Protocol

Protocol for: Creech CB, Anderson E, Berthaud V, et al. Evaluation of mRNA-1273 Covid-19 vaccine in children 6 to 11 years of age. N Engl J Med. DOI: 10.1056/NEJMoa2203315

This trial protocol has been provided by the authors to give readers additional information about the work.

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original statistical analysis plan, final statistical analysis plan (summary of changes for statistical analysis plan is integrated in summary of changes in final statistical analysis plan)

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age
Protocol Number:	mRNA-1273-P204
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	Brett Leav, MD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: 1-617-682-2724 e-mail: Brett.Leav@modernatx.com
Regulatory Agency Identifier Number(s):	IND: 019745
Approval Date:	24 Feb 2021

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title: A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age

Protocol Number: mRNA-1273-P204

Protocol Date: 24 Feb 2021

Protocol accepted and approved by:

See esignature and date signed on last page of document

Brett Leav, MD
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ModernaTX, Inc
200 Technology Square
Cambridge, MA 02139
Telephone: 1-617-682-2724

Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol titled "A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age" 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 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	

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1273 for injection

Name of Active Ingredient: mRNA-1273

Protocol Title: A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age

Protocol Number: mRNA-1273-P204

Study Period (years): Approximately 14 months

Phase of Development: Phase 2/3

Estimated date first participant enrolled: 15 Mar 2021

Estimated date last participant completed: 12 Jun 2023

Total Number of Sites: Approximately 75 to 100 study sites in the United States and Canada.

Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of up to 3 dose levels (25, 50, and 100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart in 3 age groups	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESIs, including MIS-C, through the entire study period

• To infer the efficacy of mRNA-1273 (25, 50, and 100 µg, administered as 2 doses 28 days apart) based on immunogenicity in 3 age groups	• The proportion of participants with a serum Ab level at Day 57 ≥ Ab threshold of protection[1] • The GM value of serum nAb level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301)[2] 1. If an accepted serum nAb threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy 2. If a threshold is not available, efficacy will be inferred by establishing noninferiority among 6-month-old to < 12-year-old participants (Study P204) to 18- to 25-year-old participants (Study P301) by both GM value of serum nAb level and seroresponse rate. A definition of seroresponse will be provided in the statistical analysis plan based on forthcoming information about assay performance.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 µg) administered as 2 doses 28 days apart	• The GM values of SARS-CoV-2 S protein-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2) • The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)

• To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or RT-PCR) starting 14 days after the second dose of IP Seroconversion due to SARS-CoV-2 will be measured by bAb against SARS-CoV-2 nucleocapsid protein. – Participants seronegative at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein from below the LOD at Day 1 that increase to equal to or above LOD starting 14 days after the second dose of IP. In addition, any postbaseline positive RT-PCR results (symptom-prompted or prescheduled tests) will be counted as SARS-CoV-2 infection.
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR of nasal swabs and/or serology tests obtained at prescheduled study visits
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with COVID-19 AND positive RT-PCR for SARS-CoV-2	• The incidence of the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria: – The participant must have at least 1 nasal swab (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR AND – Either o The participant must have experienced at least TWO of the following systemic symptoms: fever (≥ 38ºC/≥ 100.4ºF), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new

	loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding OR o The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence
• To describe the ratio or profile of specific S protein bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb titers in serum
• 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 assess, in a subset of participants, the SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points after vaccination relative to baseline

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; GM = geometric mean; IP = investigational product; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralizing antibody; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Overall Study Design

This is a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study intended to infer the effectiveness of mRNA-1273 in children aged 6 months to < 12 years. The study population will be divided

into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years), and up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 will be evaluated.

The study will be conducted in 2 parts. Part 1 of the study will be open label and consist of dose escalation and age de-escalation in 750 participants to select the dose for each age group (the table below provides the number of participants in each age group). Part 2 of the study will be placebo-controlled observer-blind evaluation of the selected dose in 6,000 participants (2,000 participants in each age group). No participants in Part 1 will participate in Part 2 of the study.

The study will begin with the oldest age group (6 to < 12 years) and age de-escalate. Each age group will begin with Part 1 and advance to Part 2. The mRNA-1273 investigational vaccine or placebo will be administered as 2 intramuscular (IM) injections approximately 28 days apart.

The mRNA-1273 dose levels that will be evaluated in each age group in Part 1 and Part 2 of the study are given in the following table. Only the 6 month to < 2 year age group will receive the 25 µg dose level.

	Part 1			**Part 2**	
Age Group	**mRNA-1273 25 µg**	**mRNA-1273 50 µg**	**mRNA-1273 100 µg**	**Selected Dose Level of mRNA-1273 From Part 1**	**Placebo**
6 to < 12 year		Study Arm 1 (n=75)	Study Arm 2 (n=75)	Study Arm 8 (n=1,500)	Study Arm 9 (n=500)
2 to < 6 year		Study Arm 3 (n=75)	Study Arm 4 (n=75)	Study Arm 10 (n=1,500)	Study Arm 11 (n=500)
6 month to < 2 year	Study Arm 5 (n=150)	Study Arm 6 (n=150)	Study Arm 7 (n=150)	Study Arm 12 (n=1,500)	Study Arm 13 (n=500)

Part 1 of the study will be open label. The study will begin with enrollment of 75 participants in the 6 to < 12 year age group (Study Arm 1), and dosing with 50 µg of mRNA-1273. After the 75 participants in Study Arm 1 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an internal safety team (IST) will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 6 to < 12 year age group (Study Arm 2; n=75) and independently whether to begin dosing at the 50 µg dose level in the 2 to < 6 year age group (Study Arm 3; n = 75). After the 75 participants in Study Arm 1 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will again review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 2 and whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 3. Once the 150 participants from Study Arms 1 and 2 reach Day 57 (1 month

after Dose 2 of mRNA-1273 50 and 100 µg, respectively), an interim analysis will be conducted to review the tolerability and immunogenicity data. This analysis will result in the selection of either the 50 or 100 µg mRNA-1273 dose level and expansion of the 6 to < 12 year age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 8; n = 1,500) or placebo (Study Arm 9; n = 500). The primary analysis of safety and immunogenicity for Study Arms 8 and 9 will be conducted after all participants reach Day 57.

Similarly, after 75 participants in Study Arm 3 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an IST will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 2 to < 6 year age group (Study Arm 4; n = 75) and whether to begin dosing in the 6 month to < 2 year age group at the 25 µg dose level (Study Arm 5; n = 150). After the 75 participants in Study Arm 3 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 4 and whether to administer Dose 2 of mRNA-1273 25 µg in Study Arm 5. Once all participants in Study Arms 3 and 4 reach Day 57 (1 month after Dose 2 of mRNA-1273 50 and 100 µg, respectively), an interim analysis will be conducted to review tolerability and immunogenicity data. This analysis will result in the selection of either the 50 or 100 µg mRNA-1273 dose level and expansion of the 2 to < 6 year age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 10; n = 1,500) or placebo (Study Arm 11; n = 500). The primary analysis of safety and immunogenicity for Study Arms 10 and 11 will be conducted after all participants reach Day 57.

In Study Arm 5, after 150 participants have completed Day 8 (1 week after Dose 1 of mRNA-1273 25 µg), an IST will review the available safety data and provide a recommendation whether to escalate the dose to 50 µg (Study Arm 6; n = 150). After 150 participants in Study Arm 6 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an IST will review the safety data and provide a recommendation whether to escalate the dose to 100 µg (Study Arm 7; n = 150). After the 150 participants in Study Arm 5 reach Day 36 (1 week after Dose 2 of mRNA-1273 25 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 6. After the 150 participants in Study Arm 6 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 7. Once all participants in Study Arms 5, 6, and 7 reach Day 57 (1 month after Dose 2 of mRNA-1273 25, 50, and 100 µg, respectively), an interim analysis will be conducted to review the tolerability and immunogenicity data. This analysis will result in selection of the 25, 50, or

100 µg mRNA-1273 dose level and expansion of the 6 month to < 2 year age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 12; n = 1,500) or placebo (Study Arm 13; n = 500). The primary analysis of safety and immunogenicity for Study Arms12 and 13 will be conducted after all participants reach Day 57.

In general, if a decision is made not to proceed with administration of a second dose in a given arm (eg, due to safety concerns), the second injection will likely be given at a lower dose level and the higher dose level in question will not be administered in the younger age group(s).Within an age group, if one of the dose levels is found to have an unacceptable tolerability profile, the age group may progress to Part 2 at a lower dose level based on Day 57 interim analysis of the tolerated dose level(s).

The final analysis will be performed when all participants (Study Arms 1 to 13) conclude the safety follow-up.

The goal of the study is to support an indication for use of mRNA-1273 50 or 100 µg IM, given as 2 injections, approximately 28 days apart in the 2 to < 6 year and 6 to < 12 year age groups and mRNA-1273 25, 50, or 100 µg IM, given as 2 injections, approximately 28 days apart in the 6 month to < 2 year age group. The basis for demonstrating vaccine effectiveness is proposed to be met by measuring serum neutralizing antibody (nAb) responses in the study participants. The approach to inferring vaccine effectiveness will depend on whether an accepted serum nAb threshold conferring protection against coronavirus disease 2019 (COVID-19) has been established. If a nAb threshold of protection has been established, effectiveness will be inferred based on the proportion of study participants with serum nAb levels (on Day 57) that meet or exceed the nAb threshold. If a nAb threshold of protection has not been established, effectiveness will be inferred based on demonstrating noninferiority among 6-month-old to < 12-year-old participants (Study P204) to young adult (18 to 25 years of age) participants enrolled in the ongoing clinical endpoint efficacy trial (Study P301) by both geometric mean (GM) values and seroresponse rate.

This study in children 6 months to < 12 years of age will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. Safety assessments will include solicited adverse reactions (ARs) (7 days after each injection), unsolicited adverse events (AEs; 28 days after each injection), and medically attended adverse events (MAAEs), serious AEs (SAEs), and adverse events of special interest (AESIs; including multisystem inflammatory syndrome in children [MIS-C]) throughout the study period.

Blood samples will be collected from participants in Part 1 and Part 2 of the study for assessment of immunogenicity. If a Day 1 (Baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability

to satisfy inclusion criteria 3 or could be rescheduled for rescreening (allowed once) within the screening period. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3. Participants in Part 1 of the study will provide blood specimens for immunogenicity on Day 1 (prior to the first dose) and 1, 6, and 12 months after the second dose of mRNA-1273. Participants in each age group in Part 2 will be assigned to 1 of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1 (prior to randomization and before the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and before the first dose). A fifth cohort of participants (selected Vaccine and Treatment Evaluation Units [VTEU] sites only) will provide blood samples for assessment of exploratory serology and cell-mediated immunity (CMI; spike [S]-protein-specific T-cell responses) on Day 1 (prior to randomization and before the first dose), Day 43, Day 209, and Day 394. Blood samples will also be tested for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients.

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. For Part 1 dose escalation and age de-escalation, based on the review of all available safety data through Day 7 (1 week after Dose 1 of mRNA-1273) and beyond for all participants at each dose level within the 6 to < 12 year and 2 to < 6 year age group, the IST will recommend whether dose escalation and age de-escalation are appropriate. This process will then be repeated for all participants in the 25, 50, and 100 µg dose levels within the lower age group of 6 months to < 2 years of age. An IST review on Day 36 (1 week after Dose 2 of mRNA-1273 at each dose level) will be required prior to the administration of the second injection of the next higher dose. 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 the study conduct and free of conflict of interest. The DSMB will meet on a regular basis to assess safety throughout the study conduct. Recruitment will continue, as applicable, during the DSMB review period. 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 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 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.

Study Duration: The study duration for each participant will be approximately 14 months, which includes 1 month for screening (Day -28 to Day -1), 1 month for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose of investigational product (IP).

Number of Participants:

Part 1: 750 participants (approximately 150 participants each in the 6 to < 12 year and 2 to < 6 year age groups and approximately 450 participants in the 6 month to < 2 year age group).

Part 2: 6,000 participants (approximately 1,500 participants each in the 6 to < 12 year, 2 to < 6 year, and 6 month to < 2 year age group exposed to mRNA-1273 and 500 participants each in the 6 to < 12 year, 2 to < 6 year, and 6 month to < 2 year age group exposed to placebo).

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, 6 months to < 12 years of age at the time of

consent/assent (Screening Visit), who is in good general health, in the opinion of the investigator, based on review of medical history and screening physical examination.

2. If the participants has a chronic disease (eg, asthma, diabetes mellitus, cystic fibrosis, human immunodeficiency virus [HIV] infection), the disease should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion. Stable diseases are those which have had no change in their status or in the medications required to control them in the 6 months prior to Screening Visit.

   Note: a change in medication for dose optimization (eg, insulin dose changes), change within class of medication, or reduction in dose are not considered signs of instability.

3. In the investigator's opinion, the parent(s)/legally acceptable representative(s) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures, and provide written informed consent and participants are willing to provide assent.

4. The participant has a body mass index at or above the third percentile according to WHO Child Growth Standards at the Screening Visit.

5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche.

Special inclusion criteria for female participants who have reached menarche:

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all of the following criteria:

   - Has a negative pregnancy test at Screening. Pregnancy test will be performed if deemed appropriate by the investigator.
   - Has practised adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
   - Has agreed to continue adequate contraception or abstinence through 3 months following the second injection (Day 29).
   - Is not currently breastfeeding.

   Adequate female contraception is defined as abstinence or consistent and correct use of a US Food and Drug Administration-approved contraceptive method in accordance with the product label.

Special inclusion criteria for children 6 months to < 2 years of age:

7. The participant was born at full-term (≥ 37 weeks gestation) with a minimum birth weight of 2.5 kg.

Exclusion Criteria:

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

1. Has a known history of SARS-CoV-2 infection within 2 weeks prior to administration of IP or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of IP.
2. Is acutely ill or febrile 24 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. Has previously been administered an investigational or approved CoV (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome-CoV) vaccine.
4. Has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (eg, receipt of SARS-CoV-2 monoclonal antibodies) within 6 months prior to enrollment.
5. 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 a previous dose of messenger RNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG] or immediate allergic reaction of any severity to polysorbate).
6. Has a medical or psychiatric condition 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. Has a history of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically the following:
    - Congenital or acquired immunodeficiency, excluding HIV infection, as described in Inclusion Criteria 2
    - Chronic hepatitis or suspected active hepatitis
    - A bleeding disorder that is considered a contraindication to IM injection or

phlebotomy

- Dermatologic conditions that could affect local solicited AR assessments
- Any prior diagnosis of malignancy (excluding nonmelanoma skin cancer)
- Febrile seizures

8. Has received the following:
   - Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to first vaccination or plans to receive such a vaccine through 14 days following the last study vaccination.
   - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 1 mg/kg/day or ≥ 10 mg/day prednisone equivalent, if participant weighs > 10 kg). 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.
   - Intravenous or subcutaneous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment.
9. 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.
10. Is an immediate family member, or household contact, of an employee of the study site or Moderna 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.

Study Treatment:

Investigational Product:

The term IP refers to mRNA-1273 (25, 50, and 100 μg) vaccine or placebo (0.9% sodium chloride) in this study.

mRNA-1273 is a lipid nanoparticle (LNP) dispersion of an mRNA that encodes the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with PEG of average molecular

weight 2000 (1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000 [PEG2000-DMG]). mRNA-1273 injection is provided as a sterile liquid for injection and is a white to off-white dispersion at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

Mode of Administration:

Each participant will receive 2 doses of IP by IM injection approximately 28 days apart (Day 1 and Day 29) into the deltoid muscle or anterolateral thigh (per investigator's discretion).

Procedures and Assessments:

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 eDiaries.
- Unsolicited 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 dosing and/or study participation from Day 1 through the last day of study participation.
- MAAEs from first dose on Day 1 through the entire study period.
- SAEs from first dose on Day 1 through the entire study period.
- AESIs including MIS-C through the entire study period.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

Immunogenicity Assessments:

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

- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays.

- Serum binding antibody (bAb) titer as measured by enzyme-linked immunosorbent assay specific to the SARS-CoV-2 S protein.
- For Part 1, testing for serologic markers for SARS-CoV-2 infection using a nonvaccine antigen-based blood test at Day 1 (prior to the first dose), Day 57, Day 209, and Day 394.
- For Part 2, participants in each age group will be assigned to 5 phlebotomy cohorts. Blood sampling will be performed in 3 of these 5 cohorts for immunogenicity at 3 of the following time points: Day 1 (prior to randomization and the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, and Day 394. Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and the first dose). A fifth cohort of participants at selected VTEU sites only, will provide blood samples for assessment of exploratory serology and CMI on Day 1 (prior to randomization and the first dose), Day 43, Day 209, and Day 394.

Efficacy Assessments:

Vaccine effectiveness for children 6 months to < 12 years of age will be inferred based on serum nAb responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the nAb responses against the following:

1. *If available at the time of analysis*, nAb responses will be assessed against an accepted serum nAb threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, noninferiority of the geometric mean (GM) value of serum nAb and seroresponse rate of children 6-month-old to < 12-year-old (Study P204) compared with the GM value of serum nAb and seroresponse rate from young adults (18 to 25 years of age) enrolled in the ongoing clinical endpoint efficacy trial (Study P301) will be assessed.

Statistical Methods:

Hypothesis Testing:

If an accepted nAb threshold of protection against COVID-19 is established for the primary immunogenicity endpoint, the null hypothesis is that the percentage of participants on mRNA-1273 with serum nAb above the established threshold at Day 57 is $\leq 70\%$ (ie, H_0: percentage of participants on mRNA-1273 with serum nAb at Day 57 above the established threshold $\leq 70\%$).

For each age group, the study will be considered to meet the immunogenicity endpoint if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 70% (lower bound of the 95% CI is > 70%).

The null hypotheses may be updated when the information on an acceptable nAb threshold becomes available. In this case, the null hypothesis update will be provided in the statistical analysis plan (SAP).

If an accepted serum nAb threshold of protection against COVID-19 is not available for the primary immunogenicity endpoint, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 nAb levels will be compared to Day 57 nAb levels from young adults (18 to 25 years of age) in Study P301. Noninferiority tests of 2 null hypotheses based on 2 coprimary endpoints will be performed, respectively.

Coprimary endpoint 1: nAb GM value at Day 57

The null hypothesis H^1_0: immunogenicity response to mRNA-1273, as measured by nAb GM value at Day 57, is inferior in children (in age groups 6 months to < 2 years, 2 to < 6 years, and 6 to < 12 years) compared with that in young adults (18 to 25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in nAb GM value in children compared with that in young adults (18 to 25 years of age) is demonstrated by the lower bound of the 95% CI of the geometric mean ratio (GMR) ruling out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5. The GMR is the ratio of the GM value of SARS-CoV-2-specific nAb in children in an age group receiving mRNA-1273 in this Study P204 compared with the GM value of young adults (18 to 25 years of age) receiving mRNA-1273 in Study P301 at Day 57.

Coprimary endpoint 2: nAb seroresponse at Day 57

A definition of seroresponse will be provided in the statistical analysis plan (SAP) based on forthcoming information about assay performance.

The null hypothesis H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in children compared with that in young adults (18 to 25 years of age) in Study P301.

The noninferiority in seroresponse rate in children compared with that in young adults (18 to 25 years of age) is demonstrated by the lower bound of the 95% CI of the seroresponse rate difference ruling out -10% (ie, lower bound > -10%) using the noninferiority margin of 10%. The seroresponse rate difference is defined as the seroresponse rate in children receiving

mRNA-1273 minus the seroresponse rate in young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301.

The study would be considered to meet the primary immunogenicity endpoint in an age group if the noninferiority in the age group compared with the young adults (18 to 25 years of age) is demonstrated based on both coprimary endpoints.

Power and Sample Size:

The initial age groups in Part 1 are for estimation purposes. With 150 participants each in the initial 6 to < 12 year and 2 to < 6 year age groups and approximately 450 participants in the 6 month to < 2 year age group exposed to a dose level of mRNA-1273, there is at least a 90% probability to observe at least 1 participant with an AE at a true AE rate of 2.5%.

The sample size in the expansion (Part 2) is considered to be sufficient to support a safety database in pediatric participants 6 months to < 12 years of age. With approximately 4,500 participants exposed to mRNA-1273 across the 3 age groups in Part 2, the study has at least a 90% probability to observe at least 1 participant with an AE at a true 0.2% AE rate.

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group will be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset will be processed, and the analysis of primary immunogenicity endpoint will be based on the Immunogenicity Per-Protocol (PP) Subset.

If a threshold of protection is available, for the primary immunogenicity endpoint, with approximately 289 participants on mRNA-1273 in the Immunogenicity PP Subset of an age group, there will be at least 90% power to rule out 70% with a 2-sided 95% CI (lower bound of the 95% CI > 70%) for the percentage of mRNA-1273 participants exceeding the accepted threshold if the true rate of participants exceeding the threshold is 80%.

If an acceptable nAb threshold of protection against COVID-19 is not available at the time of analysis for the primary immunogenicity endpoint, noninferiority tests of the 2 null hypotheses based on the 2 coprimary endpoints, respectively, will be performed. The sample size calculation for each of the 2 noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be 90% power to demonstrate noninferiority of the immune response, as measured by the nAb GM value, in pediatric population at a 2-sided alpha of 0.05, compared with that in young adults (18 to 25 years of age) in Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1 and a

noninferiority margin of 0.67 (or 1.5). The standard deviation of the natural log-transformed levels is assumed to be 1.5.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in children at a 2-sided alpha of 0.05, compared with that in young adults 18 to 25 years of age in Study P301 receiving mRNA-1273, assuming seroresponse rate of 85% in young adults of 18 to 25 years of age from Study P301, true seroresponse rate of 85% in children (or true rate difference is 0 compared to young adults from Study P301), and a noninferiority margin of 10%.

Assuming approximately 25% of participants in the Immunogenicity Subset will not meet the criteria to be included in the Immunogenicity PP subset, approximately 528 participants in Part 2 (~396 receiving mRNA-1273 and ~132 receiving placebo) will be selected for the Immunogenicity Subset from which approximately 289 participants on mRNA-1273 will be suitable for the Immunogenicity PP subset.

Analysis Sets:

The analysis sets are defined in the following table:

Analysis Set	Description
Randomization Set	Part 2: All participants who are randomly assigned, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	Part 1: All enrolled participants in Part 1 who receive at least 1 injection of IP Part 2: All randomly assigned participants who receive at least 1 injection of IP
Per-Protocol (PP) Set	All participants in the FAS who receive planned doses of IP per schedule, comply with the immunogenicity schedule, and have no major protocol deviations that impact key or critical data. Participants who are RT-PCR positive or seropositive at Baseline will be excluded from the PP Set. The PP Set in Part 1 will be used for all analyses of immunogenicity in Part 1 unless specified otherwise.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity sampling and testing.

Per-protocol Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset 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. Participants who are RT-PCR positive or seropositive at Baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for all analyses of immunogenicity unless specified otherwise.
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	The Solicited Safety Set consists of participants in the Safety Set who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at Baseline
Modified Intent-to-Treat-1 (mITT1) 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)

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; IP = investigational product; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 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 and placebo) and by age group. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level will be combined for safety analysis.

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, AEs leading to discontinuation, and physical examination findings.

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.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Immunogenicity Analyses:

The primary analysis population for immunogenicity will be the Immunogenicity PP Subset, unless specified otherwise. The primary objective of this study is to use the immunogenicity response to infer efficacy in participants aged 6 months to < 12 years at the dose level selected for expansion. For this objective, analyses of immunogenicity will be performed for each pediatric age group separately at the selected dose level based on the participants in the Immunogenicity PP Subset. For each pediatric age group, participants from Part 1 and Part 2 in the Immunogenicity PP Subset who receive the same mRNA-1273 dose level selected for expansion will be combined for immunogenicity analyses. If the same dose level is selected for expansion for more than one age group, these age groups may be combined for immunogenicity analyses.

An accepted nAb threshold of protection against COVID-19 may be available based on data from other mRNA-1273 studies or external data. If such a threshold of protection against COVID-19 is available, the number and percentage of participants with nAb greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. For an age group, if the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity endpoint of this study will be considered to be met for that age group.

The number and percentage of participants with serum nAb greater than or equal to the threshold with 2-sided 95% CI will be provided at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum nAb threshold of protection against COVID-19 is not established, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 nAb levels will be compared to that in young adults (18 to 25 years of age) using data from Study P301. An analysis of covariance model will be carried out with nAb at Day 57 as dependent variable and a group variable (pediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable for each pediatric age group. The GM values of the pediatric age group at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI will be provided to assess the difference in immune response between the pediatric age group (Study P204) compared to the young adults (18 to 25 years of age) in Study P301 at Day 57. For each pediatric age group, the noninferiority of GM value will be considered demonstrated if the lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5.

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 postbaseline time point with Day 57 being the primary interest. The seroresponse rate difference with 95% CI at Day 57 will be provided between children receiving mRNA-1273 in Study P204 and young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301. For each pediatric age group, the noninferiority of seroresponse rate will be considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is > -10% based on the noninferiority margin of 10%.

In addition, the GM value of anti-SARS-CoV-2-specific Ab 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 values then back transformed to the original scale. For each age group, the geometric mean fold-rise of specific nAb and bAb with corresponding 95% CI at each postbaseline time point over preinjection baseline at Day 1 will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided.

Efficacy Analyses:

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, dose level, and age group, calculated as the number of cases divided by the total person-time. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level (if applicable) will be combined in the analysis.

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

The secondary efficacy analyses will be performed in the PP set, with sensitivity analyses in FAS, mITT Set, and mITT1 Set.

Study Analyses:

Interim Analyses:

Part 1: Interim analyses will be performed after all participants in Part 1 within each age group and dose level have completed Day 57. Analyses of safety and immunogenicity will be conducted at each analysis and these interim results will be used to decide the expansion dose in Part 2 for each age group.

Part 2: An interim analysis of immunogenicity and safety will be performed after all participants assigned to the Immunogenicity Subset have completed Day 57 (1 month after the second dose) in Part 2 within an age group. This interim analysis will be considered the primary analysis of immunogenicity for a given age group. Another interim analysis on safety may be performed after a subset or all participants have completed Day 57 in an age group.

Final Analysis:

The final analysis of all endpoints will be performed after all 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.

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LIST OF ABBREVIATIONS AND TERMS

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

Abbreviation or Specialist Term	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CD	cluster of differentiation
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMI	cell-mediated immunity
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	data safety monitoring board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ERD	enhanced respiratory disease
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Definition
GLSM	geometric least squares mean
GM	geometric mean
GMR	geometric mean ratio
GMT	geometric mean titer
HCP	healthcare practitioner
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IgG	immunoglobulin G
IM	intramuscular(ly)
IND	investigational new drug
IP	investigational product
IRB	institutional review board
IST	internal safety team
LAR	legally acceptable representative
LNP	lipid nanoparticle
LOD	limit of detection
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
mRNA	messenger RNA
nAb	neutralizing antibody(ies)
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases

Abbreviation or Specialist Term	Definition
PEG	polyethylene glycol
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000
PP	per protocol
QA	quality assurance
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike
S2P	S protein stabilized with 2 proline mutations
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SoA	schedule of assessments
Study P301	Study mRNA-1273-P301; NCT04470427
Th	T helper cell
VTEU	Vaccine and Treatment Evaluation Units
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. INTRODUCTION

1.1. Study Rationale

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). Coronaviruses are zoonotic, meaning that they are transmitted between animals and people. An outbreak of the CoV disease 2019 (COVID-19) caused by SARS coronavirus 2 (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 215 other countries, territories, and areas, including the United States (WHO 2020a). On 11 Mar 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic. As of 30 Jan 2021, the WHO dashboard (WHO 2020b) reported that there have been more than 2.1 million COVID-19 deaths worldwide. As of 29 Jan 2021, the US Centers for Disease Control and Prevention (CDC) reported over 25 million cases of COVID-19 in all 50 states and 5 jurisdictions, with 431,619 attributed and probable deaths (CDC 2020a). While the CDC reports that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease, a substantial burden in children is now being recognized. Evidence is emerging (described below) to suggest that children < 18 years of age, particularly adolescents, may be disproportionately contributing to the number of new cases as schools re-open at varying degrees of in-person learning. As of 29 Jan 2021, the CDC reported 2,125,186 cases of COVID-19 in children less than 18 years of age (11.1% of all US cases) and 267 deaths (approximately 0.1% of all US deaths; CDC 2020b).

During incubation, those infected can also transmit the virus before developing symptoms (Chen et al 2020). Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual, whether symptomatic or not (Chen et al 2020; Licciardi et al 2020; Rothan and Byrareddy 2020; Shen et al 2020). SARS-CoV-2 can also be transmitted via the fecal-oral pathway (Cruz and Zeichner 2020).

During the COVID-19 pandemic, children throughout much of the world have had school attendance limited in an attempt to control infection. Therefore, the main source of infection for SARS-CoV-2 in children, with or without clinical symptoms, is infected household contacts. Indeed, a retrospective cohort study of high school students, parents and siblings of students, teachers, and staff conducted in France in early April 2020 suggests that there was little to no transmission from infected students to other students or school staff. Rather, a high prevalence of antibodies against SARS-CoV-2 among families suggests familial clustering of COVID-19 cases (Fontanet et al 2020).

