in a large hospital in Tshwane, South Africa. Int J Infect Dis. 2022;116:38-42.

Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1(1):3-14.

Ayoub HH, Chemaitelly H, Seedat S, Mumtaz GR, Makhoul M, Abu-Raddad LJ. Age could be driving variable SARS-CoV-2 epidemic trajectories worldwide. PLoS One. 2020;15(8):e0237959.

Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142(5):429-436.

Centers for Disease Control and Prevention (CDC). COVID-19: Symptoms of COVID-19 [Internet]. 2020a [updated 2020 Dec 22; cited 2021 Jan 29]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.

Centers for Disease Control and Prevention (CDC). Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) [Internet]. 2020b [updated 2020 Mar 27; cited 2022 May 04]. Available from: https://emergency.cdc.gov/han/2020/han00432.asp.

Centers for Disease Control and Prevention (CDC). COVID Data Tracker [database on the Internet]. Atlanta (GA): US Department of Health and Human Services. 2022a – [cited 2022 Apr 21]. Available from: https://covid.cdc.gov/covid-data-tracker/#datatracker-home.

Centers for Disease Control and Prevention (CDC). Demographic Trends of COVID-19 cases and deaths in the US reported to CDC [database on the Internet]. Atlanta (GA): US Department of Health and Human Services. 2022b - [cited 2022 April 20]. Available from: https://covid.cdc.gov/covid-data-tracker/#demographics.

Centers for Disease Control and Prevention (CDC). Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States [database on the Internet]. Atlanta (GA): US Department of Health and Human Services. 2022c - [cited 2022 April 20]. Available from: https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance.

Centers for Disease Control and Prevention (CDC). United States Trends in Emergency Department (ED) Visits [database on the Internet]. Atlanta (GA): US Department of Health and Human Services. 2022d - [cited 2022 April 20]. Available from: https://covid.cdc.gov/covid-data-tracker/#ed-visits.

Chalkias S, Eder F, Essink B, Khetan S, Nestorova B, Feng J, et al. Safety, Immunogenicity and Antibody Persistence of a Bivalent Beta-Containing Booster Vaccine. Research Square. Preprint posted online April 15, 2022. https://doi.org/10.21203/rs.3.rs-1555201/v1.

Delahoy MJ, Ujamaa D, Whitaker M, O'Halloran A, Anglin O, Burns E, et al; and COVID-NET Surveillance Team. Hospitalizations Associated with COVID-19 Among Children and Adolescents - COVID-NET, 14 States, March 1, 2020–August 14, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(36):1255-60.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September 2007 [cited 2022 May 04]. Available from: https://www.fda.gov/media/73679/download.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (US). Guidance for industry, investigators, and institutional review boards: Conduct of clinical trials of medical products during the COVID-19 public health emergency. March 2020 [updated 2021 Jan 27; cited 2021 Jan 29]. Available from: https://www.fda.gov/media/136238/download.

Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-4.

Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med. 2020;383(4):347-58.

Ferdinands JM, Rao S, Dixon BE, Mitchell PK, DeSilva MB, Irving SA, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance - VISION Network, 10 States, August 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(7):255-63.

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, 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):977-82.

Goga A, Bekker LG, Garrett N, Reddy T, Yende-Zuma N, Fairall L, et al. Breakthrough COVID-19 infections during periods of circulating Beta, Delta and Omicron variants of concern, among health care workers in the Sisonke Ad26.COV2.S vaccine trial, South Africa. medRxiv. Preprint posted online December 22, 2021. Available from: https://doi.org/10.1101/2021.12.21.21268171.

Goldstein B, Giroir B, Randolph A; and Members of the International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2-8.

LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M, et al; and Overcoming COVID-19 Investigators. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021;78(5):536–47.

Halasa NB, Olson SM, Staat MA, Newhams MM, Price AM, Boom JA, et al; and Overcoming COVID-19 Investigators. Effectiveness of Maternal Vaccination with mRNA COVID-19 Vaccine During Pregnancy Against COVID-19-Associated Hospitalization in Infants Aged < 6 Months – 17 States, July-2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71(7):264–70.