A recent report of COVID-19 trends in school-aged children in the United States from 01 Mar 2020 to 19 Sep 2020 indicates that 37% of laboratory-confirmed cases of COVID-19 in school-aged children occurred in children 5 to 11 years of age while 63% occurred in adolescents 12 to 17 years of age (Leeb et al 2020). The weekly incidence among adolescents was 37.4 cases per 100,000 compared with 19.0 cases per 100,000 for younger children. Among school-aged children with laboratory-confirmed COVID-19, 58% reported at least one symptom and 5% reported no symptoms, although information on symptoms was missing or unknown for 37%. Overall, 1.2% of school-aged children with COVID-19 were hospitalized, 0.1% required intensive care unit (ICU) admission, and < 0.01% died of COVID-19. Furthermore, at least one underlying condition was reported in 3% of adolescents and 2% of younger children. Chronic lung disease, including asthma, was most commonly reported (55%), followed by disability (neurologic or neurodevelopmental disorders, intellectual or physical disability, and vision or hearing impairment; 9%), immunosuppressive conditions (7%), diabetes (6%), psychological conditions (6%), cardiovascular disease (5%), and severe obesity (4%) (Leeb et al 2020). Based on the COVID-NET report, in 42.3% of children with at least 1 underlying condition, the most prevalent conditions were obesity (37.8%), chronic lung disease (18.0%), and prematurity (15.4%) (Kim et al 2020). Of particular interest is the phenomenon known as multisystem inflammatory syndrome in children (MIS-C) that was first described in critically ill children with SARS-CoV-2 infection and a Kawasaki syndrome (PICS 2020). Since those early reports, a number of articles have been published describing a hyperinflammatory syndrome with features of Kawasaki disease in children and adolescents infected with SARS-CoV-2 (Belhadjer et al 2020; Dufort et al 2020; Verdoni et al 2020). Targeted surveillance in the United States from March through May 2020 revealed 186 patients across 26 states who met a prespecified case definition of MIS-C (Feldstein et al 2020). The median age was 8.3 years (interquartile range: 3.3 to 12.5 years). Most (73%) were previously healthy, and 70% were positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) or antibody testing. The condition affected a variety of organ systems, most commonly the gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory systems. More recently, the Brighton Collaboration has drafted a manuscript proposing case definitions of MIS-C based on 5 levels of diagnostic certainty (Vogel et al 2020).

Evidence suggests that there is substantial burden of COVID-19 in younger age groups. Another study examined the age distribution of COVID-19 in the United States from May to August 2020 based on 3 indicators: COVID-19-like illness-related emergency department visits, positive RT-PCR results for SARS-CoV-2, and confirmed COVID-19 cases (Boehmer et al 2020). These authors report an estimated mean COVID-19 incidence during this time period of 179.3 cases per 100,000 in individuals 10 to 19 years of age. Finally, a recent report describes an adolescent (13-year-old female), whose only symptom was nasal congestion, yet she was the index case in an outbreak of COVID-19 linked to a family gathering that ultimately crossed 4 states and included

5 households and 11 individuals (Schwartz et al 2020). A June COVID-19 outbreak in a Georgia overnight camp demonstrated that children 6 to 19 years of age are susceptible to SARS-CoV-2 infection and transmission (Szablewski et al 2020). In addition, in the second half of July, Rhode Island childcare programs reported 52 confirmed and probable childcare-associated COVID-19 cases, 30 (58%) cases of which were among children with a median age of 5 years (Link-Gelles et al 2020). This suggests that adolescents and children can serve as the source of COVID-19 outbreaks, even when their symptoms are mild, as in these cases.

There is currently no approved vaccine against SARS-CoV-2 for children. In December 2020, following review of safety and efficacy data observed to date, the Food and Drug Administration (FDA) granted emergency use authorization (EUA) to 2 mRNA-based SARS-CoV-2 vaccines, including mRNA-1273, for adults. 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.

The objective for this Phase 2/3 study is to evaluate the safety, tolerability, reactogenicity, and effectiveness of up to 3 dose levels (25, 50, and 100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart (Section 3.1) to healthy children 6 months to < 12 years of age divided into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years). Another Phase 2/3 study to evaluate the safety and reactogenicity of a single dose level (100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart to an adolescent population (12 to < 18 years of age) is ongoing.

1.2. Background and Overview

The Sponsor has developed a rapid-response proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is based on the principle and observations that cells *in vivo* can take up mRNA, translate it, and then present viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. Messenger RNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (NCT03382405), human metapneumovirus and parainfluenza virus type 3 (NCT03392389), and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). mRNA-1273 encodes for the full-length spike (S) protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S2P). It has been confirmed that the stabilized SARS-CoV-2 S2P expresses well and is in the prefusion conformation (Wrapp et al 2020). The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target

for neutralizing antibodies (nAb) that prevent infection (Corti et al 2015; Wang et al 2015; Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019; Corbett et al 2020a; Ju et al 2020; Robbiani et al 2020).

1.2.1. Nonclinical Studies

The National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center and the Sponsor performed nonclinical studies in young and aged wild-type mice, Syrian Golden hamsters, and rhesus macaques (nonhuman primates [NHPs]) to evaluate dose-ranging responses to mRNA-1273 (immunogenicity) and high-dose virus SARS-CoV-2 challenge (protection) and to address the theoretical concern of enhanced respiratory disease (ERD) mediated by vaccine-induced antibody responses and/or T helper cell (Th) 2-directed T-cell responses observed with other vaccines against viral respiratory diseases (Graham 2020).

Nonclinical animal studies demonstrated that mRNA-1273 is immunogenic in all species assessed, with a dose-dependent response in immunoglobulin G (IgG) binding antibody (bAb) titers and a correlation that is statistically significant between binding and neutralizing antibody (Ab) activity. In addition, antigen-specific T-cell responses were observed in studies in mice and NHPs. The Th1-directed cluster of differentiation (CD) 4 and CD8 T-cell responses were measured post boost in animals that were vaccinated with mRNA-1273. In various animal models, immunological measurements suggested that Th1 responses predominated, IgG2a/c/IgG1 ratios were favorable, and high levels of SARS-CoV-2 nAb were observed, suggesting that ERD after mRNA-1273 administration would be unlikely. In addition to measuring the immune response, mice, hamsters, and NHPs were challenged with high-dose SARS-CoV-2 virus. In these studies, dose levels were included that were predicted to be optimal (fully protective) and suboptimal (subprotective). At higher doses, mice and NHPs were fully protected from viral replication in both lungs and nasal passages. At subprotective dose levels, animals either remained fully protected or had reduced viral lung burden post challenge versus control animals (Corbett et al 2020a; Corbett et al 2020b).

Overall, nonclinical animal studies demonstrated that mRNA-1273 is safe and well tolerated, is immunogenic, fully protects animals from challenge at optimal dose levels, and does not result in ERD at protective or subprotective dose levels.

In support of the development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

A detailed review of nonclinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.2.2. Clinical Studies

The mRNA-1273 vaccine is currently being evaluated in 4 ongoing trials.

The first is a safety and immunogenicity Phase 1 study (NCT04283461) sponsored and conducted by the Division of Microbiology and Infectious Diseases (DMID; investigational new drug [IND] application 019635) of the NIAID. The Phase 1 study is an open-label dose-ranging study of mRNA-1273 in healthy adult male and nonpregnant female participants in 3 age groups: 18 to 55 years, inclusive (60 participants); 56 to 70 years, inclusive (30 participants); and ≥ 71 years (30 participants). Participants were randomly assigned to 1 of 4 dose levels of mRNA-1273: 25 µg, 50 µg, 100 µg, and 250 µg. Each participant received the same dose by intramuscular (IM) injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle. Blood samples were obtained at Baseline, Days 8, 15, 29 (prior to Dose 2), 36, 43, and 57, as well as 3, 6, and 12 months after the second vaccination (Days 119, 209, and 394, respectively). Safety monitoring is ongoing for 12 months after the second injection.

On 14 Jul 2020, a preliminary report of findings in this Phase 1 study through Day 57 for the 18- to 55-year age cohort (25, 100, and 250 µg dosage groups) was published (Jackson et al 2020). After the second injection, serum viral neutralizing activity was detected by 2 methods in all 42 participants evaluated (of 45 enrolled), with values that were comparable to or greater than the geometric mean titers (GMT) measured in the convalescent serum samples. Regarding safety, no serious adverse events (SAEs) were reported and no study-halting rules were triggered. In general, solicited systemic adverse reactions (ARs) were more common after the second injection. Solicited ARs that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. While none of the participants (N=45) at any dose level experienced fever following the first dose, mild fever was observed in 5 participants (33%), moderate fever was observed in 1 participant (6.7%), and no participants experienced severe fever at 100 µg following the second dose. Data on 40 older adults > 55 years of age who received 2 doses of either 25 or 100 µg in the same Phase 1 DMID study were recently published (Anderson et al 2020). After the second injection, serum neutralizing activity was detected in all participants by multiple methods with binding and neutralizing Ab titers similar to those reported in adults 18 to 55 years of age and above the median for convalescent serum. Solicited ARs were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Specifically regarding fever, no participant reported fever of any severity following the first injection. Following the second injection, 2 participants in the 100 µg dose group reported fever categorized as mild. All participants have been vaccinated, and safety and immunogenicity follow-up is ongoing. Indeed, immunogenicity data through 119 days after the first vaccination for 34 participants revealed binding and neutralizing GMTs that exceeded the median GMTs in a panel of convalescent sera from 41 controls. No SAEs were noted,

no study-halting rules were met, and no new related adverse events (AEs) were reported after Day 57 (Widge et al 2021).

Additionally, an ongoing, placebo-controlled, dose-finding Phase 2a study (mRNA-1273-P201; NCT04405076) conducted by the Sponsor under IND 19745 aims to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 administered as 2 doses 28 days apart at dose levels of 50 and 100 µg. The study is being conducted in 600 healthy adults in 2 age cohorts: 18 to 54 years of age (300 participants) and at least 55 years of age (300 participants). All participants were randomly assigned in a ratio of 1:1:1 to receive either placebo or mRNA-1273 at 1 of 2 doses, either 50 µg or 100 µg. The study was designed to begin with parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old). An independent safety monitoring committee (SMC) reviewed all blinded and unblinded safety data through Day 57 (1 month after Dose 2) for both cohorts and found the vaccine tolerable, saw no safety concerns, and recommended continuing the study as planned. The study is now completely enrolled, and all dosing is complete; participants are undergoing additional serologic testing and safety follow-up.

The 100 µg dose level is currently being investigated in a large Phase 3 efficacy study (mRNA-1273-P301; NCT04470427) in approximately 30,000 adults 18 years of age and older, randomly assigned 1:1 to receive either vaccine or placebo. Recently published data show a vaccine efficacy of 94.1% against symptomatic COVID-19 illness with onset at least 14 days after the second injection (Baden et al 2021). Although moderate transient reactogenicity occurred more frequently in the mRNA-1273 group, SAEs were rare and the incidence was similar between the 2 groups. On 18 Dec 2020, the Moderna COVID-19 vaccine was authorized by the US FDA for emergency use in individuals ≥ 18 years of age. The participants in this Phase 3 study are currently undergoing assessments for long-term safety and durability of vaccine efficacy.

Finally, a Phase 2/3, randomized, observer-blind, placebo-controlled study (mRNA-1273-P203) conducted by the Sponsor under IND 19745 is evaluating the safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents 12 to < 18 years of age. This study began enrolling in December 2020 and will enroll 3,000 participants randomly assigned 2:1 to receive mRNA-1273 100 µg or placebo administered as 2 doses 28 days apart. Participants will be followed for 12 months after the second dose.

A detailed review of the clinical experience with LNPs containing SM-102 (mRNA vaccines and placebo) is provided in the IB.

1.3. Benefit/Risk Assessment

1.3.1. Potential Benefits From Participation

The following benefits may accrue to participants:

- The mRNA-1273 vaccine may be an effective vaccine against COVID-19 in the study population.
- 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 vaccine against COVID-19 for children 6 months to < 12 years of age.

1.3.2. Risks From Study Participation and Their Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after injection.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures are followed to avoid injury from fainting.

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. In the large Phase 3 efficacy study of mRNA-1273 described above, delayed injection site reactions occurred with an incidence of approximately 1%. These reactions typically began 8 days or more following injection, were mostly not severe, and were rarely observed after the second dose.

The majority of local and systemic solicited ARs observed after injection with mRNA-1273 at the 100 µg dose level have been mild to moderate in severity (Section 1.2.2). The most commonly reported systemic ARs were headache, myalgia, fatigue, chills, and fever. In the majority of cases, the reactions resolved spontaneously within several days.

Laboratory abnormalities (including increases in hepatic enzymes and serum lipase levels) following injection were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown. Further details are provided in the current IB.

There is a theoretical risk that active vaccination to prevent SARS-CoV-2 infection may cause a paradoxical increase in the risk of severe COVID-19. This possibility is based on the rare phenomenon of vaccine-associated ERD, which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with respiratory syncytial virus (Chin et al 1969) or measles virus (Fulginiti et al 1967). It is noteworthy that these vaccines were the result of a completely different formulation and with an entirely different mechanism of action than mRNA-based vaccines such as mRNA-1273. Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination (Thomas and Yoon 2019; WHO 2019). It is not known if mRNA-1273 will increase the risk of enhanced disease; however, preliminary data from the ongoing Phase 3 study suggests no evidence of enhanced disease, as fewer cases of severe COVID-19 and COVID-19 were observed in participants who received mRNA-1273 than in those who received placebo.

In order to address this theoretical risk, animal studies have been performed in young and aged wild-type mice and rhesus macaques (NHPs). These studies were designed to capture immunogenicity endpoints that would be predictive of ERD and also to evaluate if, at protective or subprotective dose levels of mRNA-1273, evidence of disease enhancement would be observed after challenge of the animals with SARS-CoV-2. These nonclinical studies demonstrated that mRNA-1273 is safe and well tolerated in different animal species; is immunogenic; drives a robust SARS-CoV-2-specific Ab, neutralization, and Th1-directed CD4 T-cell response; fully protects animals from challenge at dose levels as low as 1 μg/dose in mice and 30 μg/dose in NHPs; and does not lead to ERD at protective or subprotective dose levels (Corbett et al 2020a; Corbett et al 2020b). Clinical immunogenicity data from the DMID Phase 1 study of mRNA-1273 demonstrated high levels of nAbs and Th1-polarized CD4 T-cell responses (Jackson et al 2020), consistent with the immunogenicity observed in the nonclinical studies. These data suggest that the risk of paradoxical ERD, while not eliminated, is likely to be low.

1.3.3. Overall Benefit/Risk Conclusion

Based on the Phase 3 data and the results of the Phase 1 and Phase 2 studies described above, the Sponsor intends to study 3 dose levels (25, 50, and 100 μg) in the proposed Phase 2/3 study in participants 6 months to < 12 years of age. Briefly, the proposed study is designed to dose escalate and age de-escalate through 3 sequential age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years). Participants at each dose level will receive 2 doses at that dose level approximately 28 days apart. The mRNA-1273 dose levels that will be evaluated in each age group are given in Table 1.

Table 1: Age Groups and mRNA-1273 Dose Levels

Age Group	mRNA-1273 Dose Levels Planned to be Evaluated
6 to < 12 year	50 and 100 µg
2 to < 6 year	50 and 100 µg
6 month to < 2 year	25, 50, and 100 µg

The study will be conducted in 2 parts. Part 1 of the study will be open label and consist of dose escalation and age de-escalation to select the dose for each age group. Part 2 of the study will be a placebo-controlled observer-blind evaluation of the selected dose in each age group.

Immunogenicity data from participants who receive the mRNA-1273 vaccine at the selected dose level will be used to infer vaccine effectiveness. All participants will be followed up for 12 months after receipt of the second injection.

Safety will be monitored throughout the study (Section 7.5).

Given that the preliminary data from Phase 1 to 3 studies have shown no significant safety concerns and robust immunogenicity, mRNA-1273 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 in children will help facilitate a return to school as an additional step towards normalization of daily activities.

Considering the lack of approved vaccines for COVID-19, the participants' risk of COVID-19 outside the study during a pandemic, and the nonclinical and clinical data to date, the Sponsor considers the potential benefits of participation to exceed the risks.

2. OBJECTIVES AND ENDPOINTS

The objectives that will be evaluated in this study and the endpoints associated with each objective are provided in Table 2.

Table 2: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 vaccine administered as 2 doses 28 days apart in 3 age groups	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESIs, including MIS-C, through the entire study period
• To infer the efficacy of mRNA-1273 (25, 50, and 100 µg, administered as 2 doses 28 days apart) based on immunogenicity in 3 age groups	• The proportion of participants with a serum nAb level at Day 57 ≥ nAb threshold of protection[1] • The GM value of serum nAb level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301)[2] 1. If an accepted serum nAb threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy 2. If a threshold is not available, efficacy will be inferred by establishing noninferiority among 6-month-old to < 12-year-old participants (Study P204) to 18- to 25-year-old participants (Study P301) by both GM value of serum nAb level and seroresponse rate. A definition of seroresponse will be provided in the statistical analysis plan based on

Objectives	Endpoints
	forthcoming information about assay performance.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 μg) administered as 2 doses 28 days apart	• The GM values of SARS-CoV-2 S protein-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2) • The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)
• To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or RT-PCR) starting 14 days after the second dose of IP Seroconversion due to SARS-CoV-2 infection will be measured by bAb against SARS-CoV-2 nucleocapsid protein. – Participants seronegative at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein from below the LOD at Day 1 that increase to equal to or above LOD starting 14 days after the second dose of IP. In addition, any postbaseline positive RT-PCR results (symptom-prompted or prescheduled tests) will be counted as SARS-CoV-2 infection.
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR of nasal swabs and/or serology tests obtained at prescheduled study visits
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with COVID-19 AND positive RT-PCR for SARS-CoV-2	• The incidence of the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria:

Objectives	Endpoints
	– The participant must have at least 1 nasal swab (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR AND – Either o The participant must have experienced at least TWO of the following systemic symptoms: fever (≥ 38ºC/≥ 100.4ºF), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding OR o The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence
• To describe the ratio or profile of specific S protein bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb titers in serum

Objectives	Endpoints
• 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 assess, in a subset of participants, the SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points after vaccination relative to baseline

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; GM = geometric mean; IP = investigational product; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralizing antibody; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

3. STUDY DESIGN

3.1. General Design

This is a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study intended to infer the effectiveness of mRNA-1273 in children aged 6 months to < 12 years. The study population will be divided into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years), and up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 will be evaluated.

The study will be conducted in 2 parts. Part 1 of the study will be open label and consist of dose escalation and age de-escalation in 750 participants to select the dose for each age group (Table 3). Part 2 of the study will be a placebo-controlled observer-blind evaluation of the selected dose in 6,000 participants (2,000 participants in each age group). No participants in Part 1 will participate in Part 2 of the study.

The study will begin with the oldest age group (6 to < 12 years) and age de-escalate. Each age group will begin with Part 1 and advance to Part 2 after dose selection in Part 1 is complete. The mRNA-1273 investigational vaccine or placebo will be administered as 2 IM injections approximately 28 days apart.

The mRNA-1273 dose levels that will be evaluated in each age group in Part 1 and Part 2 of the study are given in Table 3. Only the 6 month to < 2 year age group will receive the 25 µg dose level.

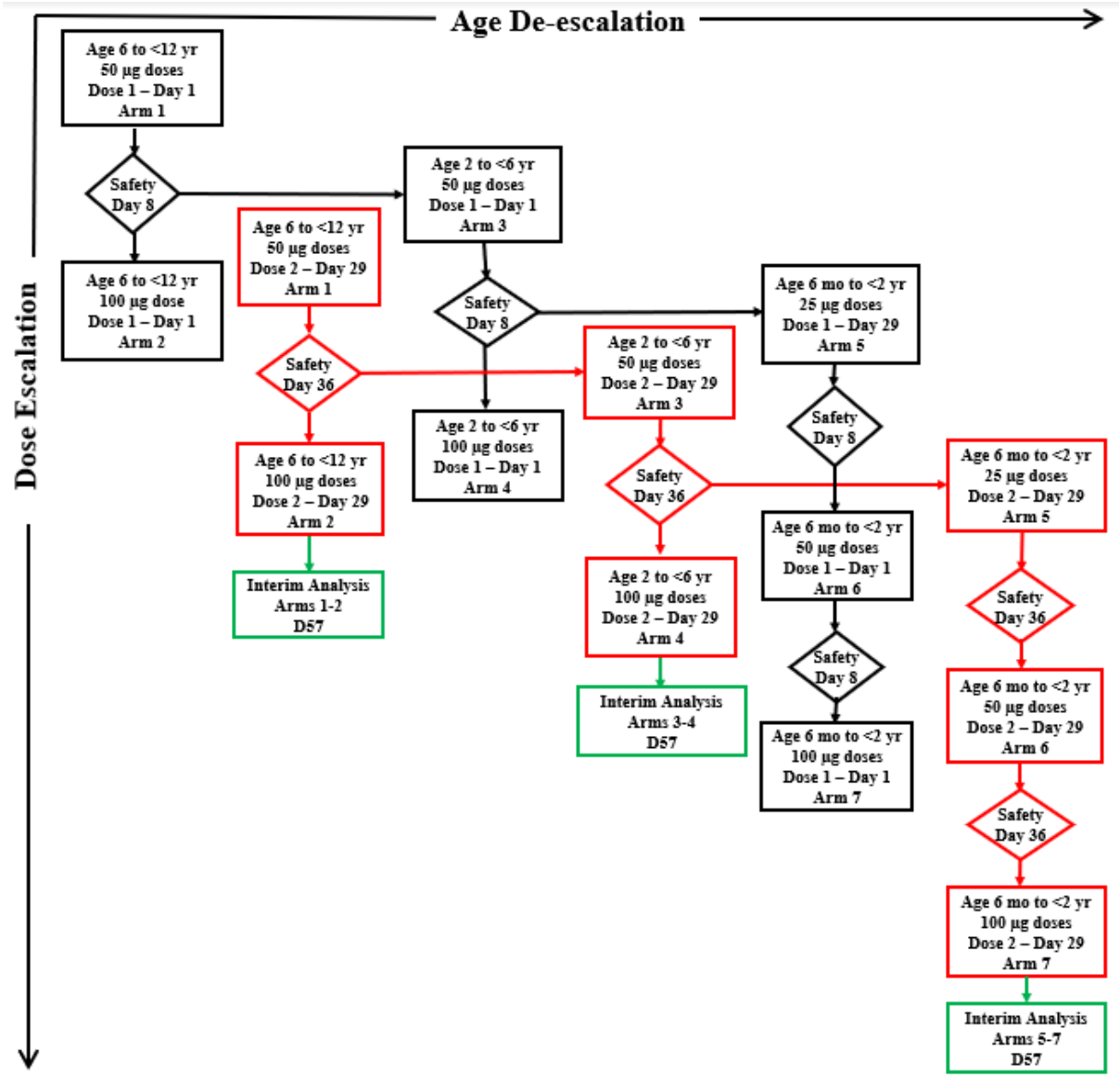
Table 3: Age Groups and mRNA-1273 Dose Levels in Part 1 and Part 2 of the Study

	Part 1			Part 2	
Age Group	**mRNA-1273 25 µg**	**mRNA-1273 50 µg**	**mRNA-1273 100 µg**	**Selected Dose Level of mRNA-1273 From Part 1**	**Placebo**
6 to < 12 year		Study Arm 1 (n=75)	Study Arm 2 (n=75)	Study Arm 8 (n=1,500)	Study Arm 9 (n=500)
2 to < 6 year		Study Arm 3 (n=75)	Study Arm 4 (n=75)	Study Arm 10 (n=1,500)	Study Arm 11 (n=500)
6 month to < 2 year	Study Arm 5 (n=150)	Study Arm 6 (n=150)	Study Arm 7 (n=150)	Study Arm 12 (n=1,500)	Study Arm 13 (n=500)

The schematic of study arms and major study events is provided in Figure 1.

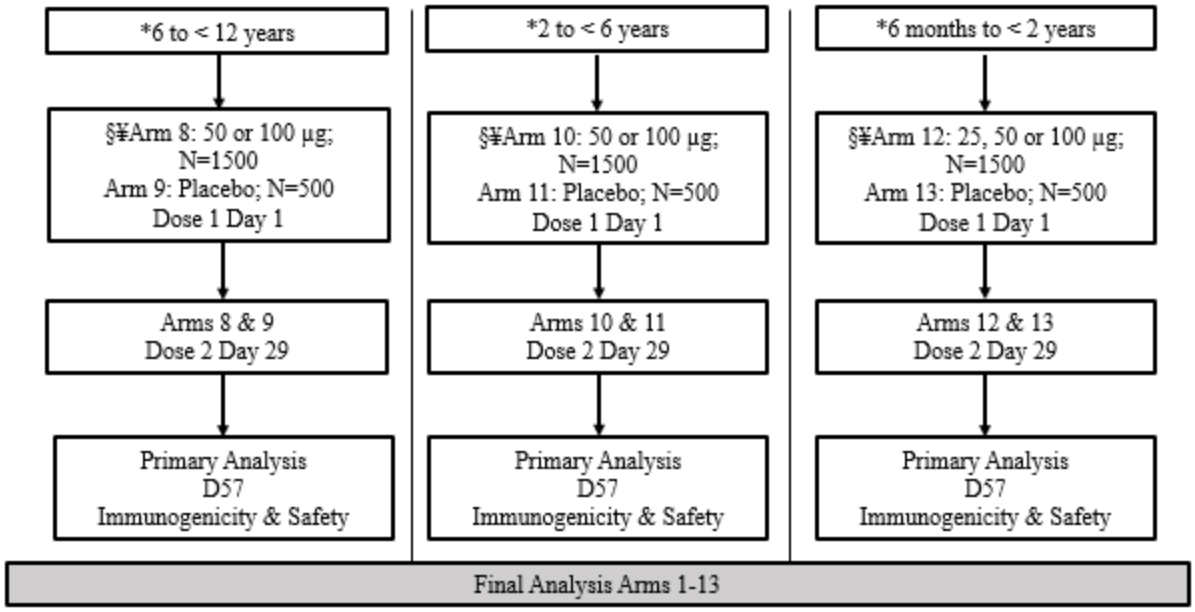
Figure 1: Study Schema

(a) Part 1: Dose Escalation, Age De-escalation



Abbreviations: D = Day; mo = months; yr = year.

(b) Part 2: Expansion



Abbreviations: CMI = cell-mediated immunity; D = Day; S = spike; VTEU = Vaccine and Treatment Evaluation Units.
*Expansion and primary analysis for each age group may occur at different times
§Arms 8-13 are contingent upon results of D57 Interim Analyses (Arms 1-7)
¥ Participants in each age group will be assigned to one of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity on D1 (prior to randomization and first dose), D57, and one of D29 (prior to the second dose), D209, or D394 (such that each participant provides a total of 3 blood samples only). Participants in the fourth cohort (remainder of the age group) will provide a blood sample on D1 (prior to randomization and before the first dose). A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on D1 (prior to randomization and before the first dose), D43, D209, and D394.

Part 1 of the study will be open label. The study will begin with enrollment of 75 participants in the 6 to < 12 year age group (Study Arm 1) and dosing with 50 µg of mRNA-1273. After the 75 participants in Study Arm 1 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an internal safety team (IST) will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 6 to < 12 year age group (Study Arm 2; n = 75) and independently whether to begin dosing at the 50 µg dose level in the 2 to < 6 year age group (Study Arm 3; n = 75). After the 75 participants in Study Arm 1 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will again review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 2 and whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 3. Once the 150 participants from Study Arms 1 and 2 reach Day 57 (1 month after Dose 2 of mRNA-1273 50 and 100 µg, respectively), an interim analysis will be conducted to review the tolerability and immunogenicity data. This analysis will result in the selection of either the 50 or 100 µg mRNA-1273 dose level and expansion of the 6 to < 12 year age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 8; n = 1,500) or placebo (Study Arm 9; n = 500). The primary analysis of

safety and immunogenicity for Study Arms 8 and 9 will be conducted after all participants reach Day 57.

Similarly, after 75 participants in Study Arm 3 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an IST will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 2 to < 6 year age group (Study Arm 4; n = 75) and whether to begin dosing in the 6 month to < 2 year age group at the 25 µg dose level (Study Arm 5; n = 150). After the 75 participants in Study Arm 3 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 4 and whether to administer Dose 2 of mRNA-1273 25 µg in Study Arm 5. Once all participants in Study Arms 3 and 4 reach Day 57 (1 month after Dose 2 of mRNA-1273 50 and 100 µg, respectively), an interim analysis will be conducted to review tolerability and immunogenicity data. This analysis will result in the selection of either the 50 or 100 µg mRNA-1273 dose level and expansion of the 2 to < 6 year age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 10; n = 1,500) or placebo (Study Arm 11; n = 500). The primary analysis of safety and immunogenicity for Study Arms 10 and 11 will be conducted after all participants reach Day 57.

In Study Arm 5, after 150 participants have completed Day 8 (1 week after Dose 1 of mRNA-1273 25 µg), an IST will review the available safety data and provide a recommendation whether to escalate the dose to 50 µg (Study Arm 6; n = 150). After 150 participants in Study Arm 6 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an IST will review the safety data and provide a recommendation whether to escalate the dose to 100 µg (Study Arm 7; n = 150). After the 150 participants in Study Arm 5 reach Day 36 (1 week after Dose 2 of mRNA-1273 25 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 6. After the 150 participants in Study Arm 6 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 7. Once all participants in Study Arms 5, 6, and 7 reach Day 57 (1 month after Dose 2 of mRNA-1273 25, 50, and 100 µg, respectively), an interim analysis will be conducted to review the tolerability and immunogenicity data. This analysis will result in selection of the 25, 50, or 100 µg mRNA-1273 dose level and expansion of the 6 month to < 2 year age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 12; n = 1,500) or placebo (Study Arm 13; n = 500). The primary analysis of safety and immunogenicity for Study Arms 12 and 13 will be conducted after all participants reach Day 57.

In general, if a decision is made not to proceed with administration of a second dose in a given arm (eg, due to safety concerns), the second injection will likely be given at a lower dose level and the higher dose level in question will not be administered in the younger age group(s). Within an

age group, if one of the dose levels is found to have an unacceptable tolerability profile, the age group may progress to Part 2 at a lower dose level based on the Day 57 interim analysis of the tolerated dose level(s).

The final analysis will be performed when all participants (Study Arms 1 to 13) conclude the safety follow-up.

The goal of the study is to support an indication for use of mRNA-1273 50 or 100 µg IM, given as 2 injections, approximately 28 days apart, in the 2 to < 6 year and 6 to < 12 year age groups and mRNA-1273 25, 50, or 100 µg IM, given as 2 injections, approximately 28 days apart, in the 6 month to < 2 year age group. The basis for demonstrating vaccine effectiveness is proposed to be met by measuring serum nAb responses in the study participants. The approach to inferring vaccine effectiveness will depend on whether an accepted serum nAb threshold conferring protection against COVID-19 has been established. If a nAb threshold of protection has been established, effectiveness will be inferred based on the proportion of study participants with serum nAb levels (on Day 57) that meet or exceed the nAb threshold. If a nAb threshold of protection has not been established, effectiveness will be inferred by demonstrating noninferiority among 6-month-old to < 12-year-old participants (Study P204) to young adult (18 to 25 years of age) participants enrolled in the ongoing clinical endpoint efficacy trial (Study P301) by both geometric mean (GM) values and seroresponse rate. The statistical parameters to infer effectiveness are described in Section 2.

This study in children 6 months to < 12 years of age will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. Safety assessments will include solicited ARs (7 days after each injection), unsolicited AEs (28 days after each injection), and medically attended adverse events (MAAEs), SAEs, and adverse events of special interest (AESIs) (including MIS-C) throughout the study period.

Blood samples will be collected from participants in Part 1 and Part 2 of the study for assessment of immunogenicity as specified in Section 3.1.1.2. If a Day 1 (Baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability to satisfy inclusion criteria 3 or could be rescheduled for rescreening (allowed once) within the screening period. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3. Blood samples will also be tested for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2. The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients.

3.1.1. Study Periods

This study involves up to 8 scheduled visits including 6 in-person visits and 2 telemedicine visits (Visit 2 and Visit 4; remote visit by means of telecommunication technology). An additional in-clinic visit (Visit 4S) will be conducted for a cohort of participants from selected Vaccine and Treatment Evaluation Units (VTEU) sites on Day 43 (2 weeks after Dose 2 of mRNA-1273 or placebo) for exploratory serology and cell-mediated immunity (CMI; S protein-specific T-cell responses) in Part 2 of the study.

The study duration for each participant will be approximately 14 months, which includes 1 month for screening (Day -28 to Day -1), 1 month for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose to monitor for safety, tolerability, reactogenicity, immunogenicity, and efficacy.

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 telemedicine visit should be conducted in place of the study site visit. The telemedicine visit 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 institutional review board (IRB) and the participant's parent(s)/legally acceptable representatives (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, Good Clinical Practice (GCP), and all applicable regulatory requirements (Section 10.2.1).

3.1.1.1. Screening Period

After providing informed consent/assent, participants will undergo screening assessments to determine study eligibility. Screening assessments (Table 10) must be completed after the participant's parent(s)/LAR(s) signs the informed consent form (ICF) and the participant, where applicable, signs the assent form. 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 10).

Eligible participants will enter the Treatment Period.

3.1.1.2. Treatment and Follow-up Period

On Day 1, after the completion of the scheduled assessments (Table 10), participants will be administered a single IM dose of the investigational product (IP) mRNA-1273 (25, 50, or 100 µg) or placebo. Placebo will be administered only to those participating in Part 2 of the study. The procedures for IP administration will be detailed in the mRNA-1273-P204 Pharmacy Manual. Participants will be closely monitored for safety and will remain at the study site for observation for at least 30 minutes after dosing. On Day 29, the second dose of IP will be administered. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+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 29 + 21 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 monitored for 12 months after the second dose of IP for safety and immunogenicity assessments.

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 and on Day 43 (if visit is applicable), Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (12 months after Dose 2) according to the schedule of assessments (SoA; Table 10).

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 reported in an expedited time frame to the Sponsor (Section 7.4.4).

All participants will be monitored for safety and reactogenicity. Participants in Part 1 of the study will provide blood specimens for immunogenicity on Day 1 (prior to the first dose) and 1, 6, and 12 months after the second dose of mRNA-1273. Participants in each age group in Part 2 will be assigned to 1 of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1 (prior to randomization and before the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and before the first dose). A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on Day 1 (prior to randomization and before the first dose), Day 43, Day 209, and Day 394. Table 11 provides the blood sampling schedule for Part 2 of the study.

Participants and their parent(s)/LAR(s) will be instructed on the day of the first dose (Day 1) and reminded on the day of the second dose (Day 29) how to document and report solicited local or systemic ARs in a provided electronic diary (eDiary). Solicited ARs, unsolicited AEs, MAAEs, AEs leading to withdrawal, AESIs, and SAEs will be assessed as described in Section 7.1, according to the time points in the SoA (Table 10).

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 prespecified 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.

A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis of COVID-19. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.

3.2. Scientific Rationale for Study Design

This Phase 2/3 study in children 6 months to < 12 years of age is planned to understand the tolerability and immunogenicity of mRNA-1273 in a pediatric population. This study follows a pivotal Phase 3 study (Study P301) in 30,000 adults 18 years and older to demonstrate the tolerability, safety, and high efficacy of mRNA-1273 (100 µg on Days 1 and 29) against COVID-19. This pediatric study is intended to confirm safety in children between 6 months and 12 years of age and bridge immunogenicity between children and young adults (18 to 25 years of age) enrolled in the pivotal adult Phase 3 study (Study P301). It is necessary to demonstrate noninferiority of the induced immune response in children compared with that in adults to infer vaccine effectiveness in this age group.

Part 1 of the study is designed to dose escalate and age de-escalate through 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 year)s. Each age group will begin dosing with the lowest dose planned for that group. Dose escalation and age de-escalation will progress only after confirming the safety of a dose level in each age group after each IP injection. The placebo-controlled dose-expansion Part 2 of the study will begin only after an interim analysis is performed for safety and immunogenicity in each of the age groups at the selected dose level.

With SARS-CoV-2 expected to be circulating in the general population during the study, some participants will provide blood samples for Ab analysis starting on Day 29 and continuing through 12 months after the last dose of IP. In addition, participants will have nasal swab samples collected, before the injections on Day 1 and Day 29 and on Day 57, Day 209, and Day 394. Furthermore, an additional nasal swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via RT-PCR and serology, respectively, if there are any signs or symptoms or an MAAE suggesting SARS-CoV-2 infection in a participant. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

As 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 for Ab responses to nonvaccine antigen(s) may help discriminate between natural infection and vaccine-induced Ab responses, should such discrimination be needed.

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

Based on the Phase 3 data and the results of the Phase 1 and 2 studies described in Section 1.2.2, the Sponsor intends to study 3 dose levels (25, 50, and 100 µg) in the Phase 2/3 study in children 6 months to < 12 years of age. On 18 Dec 2020, the mRNA-1273 vaccine (100 µg dose) was authorized by the US FDA for emergency use in individuals ≥ 18 years of age.

As there are currently no licensed SARS-CoV-2 vaccines available for children 6 months to 12 years of age, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments in Part 2. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded (Section 8.1).

3.4. 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 10) for the last participant in this study.

4. STUDY POPULATION

Participants will be enrolled at approximately 75 to 100 study sites in the United States and Canada.

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

4.1. 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, 6 months to < 12 years of age at the time of consent/assent (Screening Visit), who is in good general health, in the opinion of the investigator, based on review of medical history and screening physical examination.
2. If the participant has a chronic disease (eg, asthma, diabetes mellitus, cystic fibrosis, human immunodeficiency virus [HIV] infection), the disease should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion. Stable diseases are those which have had no change in their status or in the medications required to control them in the 6 months prior to Screening Visit.

   Note: a change in medication for dose optimization (eg, insulin dose changes), change within class of medication, or reduction in dose are not considered signs of instability.
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 and participants are willing to provide assent.
4. The participant has a body mass index (BMI) at or above the third percentile according to WHO Child Growth Standards at the Screening Visit (Section 10.2.18).
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche.

Special inclusion criteria for female participants who have reached menarche:

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all of the following criteria:

   - Has a negative pregnancy test at Screening. Pregnancy test will be performed if deemed appropriate by the investigator.
   - Has practised adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).

- Has agreed to continue adequate contraception or abstinence through 3 months following the second injection (Day 29).
- Is not currently breastfeeding.

Adequate female contraception is defined as abstinence or consistent and correct use of a US FDA-approved contraceptive method in accordance with the product label (Section 10.3).

Special inclusion criteria for children 6 months to < 2 years of age:

7. The participant was born at full-term (≥ 37 weeks gestation) with a minimum birth weight of 2.5 kg.

4.2. Exclusion Criteria

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

1. Has a known history of SARS-CoV-2 infection within 2 weeks prior to administration of IP or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of IP.
2. Is acutely ill or febrile 24 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. Has previously been administered an investigational or approved CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.
4. Has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (eg, receipt of SARS-CoV-2 monoclonal antibodies) within 6 months prior to enrollment.
5. 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 a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG] or immediate allergic reaction of any severity to polysorbate).
6. Has a medical or psychiatric condition 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. 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:
    - Congenital or acquired immunodeficiency, excluding HIV infection, as described in Inclusion Criteria 2
    - Chronic hepatitis or suspected active hepatitis
    - A bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - Dermatologic conditions that could affect local solicited AR assessments
    - Any prior diagnosis of malignancy (excluding nonmelanoma skin cancer)
    - Febrile seizures
8. Has received the following:
    - Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to first vaccination or plans to receive such a vaccine through 14 days following the last study vaccination.
    - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 1 mg/kg/day or ≥ 10 mg/day prednisone equivalent, if participant weighs > 10 kg). 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.
    - Intravenous or subcutaneous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment.
9. 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.
10. Is an immediate family member, or household contact, of an employee of the study site or Moderna 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.

4.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before their temperature is taken.

4.4. Screen Failures

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

5. STUDY TREATMENT

5.1. Investigational Product Administered

The term IP refers to mRNA-1273 (25, 50, and 100 µg) vaccine or placebo (0.9% sodium chloride) in this study.

mRNA-1273 is an LNP dispersion of an mRNA that encodes the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with PEG of average molecular weight 2000 (1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000 [PEG2000-DMG]). mRNA-1273 injection is provided as a sterile liquid for injection and is a white to off-white dispersion at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

5.2. Randomization

Random assignment of participants in Part 2 of the study will use a centralized interactive response technology, in accordance with pregenerated randomization schedules. Within each age group, approximately 2,000 participants will be randomized in a 3:1 ratio to the mRNA-1273 arm (n = ~1500) or placebo arm (n = ~500).

5.3. Dosing and Management of mRNA-1273 Vaccine

5.3.1. Preparation of Study Vaccine for Injection

Each dose of IP will be prepared for each participant based on the assigned treatment, as detailed in the mRNA-1273-P204 Pharmacy Manual. The volume of IP injected will be 0.5 mL consisting of a 25-µg dose of mRNA-1273, a 50-µg dose of mRNA-1273, a 100-µg dose of mRNA-1273, or placebo (normal saline), as detailed in the mRNA-1273-P204 Pharmacy Manual.

5.3.2. Administration of Study Vaccine

Each participant will receive 2 doses of IP by IM injection approximately 28 days apart (Day 1 and Day 29) into the deltoid muscle or anterolateral thigh (per investigator's discretion), according to their assigned regimen and according to the procedures specified in the mRNA-1273-P204 Pharmacy Manual.

At each visit when IP is administered, participants will be monitored for a minimum of 30 minutes after administration. Assessments will include body temperature measurements (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]) and monitoring for local or systemic reactions (Table 10).

Eligibility for the subsequent dose of IP will be determined by following the criteria outlined in Section 6.

The study sites will be appropriately staffed with individuals with basic 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.

5.3.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the IP
- Confirming the appropriate labeling of the IP, so that it complies with the legal requirements of the United States and Canada.

The investigator is responsible for acknowledging the receipt of the IP by a designated staff member at the study site, including the following:

- Confirming that the IP was received in good condition
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming that the Sponsor has authorized the IP for use
- Ensuring the appropriate dose level of IP is properly prepared using aseptic technique

Further description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IP are described in the mRNA-1273-P204 Pharmacy Manual.

5.3.4. Study Vaccine 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 10R glass vials with a 5.0-mL fill volume. 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, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

5.3.5. Study Vaccine Storage

The IP must be stored at -15°C to -25°C in a secure area with limited access and be protected from moisture and light until it is prepared for administration (Section 5.3.1). 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 backup freezer. The freezers must be connected to a backup generator. 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.

5.3.6. Study Vaccine 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-P204 Pharmacy Manual.

5.3.7. Study Vaccine 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 or at the end of the study, 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.

5.4. 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 electronic case report form (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/assent is withdrawn, a participant who withdraws or 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 (Table 10). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and 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.

5.5. Prior and Concomitant Medications

5.5.1. 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 his/her parent(s)/LAR(s) provided informed consent and the participant provided assent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

5.5.2. Concomitant Medications and Therapies

At each study visit, study site staff must question the participant and/or 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 14 days before the first dose of IP and through 14 days after the last dose of IP.
- 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. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE or an MAAE.

Participants will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each IP dose, including on the day of dosing. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study visits or via other participant interactions (eg, telephone calls).

Data regarding nutritional supplements, eg, vitamins, probiotics, and herbal supplements, will not be collected.

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (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.

5.5.3. 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 per-protocol (PP) analysis (analysis sets are described in Section 8.4):

- 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) 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 administered during the study period.

5.6. Intervention After the End of the Study

Any SAE, including death, occurring after the end of the study and considered to be caused by the IP must be reported to the Sponsor.

6. DELAYING OR DISCONTINUING STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

6.1. Criteria for Delay of Vaccine Administration

6.1.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]) must be measured on dosing visits before vaccine administration. The following events constitute criteria for delay of injection, and if either 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 10), or the participant may be discontinued from dosing at the discretion of the investigator (Section 6.2):

- 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 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 5.5.2).

6.2. Discontinuing Study Vaccination

Participants can 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 a participant from further injection under the following circumstances:

- The participant becomes pregnant.
- The participant's parent(s)/LAR(s) withdraw consent or the participant withdraws assent.
- An RT-PCR result from an illness visit (Section 7.1.5) is positive for SARS-CoV-2 and the participant is symptomatic at the time of next injection.
- The participant develops, during the course of the study, symptoms or conditions listed in the exclusion criteria (Section 4.2).

- The participant experiences an AE (other than solicited reactogenicity) after injection that is considered by the investigator to be related to IP (Section 7.4.9) and is of Grade 3 (severe) or greater severity.
- 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 (eg, MIS-C).
- 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 7.4.4) clearly related to IP.
- The participant experiences generalized urticaria related to IP.

The reason(s) for withdrawal from further injection will 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 5.5.2).

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

6.3. 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 or the participant can withdraw assent and withdraw from the study at any time, 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 a participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant 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 or by the investigator, as well as which of the following possible reasons was the cause for withdrawal:

- AE (specify)
- SAE (specify)
- Death
- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant's parent(s)/LAR(s) or withdrawal of assent by the participant (specify)
- 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 participants who are withdrawn from the study as result of an SAE or AE until resolution of the event.

A participant who withdraws from the study may request destruction of any samples taken and not tested, and the investigator must document this in the study site study records.

If the participant's parent(s)/LAR(s) withdraw consent or the participant withdraws assent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent/assent (Section 10.2.10).

The Sponsor will continue to retain and use all research data that have already been collected for the study evaluation, unless the participant has 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).

6.4. 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
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any SAE or Grade 4 AE that cannot be reasonably attributed to a cause other than vaccination	≥ 1
3	ICU Admission due to COVID-19	≥ 1
4[1]	Individual Grade 3 or higher solicited local AR lasting ≥ 24 hours and occurring within 7 days of injection (Days 1-7)	At least 2 participants and ≥ 5% of the dosed participants in an age group
5[1]	Individual Grade 3 or higher solicited systemic AR lasting ≥ 24 hours and occurring within 7 days of injection (Days 1-7)	At least 2 participants and ≥ 10% of the enrolled participants in an age group
6[1]	Any ≥ Grade 3 or higher unsolicited AE that cannot be reasonably attributed to a cause other than vaccination	At least 2 participants and ≥ 5% of the enrolled participants in an age group

Abbreviations: AE = adverse event; AR = adverse reaction; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[1] "Individual AR" is defined as 1 AR type, eg, pain, erythema, or headache could each be an "individual AR."

If any of the thresholds for a study pause is met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators. Such a suspension will remain in force until the threshold events are reviewed by the data safety monitoring board (DSMB) and a recommendation to continue is provided to the Sponsor.

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system, each event that potentially meets any pause rule criterion within 24 hours of observation. The Sponsor will inform the DSMB of any event that potentially meets any pause rule criterion. The DSMB will review all available study data to help adjudicate such events in accordance with the DSMB charter.

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.

6.5. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent/assent 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 and reschedule the missed visit as soon as possible, counsel the participant and his/her parent(s)/LAR(s) on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes 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 (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 who continues to be unreachable or continues 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.

7. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants and/or participants' parent(s)/LAR(s) will sign an ICF (as detailed in Section 10.2.6). Participants will undergo study procedures at the time points specified in the SoA (Table 10). 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 and/or 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 approval of the Sponsor. 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.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in Table 10. Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue study treatment or participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, pregnancy test) 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 10).

7.1. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoA (Table 10):

- Solicited local and systemic ARs (Section 7.4.3) 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 7.1.1).
- 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 7.4.1.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation.
- MAAEs (Section 7.4.4) from first dose on Day 1 through the entire study period.
- SAEs (Section 7.4.2) from first dose on Day 1 through the entire study period.
- AESIs (Section 7.4.5) including MIS-C through the entire study period.
- Physical examination findings (Section 7.1.4).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 7.1.5).
- Details of all pregnancies in female participants after the start of study treatment and until the end of their participation in the study (Section 7.4.6).

7.1.1. 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 7.4.3) 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 29) on thermometer (oral/tympanic) 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 7.4.3, 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). If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs, whichever occurs first. Capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
- Daily oral (for participants > 4 years of age) or tympanic (for participants ≤ 4 years of age) 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.
- 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. The participant's parent(s)/LAR(s) will have a limited window on the following day to complete assessments for the previous day; 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.

Any new safety information reported during safety telephone calls or at study site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. An event reported in this manner must be described as a solicited event and entered on the solicited AR eCRF.

Study site staff will review eDiary data with participants' parent(s)/LAR(s) at visits 7 days after each injection.

The eDiary will also be used every 4 weeks, starting at Day 71 through Day 183 and again starting at Day 223 through Day 363, to capture the occurrence of AEs, MAAEs, SAEs, AESI, or AEs leading to withdrawal. As specified in the SoA (Table 10), 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. 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 safety telephone call will be triggered.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 7.1.2) as the procedure for safety follow-up approximately every 4 weeks; these safety telephone calls will take place from Day 85 through Day 197 and again from Day 237 through Day 377 (Table 10).

7.1.1.1. Ancillary Supplies for Participant Use

Study sites will distribute Sponsor-provided oral or tympanic 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.

7.1.2. 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 10). The participants' parent(s)/LAR(s) will be interviewed according to the script about the occurrence of AEs, MAAEs, SAEs, AESI, AEs leading to study withdrawal, concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.4.7). 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 7.1.1, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

7.1.3. 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.

A point-of-care urine pregnancy test will be performed, if deemed appropriate by the investigator, at the Screening Visit and before each vaccine dose in female participants of childbearing potential. At any time during the study, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.

Febrile participants at dosing visits (fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F) may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses may receive the IP at the discretion of the investigator.

7.1.4. Physical Examinations

A full physical examination, including body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]), length/height and weight, will be performed at the Screening Visit or on Day 1. The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Symptom-directed physical examinations will be performed on Day 1, Day 29, Day 43 (if the visit is applicable), Day 57, Day 209, and Day 394 and may be performed at other time points at the

discretion of the investigator. Body temperature (oral/tympanic) should be measured on each injection day prior to injection. On each injection day before injection and again 7 days after injection (ie, the day of injection and 6 subsequent days), 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 (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1 or Day 29 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.

Body mass index will be calculated at the Screening Visit only.

7.1.5. Assessment for SARS-CoV-2 Infection

Study participants will have nasal swab samples collected for SARS-CoV-2 testing at the time points specified in the SoA (Table 10).

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

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020b)
- Exposure (close contact [definition in Section 7.1.1]) to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

If the participant had known exposure (close contact) to COVID-19 (eg, exposure to someone with confirmed COVID-19), it will be captured in the COVID-19 exposure form.

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

If scheduled, the study illness visit (study site visit or home visit) may collect additional clinical information, including assessments such as 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. 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.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant's parent(s)/LAR(s) and the participant's primary care physician of the diagnosis. If the study participant does not have a primary care physician, the investigator will assist them to obtain one. The participant 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.

Any confirmed symptomatic SARS-CoV-2 infection that occurs in participants will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.3). At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.

7.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoA (Table 10 and Table 11). The following analytes will be measured:

- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays.
- Serum bAb titer as measured by enzyme-linked immunosorbent assay specific to the SARS-CoV-2 S protein.
- For Part 1, testing for serologic markers for SARS-CoV-2 infection using a nonvaccine antigen-based blood test at Day 1 (prior to the first dose), Day 57, Day 209, and Day 394.
- For Part 2, participants in each age group will be assigned to 5 phlebotomy cohorts. Blood sampling will be performed in 3 of these 5 cohorts for immunogenicity at 3 of the following time points: Day 1 (prior to randomization and the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, and Day 394. Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and the first dose). A fifth cohort of participants at selected VTEU sites only, will provide blood samples for assessment of exploratory serology and CMI on Day 1 (prior to randomization and the first dose), Day 43, Day 209, and Day 394.

Sample aliquots will be designed to have backup 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 10.2.6), 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 CoVs.

The planned volume of blood to be sampled per participant in Part 1 and Part 2 (serology cohorts) for each age group for immunogenicity assessments in 1 day is as follows:

- 6 months to < 2 years: approximately 8 mL
- 2 to < 6 years: approximately 16 mL
- 6 to < 12 years: approximately 24 mL

The planned volume of blood to be sampled per participant in the exploratory serology and CMI cohort for each age group in 1 day is as follows:

- 6 months to < 2 years: approximately 9 mL
- 2 to < 6 years: approximately 9 mL
- 6 to < 12 years: approximately 17 mL

7.3. Efficacy Assessments

7.3.1. Vaccine Effectiveness Assessments

Vaccine effectiveness for children 6 months to < 12 years of age will be inferred based on serum nAb responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the nAb responses against the following:

1. *If available at the time of analysis*, nAb responses will be assessed against an accepted serum nAb threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, noninferiority of the GM value of serum nAb and seroresponse rate of children 6-month-old to < 12-year-old (Study P204) compared with the GM value of serum nAb and seroresponse rate from young adults (18 to 25 years of age) enrolled in the ongoing clinical endpoint efficacy trial (Study P301) will be assessed. The statistical parameters to infer effectiveness are described in Section 2.

COVID-19:

To be considered as a case of COVID-19 for the evaluation of the efficacy endpoint, 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

- Either
  - The participant must have experienced at least TWO of the following systemic symptoms: fever (≥ 38ºC/≥ 100.4ºF), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding

    OR
  - The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia.

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, OR
  - Admission to an ICU or death.

Table 5: Age-Specific Cut-Offs 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			
0 days to 1 week	> 180	< 100	> 50	> 34	< 65
1 week to 1 month	> 180	< 100	> 40	> 19.5 or < 5	< 75
1 month to 1 year	> 180	< 90	> 34	> 17.5 or < 5	< 100
2 to 5 year	> 140	NA	> 22	> 15.5 or < 6	< 94
6 to 12 year	> 130	NA	> 18	> 13.5 or < 4.5	< 105
13 to < 18 year	> 110	NA	> 14	> 11 or < 4.5	< 117

Abbreviations: NA = not applicable.
Note: Lower values for heart rate, leukocyte count, and systolic blood pressure are for the 5th percentile and upper values for heart rate, respiratory rate, or leukocyte count are for the 95th percentile for that age group.
Source: Goldstein et al 2005

The secondary case definition of COVID-19 includes the following systemic symptoms: fever (temperature > 38ºC/≥ 100.4ºF), chills, cough, shortness of breath or difficulty breathing, fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding AND a positive nasal swab for SARS-CoV-2 by RT-PCR.

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 by seroconversion measured by bAb against SARS-CoV-2 nucleocapsid protein.
  - For participants seronegative at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein from below the limit of detection (LOD) at Day 1 which increase to equal to or above LOD starting 7 days after the second dose of IP.
- Any postbaseline positive RT-PCR results (symptom-prompted or prescheduled tests) will also be counted as SARS-CoV-2 infection.

7.3.2. Surveillance for COVID-19 Symptoms:

Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary prompts as specified in Section 7.1.1 and Figure 2; starting after participant enrollment and continuing throughout the study.

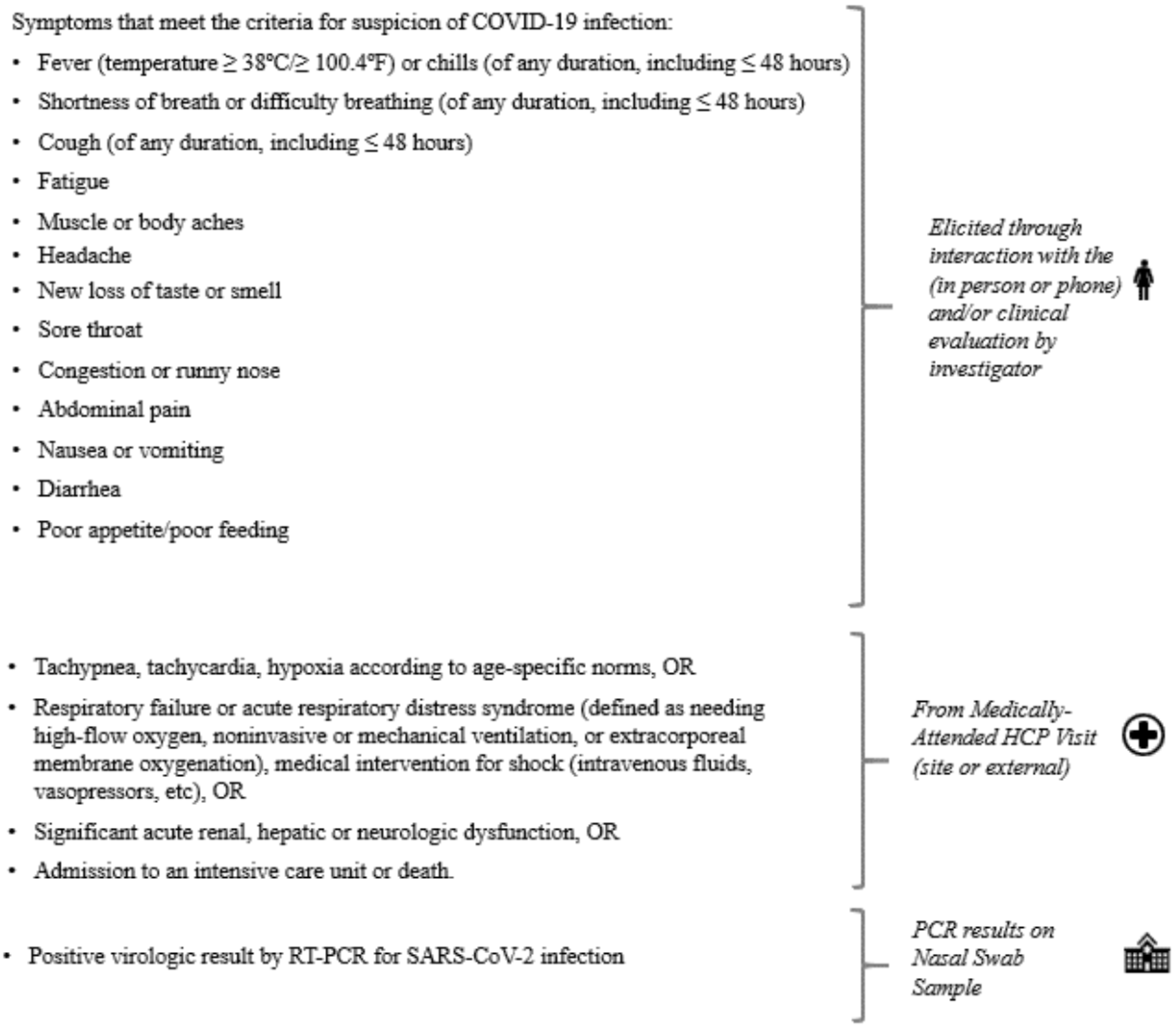
If there is no response to an eDiary prompt for 2 days, the study site staff will contact the study participant by telephone.

According to the CDC, as of 22 Dec 2020 (CDC 2020c), 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 prespecified symptoms that meet the criteria for suspicion of COVID-19 will be elicited weekly 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.

- 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, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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 (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 29, and then at all subsequent study visits (Day 43 [if visit is applicable], Day 57, Day 209, and Day 394) 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 (ie, influenza) should be evaluated for COVID-19.