Havers FP, Whitaker M, Self JL, Chai SJ, Kirley PD, Alden NB, et al; and COVID-NET Surveillance Team. Hospitalization of Adolescents Aged 12–17 Years with Laboratory-Confirmed COVID-19 – COVID-NET, 14 States, March 1, 2020–April 24, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(23):851-7.

Hay JA, Haw DJ, Hanage WP, Metcalf JE, Mina MJ. Implications of the age profile of the novel coronavirus. Digital Access to Scholarship at Harvard. 2020. Available from: http://nrs.harvard.edu/urn-3:HUL.InstRepos:42639493.

Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al; and COVID-NET Surveillance Team. Hospitalization Rates and Characteristics of Children Aged < 18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8.

Marks KJ, Whitaker M, Anglin O, Milucky J, Patel K, Pham H, et al; and COVID-NET Surveillance Team. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, July 2021–January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(7):271-8.

Martin MA, VanInsberghe D, Koelle K. Insights from SARS-CoV-2 sequences. Science. 2021;371(6528):466-7.

Paediatric Intensive Care Society (PICS). PICS Statement: Increased number of reported cases of novel presentation of multi-system inflammatory disease. 27 April 2020. Available at https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf.

Pajon R, Doria-Rose NA, Shen X, Schmidt SD, O'Dell S, McDanal C, et al. SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination. N Engl J Med. 2022;386(11):1088-91.

Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al; and Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84.

Shook LL, Atyeo CG, Yonker LM, Fasano A, Gray KJ, Alter G, et al. Durability of anti-spike antibodies in infants after maternal COVID-19 vaccination or natural infection. JAMA. 2022;327(11):1087-9.

Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner BL Jr, et al; and Pediatric Basic and Advanced Life Support Collaborators. Part 4: Pediatric basic and advanced life support: 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2020;142(16_suppl_2):S469-S523.

Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med. 2022;28(5):1063-71.

UNICEF. COVID-19 confirmed cases and deaths. Updated March 2022. Available from: https://data.unicef.org/resources/covid-19-confirmed-cases-and-deaths-dashboard/.

United Kingdom Health Security Agency (UKHSA). SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing: Update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529). December 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045619/Technical-Briefing-31-Dec-2021-Omicron_severity_update.pdf.

Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawaski-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771-8.

World Health Organization (WHO). Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV) [Internet]. Geneva, Switzerland: WHO; 2020 January 30 [cited 2022 May 04]. Available

from: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020 [Internet]. Geneva, Switzerland: WHO; 2020 March 11 [cited 2022 May 04]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al; and Overcoming COVID-19 Investigators. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12-18 Years - United States, July-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52-8.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. APPENDIX 1: Study Governance Considerations

11.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

11.1.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This

will be documented in a clinical study agreement between the Sponsor, designated CRO, and the investigator.

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the Clinical Monitoring Plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the investigational site, for the following purposes:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the SAE Hotline, and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

11.1.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow the Sponsor, their designee(s), the IRB, or regulatory authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and any IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP (R2), and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The principal investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

11.1.4. Financial Disclosure

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The Sponsor, the CRO, and the study site are not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor, the CRO, and the study site are not financially responsible for further treatment of the disease under study.

11.1.5. Recruitment Strategy

Enrollment targets will be established to ensure the participant population reflects those that are most at risk for the condition, or those that are most reflective of the general population, if appropriate.

Participant recruitment and retention initiatives will be incorporated into the trial. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical trial sites, participant support services such as concierge, and trial information and support collateral for both the participant and the site. Advertisements to be

used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant's parent(s)/LAR(s) should be submitted to the Sponsor for approval. All documents must be approved by the IRB.

11.1.6. Informed Consent Process

The informed consent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study site. All consent documents will be approved by the appropriate IRB. The actual ICF used at each site may differ, depending on local regulations and IRB requirements. However, all versions of the ICF must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB prior to the ICF being used.

If new information becomes available that may be relevant to the participant's parent(s)/LAR(s) willingness to continue participation of their child in the study, this will be communicated to them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF

The investigator or his/her representative will explain the nature of the study to the participant's parent(s)/LAR(s) and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant's parent(s)/LAR(s) fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. The participant's parent(s)/LAR(s) must be informed that participation is voluntary. The participant's relatives, guardians, or (if applicable) LARs must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

The participant's parent(s)/LAR(s) must be allowed sufficient time to decide whether they wish to let their child participate in the study.