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 7.1.5). Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.3). At this visit, a nasal swab sample for viral RT-PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.

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 7.3.1.

All clinical findings will be recorded in the eCRF. All confirmed cases of COVID-19 will be captured as MAAEs, along with relevant concomitant medications and details about severity, seriousness, and outcome, and will be reported immediately to the Sponsor or designee (Section 7.4.4).

7.3.3. Follow-up/Convalescent Period After Diagnosis with COVID-19

Any confirmed COVID-19 occurring in a participant will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Study participants will be monitored by trained study site personnel for a 28-day period after diagnosis. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected (Table 10). 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.

7.4. Safety Definitions and Related Procedures

7.4.1. 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 AE unless complications arise.

An AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 7.4.9). 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 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 dose of injection and the 6 days after the day of dosing).

7.4.2. 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 one 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.

7.4.3. 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 7.1.1). 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 6 and Table 7, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs, whichever occurs first. Capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit. All solicited ARs (local and systemic) will be considered related to the IP.

Table 6: Solicited Adverse Reactions and Grades: Age 37 Months to < 12 Years[1]

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[2]
Injection site pain	None	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires emergency room visit[3] or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit[3] or hospitalization
Headache	None	No interference with activity	Some interference with activity	Significant; Prevents daily activity	Requires emergency room visit[3] or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit[3] or hospitalization

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[2]
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit[3] or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit[3] or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity,	Requires emergency room visit[3] or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit[3] or hospitalization
Fever	< 38.0°C < 100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	> 40.0°C > 104.0°F

[1] Age at time of enrollment determines the scale to be used.
[2] Grading for Grade 4 events per investigator assessment (with exception of fever).
[3] 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).

Table 7: Solicited Adverse Reactions and Grades: Age 6 to ≤ 36 Months[1]

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[2]
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[3] 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[2]
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[3] or hospitalization
Systemic Reaction					
Fever	< 38.0°C < 100.4°F	38.0-38.5°C 100.4-101.3°F	38.5-39.5°C 101.3-103.1°F	39.6-40.0°C 103.1-104.0°F	> 40.0°C > 104.0°F
Irritability/crying	None	Lasting < 1 hour or easily consolable	Lasting 1-3 hours or requiring increased attention	Lasting > 3 hours or inconsolable	Requires emergency room visit[3] 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[3] or hospitalization

[1] Age at time of enrollment determines the scale to be used.
[2] Grading for Grade 4 events per investigator assessment (with exception of fever).
[3] 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 a healthcare practitioner (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

7.4.4. 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 7.3.1]) 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. All MAAEs must be fully reported on the MAAE page of the eCRF.

All confirmed COVID-19 cases (Section 7.3.1) will be recorded as MAAEs and 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 7.4.11). 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 should be recorded as MAAEs and reported as an 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 7.4.11. 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

7.4.5. 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. Such events may require further investigation to characterize and understand them. A list of AESIs pertinent to this study may be referenced in the list of AESIs that is maintained by the Sponsor and provided to each investigator throughout the 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 7.4.11).

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

- An individual aged < 21 years presenting with fever, laboratory evidence of inflammation, 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:
  - Fever ≥ 38.0°C/≥ 100.4ºF for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours
  - 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

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.

7.4.6. Recording and Follow-up of Pregnancy

Female participants who have a positive pregnancy test at Screening should not be enrolled; participants who have a positive pregnancy test any time during the study should receive no further dosing with IP but should be asked to remain in the study and be monitored for safety.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancies occurring in participants after enrollment must be reported to the Sponsor or designee within 24 hours of the study site learning of its occurrence, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11). If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

7.4.7. Eliciting and Documenting Adverse Events

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 from Day 1 through 7 days after each dose (ie, the day of injection and 6 subsequent days). Other (unsolicited) AEs will be collected from Day 1 through 28 days after each dose.

Both MAAEs and SAEs will be collected from participants as specified in the SoA (Table 10) 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, participants or 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) according to the scripts provided. Participants or 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 6.5).

7.4.8. 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 7.4.2), 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 children 37 months to < 12 years of age (Table 6) and 6 to ≤ 36 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 7.4.3.

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 or the 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.

7.4.9. 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.

7.4.10. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, 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. The Medical Dictionary for Regulatory Activities (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.

7.4.11. 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 7.4.2) 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 following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (United States and Canada): +1-866-599-1341
- SAE Fax line (United States and Canada): +1-866-599-1342

Regulatory reporting requirements for SAEs are described in Section 7.4.15.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, 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.

7.4.12. Time Period and Frequency for Collecting AE, AESI, 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 or participant’s parent(s)/LAR(s)
- Questioning the participant or 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 (including AESIs) will be collected from the start of IP dosing until the last day of study participation.

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 7.4.11).

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). 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 end of the study participation. However, if the investigator learns of any SAE (including a death) at any time after a participant has withdrawn from or completed the study, and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

7.4.13. 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 and participant's parent(s)/LAR(s) is the preferred method to inquire about the occurrence of AE.

7.4.14. 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 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 6.5.

7.4.15. 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 adverse reactions 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.

7.5. Safety Monitoring

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

7.5.1. Internal Safety Team

An IST will review safety data throughout the study. For Part 1 dose escalation and age de-escalation, based on the review of all available safety data through Day 7 (1 week after Dose 1 of mRNA-1273) and beyond for all participants at each dose level within the 6 to < 12 year and 2 to < 6 year age group, the IST will recommend whether dose escalation and age de-escalation are appropriate. This process will then be repeated for all participants in the 25, 50, and 100 µg dose levels within the lower age group of 6 months to < 2 years of age. An IST review on Day 36 (1 week after Dose 2 of mRNA-1273 at each dose level) will be required prior to the administration of the second injection of the next higher dose. 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.

7.5.2. 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 meet on a regular basis to assess safety throughout study conduct. Recruitment will continue, as applicable, during the DSMB review period. 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, described in Section 6.4, 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 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.

7.6. Treatment of Overdose

As the study treatment is to be administered by a healthcare professional, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 10.2.8).

7.7. Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

7.8. Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

7.9. Biomarkers

Immunogenicity assessments are presented in Section 7.2. Biomarkers will not be evaluated in this study.

7.10. Health Economics

Health economics will not be evaluated in this study.

8. 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 statistical analysis plan (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 clinical study report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

8.1. 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 participants, 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) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of IP to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- 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 unblinded statistical and programming team will perform the primary analyses in Part 2 (Section 8.6.2). Sponsor team members will be prespecified 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 dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the IP in a secure location that is not accessible or visible to other study staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different from those of placebo. Only delegated unblinded study site staff

will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

The planned study analyses are described in Section 8.6.

8.1.1. Breaking the Blind

A participant's treatment assignment may be unblinded (Part 2 of the study) in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for interim analyses as outlined in Section 8.6.1.

8.2. Statistical Hypothesis

If an accepted nAb threshold of protection against COVID-19 is established for the primary immunogenicity endpoint, the null hypothesis is that the percentage of participants on mRNA-1273 with serum nAb above the established threshold at Day 57 is $\leq 70\%$ (ie, H_0: percentage of participants on mRNA-1273 with serum nAb at Day 57 above the established threshold $\leq 70\%$).

For each age group, the study will be considered to meet the immunogenicity endpoint if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 70% (lower bound of the 95% CI is > 70%).

The null hypotheses may be updated when the information on an acceptable nAb threshold becomes available. In this case, the null hypothesis update will be provided in the SAP.

If an accepted serum nAb threshold of protection against COVID-19 is not available for the primary immunogenicity endpoint, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 nAb levels will be compared to Day 57 nAb levels from young adults (18 to 25 years of age) in Study P301. Noninferiority tests of 2 null hypotheses based on 2 coprimary endpoints will be performed, respectively.

Coprimary endpoint 1: nAb GM value at Day 57

The null hypothesis H^1_0: immunogenicity response to mRNA-1273, as measured by nAb GM value at Day 57, is inferior in children (in age groups 6 months to < 2 years, 2 to < 6 years, and 6 to < 12 years) compared with that in young adults (18 to 25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in nAb GM value in children compared with that in young adults (18 to 25 years of age) is demonstrated by the lower bound of the 95% CI of the geometric mean ratio (GMR) ruling out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5. The GMR is the ratio of the GM value of SARS-CoV-2-specific nAb in children in an age group receiving mRNA-1273 in this Study P204 compared with the GM value of young adults (18 to 25 years of age) receiving mRNA-1273 in Study P301 at Day 57.

Coprimary endpoint 2: nAb seroresponse rate at Day 57

A definition of seroresponse will be provided in the SAP based on forthcoming information about assay performance.

The null hypothesis H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in children compared with that in young adults (18 to 25 years of age) in Study P301.

The noninferiority in seroresponse rate in children compared with that in young adults (18 to 25 years of age) is demonstrated by the lower bound of the 95% CI of the seroresponse rate difference ruling out -10% (ie, lower bound > -10%) using the noninferiority margin of 10%. The seroresponse rate difference is defined as the seroresponse rate in children receiving mRNA-1273 minus the seroresponse rate in young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301.

The study would be considered to meet the primary immunogenicity endpoint in an age group if the noninferiority in the age group compared with the young adults (18 to 25 years of age) is demonstrated based on both coprimary endpoints.

8.3. Power and Sample Size

The initial age groups in Part 1 are for estimation purposes. With 150 participants each in the initial 6 to < 12 year and 2 to < 6 year age groups and approximately 450 participants in the 6 month to < 2 year age group exposed to a dose level of mRNA-1273, there is at least a 90% probability to observe at least 1 participant with an AE at a true AE rate of 2.5%.

The sample size in the expansion (Part 2) is considered to be sufficient to support a safety database in pediatric participants 6 months to < 12 years of age. With approximately 4,500 participants

exposed to mRNA-1273 across the 3 age groups in Part 2, the study has at least a 90% probability to observe at least 1 participant with an AE at a true 0.2% AE rate.

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group will be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset will be processed, and the analysis of primary immunogenicity endpoint will be based on the Immunogenicity PP Subset.

If a threshold of protection is available, for the primary immunogenicity endpoint, with approximately 289 participants on mRNA-1273 in the Immunogenicity PP Subset of an age group, there will be at least 90% power to rule out 70% with a 2-sided 95% CI (lower bound of the 95% CI > 70%) for the percentage of mRNA-1273 participants exceeding the accepted threshold if the true rate of participants exceeding the threshold is 80%.

If an acceptable nAb threshold of protection against COVID-19 is not available at the time of analysis for the primary immunogenicity endpoint, noninferiority tests of the 2 null hypotheses based on the 2 coprimary endpoints will be performed, respectively. The sample size calculation for each of the 2 noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be 90% power to demonstrate noninferiority of the immune response, as measured by the nAb GM value, in pediatric population at a 2-sided alpha of 0.05, compared with that in young adults (18 to 25 years of age) in Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1 and a noninferiority margin of 0.67 (or 1.5). The standard deviation of the natural log-transformed levels is assumed to be 1.5.
- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in children at a 2-sided alpha of 0.05, compared with that in young adults 18 to 25 years of age in Study P301 receiving mRNA-1273, assuming seroresponse rate of 85% in young adults of 18 to 25 years of age from Study P301, true seroresponse rate of 85% in children (or true rate difference is 0 compared to young adults from Study P301), and a noninferiority margin of 10%.

Assuming approximately 25% of participants in the Immunogenicity Subset will not meet the criteria to be included in the Immunogenicity PP subset, approximately 528 participants in Part 2 (~396 receiving mRNA-1273 and ~132 receiving placebo) will be selected for the Immunogenicity

Subset from which approximately 289 participants on mRNA-1273 will be suitable for the Immunogenicity PP subset.

8.4. Analysis Sets

The analysis sets are defined in Table 8. The analysis sets may be defined for Part 1 and Part 2 separately.

Table 8: Analysis Sets

Analysis Set	Description
Randomization Set	Part 2: All participants who are randomly assigned, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	Part 1: All enrolled participants in Part 1 who receive at least 1 injection of IP Part 2: All randomly assigned participants who receive at least 1 injection of IP
Per-Protocol (PP) Set	All participants in the FAS who receive planned doses of IP per schedule, comply with the immunogenicity schedule, and have no major protocol deviations that impact key or critical data. Participants who are RT-PCR positive or seropositive at Baseline will be excluded from the PP Set. The PP Set in Part 1 will be used for all analyses of immunogenicity in Part 1 unless specified otherwise.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity sampling and testing.
Per-Protocol Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset 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. Participants who are RT-PCR positive or seropositive at Baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for all analyses of immunogenicity unless specified otherwise.
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.

Analysis Set	Description
Solicited Safety Set	The Solicited Safety Set consists of participants in the Safety Set who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at Baseline
Modified Intent-to-Treat-1 (mITT1) 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)

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; IP = investigational product; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

8.5. Statistical Methods

8.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, race, ethnicity) and baseline characteristics (eg, length/height, weight, and BMI) will be summarized by treatment group. Summary statistics (mean, standard deviation for continuous variables, and number and percentage for categorical variables) will be provided.

8.5.2. 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 and placebo) and by age group. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for safety analysis.

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, AEs leading to discontinuation, and physical examination findings.

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.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs 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 parameters. 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	—

Abbreviations: AE = adverse event; 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.

8.5.3. Immunogenicity Analyses

The primary analysis population for immunogenicity will be the Immunogenicity PP Subset, unless specified otherwise. The primary objective of this study is to use the immunogenicity response to infer efficacy in participants aged 6 months to < 12 years at the dose level selected for expansion. For this objective, analyses of immunogenicity will be performed for each pediatric age group separately at the selected dose level based on the participants in the Immunogenicity PP Subset. For each pediatric age group, participants from Part 1 and Part 2 in the Immunogenicity PP Subset who receive the same mRNA-1273 dose level selected for expansion will be combined for immunogenicity analyses. If the same dose level is selected for expansion for more than one age group, these age groups may be combined for immunogenicity analyses.

An accepted nAb threshold of protection against COVID-19 may be available based on data from other mRNA-1273 studies or external data. If such a threshold of protection against COVID-19 is

available, the number and percentage of participants with nAb greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. For an age group, if the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity endpoint of this study will be considered to be met for that age group.

The number and percentage of participants with serum nAb greater than or equal to the threshold with 2-sided 95% CI will be provided at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum nAb threshold of protection against COVID-19 is not established, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 nAb levels will be compared to that in young adults (18 to 25 years of age) using data from Study P301. An analysis of covariance model will be carried out with nAb at Day 57 as dependent variable and a group variable (pediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable for each pediatric age group. The GM values of the pediatric age group at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI will be provided to assess the difference in immune response between the pediatric age group (Study P204) compared to the young adults (18 to 25 years of age) in Study P301 at Day 57. For each pediatric age group, the noninferiority of GM value will be considered demonstrated if the lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5.

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 postbaseline time point with Day 57 being of the primary interest. The seroresponse rate difference with 95% CI at Day 57 will be provided between children receiving mRNA-1273 in Study P204 and young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301. For each pediatric age group, the noninferiority of seroresponse rate will be considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is > -10% based on the noninferiority margin of 10%.

In addition, the GM value of anti-SARS-CoV-2-specific Ab 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 values then back transformed to the original scale. For each age group, the geometric mean fold-rise of specific nAb and bAb with corresponding 95% CI at each postbaseline time point over preinjection baseline at Day 1 will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided.

8.5.4. Efficacy Analysis

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, dose level, and age group, calculated as the number of cases divided by the total person-time. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level (if applicable) will be combined in the analysis.

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

The secondary efficacy analyses will be performed on the PP set, with sensitivity analyses in FAS, mITT Set, and mITT1 Set.

8.5.5. Exploratory Analyses

Exploratory analyses will be described in the SAP before database lock.

8.5.6. Subgroup Analyses

Subgroup analyses will be performed as described in the SAP.

8.6. Study Analyses

8.6.1. Interim Analyses

Part 1: Interim analyses will be performed after all participants in Part 1 within each age group and dose level have completed Day 57. Analyses of safety and immunogenicity will be conducted at each analysis and these interim results will be used to decide the expansion dose in Part 2 for each age group.

Part 2: An interim analysis of immunogenicity and safety will be performed after all participants assigned to the Immunogenicity Subset have completed Day 57 (1 month after the second dose) in Part 2 within an age group. This interim analysis will be considered the primary analysis of immunogenicity (Section 8.5.3) for a given age group. Another interim analysis on safety may be performed after a subset or all participants have completed Day 57 in an age group.

8.6.2. Final Analysis

The final analysis of all endpoints will be performed after all 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.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Schedule of Assessments

The SoA is presented in Table 10.

If a participant cannot attend a study site visit (scheduled or unscheduled), with the exception of Screening, Day 1, and Day 29, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor (Section 7). If neither a participant visit to the study site nor a home visit to the participant is possible (with the aforementioned exceptions), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls.

The blood sampling schedule for exploratory serology and CMI in Part 2 of the study is presented in Table 11.

Table 10: Schedule of Assessments

Visit Number	0	1	2	3	4	4S	5			6			7
Type of Visit	C	C	TMV	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	7	-	28	-	-	180	-	-	365
Informed consent/assent form, demographics, concomitant medications, medical history	X												
Review of inclusion and exclusion criteria	X	X											
Physical examination including body temperature, length/height, weight, and BMI[7]	X	X		X		X	X			X			X
Pregnancy test[8]	X	X		X									
Randomization		X											
Study injection (including 30-minute postdose observation period)		X		X									
Blood sample for vaccine immunogenicity (Part 1)[9]		X					X			X			X
Blood sample for vaccine immunogenicity (Part 2)[10]		X		X			X			X			X
Blood sample for exploratory serology and cell-mediated immunity (Part 2)[3,10]		X				X				X			X
Nasal swab sample for SARS-CoV-2[11]		X		X		X	X			X			X
Surveillance for COVID-19/illness visit/ unscheduled visit[12]			X	X	X	X	X	X	X	X	X	X	X
Convalescent visit[13]					X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[14]		X		X									

Visit Number	0	1	2	3	4	4S	5			6			7
Type of Visit	C	C	TMV	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	7	-	28	-	-	180	-	-	365
Review of eDiary data			X		X								
Follow-up safety telephone calls[15]									X			X	
Recording of unsolicited AEs		X	X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[16]		X	X	X	X	X	X	X		X	X		X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[16,17]		X	X	X	X	X	X	X		X	X		X
Recording of AESIs (eg, MIS-C)[17]		X	X	X	X	X	X	X		X	X		X
Recording of concomitant medications and nonstudy vaccinations[16]		X	X	X	X	X	X						
Study completion													X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BMI = body mass index; 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; IP = investigational product; IRB = institutional review board; LAR = legally acceptable representative; M = month; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; 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; TMV = telemedicine visit; VTEU = Vaccine and Treatment Evaluation Units.

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, and Day 29) with the approval of the Sponsor.

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. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+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 29 + 21 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.
3. To be conducted during Part 2 of the study in a cohort of participants at selected VTEU sites only.

4. 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 telemedicine visit should be conducted in place of the study site visit. The telemedicine visit 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).
5. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
6. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
7. A full physical examination, including body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]), length/height, and weight, will be performed at the Screening Visit or on Day 1. Symptom-directed physical examination will be performed on Day 1, Day 29, Day 43 (if the visit is applicable), Day 57, Day 209, and Day 394 and may be performed at other time points at the discretion of the investigator. Body mass index will be calculated only at Screening Visit. Body temperature (oral/tympanic) should be measured on each injection day prior to injection. 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 (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1 or Day 29 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.
8. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test and will be performed if deemed appropriate by the investigator. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time during the study.
9. On Day 1, sample must be collected prior to randomization and dosing. If a Day 1 (Baseline) blood sample cannot be obtained, the participant will be considered either a screen failure due to inability to satisfy inclusion criteria 3 or could be scheduled for rescreening (allowed once) within the Screening Period. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3.
10. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing. Participants in each age group will be assigned to 1 of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1, Day 57, and one of Day 29, Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1. A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on Day 1, Day 43, Day 209, and D394. Table 11 provides the blood sampling schedule in Part 2 of the study. If a Day 1 (Baseline) blood sample cannot be obtained, the participant will be considered either a screen failure due to inability to satisfy inclusion criteria 3 or could be scheduled for rescreening (allowed once) within the Screening Period. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3.
11. The nasal swab sample (collected before dosing on injection day) will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.
12. 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 prespecified criteria of suspicion for COVID-19 (Section 7.1.5), 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.
13. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis of COVID-19. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.
14. 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. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolved or the next IP injection occurs, whichever occurs first. Capturing details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.

15. Trained study site personnel will call all participants to collect information relating to any AEs, 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.
16. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).
17. In addition to MIS-C, a list of AESIs pertinent to this study may be referenced in the list of AESIs that 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 (Section 7.4.11).

Table 11: Phlebotomy Schedule for Serology and Cell-Mediated Immunity for Part 2 (Expansion) of the Study

Cohort	Number of subjects	Study Visit Day					
		D1[1,2]	D29[1]	D43	D57	D209	D394
Phlebotomy Schedule for Serology: To be Executed Within Age Group							
A	First 176 (132 mRNA-1273: 44 placebo)	X	X		X		
B	Next 176 (132 mRNA-1273: 44 placebo)	X			X	X	
C	Next 176 (132 mRNA-1273: 44 placebo)	X			X		X
D	Remainder of the age group	X					
Phlebotomy Schedule for Cell-Mediated Immunity: To be Executed Within Each Age Group at Selected VTEU Sites only							
E (CMI with exploratory serology)	24 (18 mRNA-1273: 6 placebo)	X		X		X	X

Abbreviations: CMI = cell-mediated immunity; D = day; VTEU = Vaccine and Treatment Evaluation Units.

1. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing.
2. If a Day 1 (Baseline) blood sample cannot be obtained, the participant will be considered either a screen failure due to inability to satisfy inclusion criteria 3 or could be scheduled for rescreening (allowed once) within the Screening Period. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3.

10.2. APPENDIX 2: Study Governance Considerations

10.2.1. 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.

10.2.2. 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 do the following:

- 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, the designated CRO, and the investigator.

According to ICH GCP guidelines, 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 the 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 that AEs and SAEs have been properly documented on eCRFs, that any SAEs have been forwarded to the SAE Hotline, and that those SAEs that meet criteria for reporting have been forwarded to the IRB.

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

10.2.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct study 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 study 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 E6(R2) GCP, 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 informed consent/assent forms and recruitment materials, must be maintained by the investigator and made available for inspection.

10.2.4. 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.

10.2.5. Recruitment Procedures

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.

10.2.6. Informed Consent/Assent Process

The informed consent and assent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, the Health Insurance Portability and Accountability Act, where applicable, and the IRB or study site. All consent/assent documents will be approved by the appropriate IRB. The actual ICF used at each study 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 willingness to continue participation 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 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 he/she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participants' 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.

10.2.7. 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 that may impact the conduct of the study or 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 an amendment will be released by the Sponsor, agreed to 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 to by the investigators, and notified to the IRB(s).

10.2.8. Protocol Deviations

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

It is the responsibility of the study 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 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.

10.2.9. 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 that 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 quality assurance (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 health care 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, the 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.

10.2.10. Sample Retention and Future Biomedical Research

The retention period of laboratory samples will be 20 years, or as permitted by local regulations, to address further scientific questions related to mRNA-1273 or anti-respiratory virus immune response. In addition, identifiable samples can be destroyed at any time at the request of the participant. 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. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1273, 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.

10.2.11. 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), and 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.

10.2.12. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the study site under the supervision of the study 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 study 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 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 less than 2 years. 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.

10.2.13. 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 WHO - Drug Dictionary.

10.2.14. 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.

10.2.15. 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.

10.2.16. 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 participants and should ensure 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 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.

10.2.17. 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.

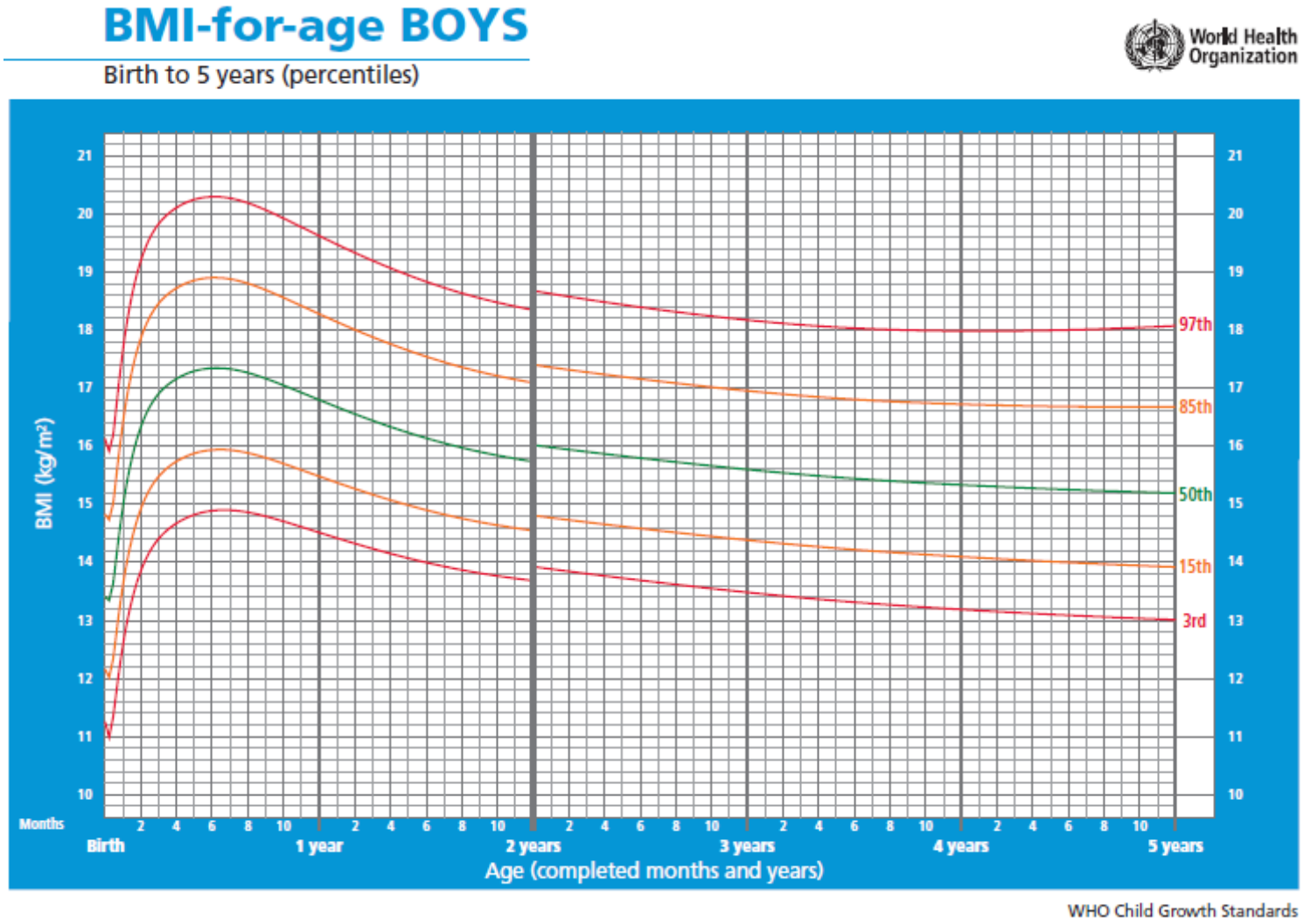
The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating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

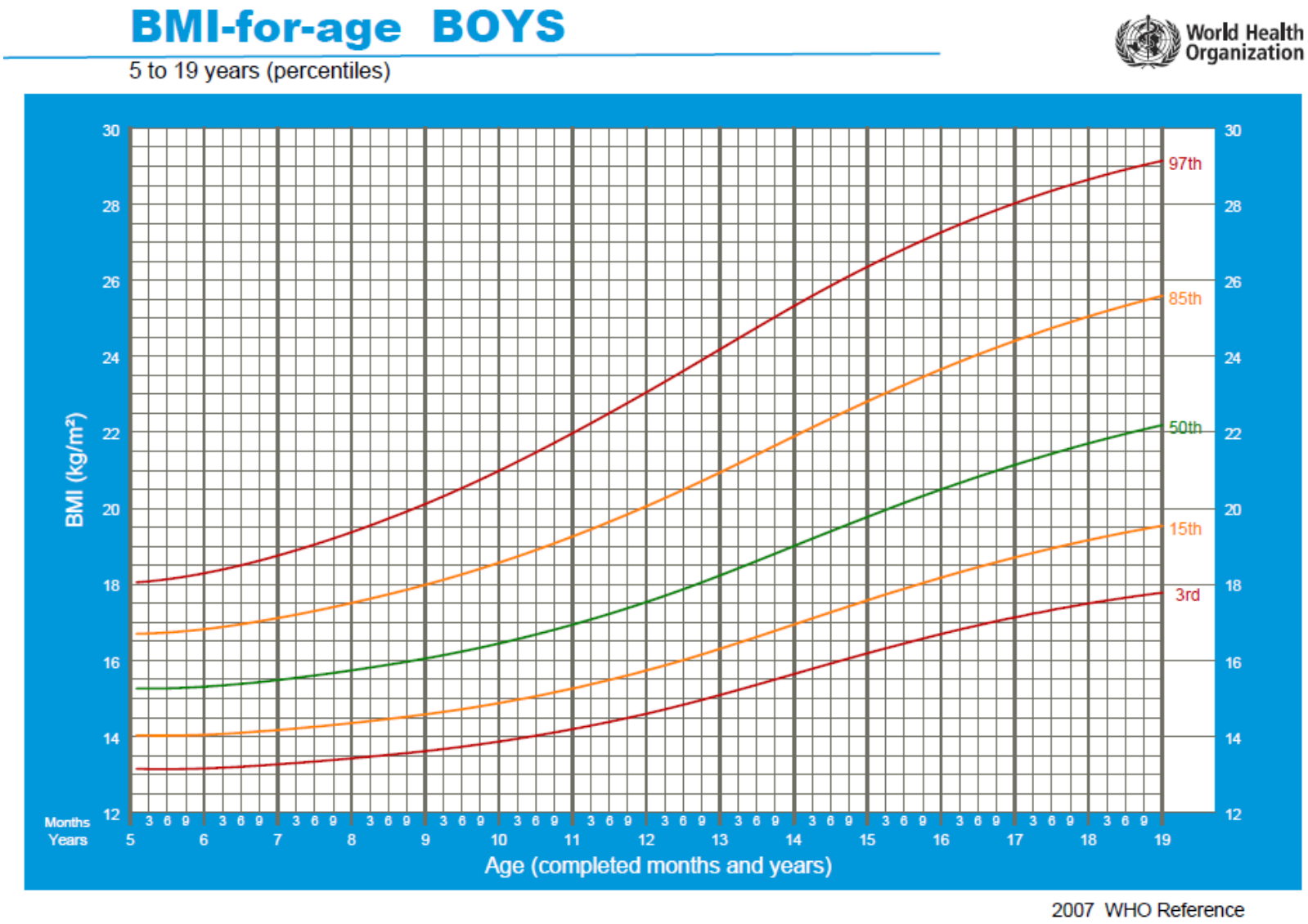
The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results and data from this study belong to the Sponsor.

10.2.18. Body Mass Index Charts for Boys and Girls

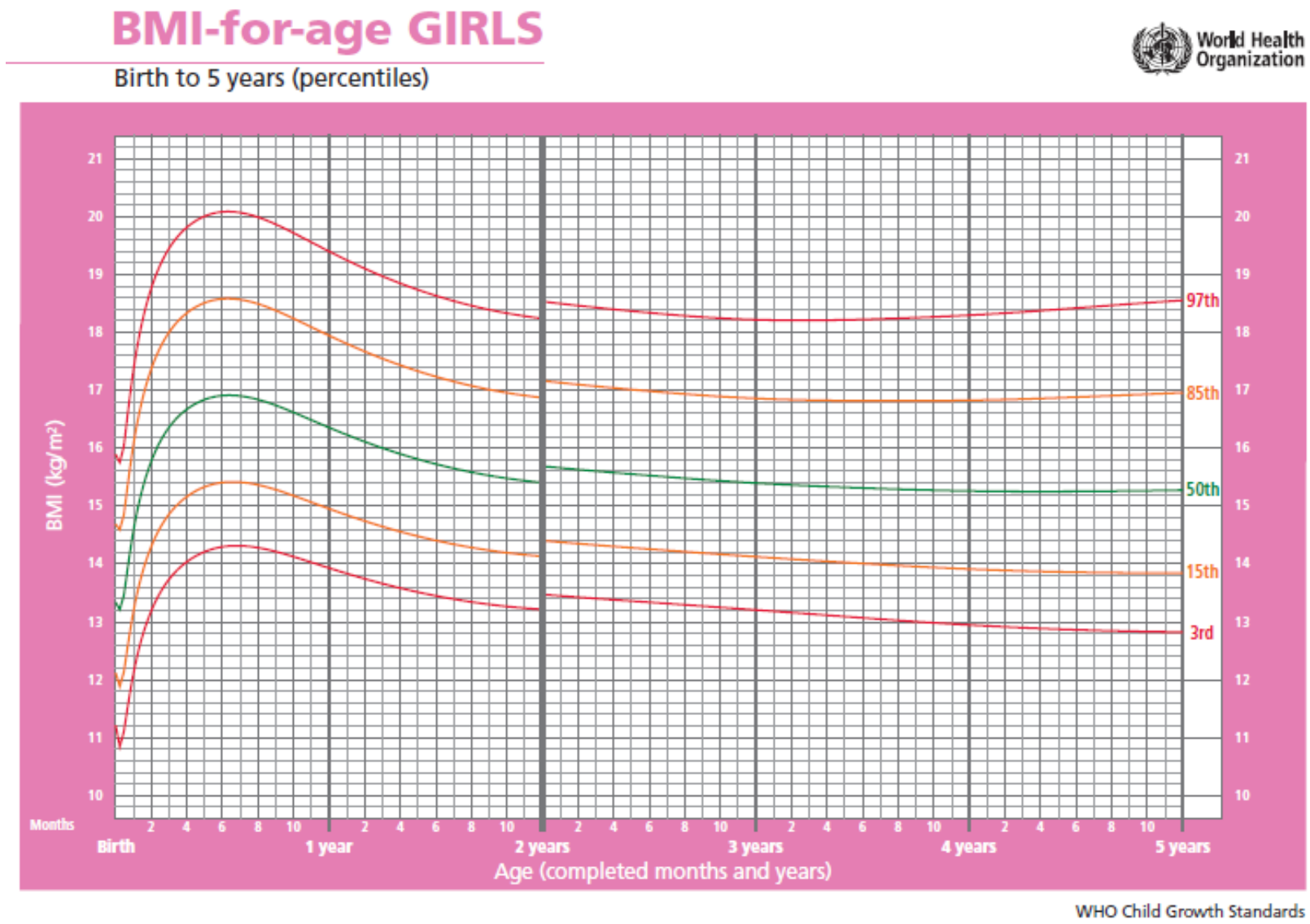
For boys from birth to 5 years:



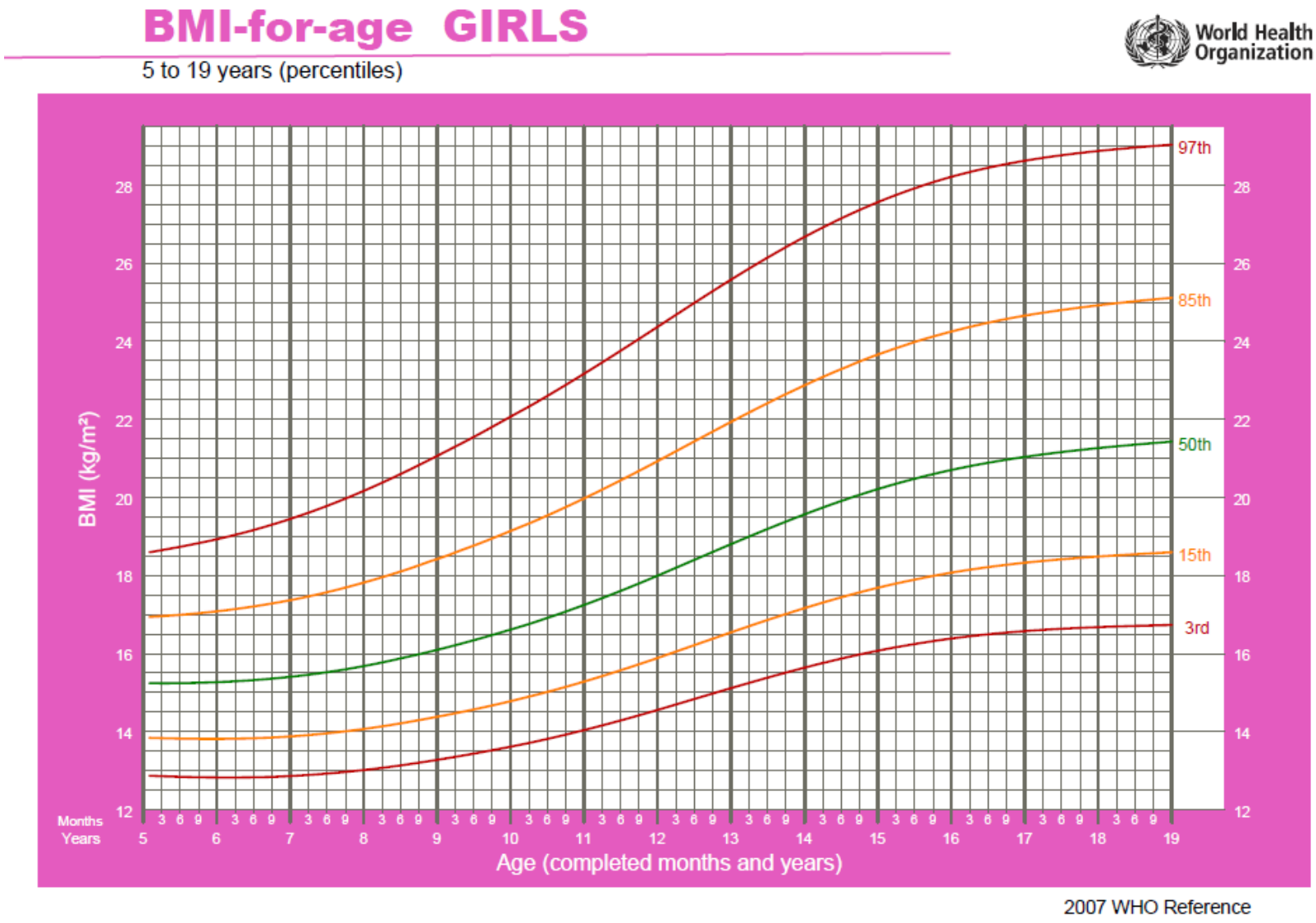
For boys aged 5 through 19 years:



For girls from birth to 5 years:



For girls aged 5 through 19 years:



10.3. APPENDIX 3: Contraceptive Guidance

Woman of Childbearing Potential (WOCBP)

Females of childbearing potential are those who are considered fertile following menarche and unless permanently sterile (see below). If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Surgically sterile female with one of the following:
    a. Documented complete hysterectomy
    b. Documented surgical sterilization

    For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study entry.

    Note: Documentation can come from the study site personnel's review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

Adequate female contraception is defined as consistent and correct use of an FDA-approved contraceptive method in accordance with the product label, for example:

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via the oral (pill), transdermal (patch), subdermal, or IM route

Note: While **complete abstinence is accepted** as adequate female contraception in this age group, periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

Signature Page for VV-CLIN-002040 v2.0

Approval	Conor Knightly Clinical 25-Feb-2021 00:29:44 GMT+0000

Approval	Jacqueline Miller Clinical 25-Feb-2021 00:46:27 GMT+0000

Approval	Charbel Haber Regulatory 25-Feb-2021 00:53:02 GMT+0000

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Approval	David Martin Pharmacovigilance 25-Feb-2021 03:21:32 GMT+0000

Signature Page for VV-CLIN-002040 v2.0

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age
Protocol Number:	mRNA-1273-P204
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	Sabine Schnyder Ghamloush, MD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: 1-617-758-9453 e-mail: sabine.schnyder.ghamloush@modernatx.com
Regulatory Agency Identifier Number(s):	IND: 019745
Amendment Number:	5
Date of Amendment 5:	29 Sep 2021
Date of Amendment 4:	25 Aug 2021
Date of Amendment 3:	23 Jul 2021
Date of Amendment 2:	17 Jun 2021
Date of Amendment 1:	30 Apr 2021
Date of Original Protocol:	24 Feb 2021

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title: A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age

Protocol Number: mRNA-1273-P204

Amendment Number: 5

Date of Amendment: 29 Sep 2021

Protocol accepted and approved by:

Please see eSignature and date in the last page of the document.

Rituparna Das, MD, PhD
Clinical Development – COVID-19 Vaccines
ModernaTX, Inc.
200 Technology Square
Cambridge, MA 02139
Telephone: 617-710-9794

Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol titled "A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age" 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 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	

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	29 Sep 2021
Amendment 4	25 Aug 2021
Amendment 3	23 Jul 2021
Amendment 2	17 Jun 2021
Amendment 1	30 Apr 2021
Original Protocol	24 Feb 2021

Amendment 5, (29 Sep 2021): Current Amendment

Main Rationale for the Amendment:

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/European Commission (EC) of the European Parliament and the Council of the European Union.

The main rationale for this amendment is to simplify the process for potential cross-over vaccination given the increased sample size of the study and to ensure retention in the study for safety follow-up, incorporate Clarification Memo #8, align with the Cardiac Event Adjudication Committee (CEAC) charter, and clarify the Data Safety Monitoring Board (DSMB) safety data review process for the younger age groups (2 to < 6 years; 6 months to < 2 years) to match the process in the older age group (6 to < 12 years) and allow DSMB review of Part 1 (open-label phase) data before start of Part 2 (blinded phase) for the younger age groups. Additional updates were made to clarify the statistical analysis plan, including the inferred efficacy analysis and interim analyses.

The summary of changes table provided below describes the major changes made to Amendment 5 relative to Amendment 4, including the sections modified and corresponding rationales. The synopsis of Amendment 5 has been modified to correspond to changes in the body of the protocol. Minor copy edits and administrative updates were made throughout the protocol to align with new content as well as for clarity, readability, and/or accuracy.

Summary of Major Changes in Protocol Amendment 5:

Section # and Name	Description of Change	Brief Rationale
Section 3.1 (General Design; Figure 1), Section 3.1.1.2 (Treatment and Follow-up Period), Section 7.2 (Blood Collections for Immunogenicity	Made updates to explain that blood sample collection for participants in Cohort D will be prior to randomization and the first dose at Day 1 and within 4	For clarification.

Assessments and Biomarker Samples), Appendix 1 (Schedule of Assessments; Table 10)	days of receiving Dose 2 at Day 30 (+ 3 days).	
Section 3.3 (Justification for Dose, Control Product, and Choice of Study Population), Appendix 1 (Schedule of Assessments)	Made updates to Section 3.3 to clarify the justification for the choice of study population, including unblinding of eligible study participants, placebo recipient cross-over vaccination, booster dose eligibility for participants who received a lower dose in Part 1 than was ultimately approved for their respective age group in Part 2, and study discontinuation for participants receiving an EUA vaccine outside the protocol. In accordance with changes made to Section 3.3, updated text and Table 11 in Appendix 1 to clarify placebo recipient cross-over vaccination.	Given the increase in sample size, unblinding via clinic visit is no longer feasible and will instead be performed over the phone, if desired by the family. To ensure retention in the study for safety follow-up, cross-over vaccination will be offered to all placebo recipients per their request if any COVID-19 vaccine (mRNA-1273 or other) becomes authorized or licensed for their age group.
Section 4.2 (Exclusion Criteria)	Added text to exclusion criteria #8 to provide context related to the influenza vaccine.	For incorporation of Clarification Memo #8.
Section 6.1.1 (Individual Participant Criteria for Delay of Study Vaccination)	Provided text in Section 6.1.1 to describe additional reasons to delay study vaccination for participants.	For incorporation of Clarification Memo #8.
Section 7.3.3 (Follow-up/Convalescent Period After Diagnosis with COVID-19)	Deleted text, “Study participants will be monitored by trained study site personnel for a 28 day period after diagnosis.”	For accuracy.
Section 7.4.5 (Adverse Events of Special Interest), Section 7.5.2 (Data Safety Monitoring Board)	Clarified that the CEAC will review suspected cases of myocarditis/pericarditis to determine if they meet CDC criteria of “probable” or “confirmed” event and to assess severity, but recommendations to the Sponsor to continue vaccine dosing will be made by DSMB.	To align with CEAC charter.
Section 7.5.2 (Data Safety Monitoring Board)	Changed description of timing of DSMB review and scope for younger age groups (2 to < 6 years; 6 months to < 2 years) from separate reviews in each age group with data from Part 1 and Part 2 during the conduct of	To allow the DSMB to review data from Part 1 (open-label phase) for all doses used in < 6 year old participants before starting Part 2 for 2 to < 6 years and 6 months to < 2 years age groups.

	Part 2 to one review of all available Part 1 safety data for all doses used in < 6 years before start of Part 2 for each age group.	
Section 8.5.4 (Inferred Efficacy Analysis)	Added text to explain the following: 1) analyses of efficacy endpoints in Part 2 will be performed for the randomized blinded phase, and 2) additional exploratory analyses will be conducted in the blinded and unblinded phases for participants randomized to mRNA-1273 in Part 2, and in the unblinded phase for participants who are originally randomized to the placebo arm and cross-over to mRNA-1273 after use of any COVID-19 vaccine is authorized or licensed for the participant's age group.	For clarification.
Section 8.6.1 (Interim Analyses)	Updated description of Part 2 to indicate that an interim analysis of immunogenicity and safety will be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 1 or Part 2 within an age group.	For clarification.
Appendix 1 (Schedule of Assessments; Table 10 and Table 11)	Updated footnote #2 in Table 10 and added footnote #2 to Table 11 to include cross-references for Section 6.1.1.	For alignment.

Abbreviations: CDC = Centers for Disease Control and Prevention; CEAC = Cardiac Event Adjudication Committee; COVID-19 = coronavirus disease 2019; DSMB = Data Safety Monitoring Board; EUA = Emergency Use Authorization; mRNA = messenger RNA; SoA = Schedule of Assessments.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1273 for injection

Name of Active Ingredient: mRNA-1273

Protocol Title: A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age

Protocol Number: mRNA-1273-P204

Study Period (years): Approximately 14 months

Phase of Development: Phase 2/3

Estimated date first participant enrolled: 15 Mar 2021

Estimated date last participant completed: 12 Jun 2023

Total Number of Sites: Approximately 75 to 100 study sites in the United States and Canada.

Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of up to 3 dose levels (25, 50, and 100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart in 3 age groups	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESIs, including MIS-C and myocarditis and/or pericarditis, through the entire study period
• To infer the efficacy of mRNA-1273 (25, 50, and 100 μg, administered as	• The proportion of participants with a serum antibody level at Day 57 ≥ antibody threshold of protection

2 doses 28 days apart) based on immunogenicity in 3 age groups	– If an accepted serum antibody threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy • The GM value of serum antibody level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301) – If a threshold is not available, efficacy will be inferred by establishing noninferiority for each age group (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years in Study P204) compared to 18- to 25-year old participants (Study P301) by both GM value of serum antibody levels and seroresponse rate. A definition of seroresponse will be provided in the statistical analysis plan based on forthcoming information about assay performance
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 μg) administered as 2 doses 28 days apart	• The GM values of SARS-CoV-2 S protein-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2) • The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)
• To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• 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: – bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by Roche Elecsys) postbaseline, OR – Positive RT-PCR postbaseline
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) postbaseline in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms.
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with COVID-19 AND positive RT-PCR for SARS-CoV-2	• The incidence of the first occurrence of COVID-19 postbaseline, where COVID-19 is defined as symptomatic disease based on CDC case definition.[1]
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence
• To describe the ratio or profile of specific S protein bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb titers in serum
• 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 assess, in a subset of participants, the SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points after vaccination relative to baseline

• To explore asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; CDC = Center for Disease Control; COVID-19 = coronavirus disease 2019; GM = geometric mean; GMFR = geometric mean fold-rise; IgG = immunoglobin G; IP = investigational product; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; mRNA = messenger RNA; nAb = neutralizing antibody; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[1] 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.

Overall Study Design

This is a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study intended to infer the effectiveness of messenger RNA (mRNA)-1273 in children aged 6 months to < 12 years. The study population will be divided into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years), and up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 will be evaluated.

The study will be conducted in 2 parts. Part 1 of the study will be open-label and consist of dose-escalation and age de-escalation in approximately 1,275 participants to select the dose for each age group with the highest number enrolled in the oldest age group (the table below provides the approximate number of participants in each age group). Part 2 of the study will be a placebo-controlled observer-blind evaluation of the selected dose in up to 12,000 participants (up to 4,000 participants in each of the 6 to < 12 years, 2 to < 6 years, and the 6 months to < 2 years age groups). No participants in Part 1 will participate in Part 2 of the study.

In order to expedite the study of the safety of mRNA-1273 in school-aged children 6 to < 12 years of age; Part 1 will enroll a total of approximately 375 participants per dose (both at the 50 and 100 µg dose level) in this age group (6 to < 12 years). The first 75 of these participants per dose will be included in the safety evaluation for dose-escalation and age de-escalation as well as the immunogenicity assessment needed for dose selection, as applicable. Additionally, approximately 300 participants per dose will be enrolled to assess for any adverse event (AE) occurring at 1% or higher. Conversely, approximately 75 participants in the middle age group (2 to < 6 years) will be enrolled per dose in Part 1 for safety and dose selection and Part 2 will utilize the dose selected in Part 1 to inform on AEs occurring at a frequency of 1% or greater. In the youngest age group (6 months to < 2 years), approximately 150 participants will be enrolled per dose in Part 1 for safety and dose selection and Part 2 will utilize the dose selected in Part 1 to inform on AEs occurring at a frequency of 1% or greater. For more details, please refer to Safety Oversight.

The study will begin with the oldest age group (6 to < 12 years) and age de-escalate as described under Study Progression. Each age group will begin with Part 1 and advance to Part 2 independently.

The mRNA-1273 investigational vaccine or placebo will be administered as 2 intramuscular (IM) injections approximately 28 days apart.

The mRNA-1273 dose levels that will be evaluated in each age group in Part 1 and Part 2 of the study are given in the following table.

Planned Age Groups and mRNA-1273 Dose Levels in Part 1 and Part 2 of the Study

	Part 1			Part 2	
Age Group	**mRNA-1273 25 µg**	**mRNA-1273 50 µg**	**mRNA-1273 100 µg**	**Selected Dose Level of mRNA-1273 From Part 1**	**Placebo**
6 to < 12 years		Study Arm 1 (n=375)	Study Arm 2 (n=375)	Study Arm 8 (n= 3,000)	Study Arm 9 (n= 1,000)
2 to < 6 years	Study Arm 7 (Optional) (n=75)	Study Arm 3 (n=75)	Study Arm 4 (n=75)	Study Arm 10 (n= up to 3,000)	Study Arm 11 (n=up to 1,000)
6 months to < 2 years	Study Arm 5 (n=150)	Study Arm 6 (n=150)		Study Arm 12 (n= up to 3,000)	Study Arm 13 (n=up to 1,000)

Study Progression

Part 1 of the study will be open-label. The study will begin with enrollment of approximately 375 participants in the 6 to < 12 years age group (Study Arm 1), and dosing with 50 µg of mRNA-1273. After at least 75 participants in Study Arm 1 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an internal safety team (IST) will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 6 to < 12 years age group (Study Arm 2; n = 375) and independently whether to begin dosing at the 50-µg dose level in the 2 to < 6 years age group (Study Arm 3; n = 75). After at least 75 participants in Study Arm 1 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will again review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 2 and whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 3. Simultaneously, the enrollment of the remaining 300 planned participants in both Arms 1 and 2 will be ongoing. A preliminary safety and immunogenicity data review of Arm 1, and Arm 2 as applicable, will aid in the selection of a dose level for Part 2. Once all or a subset of participants from each of Study Arms 1 and 2 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the safety and immunogenicity data. Cumulative safety data for approximately 300 participants at the selected dose level will be reviewed by the Data Safety Monitoring Board (DSMB) before enrollment in Part 2, and the DSMB safety review recommendation will enable the expansion of the 6 to < 12 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 8; n = 3,000) or placebo (Study Arm 9; n = 1,000). The primary analysis of immunogenicity in Part 2 for Study Arm 8 (mRNA-1273 recipients) will be conducted after a pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis for Arms 8 and 9 will be conducted after a subset or all participants reach Day 57.

For the middle age group (2 to < 6 years) progression in Part 1 will be as follows: After 75 participants in Study Arm 3 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an IST will review the available safety data and provide a recommendation whether

to escalate the dose to 100 µg in the 2 to < 6 years age group (Study Arm 4; n = 75) and whether to begin dosing in the 6 months to < 2 years age group at the 25 µg-dose level (Study Arm 5; n = 150). After the 75 participants in Study Arm 3 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 4 and whether to administer Dose 2 of mRNA-1273 25 µg in Study Arm 5. An optional Arm 7 may be enrolled in this age group (approximately 75 participants) at the 25-µg dose if the 100-µg dose is eliminated at any point during dose escalation process, to maintain dose ranging for this age group. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2. Once all or a subset of participants in all applicable Arms reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review safety and immunogenicity data. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2 and for expansion of the 2 to < 6 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 10; n = up to 3,000) or placebo (Study Arm 11; n = up to 1,000). The primary analysis of immunogenicity in Part 2 for Study Arm 10 (mRNA-1273 recipients) will be conducted after a pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis for Arms 10 and 11 will be conducted after a subset or all participants in Arms 10 and 11 reach Day 57.

For the youngest age group (6 months to < 2 years) progression in Part 1 will be as follows: In Study Arm 5, after 150 participants have completed Day 8 (1 week after Dose 1 of mRNA-1273 25 µg), an IST will review the available safety data and provide a recommendation whether to escalate the dose to 50 µg (Study Arm 6; n = 150). After the 150 participants in Study Arm 5 reach Day 36 (1 week after Dose 2 of mRNA-1273 25 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 6. Once all or a subset of participants in Study Arms 5 and 6 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the tolerability and immunogenicity data at each dose level. A preliminary safety and immunogenicity data review of Arm 5 and Arm 6, as applicable, will aid in the selection of a dose level for Part 2 and allow for expansion of the 6 months to < 2 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 12; n = up to 3,000) or placebo (Study Arm 13; n = up to 1,000). The primary analysis of immunogenicity in Part 2 for Study Arm 12 (mRNA-1273 recipients) will be conducted after the pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis will be conducted after a subset or all participants in Arm 12 and 13 reach Day 57.

In general, if a decision is made not to proceed with administration of a higher dose and/or the second injection at a given dose level (eg, due to safety concerns), the participants scheduled to receive the higher dose may receive a lower dose, and the participants who had

received the higher dose level as their first injection will likely be given the next lower dose level that was tolerated for their second injection. The dose level not tolerated in the older age group will not be administered in any of the younger age groups. Within an age group, if one of the dose levels is found to have an unacceptable tolerability profile, the age group may progress to Part 2 at a lower dose level.

The final analysis will be performed when participants (Study Arms 1 to 13) conclude the safety follow-up at 12 months.

The goal of the study is to support an indication for use of mRNA-1273 50 or 100 µg IM, given as 2 injections, approximately 28 days apart in the 6 to < 12 years age group; mRNA-1273 25, 50, or 100 µg IM, given as 2 injections, approximately 28 days apart in the 2 to < 6 years age group; and mRNA-1273 25 or 50 µg IM, given as 2 injections, approximately 28 days apart in the 6 months to < 2 years age group. The basis for demonstrating vaccine effectiveness is proposed to be met by measuring serum antibody responses in the study participants. The approach to inferring vaccine effectiveness will depend on whether an accepted serum antibody threshold conferring protection against coronavirus disease 2019 (COVID-19) has been established. If an antibody threshold of protection has been established, effectiveness will be inferred based on the proportion of study participants with serum antibody levels (on Day 57) that meet or exceed the antibody threshold. If an antibody threshold of protection has not been established, effectiveness will be inferred based on demonstrating noninferiority for each age group (6 to < 12 years, 2 < 6 years, and 6 months to < 2 years in Study P204) compared to young adult (18 to 25 years of age) participants enrolled in the ongoing clinical endpoint efficacy trial (Study P301) by both geometric mean (GM) values and seroresponse rate.

This study in children 6 months to < 12 years of age will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. If a COVID-19 vaccine is authorized for a specific age group before the end of the study, please refer to the Justification for Dose, Control Product, and Choice of Study Population Section in the protocol for unblinding and/or cross-over plans. Safety assessments will include solicited adverse reactions (ARs) (the day of injection and 6 subsequent days), unsolicited adverse events (AEs; 28 days after each injection), and medically attended adverse events (MAAEs), serious AEs (SAEs), and adverse events of special interest (AESIs; including multisystem inflammatory syndrome in children [MIS-C] and myocarditis and/or pericarditis) throughout the study period.

Blood samples will be collected from participants in Part 1 and Part 2 of the study for assessment of immunogenicity. If a Day 1 (baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be rescheduled for rescreening. Participants may be rescreened 1 time, either within the same screening period for Part 1 or Part 2 or in a new

screening period of Part 2 if the initial screening was in Part 1. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3. All participants in Part 1 of the study will provide blood specimens for immunogenicity on Day 1 (prior to the first dose) and will also provide additional samples after the second dose of mRNA-1273 at Day 57, Day 209, and Day 394, except for the expansion of Arms 1 and 2 (N= ~300 participants per arm) who have a scheduled Day 1 blood draw and a voluntary blood draw on Day 57 only. Participants in each age group in Part 2 will be assigned to 1 of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1 (prior to randomization and before the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the Cohort D (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and before the first dose) and within 4 days of receiving Dose 2 at Day 30 (+3 days) for storage and potential future biomarker testing. A fifth cohort of participants (selected Vaccine and Treatment Evaluation Units [VTEU] sites only) will provide blood samples for assessment of exploratory serology and cell-mediated immunity (CMI; spike [S]-protein-specific T cell responses) on Day 1 (prior to randomization and before the first dose), Day 43, Day 209, and Day 394. Blood samples will also be tested for the development of antibodies directed against nonvaccine antigen (eg, antibodies against the nucleocapsid protein), which will signify infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients. In addition, all participants will be monitored for symptoms of COVID-19 and scheduled for illness visits if concerning symptoms occur, and a nasal swab will be collected at the illness visit.