The participant's parent(s)/LAR(s) must be made aware of, and give consent to, direct access to the participant's source medical records by study monitors, auditors, the IRB, and regulatory authorities. The participant's parent(s)/LAR(s) should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant's parent(s)/LAR(s) should also be informed that they are authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participant's parent(s)/LAR(s).

Parent(s)/LAR(s) of a participant who is rescreened (allowed once) are not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date (within the initial screening period).

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoVs.

11.1.7. Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor. Approval of the IRB is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by the Sponsor, agreed by the investigator(s), and approved by the relevant IRB(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IRB(s) must be provided to the Sponsor before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the investigator(s), and notified to the IRB(s).

11.1.8. Protocol Deviations

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report protocol deviations to the Sponsor or its designee. All protocol deviations must be addressed in

study source documents and reported to the study monitor. Protocol deviations must be sent to the reviewing IRB per their policies. The study site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

11.1.9. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant's parent(s)/LAR(s) must be informed that the participant's personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/LAR(s).

The participant's parent(s)/LAR(s) must be informed that the participant's medical records may be examined by clinical QA auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being. Each participant's parent(s)/LAR(s) will be asked to complete a form allowing the investigator to notify the participant's primary healthcare provider of his/her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant's parent(s)/LAR(s), except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

11.1.10. Sample Retention and Future Biomedical Research

ModernaTX, Inc. may store samples for the time frame specified in the ICF to achieve study objectives and to address further scientific questions related to mRNA-1273.214 or anti-respiratory virus immune response. In addition, identifiable samples can be destroyed at any

time at the request of the participant's parent(s)/LAR(s). During the study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other Ab-based methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled and samples collected and stored in Part 1 or Part 2. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1273.214, as well as to determine how changes in biomarkers may relate to exposure and clinical outcomes. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

11.1.11. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), etc., as well as some national registries.

In addition, results from clinical trials are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available, the privacy of participants in clinical studies sponsored by the Sponsor is ensured. Details on data sharing criteria and the process for requesting access can be found at this web address: clinicalstudydatarequest.com.

11.1.12. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checks of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CRO).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as described in Section 11.1.15. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A QA representative from the Sponsor or a qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

11.1.13. Data Collection and Management

This study will be conducted in compliance with ICH CGP guidelines. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the study site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using WHODrug Dictionary.

11.1.14. Source Documents

Source documents are original documents or certified copies, and include, but are not limited to, eDiaries, medical and hospital records, screening logs, ICFs, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's study site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Sponsor or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents such as any hospital, clinic, or office charts and the signed ICFs are to be included in the investigator's files with the participant's study records.

11.1.15. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is < 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

11.1.16. Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to the following:

- Continuation of the study represents a significant medical risk to participants.
- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further mRNA-1273.214 development.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