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. For Part 1 dose-escalation and age de-escalation, based on the review of all available safety data through at least Day 8 (1 week after Dose 1 of mRNA-1273) for at least 75 participants at each dose level within the 6 to < 12 years and 2 to < 6 years age group, the IST will recommend whether dose-escalation and age de-escalation are appropriate. This process will then be repeated for all participants in the 25 and 50 µg dose levels within the lower age group of 6 months to < 2 years of age. An IST review of all available safety data through at least Day 36 (1 week after Dose 2 of mRNA-1273 at each dose level) of at least 75 participants will be required prior to the administration of the second injection of the next higher dose. 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.

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 the study conduct and free of conflict of interest. The DSMB will meet at pre-specified timepoints during the study to assess safety throughout the study conduct. For the 6 to < 12 years age group, the DSMB will review cumulative safety data for approximately 300 participants enrolled at the selected dose level in Part 1 before enrollment begins in Part 2. For both the middle age group (2 to < 6 years) and the youngest age group (6 months to < 2 years) the DSMB will review cumulative safety data in both younger age groups (2 to < 6 years; 6 months to < 2 years) combined and at all dose levels administered in Part 1, before start of Part 2 (blinded phase) for each age group. 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 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.

A Cardiac Event Adjudication Committee will adjudicate any suspected cases of myocarditis, pericarditis, or myopericarditis and enable the DSMB to make recommendations to the Sponsor.

Study Duration: The study duration for each participant will be approximately 14 months, which includes 1 month for screening (Day -28 to Day -1), 1 month for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose of investigational product (IP).

Number of Participants:

Part 1: Approximately 1,275 participants (approximately 750 participants in the 6 to < 12 years age group, approximately 225 participants 2 to < 6 years age group, and approximately 300 participants in the 6 months to < 2 years age group).

Part 2: Up to 12,000 participants (up to 3,000 participants each exposed to mRNA-1273 and 1,000 participants exposed to placebo in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years age groups).

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, 6 months to < 12 years of age at the time of consent/assent (Screening Visit), who is in good general health, in the opinion of the investigator, based on review of medical history and screening physical examination.
2. If the participant has a chronic disease (eg, asthma, diabetes mellitus, cystic fibrosis, human immunodeficiency virus [HIV] infection), the disease should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion. Stable diseases are those which have had no change in their status or in the medications required to control them in the 6 months prior to Screening Visit.

   Note: a change in medication for dose optimization (eg, insulin dose changes), change within class of medication, or reduction in dose are not considered signs of instability.
3. In the investigator's opinion, the parent(s)/legally acceptable representative(s) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures, and provide written informed consent and participants are willing to provide assent.
4. The participant is 2 years or older and has a body mass index at or above the third percentile according to WHO Child Growth Standards at the Screening Visit.

   The participant is less than 2 years of age and the participant's height and weight are both at or above the 3rd percentile according to WHO Child Growth Standard at the Screening Visit.
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche.

Special inclusion criteria for female participants who have reached menarche:

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all of the following criteria:
   - Has a negative pregnancy test at Screening. Pregnancy test will be performed if deemed appropriate by the investigator.
   - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
   - Has agreed to continue adequate contraception or abstinence through 3 months

following the second injection (Day 29).

- Is not currently breastfeeding.

Adequate female contraception is defined as abstinence or consistent and correct use of a US Food and Drug Administration-approved contraceptive method in accordance with the product label.

Special inclusion criteria for children 6 months to < 12 months of age

7. The participant was born at full-term (≥ 37 weeks gestation) with a minimum birth weight of 2.5 kg.

Exclusion Criteria:

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

1. Has a known history of SARS-CoV-2 infection within 2 weeks prior to administration of IP or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of IP.
2. Is acutely ill or febrile 24 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. Has previously been administered an investigational or approved CoV (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome-CoV) vaccine.
4. Has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (eg, receipt of SARS-CoV-2 monoclonal antibodies) within 6 months prior to enrollment.
5. 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 a previous dose of messenger RNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG] or immediate allergic reaction of any severity to polysorbate).
6. Has a medical or psychiatric condition 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. Has a history of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically the following:
    - Congenital or acquired immunodeficiency, excluding HIV infection, as

described in Inclusion Criteria 2

- Chronic hepatitis or suspected active hepatitis
- A bleeding disorder that is considered a contraindication to IM injection or phlebotomy
- Dermatologic conditions that could affect local solicited AR assessments
- Any prior diagnosis of malignancy (excluding nonmelanoma skin cancer)
- Febrile seizures*

  *In Part 2 of the study, a history of a single, simple febrile seizure is allowed for children 6 years and older.

8. Has received the following:

   - Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to first vaccination or plans to receive such a vaccine through 14 days following the last study vaccination.

     - Note: This excludes influenza vaccine that may be given, however, not within 14 days prior to or post Dose 1 or Dose 2. If a participant receives an influenza vaccine, this should be captured within the concomitant medication electronic case report form (eCRF) (Section 5.5.2).

   - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 1 mg/kg/day or ≥ 10 mg/day prednisone equivalent, if participant weighs > 10 kg). 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.

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

9. 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.

10. Is an immediate family member, or household contact, of an employee of the study site or Moderna 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.

Study Treatment:

Investigational Product:

The term IP refers to mRNA-1273 (25, 50, and 100 μg) vaccine or placebo (0.9% sodium chloride) in this study.

mRNA-1273 is a lipid nanoparticle (LNP) dispersion of an mRNA that encodes the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid heptadecan-9-yl 8-((2hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with PEG of average molecular weight 2000 (1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000 [PEG2000-DMG]). mRNA-1273 injection is provided as a sterile liquid for injection and is a white to off-white dispersion at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 4.3 mM sodium acetate at pH 7.5.

Mode of Administration:

Each participant will receive 2 doses of IP by IM injection approximately 28 days apart (Day 1 and Day 29) into the deltoid muscle or anterolateral thigh (per investigator's discretion).

Procedures and Assessments:

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 (eDiary).
- Unsolicited 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 dosing and/or study participation from Day 1 through the last day of study participation.
- MAAEs from first dose on Day 1 through the entire study period.
- SAEs from first dose on Day 1 through the entire study period.
- AESIs including MIS-C and myocarditis and/or pericarditis, through the entire study period.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

Blood Collections for Immunogenicity Assessments and Biomarker Samples:

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.
- Serum binding antibody (bAb) titer as measured by enzyme-linked immunosorbent assay specific to the SARS-CoV-2 S protein.
- For Part 1, testing for serologic markers for SARS-CoV-2 infection using a nonvaccine antigen-based blood test at Day 1 (prior to the first dose), Day 57, Day 209, and Day 394.

For Part 2, participants in each age group will be assigned to 5 phlebotomy cohorts. Blood sampling will be performed in 3 of these 5 cohorts for immunogenicity at 3 of the following time points: Day 1 (prior to randomization and the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, and Day 394. Participants in the Cohort D (remainder

of the age group) will provide a blood sample at Day 1 (prior to randomization and the first dose) and within 4 days of receiving Dose 2 at Day 30 (+3 days) for storage and potential future biomarker testing (may include cardiac biomarkers). For participants already enrolled in Cohort D prior to amendment 4, this blood draw will be optional and confirmed at time of re-consenting; for all participants newly enrolled into Cohort D under amendment 4, it will be mandatory. A fifth cohort of participants at selected VTEU sites only, will provide blood samples for assessment of exploratory serology and CMI on Day 1 (prior to randomization and the first dose), Day 43, Day 209, and Day 394.

Inferred Efficacy Assessments:

Vaccine effectiveness for children 6 months to < 12 years of age will be inferred based on serum antibody responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the antibody responses against the following:

1. *If available at the time of analysis*, antibody responses will be assessed against an accepted serum antibody threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, noninferiority of the geometric mean (GM) value of serum antibody and seroresponse rate of children 6 months old to < 12 years old (Study P204) compared with the GM value of serum antibody and seroresponse rate from young adults (18 to 25 years of age) enrolled in the ongoing clinical endpoint efficacy trial (Study P301) will be assessed.

Statistical Methods:

Hypothesis Testing:

If an accepted antibody threshold of protection against COVID-19 is established for the primary immunogenicity endpoint, the null hypothesis is that the percentage of participants on mRNA-1273 with serum antibody above the established threshold at Day 57 is ≤ 70% (ie, H_0: percentage of participants on mRNA-1273 with serum antibody at Day 57 above the established threshold ≤ 70%).

For each age group, the study will be considered to meet the immunogenicity endpoint if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 70% (lower bound of the 95% CI is > 70%).

The null hypotheses may be updated when the information on an acceptable antibody threshold becomes available. In this case, the null hypothesis update will be provided in the statistical analysis plan (SAP).

If an accepted serum antibody threshold of protection against COVID-19 is not available for the primary immunogenicity endpoint, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 antibody levels will be compared to

Day 57 antibody levels from young adults (18 to 25 years of age) in Study P301. Noninferiority tests of 2 null hypotheses based on 2 coprimary endpoints will be performed, respectively.

Coprimary endpoint 1: antibody GM value at Day 57

The null hypothesis H^1_0: immunogenicity response to mRNA-1273, as measured by antibody GM value at Day 57, is inferior in children (in age groups 6 months to < 2 years, 2 to < 6 years, and 6 to < 12 years) compared with that in young adults (18 to 25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in antibody GM value in an age group in children compared with that in young adults (18 to 25 years of age) is demonstrated by meeting both success criteria:

- The lower bound of the 95% CI of the geometric mean ratio (GMR) ruling out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, AND
- The GMR point estimate > 0.8 (minimum threshold).

The GMR is the ratio of the GM value of SARS-CoV-2-specific antibody in children in an age group receiving mRNA-1273 in this Study P204 compared with the GM value of young adults (18 to 25 years of age) receiving mRNA-1273 in Study P301 at Day 57.

Coprimary endpoint 2: antibody seroresponse at Day 57

A definition of seroresponse will be provided in the statistical analysis plan (SAP) based on forthcoming information about assay performance.

The null hypothesis H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in children compared with that in young adults (18 to 25 years of age) in Study P301.

The noninferiority in seroresponse rate in an age group in children compared with that in young adults (18 to 25 years of age) is demonstrated by meeting both success criteria:

- The lower bound of the 95% CI of the seroresponse rate difference ruling out -10% (ie, lower bound > -10%) using the noninferiority margin of 10%, AND
- The seroresponse rate difference point estimate > -5% (minimum threshold)

The seroresponse rate difference is defined as the seroresponse rate in children receiving mRNA-1273 minus the seroresponse rate in young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301.

The study would be considered to meet the primary immunogenicity endpoint in an age group if the noninferiority in the age group compared with the young adults (18 to 25 years of age) is demonstrated based on both coprimary endpoints.

Power and Sample Size:

The initial age groups in Part 1 are for estimation purposes. With 750 participants (approximately 375 participants at each dose level) in the initial 6 to < 12 years age group, there is at least a 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% for a given dose level. In each of the younger age groups (2 to < 6 years and 6 months to < 2 years), the safety assessment will occur during the conduct of Part 2 after approximately 375 participants have been exposed to mRNA-1273 at the dose level selected for Part 2. For further details, please refer to the DSMB Section in this synopsis.

The sample size in the expansion (Part 2) is considered to be sufficient to support a safety database in the pediatric participants 6 months to < 12 years of age. With approximately 3,000 participants each in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years of age groups exposed to mRNA-1273 at a given dose level in Part 2, the study has at least a 95% probability to observe at least 1 participant with an AE at a true 0.1% AE rate for a given dose level.

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group will be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset will be processed, and the analysis of primary immunogenicity endpoint will be based on the Immunogenicity Per-Protocol (PP) Subset.

If a threshold of protection is available, for the primary immunogenicity endpoint, with approximately 289 participants on mRNA-1273 in the Immunogenicity PP Subset of an age group, there will be at least 90% power to rule out 70% with a 2-sided 95% CI (lower bound of the 95% CI > 70%) for the percentage of mRNA-1273 participants exceeding the accepted threshold if the true rate of participants exceeding the threshold is 80%.

If an acceptable antibody threshold of protection against COVID-19 is not available at the time of analysis for the primary immunogenicity endpoint, noninferiority tests of the 2 null hypotheses based on the 2 coprimary endpoints, respectively, will be performed. The sample size calculation for each of the 2 noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be 90% power to demonstrate noninferiority of the immune response, as measured by the antibody GM value, in pediatric population at a 2-sided alpha of 0.05, compared with that in young adults (18 to 25 years of age) in Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1, a noninferiority margin of 0.67 (or 1.5) and a point estimate minimum threshold of 0.8. The standard deviation of the natural log-transformed levels is assumed to be 1.5.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in children at a 2-sided alpha of 0.05, compared with that in young adults 18 to 25 years of age in Study P301 receiving mRNA-1273, assuming seroresponse rate of 85% in young adults of 18 to 25 years of age from Study P301, true seroresponse rate of 85% in children (or true rate difference is 0 compared to young adults from Study P301), a noninferiority margin of 10% and a point estimate minimum threshold of -5% in seroresponse rate difference.
- In the 1273-P203 interim analysis (data snapshot on 08 May 2021), the observed seroresponse rates at Day 57 were high in both 18 to 25 years of age group from Study P301 (98.6% with 95% CI: 96.6, 99.6) and 12 to17 years of age group (98.8% with 95% CI: 97.0, 99.7), based on pseudovirus nAb ID50 titers. For this Study P204, if the true seroresponse rates were assumed to be 95% or higher in both 18 to 25 years of age group from Study P301 and an age group in children, with between-group true difference within 4%, there will be a >90% power to demonstrate noninferiority by seroresponse rate in children compared with 18 to 25 years of age in Study P301, at a 2-sided alpha of 0.05

Assuming approximately 25% of participants in the Immunogenicity Subset will not meet the criteria to be included in the Immunogenicity PP Subset, approximately 528 participants in Part 2 (~396 receiving mRNA-1273 and ~132 receiving placebo) will be selected for the Immunogenicity Subset from which approximately 289 participants on mRNA-1273 will be suitable for the Immunogenicity PP Subset.

Analysis Sets:

The analysis sets are defined in the following table:

Analysis Set	Description
Randomization Set	Part 2: All participants who are randomly assigned, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	Part 1: All enrolled participants in Part 1 who receive at least 1 injection of IP Part 2: All randomly assigned participants who receive at least 1 injection of IP

Per-Protocol (PP) Set	All participants in the FAS who receive planned doses of IP per schedule, comply with the immunogenicity schedule, and have no major protocol deviations that impact key or critical data. Participants who are RT-PCR positive or seropositive at baseline will be excluded from the PP Set. The PP Set in Part 1 will be used for all analyses of immunogenicity in Part 1 unless specified otherwise.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity sampling and testing.
Per-Protocol Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset 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. Participants who are RT-PCR positive or seropositive at baseline will be excluded from the PP Immunogenicity Subset, in addition to participants with HIV who are receiving highly active anti-retroviral therapy (HAART). The PP Immunogenicity Subset will be used for all analyses of immunogenicity unless specified otherwise.
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	The Solicited Safety Set consists of participants in the Safety Set who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at Baseline
Modified Intent-to-Treat-1 (mITT1) 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)

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; IP = investigational product; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 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 and placebo) and by age group. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for safety analysis.

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, AEs leading to discontinuation, and physical examination findings.

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.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Immunogenicity Analyses:

The primary analysis population for immunogenicity will be the Immunogenicity PP Subset, unless specified otherwise. The primary objective of this study is to use the immunogenicity response to infer efficacy in participants aged 6 months to < 12 years at the dose level selected for expansion. For this objective, analyses of immunogenicity will be performed for each pediatric age group separately at the selected dose level based on the participants in the Immunogenicity PP Subset. For each pediatric age group, participants in Part 2 in the Immunogenicity PP Subset may be used for immunogenicity primary analysis. Participants from Part 1 and Part 2 who receive the same mRNA-1273 dose level selected for expansion may be combined for immunogenicity analyses. If the same dose level is selected for expansion for more than one age group, these age groups may be combined for immunogenicity analyses.

An accepted antibody threshold of protection against COVID-19 may be available based on data from other mRNA-1273 studies or external data. If such a threshold of protection against

COVID-19 is available, the number and percentage of participants with antibody greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. For an age group, if the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity endpoint of this study will be considered to be met for that age group.

The number and percentage of participants with serum antibody greater than or equal to the threshold with 2-sided 95% CI will be provided at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum antibody threshold of protection against COVID-19 is not established, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 antibody levels will be compared to that in young adults (18 to 25 years of age) using data from Study P301. An analysis of covariance model will be carried out with antibody at Day 57 as dependent variable and a group variable (a pediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable for each pediatric age group. The GM values of the pediatric age group at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI will be provided to assess the difference in immune response between the pediatric age group (Study P204) compared to the young adults (18 to 25 years of age) in Study P301 at Day 57. For each pediatric age group, the noninferiority of GM value will be considered demonstrated if:

- The lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5, AND
- The GMR point estimate > 0.8 (minimum threshold).

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 postbaseline time point with Day 57 being the primary interest. The seroresponse rate difference with 95% CI at Day 57 will be provided between children receiving mRNA-1273 in Study P204 and young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301. For each pediatric age group, the noninferiority of seroresponse rate will be considered demonstrated if:

- The lower bound of the 95% CI of the seroresponse rate difference is > -10% based on the noninferiority margin of 10%, AND
- The seroresponse rate difference point estimate > -5% (minimum threshold).

In addition, the GM value of anti-SARS-CoV-2-specific antibody 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 values then back transformed to the original scale. For

each age group, the geometric mean fold-rise of specific nAb and bAb with corresponding 95% CI at each postbaseline time point over preinjection baseline at Day 1 will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided.

Multiplicity adjustment between age groups:

A sequential hypothesis testing (fixed-sequence method) will be used to adjust multiplicity to preserve the family-wise Type I error rate (alpha = 0.05), starting with the oldest age group, followed by the middle age group, and then followed by the youngest age group. The immunogenicity coprimary endpoint hypotheses for the oldest age group (6 to < 12 years of age) will be tested first at alpha level of 0.05. If the testing in the oldest age group is statistically significant (meeting the noninferiority success criteria of the coprimary endpoints), the alpha level of 0.05 will be passed to the testing of the coprimary endpoint hypotheses in the middle age group (2 to < 6 years of age). If the testing in the middle age group is statistically significant at alpha level of 0.05, then the alpha 0.05 is preserved for testing the coprimary endpoint hypotheses in the youngest age group (6 months to < 2 years of age). The testing will continue through the sequence only until an endpoint in an age group is not statistically significant (did not meet noninferiority success criteria of any primary endpoint), in which case the testing will stop.

Inferred Efficacy Analyses:

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, dose level, and age group, calculated as the number of cases divided by the total person-time. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level (if applicable) may be combined in the analysis.

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

The secondary efficacy analyses will be performed in the PP Set, with sensitivity analyses in FAS, mITT Set, and mITT1 Set. Analyses of the efficacy endpoints in Part 2 will be performed for the randomized blinded phase. Additional exploratory analyses will be conducted in the blinded and unblinded phases for participants randomized to mRNA-1273 in Part 2, and in the unblinded phase for participants who are originally randomized to the placebo arm and cross-over to mRNA-1273 after use of any COVID-19 vaccine is authorized or licensed for the participant’s age group.

Study Analyses:

Interim Analyses:

Part 1: Interim analyses may be performed after all or a subset of participants (with immunogenicity samples collected for D1 and D57) have completed Day 57 within an age group in Part 1 (one optional interim analysis for each age group, 3 interim analyses total for the 3 age groups in Part 1). Analyses of safety and immunogenicity may be conducted at each interim analysis.

Part 2: An interim analysis of immunogenicity and safety will be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 1 or Part 2 within an age group. This interim analysis will be considered the primary analysis of immunogenicity for a given age group. Another interim analysis on safety may be performed after a different subset or all participants have completed Day 57 in an age group.

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 clinical study report, including individual listings.

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

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LIST OF ABBREVIATIONS AND TERMS

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

Abbreviation or Specialist Term	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CD	cluster of differentiation
CDC	US Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CMI	cell-mediated immunity
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ERD	enhanced respiratory disease
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Definition
GLSM	geometric least squares mean
GM	geometric mean
GMR	geometric mean ratio
GMT	geometric mean titer
HCP	healthcare practitioner
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IgG	immunoglobulin G
IM	intramuscular(ly)
IND	investigational new drug
IP	investigational product
IRB	institutional review board
IST	internal safety team
LAR	legally acceptable representative
LNP	lipid nanoparticle
LOD	limit of detection
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
mRNA	messenger RNA
nAb	neutralizing antibody(ies)
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases

Abbreviation or Specialist Term	Definition
PEG	polyethylene glycol
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000
PP	per protocol
QA	quality assurance
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike
S2P	S protein stabilized with 2 proline mutations
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SoA	schedule of assessments
Study P301	Study mRNA-1273-P301; NCT04470427
Th	T helper cell
VTEU	Vaccine and Treatment Evaluation Units
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. INTRODUCTION

1.1. Study Rationale

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). Coronaviruses are zoonotic, meaning that they are transmitted between animals and people. An outbreak of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 215 other countries, territories, and areas, including the United States (WHO 2020a). On 11 Mar 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic. As of 30 Jan 2021, the WHO dashboard (WHO 2020b) reported that there have been more than 2.1 million COVID-19 deaths worldwide. As of 29 Jan 2021, the US Centers for Disease Control and Prevention (CDC) reported over 25 million cases of COVID-19 in all 50 states and 5 jurisdictions, with 431,619 attributed and probable deaths (CDC 2020a). While the CDC reports that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease, a substantial burden in children is now being recognized. Evidence is emerging (described below) to suggest that children < 18 years of age, particularly adolescents, may be disproportionately contributing to the number of new cases as schools re-open at varying degrees of in-person learning. As of 29 Jan 2021, the CDC reported 2,125,186 cases of COVID-19 in children less than 18 years of age (11.1% of all US cases) and 267 deaths (approximately 0.1% of all US deaths; CDC 2020b).

During incubation, those infected can also transmit the virus before developing symptoms (Chen et al 2020). Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual, whether symptomatic or not (Chen et al 2020; Licciardi et al 2020; Rothan and Byrareddy 2020; Shen et al 2020). SARS-CoV-2 can also be transmitted via the fecal-oral pathway (Cruz and Zeichner 2020).

During the COVID-19 pandemic, children throughout much of the world have had school attendance limited in an attempt to control infection. Therefore, the main source of infection for SARS-CoV-2 in children, with or without clinical symptoms, is infected household contacts. Indeed, a retrospective cohort study of high school students, parents and siblings of students, teachers, and staff conducted in France in early April 2020 suggests that there was little to no transmission from infected students to other students or school staff. Rather, a high prevalence of antibodies against SARS-CoV-2 among families suggests familial clustering of COVID-19 cases (Fontanet et al 2020).

A recent report of COVID-19 trends in school-aged children in the United States from 01 Mar 2020 to 19 Sep 2020 indicates that 37% of laboratory-confirmed cases of COVID-19 in school-aged children occurred in children 5 to 11 years of age while 63% occurred in adolescents 12 to 17 years of age (Leeb et al 2020). The weekly incidence among adolescents was 37.4 cases per 100,000 compared with 19.0 cases per 100,000 for younger children. Among school-aged children with laboratory-confirmed COVID-19, 58% reported at least one symptom and 5% reported no symptoms, although information on symptoms was missing or unknown for 37%. Overall, 1.2% of school-aged children with COVID-19 were hospitalized, 0.1% required intensive care unit (ICU) admission, and < 0.01% died of COVID-19. Furthermore, at least one underlying condition was reported in 3% of adolescents and 2% of younger children. Chronic lung disease, including asthma, was most commonly reported (55%), followed by disability (neurologic or neurodevelopmental disorders, intellectual or physical disability, and vision or hearing impairment; 9%), immunosuppressive conditions (7%), diabetes (6%), psychological conditions (6%), cardiovascular disease (5%), and severe obesity (4%) (Leeb et al 2020). Based on the COVID-NET report, in 42.3% of children with at least 1 underlying condition, the most prevalent conditions were obesity (37.8%), chronic lung disease (18.0%), and prematurity (15.4%) (Kim et al 2020). Of particular interest is the phenomenon known as multisystem inflammatory syndrome in children (MIS-C) (PICS 2020). Since those early reports, a number of articles have been published describing a hyperinflammatory syndrome with features of Kawasaki disease in children and adolescents infected with SARS-CoV-2 (Belhadjer et al 2020; Dufort et al 2020; Verdoni et al 2020). Targeted surveillance in the United States from March through May 2020 revealed 186 patients across 26 states who met a pre-specified case definition of MIS-C (Feldstein et al 2020). The median age was 8.3 years (interquartile range: 3.3 to 12.5 years). Most (73%) were previously healthy, and 70% were positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) or antibody testing. The condition affected a variety of organ systems, most commonly the gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory systems. More recently, the Brighton Collaboration has drafted a manuscript proposing case definitions of MIS-C based on 5 levels of diagnostic certainty (Vogel et al 2020).

Evidence suggests that there is substantial burden of COVID-19 in younger age groups. Another study examined the age distribution of COVID-19 in the United States from May to August 2020 based on 3 indicators: COVID-19-like illness-related emergency department visits, positive RT-PCR results for SARS-CoV-2, and confirmed COVID-19 cases (Boehmer et al 2020). These authors report an estimated mean COVID-19 incidence during this time period of 179.3 cases per 100,000 in individuals 10 to 19 years of age. Finally, a recent report describes an adolescent (13-year-old female), whose only symptom was nasal congestion, yet she was the index case in an outbreak of COVID-19 linked to a family gathering that ultimately crossed 4 states and included 5 households and 11 individuals (Schwartz et al 2020). A June COVID-19 outbreak in a Georgia

overnight camp demonstrated that children 6 to 19 years of age are susceptible to SARS-CoV-2 infection and transmission (Szablewski et al 2020). In addition, in the second half of July, Rhode Island childcare programs reported 52 confirmed and probable childcare-associated COVID-19 cases, 30 (58%) cases of which were among children with a median age of 5 years (Link-Gelles et al 2020). This suggests that adolescents and children can serve as the source of COVID-19 outbreaks, even when their symptoms are mild, as in these cases.

There is currently no approved vaccine against SARS-CoV-2 for children. In December 2020, following review of safety and efficacy data observed to date, the Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) to 2 messenger RNA (mRNA)-based SARS-CoV-2 vaccines, including mRNA-1273, for adults. 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.

The objective for this Phase 2/3 study is to evaluate the safety, tolerability, reactogenicity, and effectiveness of up to 3 dose levels (25, 50, and 100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart (Section 3.1) to healthy children 6 months to < 12 years of age divided into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years). Another Phase 2/3 study to evaluate the safety and reactogenicity of a single dose level (100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart to an adolescent population (12 to < 18 years of age) is ongoing.

1.2. Background and Overview

The Sponsor has developed a rapid-response proprietary vaccine platform based on a mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then present viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. Messenger RNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (NCT03382405), human metapneumovirus and parainfluenza virus type 3 (NCT03392389), and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). mRNA-1273 encodes for the full-length spike (S) protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S2P). It has been confirmed that the stabilized SARS-CoV-2 S2P expresses well and is in the prefusion conformation (Wrapp et al 2020). The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies (nAb) that prevent infection (Corti et al 2015; Wang et al 2015;

Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019; Corbett et al 2020a; Ju et al 2020; Robbiani et al 2020).

1.2.1. Nonclinical Studies

The National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center and the Sponsor performed nonclinical studies in young and aged wild-type mice, Syrian Golden hamsters, and rhesus macaques (nonhuman primates [NHPs]) to evaluate dose-ranging responses to mRNA-1273 (immunogenicity) and high-dose virus SARS-CoV-2 challenge (protection) and to address the theoretical concern of enhanced respiratory disease (ERD) mediated by vaccine-induced antibody responses and/or T helper cell (Th) 2-directed T-cell responses observed with other vaccines against viral respiratory diseases (Graham 2020).

Nonclinical animal studies demonstrated that mRNA-1273 is immunogenic in all species assessed, with a dose-dependent response in immunoglobulin G (IgG) binding antibody (bAb) titers and a correlation that is statistically significant between bAb and (nAb) activity. In addition, antigen-specific T-cell responses were observed in studies in mice and NHPs. The Th1-directed cluster of differentiation (CD) 4 and CD8 T-cell responses were measured after boost in animals that were vaccinated with mRNA-1273. In various animal models, immunological measurements suggested that Th1 responses predominated, IgG2a/c/IgG1 ratios were favorable, and high levels of SARS-CoV-2 nAb were observed, suggesting that ERD after mRNA-1273 administration would be unlikely. In addition to measuring the immune response, mice, hamsters, and NHPs were challenged with high-dose SARS-CoV-2 virus. In these studies, dose levels were included that were predicted to be optimal (fully protective) and suboptimal (subprotective). At higher doses, mice and NHPs were fully protected from viral replication in both lungs and nasal passages. At subprotective dose levels, animals either remained fully protected or had reduced viral lung burden post challenge versus control animals (Corbett et al 2020a; Corbett et al 2020b).

Overall, nonclinical animal studies demonstrated that mRNA-1273 is safe and well tolerated, is immunogenic, fully protects animals from challenge at optimal dose levels, and does not result in ERD at protective or subprotective dose levels.

In support of the development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

A detailed review of nonclinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.2.2. Clinical Studies

The mRNA-1273 vaccine is currently being evaluated in 4 ongoing trials.

The first is a safety and immunogenicity Phase 1 study (NCT04283461) sponsored and conducted by the Division of Microbiology and Infectious Diseases (DMID; investigational new drug [IND] application 019635) of the NIAID. The Phase 1 study is an open-label dose-ranging study of mRNA-1273 in healthy adult male and nonpregnant female participants in 3 age groups: 18 to 55 years, inclusive (60 participants); 56 to 70 years, inclusive (30 participants); and ≥ 71 years (30 participants). Participants were randomly assigned to 1 of 4 dose levels of mRNA-1273: 25 µg, 50 µg, 100 µg, and 250 µg. Each participant received the same dose by intramuscular (IM) injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle. Blood samples were obtained at baseline, Days 8, 15, 29 (prior to Dose 2), 36, 43, and 57, as well as 3, 6, and 12 months after the second vaccination (Days 119, 209, and 394, respectively). Safety monitoring is ongoing for 12 months after the second injection.

On 14 Jul 2020, a preliminary report of findings in this Phase 1 study through Day 57 for the 18- to 55-year age-cohort (25, 100, and 250 µg dosage groups) was published (Jackson et al 2020). After the second injection, serum viral neutralizing activity was detected by 2 methods in all 42 participants evaluated (of 45 enrolled), with values that were comparable to or greater than the geometric mean titers (GMT) measured in the convalescent serum samples. Regarding safety, no serious adverse events (SAEs) were reported and no study-halting rules were triggered. In general, solicited systemic adverse reactions (ARs) were more common after the second injection. Solicited ARs that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. While none of the participants (N= 45) at any dose level experienced fever following the first dose, mild fever was observed in 5 participants (33%), moderate fever was observed in 1 participant (6.7%), and no participants experienced severe fever at 100 µg following the second dose. Data on 40 older adults > 55 years of age who received 2 doses of either 25 or 100 µg in the same Phase 1 DMID study were recently published (Anderson et al 2020). After the second injection, serum neutralizing activity was detected in all participants by multiple methods with binding and neutralizing antibody titers similar to those reported in adults 18 to 55 years of age and above the median for convalescent serum. Solicited ARs were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Specifically, regarding fever, no participant reported fever of any severity following the first injection. Following the second injection, 2 participants in the 100-µg dose group reported fever categorized as mild. All participants have been vaccinated, and safety and immunogenicity follow-up is ongoing. Indeed, immunogenicity data through 119 days after the first vaccination for 34 participants revealed binding and neutralizing GMTs that exceeded the median GMTs in a panel of convalescent sera from

41 controls. No SAEs were noted, no study-halting rules were met, and no new related adverse events (AEs) were reported after Day 57 (Widge et al 2021).

Additionally, an ongoing, placebo-controlled, dose-finding Phase 2a study (mRNA-1273-P201; NCT04405076) conducted by the Sponsor under IND 19745 aims to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 administered as 2 doses 28 days apart at dose levels of 50 and 100 µg. The study is being conducted in 600 healthy adults in 2 age cohorts: 18 to 54 years of age (300 participants) and at least 55 years of age (300 participants). All participants were randomly assigned in a ratio of 1:1:1 to receive either placebo or mRNA-1273 at 1 of 2 doses, either 50 µg or 100 µg. The study was designed to begin with parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old). An independent safety monitoring committee (SMC) reviewed all blinded and unblinded safety data through Day 57 (1 month after Dose 2) for both cohorts and found the vaccine tolerable, saw no safety concerns, and recommended continuing the study as planned. The study is now completely enrolled, and all dosing is complete; participants are undergoing additional serologic testing and safety follow-up.

The 100 µg dose level is currently being investigated in a large Phase 3 efficacy study (mRNA-1273-P301; NCT04470427) in approximately 30,000 adults 18 years of age and older, randomly assigned 1:1 to receive either vaccine or placebo. Recently published data show a vaccine efficacy of 94.1% against symptomatic COVID-19 illness with onset at least 14 days after the second injection (Baden et al 2021). Although moderate transient reactogenicity occurred more frequently in the mRNA-1273 group, SAEs were rare and the incidence was similar between the 2 groups. On 18 Dec 2020, the Moderna COVID-19 vaccine was authorized by the US FDA for emergency use in individuals ≥ 18 years of age. The participants in this Phase 3 study are currently undergoing assessments for long-term safety and durability of vaccine efficacy.

Finally, a Phase 2/3, randomized, observer-blind, placebo-controlled study (mRNA-1273-P203) conducted by the Sponsor under IND 19745 is evaluating the safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents 12 to < 18 years of age. This study began enrolling in December 2020 and will enroll 3,000 participants randomly assigned 2:1 to receive mRNA-1273 100 µg or placebo administered as 2 doses 28 days apart. Participants will be followed for 12 months after the second dose.

A detailed review of the clinical experience with LNPs containing SM-102 (mRNA vaccines and placebo) is provided in the IB.

1.3. Benefit/Risk Assessment

1.3.1. Potential Benefits From Participation

The following benefits may accrue to participants:

- The mRNA-1273 vaccine may be an effective vaccine against COVID-19 in the study population.
- 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 vaccine against COVID-19 for children 6 months to < 12 years of age.

1.3.2. Risks From Study Participation and Their Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after injection.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures are followed to avoid injury from fainting.

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. In the large Phase 3 efficacy study of mRNA-1273 described above, delayed injection site reactions occurred with an incidence of approximately 1%. These reactions typically began 8 days or more following injection, were mostly not severe, and were rarely observed after the second dose.

The majority of local and systemic solicited ARs observed after injection with mRNA-1273 at the 100-µg dose level have been mild to moderate in severity (Section 1.2.2). The most commonly reported systemic ARs were headache, myalgia, fatigue, chills, and fever. In the majority of cases, the reactions resolved spontaneously within several days.

Laboratory abnormalities (including increases in hepatic enzymes and serum lipase levels) following injection were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown. Further details are provided in the current IB.

There is a theoretical risk that active vaccination to prevent SARS-CoV-2 infection may cause a paradoxical increase in the risk of severe COVID-19. This possibility is based on the rare phenomenon of vaccine-associated ERD, which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with respiratory syncytial virus (Chin et al 1969) or measles virus (Fulginiti et al 1967). It is noteworthy that these vaccines were the result of a completely different formulation and with an entirely different mechanism of action than mRNA-based vaccines such as mRNA-1273. Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination (Thomas and Yoon 2019; WHO 2019). It is not known if mRNA-1273 will increase the risk of enhanced disease; however, preliminary data from the ongoing Phase 3 study suggests no evidence of enhanced disease, as fewer cases of severe COVID-19 and COVID-19 were observed in participants who received mRNA-1273 than in those who received placebo.

In order to address this theoretical risk, animal studies have been performed in young and aged wild-type mice and rhesus macaques (NHPs). These studies were designed to capture immunogenicity endpoints that would be predictive of ERD and also to evaluate if, at protective or subprotective dose levels of mRNA-1273, evidence of disease enhancement would be observed after challenge of the animals with SARS-CoV-2. These nonclinical studies demonstrated that mRNA-1273 is safe and well tolerated in different animal species; is immunogenic; drives a robust SARS-CoV-2-specific Ab, neutralization, and Th1-directed CD4 T-cell response; fully protects animals from challenge at dose levels as low as 1 μg/dose in mice and 30 μg/dose in NHPs; and does not lead to ERD at protective or subprotective dose levels (Corbett et al 2020a; Corbett et al 2020b). Clinical immunogenicity data from the DMID Phase 1 study of mRNA-1273 demonstrated high levels of nAbs and Th1-polarized CD4 T-cell responses (Jackson et al 2020), consistent with the immunogenicity observed in the nonclinical studies. These data suggest that the risk of paradoxical ERD, while not eliminated, is likely to be low.

In the context of the EUA of mRNA-1273 for individuals aged 18 years and older, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with Moderna COVID-19 Vaccine. Although causality has not been established, the majority of the cases have been reported in young males 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 (Gargano et al, 2021).

1.3.3. Overall Benefit/Risk Conclusion

Based on the Phase 3 data and the results of the Phase 1 and Phase 2 studies described above, the Sponsor intends to study 3 dose levels (25, 50, and 100 µg) in the proposed Phase 2/3 study in participants 6 months to < 12 years of age. Briefly, the proposed study is designed to dose escalate and age de-escalate through 3 sequential age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years). Participants at each dose level will receive 2 doses at that dose level approximately 28 days apart. The mRNA-1273 dose levels that will be evaluated in each age group are given in Table 1.

Table 1: Age Groups and mRNA-1273 Dose Levels

Age Group	mRNA-1273 Dose Levels Planned to be Evaluated
6 to < 12 year	50 and 100 µg
2 to < 6 year	25[1], 50, and 100 µg
6 months to < 2 year	25 and 50 µg

[1] The 25-µg dose will be evaluated if 100 µg is eliminated at any point during the dose escalation process, to maintain dose ranging for this age group.

The study will be conducted in 2 parts. Part 1 of the study will be open-label and consist of dose-escalation and age de-escalation to select the dose for each age group. Part 2 of the study will be a placebo-controlled observer-blind evaluation of the selected dose in each age group.

Immunogenicity data from participants who receive the mRNA-1273 vaccine at the selected dose level will be used to infer vaccine effectiveness. All participants will be followed up for 12 months after receipt of the second injection.

Safety will be monitored throughout the study (Section 7.5).

Given that the preliminary data from Phase 1 to 3 studies have shown no significant safety concerns and robust immunogenicity, mRNA-1273 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 in children will help facilitate a return to school as an additional step towards normalization of daily activities.

Considering the lack of approved vaccines for COVID-19, the participants' risk of COVID-19 outside the study during a pandemic, and the nonclinical and clinical data to date, the Sponsor considers the potential benefits of participation to exceed the risks.

2. OBJECTIVES AND ENDPOINTS

The objectives that will be evaluated in this study and the endpoints associated with each objective are provided in Table 2.

Table 2: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 vaccine administered as 2 doses 28 days apart in 3 age groups	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESIs, including MIS-C and myocarditis and/or pericarditis, through the entire study period
• To infer the efficacy of mRNA-1273 (25, 50, and 100 µg, administered as 2 doses 28 days apart) based on immunogenicity in 3 age groups	• The proportion of participants with a serum antibody level at Day 57 ≥ antibody threshold of protection – If an accepted serum antibody threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy • The GM value of serum antibody level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301) – If a threshold is not available, efficacy will be inferred by establishing noninferiority for each age group (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years in Study P204) compared to 18- to 25-year old participants (Study P301) by both GM value of serum antibody levels and seroresponse rate. A definition of seroresponse will be provided in the

	statistical analysis plan based on forthcoming information about assay performance
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 μg) administered as 2 doses 28 days apart	• The GM values of SARS-CoV-2 S protein-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2) • The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)
• To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• 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: – bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1, that becomes positive (as measured by Roche Elecsys) postbaseline, OR – Positive RT-PCR postbaseline
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) postbaseline in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with COVID-19 AND positive RT-PCR for SARS-CoV-2	• The incidence of the first occurrence of COVID-19 postbaseline, where COVID-19 is defined as symptomatic disease based on CDC case definition[1]

Exploratory Objectives	Exploratory Endpoints
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence
• To describe the ratio or profile of specific S protein bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb titers in serum
• 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 assess, in a subset of participants, the SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points after vaccination relative to baseline
• To explore asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; GM = geometric mean; GMFR = geometric mean fold-rise; IgG = immunoglobin; IP = investigational product; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralizing antibody; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[1] 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.

3. STUDY DESIGN

3.1. General Design

This is a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study intended to infer the effectiveness of mRNA-1273 in children aged 6 months to < 12 years. The study population will be divided into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years), and up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 will be evaluated.

The study will be conducted in 2 parts. Part 1 of the study will be open-label and consist of dose-escalation and age de-escalation in approximately 1,275 participants to select the dose for each age group with the highest number enrolled in the oldest age group (Table 3). Part 2 of the study will be a placebo-controlled observer-blind evaluation of the selected dose in up to 12,000 participants (up to 4,000 participants each in the 6 to < 12 years, 2 to < 6 years, and the 6 months to < 2 years of age groups). No participants in Part 1 will participate in Part 2 of the study.

In order to expedite the study of the safety of mRNA-1273 in school-aged children 6 to < 12 years of age; Part 1 will enroll a total of approximately 375 participants per dose (both at the 50 and 100 µg dose levels) in this age group (6 to < 12 years). The first 75 of these participants per dose will be included in the safety evaluation for dose-escalation and age de-escalation as well as the immunogenicity assessment needed for dose selection, as applicable. Additionally, approximately 300 participants per dose will be enrolled to assess for any AE occurring at 1% or higher. The sample size for Part 2 in this age group (6 to < 12 years) will be adjusted to approximately 1700 participants. Conversely, approximately 75 participants in the middle age group (2 to < 6 years) will be enrolled per dose in Part 1 for safety and dose selection and Part 2 will utilize the dose selected in Part 1 to inform on AEs occurring at a frequency of 1% or greater. In the youngest age group (6 months to < 2 years), approximately 150 participants will be enrolled per dose in Part 1 for safety and dose selection and Part 2 will utilize the dose selected in Part 1 to inform on AEs occurring at a frequency of 1% or greater. For details, please refer to Section 7.5.

The study will begin with the oldest age group (6 to < 12 years) and age de-escalate as described under Study Progression. Each age group will begin with Part 1 and advance to Part 2 independently. For details, please refer to the study schematic in Figure 1.

The mRNA-1273 investigational vaccine or placebo will be administered as 2 intramuscular (IM) injections approximately 28 days apart.

The mRNA-1273 dose levels that will be evaluated in each age group in Part 1 and Part 2 of the study are given in Table 3.

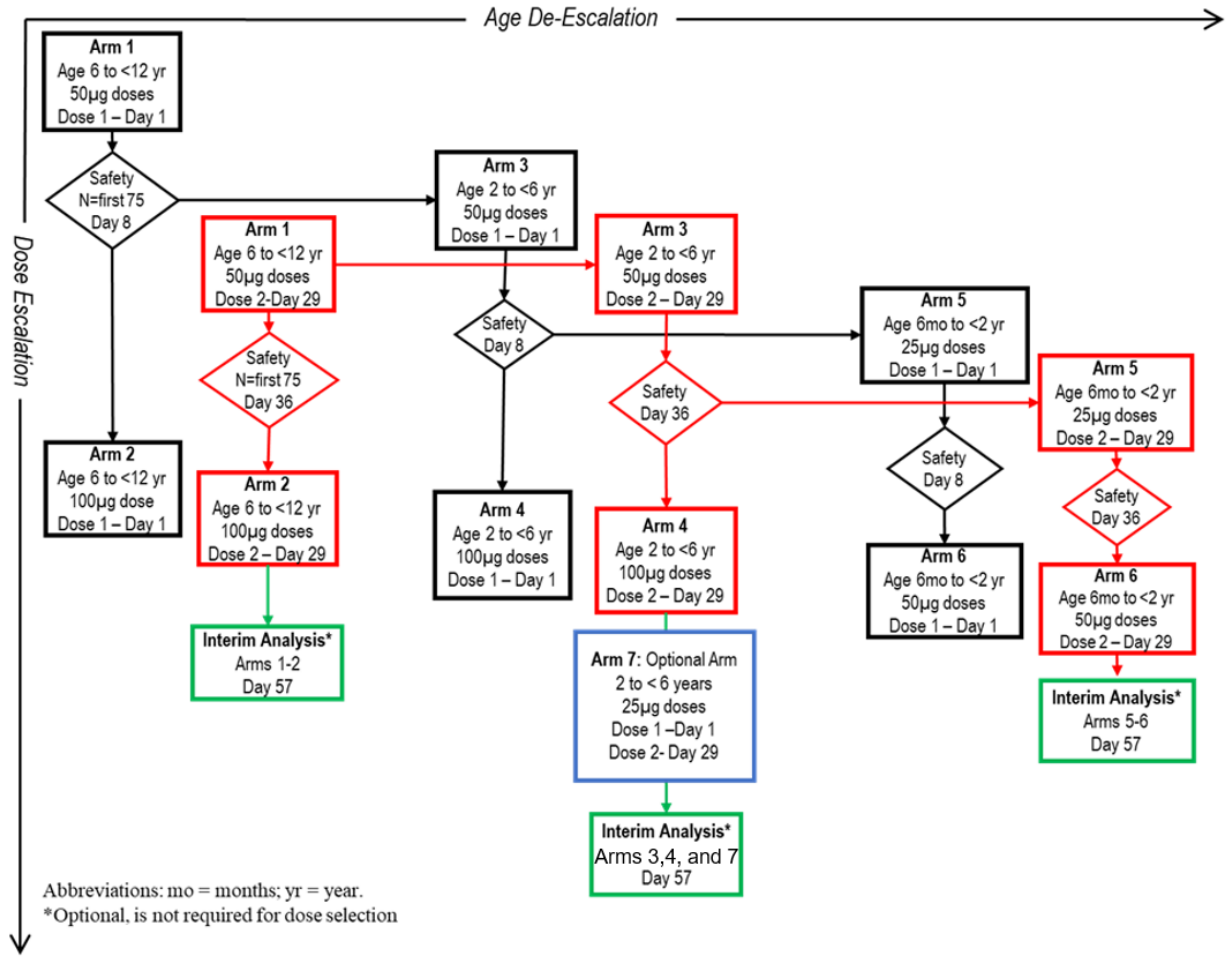
Table 3: Planned Age Groups and mRNA-1273 Dose Levels in Part 1 and Part 2 of the Study

Age Group	Part 1			Part 2	
	mRNA-1273 25 µg	mRNA-1273 50 µg	mRNA-1273 100 µg	Selected Dose Level of mRNA-1273 From Part 1	Placebo
6 to < 12 years		Study Arm 1 (n=375)	Study Arm 2 (n=375)	Study Arm 8 (n=3,000)	Study Arm 9 (n=1,000)
2 to < 6 years	Study Arm 7 (Optional) (n=75)	Study Arm 3 (n=75)	Study Arm 4 (n=75)	Study Arm 10 (n= up to 3,000)	Study Arm 11 (n= up to 1,000)
6 months to < 2 years	Study Arm 5 (n=150)	Study Arm 6 (n=150)		Study Arm 12 (n= up to 3,000)	Study Arm 13 (n= up to 1,000)

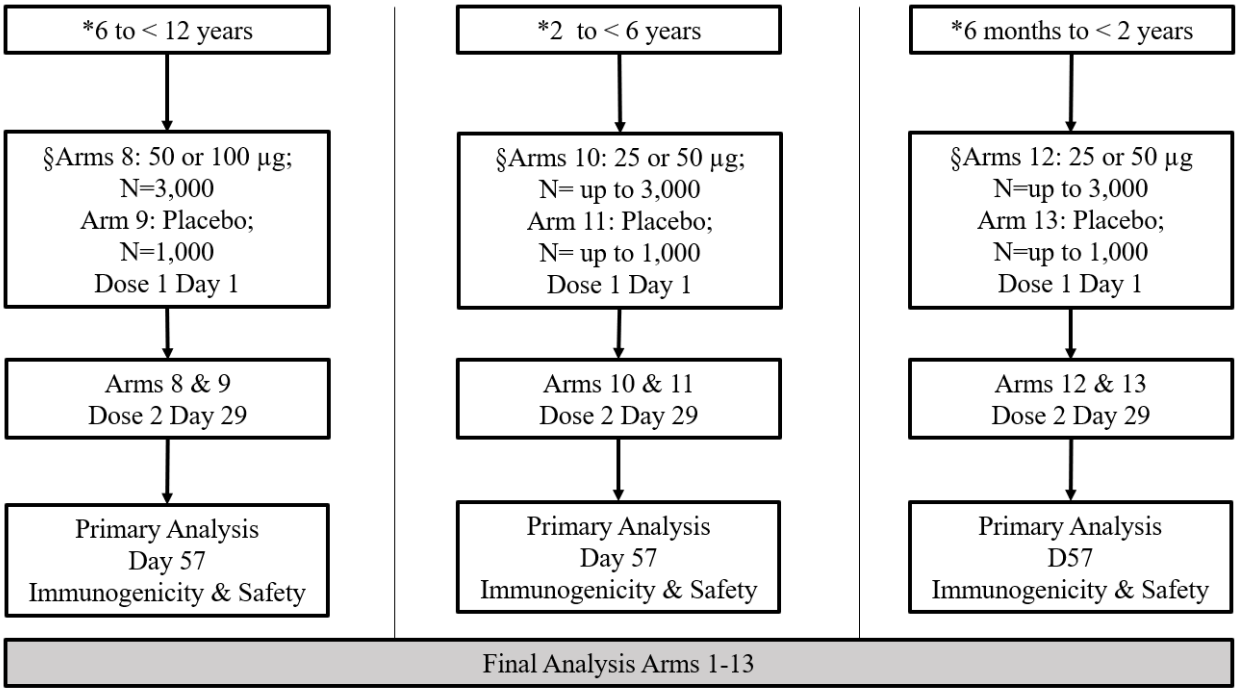
The schematic of Study Arms and major study events is provided in Figure 1.

Figure 1: Study Schema

(a) Part 1: Dose Escalation, Age De-escalation



(b) Part 2: Expansion



Abbreviations: CMI = cell-mediated immunity; D = Day; S = spike; VTEU = Vaccine and Treatment Evaluation Units.
*Expansion and primary analysis for each age group may occur at different times.
§Participants in each age group will be assigned to one of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity on D1 (prior to randomization and first dose), D57, and one of D29 (prior to the second dose), D209, or D394 (such that each participant provides a total of 3 blood samples only). Participants in the Cohort D (remainder of the age group) will provide a blood sample on D1 (prior to randomization and before the first dose) and within 4 days of receiving Dose 2 at D30 (+3 days) for storage and potential future biomarker testing. A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on D1 (prior to randomization and before the first dose), D43, D209, and D394.

Study Progression

Part 1 of the study will be open-label. The study will begin with enrollment of approximately 375 participants in the 6 to < 12 years age group (Study Arm 1) and dosing with 50 µg of mRNA-1273. After at least 75 participants in Study Arm 1 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an internal safety team (IST) will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 6 to < 12 years age group (Study Arm 2; n = 375) and independently whether to begin dosing at the 50-µg dose level in the 2 to < 6 years age group (Study Arm 3; n = 75). After at least 75 participants in Study Arm 1 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will again review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 2 and whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 3. Simultaneously, the enrollment of the remaining 300 planned participants for both Arm 1 and Arm 2 will be ongoing. A preliminary safety and immunogenicity data review of Arm 1, and Arm

2 as applicable, will aid in the selection of a dose level for Part 2. Once all or a subset of participants from each of Study Arms 1 and 2 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the safety and immunogenicity data. Cumulative safety data for approximately 300 participants at the selected dose level will be reviewed by the Data Safety Monitoring Board (DSMB) before enrollment in Part 2, and the DSMB safety review recommendation will enable the expansion of the 6 to < 12 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 8; n = 3,000) or placebo (Study Arm 9; n = 1,000). The primary analysis of immunogenicity in Part 2 for Study Arm 8 (mRNA-1273 recipients) will be conducted after the pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis will be conducted after a subset or all participants in Arms 8 and 9 reach Day 57.

For the middle age group (2 to < 6 years), progression in Part 1 will be as follows: After 75 participants in Study Arm 3 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an IST will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 2 to < 6 years age group (Study Arm 4; n = 75) and whether to begin dosing in the 6 months to < 2 years age group at the 25-µg dose level (Study Arm 5; n = 150). After the 75 participants in Study Arm 3 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 4 and whether to administer Dose 2 of mRNA-1273 25 µg in Study Arm 5. An optional Arm 7 may be enrolled in this age group (approximately 75 participants) at the 25-µg dose if the 100-µg dose is eliminated at any point during dose escalation process, to maintain dose ranging for this age group. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2. Once all or a subset of participants in all applicable Arms reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review safety and immunogenicity data. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2 and for expansion of the 2 to < 6 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 10; n = up to 3,000) or placebo (Study Arm 11; n = up to 1,000). The primary analysis of immunogenicity in Part 2 for Study Arm 10 (mRNA-1273 recipients) will be conducted after a pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis will be conducted after a subset or all participants in Arms 10 and 11 reach Day 57.

For the youngest age group (6 months to < 2 years) progression in Part 1 will be as follows: In Study Arm 5, after 150 participants have completed Day 8 (1 week after Dose 1 of mRNA-1273 25 µg), an IST will review the available safety data and provide a recommendation whether to escalate the dose to 50 µg (Study Arm 6; n = 150). After the 150 participants in Study Arm 5 reach

Day 36 (1 week after Dose 2 of mRNA-1273 25 µg), the IST will review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 6. Once all or a subset of participants in Study Arms 5 and 6 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the tolerability and immunogenicity data at each dose level. A preliminary safety and immunogenicity data review of Arm 5 and Arm 6, as applicable, will aid in the selection of a dose level for Part 2 and allow for expansion of the 6 months to < 2 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 12; n = up to 3,000) or placebo (Study Arm 13; n = up to 1,000). The primary analysis of immunogenicity in Part 2 for Study Arm 12 (mRNA-1273 recipients) will be conducted after the pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis will be conducted after a subset or all participants in Arm 12 and 13 reach Day 57.

In general, if a decision is made not to proceed with administration of the higher dose and/or the second injection at a given dose level (eg, due to safety concerns), the participants scheduled to receive the higher dose may receive a lower dose, and the participants who had received the higher dose level as their first injection will likely be given the next lower dose level that was tolerated for their second injection. The dose level not tolerated in the older age group will not be administered in any of the younger age groups. Within an age group, if one of the dose levels is found to have an unacceptable tolerability profile, the age group may progress to Part 2 at a lower dose level.

The final analysis will be performed when participants (Study Arms 1 to 13) conclude the safety follow-up at 12 months.

The goal of the study is to support an indication for use of mRNA-1273 50 or 100 µg IM, given as 2 injections, approximately 28 days apart in the 6 to < 12 years age group; mRNA-1273 25, 50, or 100 µg IM, given as 2 injections, approximately 28 days apart in the 2 to < 6 years age group; and mRNA-1273 25 or 50 µg IM, given as 2 injections, approximately 28 days apart in the 6 months to < 2 years age group. The basis for demonstrating vaccine effectiveness is proposed to be met by measuring serum antibody responses in the study participants. The approach to inferring vaccine effectiveness will depend on whether an accepted serum antibody threshold conferring protection against COVID-19 has been established. If an antibody threshold of protection has been established, effectiveness will be inferred based on the proportion of study participants with serum antibody levels (on Day 57) that meet or exceed the antibody threshold. If an antibody threshold of protection has not been established, effectiveness will be inferred by demonstrating noninferiority for each age group (6 to < 12 years, 2 < 6 years, and 6 months to < 2 years in Study P204) compared to young adult (18 to 25 years of age) participants enrolled in the ongoing clinical endpoint efficacy trial (Study P301) by both geometric mean (GM) values and seroresponse rate. The statistical parameters to infer effectiveness are described in Section 2.

This study in children 6 months to < 12 years of age will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. If a COVID-19 vaccine is authorized or licensed for a specific age group before the end of the study, please refer to Section 3.3 for unblinding and/or cross-over plans. Safety assessments will include solicited ARs 7 days after each injection (ie, the day of injection and 6 subsequent days), unsolicited AEs (28 days after each injection), and medically attended adverse events (MAAEs), SAEs, and adverse events of special interest (AESIs) (including MIS-C and myocarditis and/or pericarditis) through the entire study period.

Blood samples will be collected from participants in Part 1 and Part 2 of the study for assessment of immunogenicity as specified in Section 3.1.1.2. If a Day 1 (baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be rescheduled for rescreening. Participants may be rescreened 1 time, either within the same screening period for Part 1 or Part 2 or in a new screening period of Part 2 if the initial screening was in Part 1. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3. Blood samples will also be tested for the development of antibodies directed against nonvaccine antigen (eg, antibodies against the nucleocapsid protein), which will signify infection with SARS-CoV-2. The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients. In addition, all participants will be monitored for symptoms of COVID-19 and scheduled for illness visits if concerning symptoms occur, and a nasal swab will be collected at the illness visit.

3.1.1. Study Periods

This study involves up to 8 scheduled visits including up to 6 in-person visits (if screening and baseline are done separately) and 2 telemedicine visits (Visit 2 and Visit 4; remote visit by means of telecommunication technology). An additional in clinic visit (Visit 4S) will be conducted for a cohort of participants from selected Vaccine and Treatment Evaluation Units (VTEU) sites on Day 43 (2 weeks after Dose 2 of mRNA-1273 or placebo) for exploratory serology and cell-mediated immunity (CMI; S protein-specific T-cell responses) in Part 2 of the study.

The study duration for each participant will be approximately 14 months, which includes 1 month for screening (Day -28 to Day -1), 1 month for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose to monitor for safety, tolerability, reactogenicity, immunogenicity, and efficacy.

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 telemedicine visit should be conducted in place of the study site visit. The telemedicine visit 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 institutional review board (IRB) and the participant's parent(s)/legally acceptable representatives (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, Good Clinical Practice (GCP), and all applicable regulatory requirements (Section 10.2.1).

3.1.1.1. Screening Period

After providing informed consent/assent, participants will undergo screening assessments to determine study eligibility. Screening assessments (Table 10) must be completed after the participant's parent(s)/LAR(s) signs the informed consent form (ICF) and the participant, where applicable, signs the assent form. 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 10).

Eligible participants will enter the Treatment Period.

3.1.1.2. Treatment and Follow-up Period

On Day 1, after the completion of the scheduled assessments (Table 10), participants will be administered a single IM dose of the investigational product (IP) mRNA-1273 (25, 50, or 100 µg) or placebo. Placebo will be administered only to those participating in Part 2 of the study. The procedures for IP administration will be detailed in the mRNA-1273-P204 Pharmacy Manual. Participants will be closely monitored for safety and will remain at the study site for observation for at least 30 minutes after dosing. On Day 29, the second dose of IP will be administered. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+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 29 + 21 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 monitored for 12 months after the second dose of IP for safety, immunogenicity assessments, and biomarker samples.