11.1.17. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

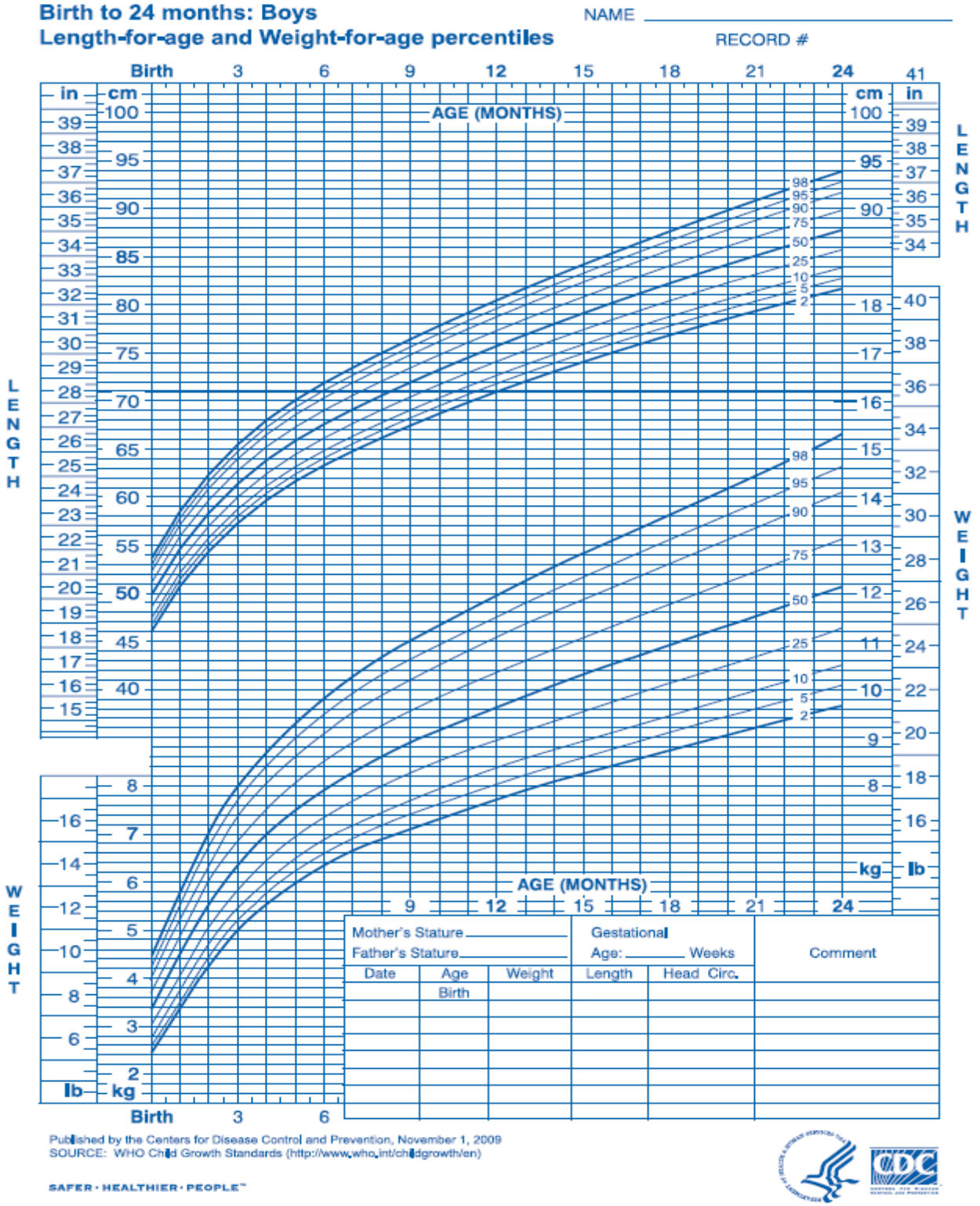
The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

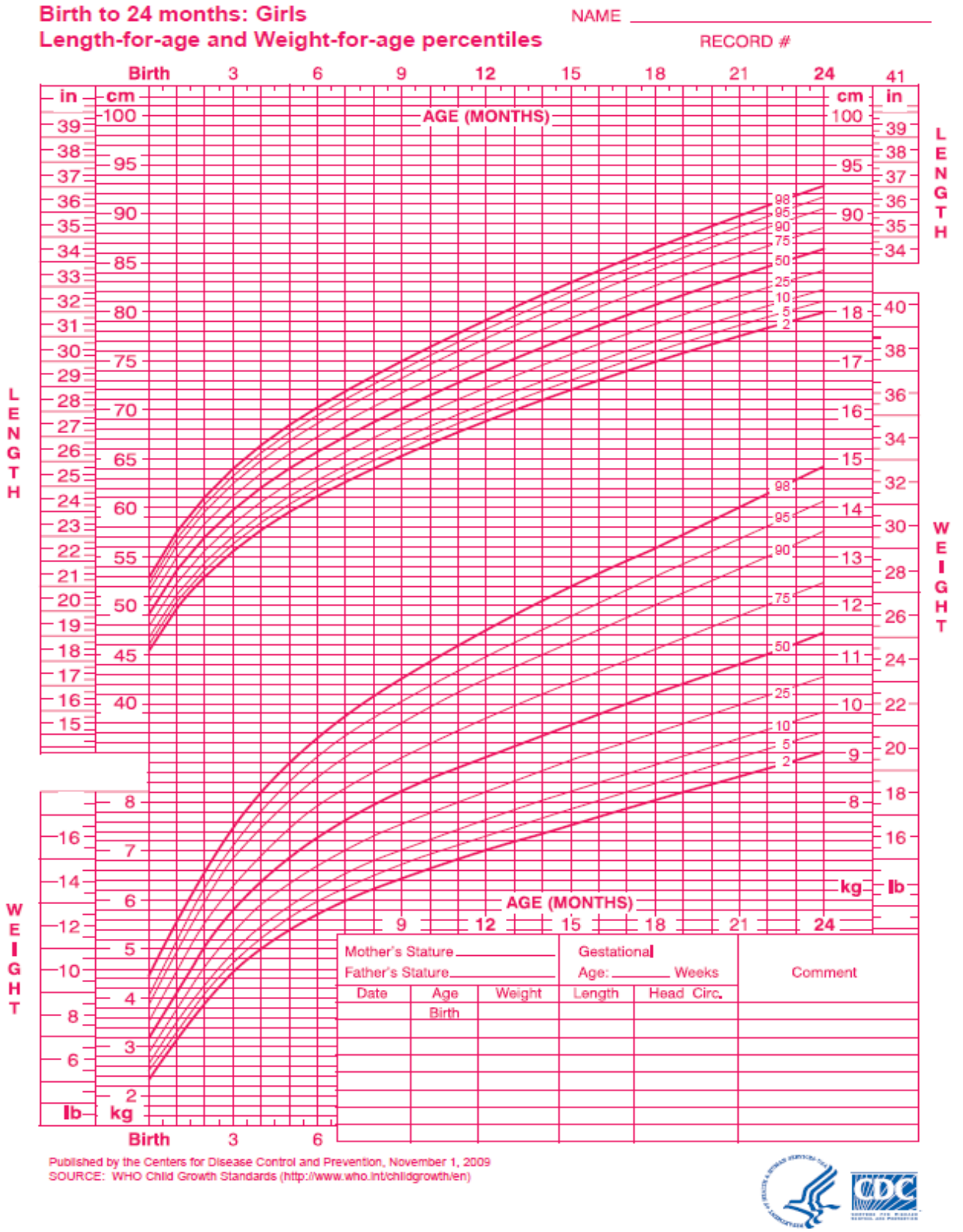
The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

11.1.18. Height and Weight Chart for Boys and Girls

For boys from birth to 2 years



For girls from birth to 2 years



11.2. APPENDIX 2: Adverse Events of Special Interest Terms

The investigator's medical judgement must be applied to assess an event as an AESI, as most AESIs are based on medical concepts. Table 10 does not provide a comprehensive list of terms.

Table 10 describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below (Table 10) should be reported as AESIs, per the reporting processes specified in Section 8.11.5, even when they occur during/following COVID infection.

It should be noted that COVID-19 itself is not an AESI.

Table 10: Adverse Events of Special Interest

Medical Concept	Medical Concept Descriptions/Guidance
Anosmia, ageusia	• New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology • DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
Subacute thyroiditis	• Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) • DOES NOT INCLUDE new onset of chronic thyroiditis
Acute pancreatitis	• New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	• Any event of appendicitis
Rhabdomyolysis	• New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute respiratory distress syndrome	• New onset of ARDS/respiratory failure due to acute inflammatory lung injury

Medical Concept	Medical Concept Descriptions/Guidance
	• DOES NOT INCLUDE non-specific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
Coagulation disorders	• New onset of thrombosis, thromboembolic event, or non-traumatic hemorrhage/bleeding disorder (eg, stroke, DVT, pulmonary embolism, DIC, etc)
Acute cardiovascular injury	• New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia confirmed by ECG (eg, atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. • DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute kidney injury	• New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc.; • Increase in serum creatinine by ≥ 0.3 mg/dL (or ≥ 26.5 µmol/L) within 48 hours; OR • Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days
Acute liver injury	• New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc.; • > 3-fold elevation above the upper normal limit for ALT or AST; OR • > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions

Medical Concept	Medical Concept Descriptions/Guidance
	• Single organ cutaneous vasculitis • Erythema multiforme • Bullous rash • Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, fixed drug eruptions, and necrotic or exfoliative reactions
Systemic inflammatory syndromes	• MIS-A or MIS-C • Kawasaki's disease • Hemophagocytic lymphohistiocytosis
Thrombocytopenia	• Platelet count < 150 $\times 10^9$/L (thrombocytopenia) • New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture, and/or PCR • DOES NOT INCLUDE new onset of chronic arthritic conditions
New onset, or worsening, of neurological disease	• Immune-mediated neurological disorders • Guillain-Barre syndrome • Acute disseminated encephalomyelitis • Peripheral facial nerve palsy (Bell's palsy) • Transverse myelitis • Encephalitis/encephalomyelitis • Aseptic meningitis

Medical Concept	Medical Concept Descriptions/Guidance
	• Seizures/convulsions/epilepsy • Narcolepsy/hypersomnia
Anaphylaxis	• Anaphylaxis associated with study drug administration
Other syndromes	• Fibromyalgia • Postural orthostatic tachycardia syndrome • Chronic fatigue syndrome • Myalgic encephalomyelitis • Post viral fatigue syndrome • Myasthenia gravis

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; COVID-19 = coronavirus disease 2019; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; HELLP = hemolysis, elevated liver enzymes, and low platelets; MIS-A = multisystem inflammatory syndrome in adults; MIS-C = multisystem inflammatory syndrome in children; PCR = polymerase chain reaction.

11.3. APPENDIX 3: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

The investigator's medical judgment must be applied when parent(s)/LAR(s) report that a participant has symptoms concerning for myocarditis and/or pericarditis contained within the CDC case definition. Diagnostic evaluation (eg, electrocardiogram, echocardiogram) and laboratory testing (eg, troponin) included in the CDC definition (Table 11) must promptly be obtained in any participant with concerning signs/symptoms. Referral to a pediatric cardiologist should be obtained in those with positive test results or clinically significant symptoms without other identifiable causes. Additional testing and evaluation may be indicated. The investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available.

Table 11: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	**Definition**	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥ 1 new or worsening of the following clinical symptoms:	Presence of ≥ 1 new or worsening of the following clinical symptoms:
	• chest pain, pressure, or discomfort	• chest pain, pressure, or discomfort
	• dyspnea, shortness of breath, or pain with breathing	• dyspnea, shortness of breath, or pain with breathing
	• palpitations	• palpitations
	• syncope	• syncope
	OR, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:	OR, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:
	• irritability	• irritability
	• vomiting	• vomiting
	• poor feeding	• poor feeding
	• tachypnea	• tachypnea

Condition	Definition	
	• lethargy	• lethargy
	AND	AND
	≥ 1 new finding of:	≥ 1 new finding of:
	• troponin level above upper limit of normal (any type of troponin)	• Histopathologic confirmation of myocarditis[a]
	• abnormal ECG or EKG or rhythm monitoring findings consistent with myocarditis[b]	
	• abnormal cardiac function or wall motion abnormalities on echocardiogram	• cMRI findings consistent with myocarditis[c] in the presence of troponin level above upper limit of normal (any type of troponin)
	• cMRI findings consistent with myocarditis[c]	
	AND	AND
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings
Acute pericarditis[d]	Presence of ≥ 2 new or worsening of the following clinical features:	
	• acute chest pain[e]	
	• pericardial rub on examination	
	• new ST-elevation or PR-depression on EKG	
	• new or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

Abbreviations: AV = atrioventricular; CEAC = cardiac event adjudication committee; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging.
Note: An independent cardiac event adjudication committee (CEAC; see Section 8.12.3) comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet Center for Disease Control and Prevention criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
[a.] Using the Dallas criteria (Aretz et al 1987).

b. 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.
c. Using either the original or the revised Lake Louise criteria (https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon).
d. https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon.
e. 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.

Reference: Gargano et al 2021.

Signature Page for CCI [redacted]

2nd Approval	PPD 22-Jun-2022 13:13:03 GMT+0000

Signature Page for CCI [redacted]