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 and on Day 43 (if visit is applicable), Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (12 months after Dose 2) according to the schedule of assessments (SoA; Table 10). Participants who test positive at baseline may receive Dose 2 as long as they remain asymptomatic at the time of dosing.

During the course of the study, participants who meet pre-specified 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 reported in an expedited time frame to the Sponsor (Section 7.4.4).

All participants will be monitored for safety and reactogenicity. All participants in Part 1 of the study will provide blood specimens for immunogenicity on Day 1 (prior to the first dose) and will also provide additional samples after the second dose of mRNA-1273 at Day 57, Day 209, and Day 394, except for the expansion of Arms 1 and 2 (N= ~300 participants per arm) who have a scheduled Day 1 blood draw and a voluntary blood draw on Day 57 only. Participants in each age group in Part 2 will be assigned to 1 of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1 (prior to randomization and before the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the Cohort D (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and before the first dose) and within 4 days of receiving Dose 2 at Day 30 (+3 days) for storage and potential future biomarker testing. For participants already enrolled in Cohort D prior to protocol amendment 4, this blood draw will be optional and confirmed at time of re-consenting; for all participants newly enrolled into Cohort D under amendment 4, it will be mandatory.

A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on Day 1 (prior to randomization and before the first dose), Day 43, Day 209, and Day 394. Table 12 provides the blood sampling schedule for Part 2 of the study.

Participants and their parent(s)/LAR(s) will be instructed on the day of the first dose (Day 1) and reminded on the day of the second dose (Day 29) how to document and report solicited local or systemic ARs in a provided electronic diary (eDiary). Solicited ARs, unsolicited AEs, MAAEs,

AEs leading to withdrawal, AESIs, and SAEs will be assessed as described in Section 7.1, according to the time points in the SoA (Table 10).

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.

A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis of COVID-19. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.

For treatment and follow-up assessments of placebo participants in the case that a COVID-19 vaccine is authorized or licensed for a specific age group during conduct of the trial, please refer to Section 3.3.

3.2. Scientific Rationale for Study Design

This Phase 2/3 study in children 6 months to < 12 years of age is planned to understand the tolerability and immunogenicity of mRNA-1273 in a pediatric population. This study follows a pivotal Phase 3 study (Study P301) in 30,000 adults 18 years and older to demonstrate the tolerability, safety, and high efficacy of mRNA-1273 (100 µg on Days 1 and 29) against COVID-19. This pediatric study is intended to confirm safety in children between 6 months and 12 years of age and bridge immunogenicity between children and young adults (18 to 25 years of age) enrolled in the pivotal adult Phase 3 study (Study P301). It is necessary to demonstrate noninferiority of the induced immune response in children compared with that in adults to infer vaccine effectiveness in this age group.

Part 1 of the study is designed to dose escalate and age de-escalate through 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years). Each age group will begin dosing with the lowest dose planned for that group. Dose-escalation and age de-escalation will progress only after confirming the safety of a dose level in each age group after each IP injection. The placebo-controlled dose-expansion Part 2 of the study will begin only after an interim analysis is performed for safety and immunogenicity in each of the age groups at the selected dose level.

With SARS-CoV-2 expected to be circulating in the general population during the study, a pre-defined subset of participants will provide blood samples for antibody analysis starting on Day 29 and continuing through 12 months after the last dose of IP. In addition, participants will have nasal swab samples collected, before the injections on Day 1, Day 29, Day 43 (if applicable), Day 57, Day 209, and Day 394. Furthermore, an additional nasal swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via RT-PCR and serology, respectively, if there are any signs or symptoms or an MAAE suggesting SARS-CoV-2 infection in a participant. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

As 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 for antibody responses to nonvaccine antigen(s) may help discriminate between natural infection and vaccine-induced antibody responses, should such discrimination be needed.

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

Based on the Phase 3 data and the results of the Phase 1 and 2 studies described in Section 1.2.2, the Sponsor intends to study 3 dose levels (25, 50, and 100 µg) in the Phase 2/3 study in children 6 months to < 12 years of age. On 18 Dec 2020, the mRNA-1273 vaccine (100 µg dose) was authorized by the US FDA for emergency use in individuals ≥ 18 years of age.

As there are currently no licensed SARS-CoV-2 vaccines available for children 6 months to 12 years of age, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments in Part 2. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded (Section 8.1).

If a COVID-19 vaccine (mRNA-1273 or other) is authorized or licensed, eligible study participants (by virtue of their age) will be offered the opportunity to unblind via a phone call and learn what treatment they received, ideally after they have reached at least study Day 57. Participants who learn that they have received mRNA-1273 will continue in the study and will be followed per protocol. If a participant previously received placebo the participant will be offered cross-over vaccination with mRNA-1273 (first injection), followed by a second mRNA-1273 injection 28 days thereafter. The remainder of study visits will subsequently be performed as shown in the SoA for cross-over vaccination with mRNA-1273 if any COVID-19 vaccine is authorized or licensed for participant's age group (Table 11). All participants will continue to be followed until their Day 394 end-of-study visit. In addition, participants who received a lower dose in Part 1 than was ultimately approved for their respective age group in Part 2, will be eligible for a booster dose with the optimal dose once authorization or approval of mRNA-1273 has been granted for their

age group. If a decision is made to go outside the protocol to receive an EUA vaccine, the participant will be discontinued from the study.

3.4. 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 10) for the last participant in this study.

4. STUDY POPULATION

Participants will be enrolled at approximately 75 to 100 study sites in the United States and Canada.

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

4.1. 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, 6 months to < 12 years of age at the time of consent/assent (Screening Visit), who is in good general health, in the opinion of the investigator, based on review of medical history and screening physical examination.
2. If the participant has a chronic disease (eg, asthma, diabetes mellitus, cystic fibrosis, human immunodeficiency virus [HIV] infection), the disease should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion. Stable diseases are those which have had no change in their status or in the medications required to control them in the 6 months prior to Screening Visit.

   Note: a change in medication for dose optimization (eg, insulin dose changes), change within class of medication, or reduction in dose are not considered signs of instability.
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 and participants are willing to provide assent.
4. The participant is 2 years or older and has a body mass index (BMI) at or above the third percentile according to WHO Child Growth Standards at the Screening Visit (Section 10.2.18).

   The participant is less than 2 years of age and the participant's height and weight are both at or above the 3rd percentile according to WHO Child Growth Standard at the Screening Visit (Section 10.2.18).
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche.

Special inclusion criteria for female participants who have reached menarche:

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all of the following criteria:

- Has a negative pregnancy test at Screening. Pregnancy test will be performed if deemed appropriate by the investigator.
- Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
- Has agreed to continue adequate contraception or abstinence through 3 months following the second injection (Day 29).
- Is not currently breastfeeding.

- Adequate female contraception is defined as abstinence or consistent and correct use of a US FDA-approved contraceptive method in accordance with the product label (Section 10.3).

Special inclusion criteria for children 6 months to < 12 months of age

7. The participant was born at full-term (≥ 37 weeks gestation) with a minimum birth weight of 2.5 kg.

4.2. Exclusion Criteria

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

1. Has a known history of SARS-CoV-2 infection within 2 weeks prior to administration of IP or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of IP.
2. Is acutely ill or febrile 24 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. Has previously been administered an investigational or approved CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.
4. Has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (eg, receipt of SARS-CoV-2 monoclonal antibodies) within 6 months prior to enrollment.
5. 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 a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG] or immediate allergic reaction of any severity to polysorbate).

6. Has a medical or psychiatric condition 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. 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:
    - Congenital or acquired immunodeficiency, excluding HIV infection, as described in Inclusion Criteria 2
    - Chronic hepatitis or suspected active hepatitis
    - A bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - Dermatologic conditions that could affect local solicited AR assessments
    - Any prior diagnosis of malignancy (excluding nonmelanoma skin cancer)
    - Febrile seizures*

      *In Part 2 of the study, a history of a simple, single febrile seizure is allowed for children 6 years and older.
8. Has received the following:
    - Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to first vaccination or plans to receive such a vaccine through 14 days following the last study vaccination.
        - Note: This excludes influenza vaccine that may be given, however, not within 14 days prior to or post Dose 1 or Dose 2. If a participant receives an influenza vaccine, this should be captured within the concomitant medication electronic case report form (eCRF) (Section 5.5.2).
    - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 1 mg/kg/day or ≥ 10 mg/day prednisone equivalent, if participant weighs > 10 kg). 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.
    - Intravenous or subcutaneous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment.

9. 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.
10. Is an immediate family member, or household contact, of an employee of the study site or Moderna 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.

4.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before their temperature is taken.

4.4. Screen Failures

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

5. STUDY TREATMENT

5.1. Investigational Product Administered

The term IP refers to mRNA-1273 (25, 50, and 100 μg) vaccine or placebo (0.9% sodium chloride) in this study.

mRNA-1273 is an LNP dispersion of an mRNA that encodes the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with PEG of average molecular weight 2000 (1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000 [PEG2000-DMG]). mRNA-1273 injection is provided as a sterile liquid for injection and is a white to off-white dispersion at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 4.3 mM sodium acetate at pH 7.5.

5.2. Randomization

Random assignment of participants in Part 2 of the study will use a centralized interactive response technology, in accordance with pregenerated randomization schedules. Up to 4,000 participants each in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years age groups will be randomized in a 3:1 ratio to the mRNA-1273 arm (n = up to 3,000 participants in each group) or placebo arm (n = up to 1,000 participants in each group).

5.3. Dosing and Management of mRNA-1273 Vaccine

5.3.1. Preparation of Study Vaccine for Injection

Each dose of IP will be prepared for each participant based on the assigned treatment, as detailed in the mRNA-1273-P204 Pharmacy Manual. The volume of IP injected will be 0.5 mL consisting of a 25-μg dose of mRNA-1273, a 50-μg dose of mRNA-1273, a 100-μg dose of mRNA-1273, or placebo (normal saline), as detailed in the mRNA-1273-P204 Pharmacy Manual.

5.3.2. Administration of Study Vaccine

Each participant will receive 2 doses of IP by IM injection approximately 28 days apart (Day 1 and Day 29) into the deltoid muscle or anterolateral thigh (per investigator's discretion), according to their assigned regimen and according to the procedures specified in the mRNA-1273-P204 Pharmacy Manual.

At each visit when IP is administered, participants will be monitored for a minimum of 30 minutes after administration. Assessments will include body temperature measurements (oral preferred for participants > 4 years of age, tympanic preferred for participants ≤ 4 years of age, but other

methods acceptable in context of COVID-19 precautions) and monitoring for local or systemic reactions (Table 10).

Eligibility for the subsequent dose of IP will be determined by following the criteria outlined in Section 6.

The study sites will be appropriately staffed with individuals with basic 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.

5.3.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the IP
- Confirming the appropriate labeling of the IP, so that it complies with the legal requirements of the United States and Canada.

The investigator is responsible for acknowledging the receipt of the IP by a designated staff member at the study site, including the following:

- Confirming that the IP was received in good condition
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming that the Sponsor has authorized the IP for use
- Ensuring the appropriate dose level of IP is properly prepared using aseptic technique

Further description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IP are described in the mRNA-1273-P204 Pharmacy Manual.

5.3.4. Study Vaccine 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 10R glass vials with a 6.3-mL fill volume. 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, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

5.3.5. Study Vaccine Storage

The IP must be stored at -15°C to -25°C in a secure area with limited access and be protected from moisture and light until it is prepared for administration (Section 5.3.1). 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 backup 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.

5.3.6. Study Vaccine 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-P204 Pharmacy Manual.

5.3.7. Study Vaccine 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, and completion of each age cohort or at the end of the study, 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.

5.4. 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/assent is withdrawn, a participant who

withdraws or 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 (Table 10). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and 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.

5.5. Prior and Concomitant Medications

5.5.1. 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 his/her parent(s)/LAR(s) provided informed consent and the participant provided assent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

5.5.2. Concomitant Medications and Therapies

At each study visit, study site staff must question the participant and/or 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 14 days before the first dose of IP and through 14 days after the last dose of IP.
- 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. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE or an MAAE.

Participants will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each IP dose, including on the day of dosing. Reported antipyretic or analgesic medications should be recorded in the source document by the study site

staff during the postinjection period of the study visits or via other participant interactions (eg, telephone calls).

Data regarding nutritional supplements, eg, vitamins, probiotics, and herbal supplements, will not be collected.

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (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.

5.5.3. 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 per-protocol (PP) analysis (analysis sets are described in Section 8.4):

- 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) 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 administered during the study period.

5.6. Intervention After the End of the Study

Any SAE, including death, occurring after the end of the study, and considered to be caused by the IP must be reported to the Sponsor.

6. DELAYING OR DISCONTINUING STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

6.1. Criteria for Delay of Vaccine Administration

6.1.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature (oral preferred for participants > 4 years of age or tympanic preferred for participants ≤ 4 years of age, but other methods are acceptable in context of COVID-19 precautions) must be measured on dosing visits before vaccine administration. 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 10), or the participant may be discontinued from dosing at the discretion of the investigator (Section 6.2):

- 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 5.5.2).

If unforeseen circumstances out of the control of the participant's family or the Study Site (eg, extreme weather, such as hurricanes) render it impossible for the participant to receive the second dose within the specified window, Dose 2 may be delayed at the principal investigator's discretion but should be administered as soon as possible thereafter.

6.2. Discontinuing Study Vaccination

Participants can 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 a participant from further injection under the following circumstances:

- The participant becomes pregnant.
- The participant's parent(s)/LAR(s) withdraw consent or the participant withdraws assent.
- An RT-PCR result from an illness visit (Section 7.1.5) is positive for SARS-CoV-2 and the participant is symptomatic at the time of next injection.
- The participant develops, during the course of the study, symptoms or conditions listed in the exclusion criteria (Section 4.2).
- The participant experiences an AE (other than solicited reactogenicity) after injection that is considered by the investigator to be related to IP (Section 7.4.9) and is of Grade 3 (severe) or greater severity.
- 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 (eg, MIS-C and myocarditis and/or pericarditis).
- 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 7.4.4) clearly related to IP.
- The participant experiences generalized urticaria related to IP.

The reason(s) for withdrawal from further injection will 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 5.5.2).

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

6.3. 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 or the participant can withdraw assent and withdraw from the study at any time, 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 a participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant 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 or by the investigator, as well as which of the following possible reasons was the cause for withdrawal:

- AE (specify)
- SAE (specify)
- Death
- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant's parent(s)/LAR(s) or withdrawal of assent by the participant (specify)
- 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 participants who are withdrawn from the study as result of an SAE or AE until resolution of the event.

A participant who withdraws from the study may request destruction of any samples taken and not tested, and the investigator must document this in the study site study records.

If the participant's parent(s)/LAR(s) withdraw consent or the participant withdraws assent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent/assent (Section 10.2.10).

The Sponsor will continue to retain and use all research data that have already been collected for the study evaluation, unless the participant has 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).

6.4. 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
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any SAE or Grade 4 AE that cannot be reasonably attributed to a cause other than vaccination	≥ 1
3	ICU Admission due to COVID-19	≥ 1
4[1]	Individual Grade 3 or higher solicited local AR lasting ≥ 24 hours and occurring within 7 days of injection (Days 1-7)	At least 2 participants and ≥ 5% of the dosed participants in an age group
5[1]	Individual Grade 3 or higher solicited systemic AR lasting ≥ 24 hours and occurring within 7 days of injection (Days 1-7)	At least 2 participants and ≥ 10% of the enrolled participants in an age group
6[1]	Any ≥ Grade 3 or higher unsolicited AE that cannot be reasonably attributed to a cause other than vaccination	At least 2 participants and ≥ 5% of the enrolled participants in an age group

Abbreviations: AE = adverse event; AR = adverse reaction; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[1] "Individual AR" is defined as 1 AR type, eg, pain, erythema, or headache could each be an "individual AR."

If any of the thresholds for a study pause is met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators. Such a suspension will remain in

force until the threshold events are reviewed by the DSMB and a recommendation to continue is provided to the Sponsor.

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system, each event that potentially meets any pause rule criterion within 24 hours of observation. The Sponsor will inform the DSMB of any event that potentially meets any pause rule criterion. The DSMB will review all available study data to help adjudicate such events in accordance with the DSMB charter.

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.

6.5. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent/assent 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 and reschedule the missed visit as soon as possible, counsel the participant and his/her parent(s)/LAR(s) on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes 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 (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 who continues to be unreachable or continues 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.

7. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants and/or participants' parent(s)/LAR(s) will sign an ICF (as detailed in Section 10.2.6). Participants will undergo study procedures at the time points specified in the SoA (Table 10). 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 and/or 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 approval of the Sponsor. 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.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in Table 10. Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue study treatment or participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, pregnancy test) 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 10).

7.1. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoA (Table 10):

- Solicited local and systemic ARs (Section 7.4.3) 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 eDiary (Section 7.1.1).
- 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 7.4.1.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation.
- MAAEs (Section 7.4.4) from first dose on Day 1 through the entire study period.
- SAEs (Section 7.4.2) from first dose on Day 1 through the entire study period.
- AESIs (Section 7.4.5) including MIS-C and myocarditis and/or pericarditis, through the entire study period.
- Physical examination findings (Section 7.1.4).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 7.1.5).
- Details of all pregnancies in female participants after the start of study treatment and until the end of their participation in the study (Section 7.4.6).

7.1.1. 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 7.4.3) 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 29) on thermometer (oral/tympanic) 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 7.4.3, 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). If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs, whichever occurs first. Capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
- Daily oral (for participants > 4 years of age) or tympanic (for participants ≤ 4 years of age) 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.
- 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. The participant's parent(s)/LAR(s) will have a limited window on the following day to complete assessments for the previous day; 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.

Any new safety information reported during safety telephone calls or at study site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. An event reported in this manner must be described as a solicited event and entered on the solicited AR eCRF.

Study site staff will review eDiary data with participants' parent(s)/LAR(s) at telemedicine visits 7 days after each injection.

The eDiary will also be used every 4 weeks, starting at Day 71 through Day 183 and again starting at Day 223 through Day 363, to capture the occurrence of AEs, MAAEs, SAEs, AESI, or AEs leading to withdrawal. As specified in the SoA (Table 10), 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. 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 safety telephone call will be triggered.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 7.1.2) as the procedure for safety follow-up approximately every 4 weeks; these safety telephone calls will take place from Day 85 through Day 197 and again from Day 237 through Day 377 (Table 10).

7.1.1.1. Ancillary Supplies for Participant Use

Study sites will distribute Sponsor-provided oral or tympanic thermometers and rulers for use by participants' parent(s)/LAR(s) in assessing body temperature and injection site reactions for recording solicited ARs in electronic diaries (eDiary). 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.

7.1.2. 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 10). The participants' parent(s)/LAR(s) will be interviewed according to the script about the occurrence of AEs, MAAEs, SAEs, AESI, AEs leading to study withdrawal, concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.4.7). 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 7.1.1, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

7.1.3. 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.

A point-of-care urine pregnancy test will be performed, if deemed appropriate by the investigator, at the Screening Visit and before each vaccine dose in female participants of childbearing potential. At any time during the study, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.

Febrile participants at dosing visits (fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F) may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses may receive the IP at the discretion of the investigator.

7.1.4. Physical Examinations

A full physical examination, including body temperature (oral preferred for participants > 4 years of age, tympanic preferred for participants ≤ 4 years of age, but other methods are acceptable in context of COVID-19 precautions), length/height and weight, will be performed at the Screening Visit or on Day 1. The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Symptom-directed physical examinations will be performed on Day 1, Day 29, Day 43 (if the visit is applicable), Day 57, Day 209, and Day 394 and may be performed at other time points at the

discretion of the investigator. Body temperature (oral/tympanic) should be measured on each injection day prior to injection. On each injection day before injection and again 7 days after injection (ie, the day of injection and 6 subsequent days), 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 (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1 or Day 29 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.

Body mass index will be calculated for children ≥ 2 years of age at the Screening Visit only.

7.1.5. Assessment for SARS-CoV-2 Infection

Study participants will have nasal swab samples collected for SARS-CoV-2 testing at the time points specified in the SoA (Table 10).

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

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020b)
- MAAE suggesting a SARS-CoV-2 infection

A study illness visit (study site visit or home visit) will be arranged within 4 to 6 days after last exposure* if a participant experiences the following:

- Exposure (close contact [definition in Section 7.1.1]) to an individual in the household confirmed to be infected with SARS-CoV-2

*Last exposure is defined as the last day a child was in close contact with a symptomatic person in the household (if the child was then isolated from that person) or the last day of the quarantine of the person the child was exposed to, if that person was asymptomatic and/or the child was unable to isolate from that person.

If the participant had a known exposure (close contact) to COVID-19 (eg, exposure to someone with confirmed COVID-19 in the household), it will be captured in the COVID-19 exposure form.

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

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. 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.

If participants are confirmed to have SARS-CoV-2 infection, 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 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 will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.3). At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.

If a participant tests positive at baseline but remains asymptomatic, Day 29 visit can be used as the convalescent visit to obtain a convalescent blood sample; the second dose may still be administered as long as participant remains asymptomatic and no other concerns arise.

7.2. Blood Collections for Immunogenicity Assessments and Biomarker Samples

Blood samples for immunogenicity assessments and biomarker samples will be collected at the time points indicated in the SoA (Table 10, Table 11, and Table 12). The following analytes will be measured:

- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays.
- Serum bAb titer as measured by enzyme-linked immunosorbent assay specific to the SARS-CoV-2 S protein.

- For Part 1, testing for serologic markers for SARS-CoV-2 infection using a nonvaccine antigen-based blood test at Day 1 (prior to the first dose), Day 57, Day 209, and Day 394.

For Part 2, participants in each age group will be assigned to 5 phlebotomy cohorts. Blood sampling will be performed in 3 of these 5 cohorts for immunogenicity at 3 of the following time points: Day 1 (prior to randomization and the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, and Day 394. Participants in the Cohort D (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and the first dose) and within 4 days of receiving Dose 2 at Day 30 (+3 days) for storage and potential future biomarker testing (may include cardiac biomarkers). For participants already enrolled in Cohort D prior to amendment 4, this blood draw will be optional and confirmed at time of re-consenting; for all participants newly enrolled into Cohort D under amendment 4, it will be mandatory. A fifth cohort of participants at selected VTEU sites only, will provide blood samples for assessment of exploratory serology and CMI on Day 1 (prior to randomization and the first dose), Day 43, Day 209, and Day 394.

Sample aliquots will be designed to have backup 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 (Section 10.2.6), 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 CoVs.

The planned volume of blood to be sampled per participant in Part 1 and Part 2 (serology cohorts) for each age group for immunogenicity assessments in 1 day is as follows:

- 6 months to < 2 years: approximately 8 mL
- 2 to < 6 years: approximately 16 mL
- 6 to < 12 years: approximately 24 mL

The planned volume of blood to be sampled per participant at the Day 30 (+3 days) blood draw for storage and potential future biomarker testing for Cohort D in Part 2 is as follows:

- All ages: approximately 4 mL

The planned volume of blood to be sampled per participant in the exploratory serology and CMI cohort for each age group in 1 day is as follows:

- 6 months to < 2 years: approximately 9 mL
- 2 to < 6 years: approximately 9 mL
- 6 to < 12 years: approximately 17 mL

Note: If less than 8 mL of blood is obtained for any given child at baseline, the child cannot be enrolled.

7.3. Inferred Efficacy Assessments

7.3.1. Vaccine Effectiveness Assessments

Vaccine effectiveness for children 6 months to < 12 years of age will be inferred based on serum antibody responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the antibody responses against the following:

1. *If available at the time of analysis*, antibody responses will be assessed against an accepted serum antibody threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, noninferiority of the GM value of serum antibody and seroresponse rate of children 6 months to < 12 years of age (Study P204) compared with the GM value of serum antibody and seroresponse rate from young adults (18 to 25 years of age) enrolled in the ongoing clinical endpoint efficacy trial (Study P301) will be assessed. The statistical parameters to infer effectiveness are described in Section 2.

COVID-19:

To be considered as a case of COVID-19 for the evaluation of the efficacy endpoint, 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 Cut-Offs 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
2 to 5 year	> 140	NA	> 22	> 15.5 or < 6	< 70 + (age in years x 2)
6 to 10 year	> 130	NA	> 18	> 13.5 or < 4.5	< 70 + (age in years x 2)
>10 years	> 130	NA	>18	> 13.5 or < 4.5	< 90

Abbreviations: AHA = American Heart Association; NA = not applicable.

Note: Lower values for heart rate, leukocyte count, are for the 5th percentile and upper values for heart rate, respiratory rate, or leukocyte count are for the 95th percentile for that 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 times 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: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase.
Source: [a]LaRovere et al.

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:
  - bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by Roche Elecsys) postbaseline, OR
  - Positive RT-PCR postbaseline

7.3.2. Surveillance for COVID-19 Symptoms

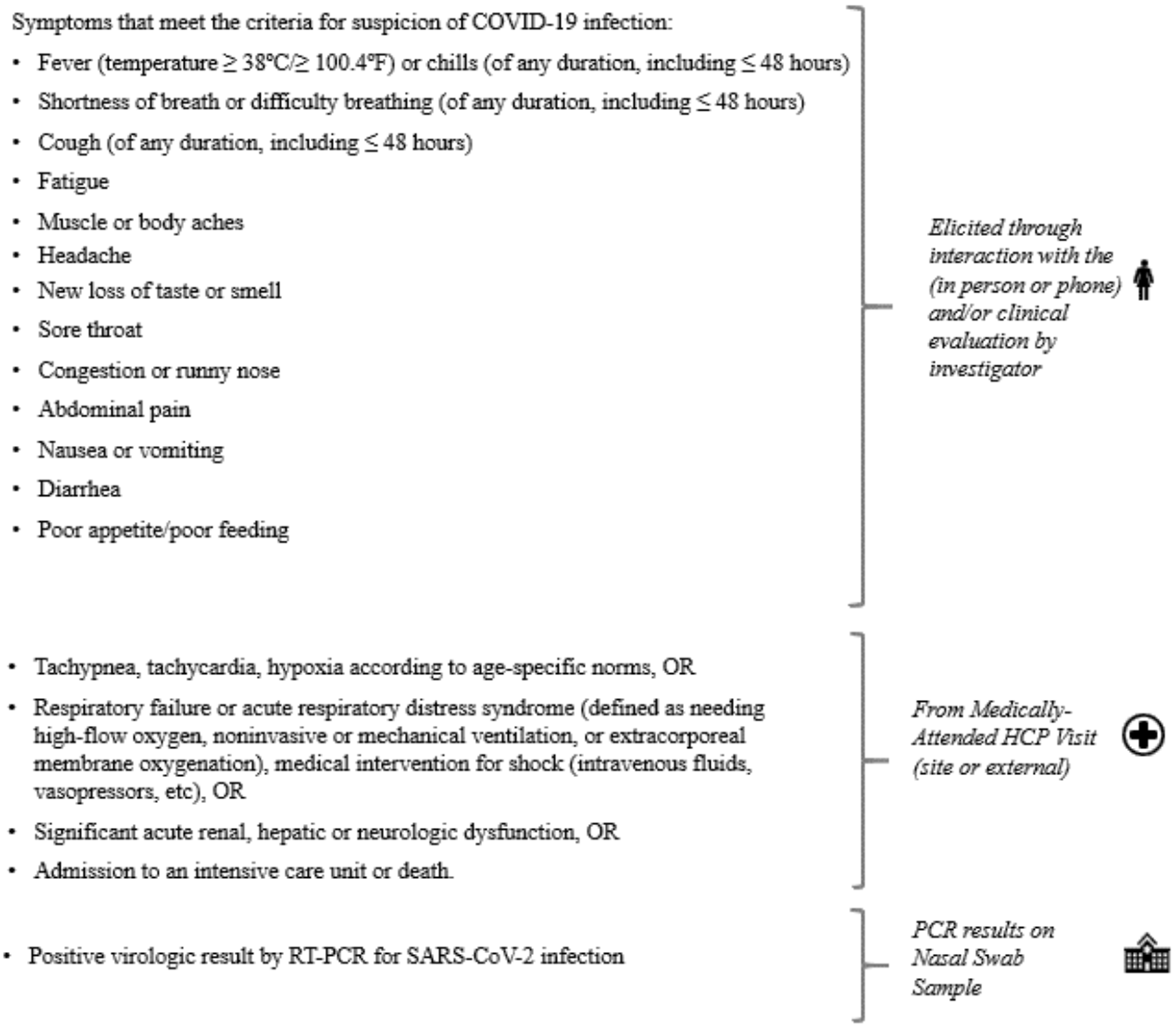
Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary prompts as specified in Section 7.1.1 and Figure 2; starting after participant enrollment and continuing throughout the study.

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 2020c), 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 weekly 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.

- 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, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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 (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 29, and then at all subsequent study visits (Day 43 [if visit is applicable], Day 57, Day 209, and Day 394) 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 RSV 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 nucleic acid amplification test performed at a CLIA-certified or CLIA-waived laboratory 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 7.1.5). Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.3). At this visit, a nasal swab sample for viral RT-PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.

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 7.3.1.

All clinical findings will be recorded in the eCRF. All confirmed cases of COVID-19 will be captured as MAAEs, along with relevant concomitant medications and details about severity, seriousness, and outcome, and will be reported immediately to the Sponsor or designee (Section 7.4.4).

7.3.3. Follow-up/Convalescent Period After Diagnosis with COVID-19

Any confirmed COVID-19 occurring in a participant will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected (Table 10). 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.

Children hospitalized with possible or confirmed MIS-C will also have the same convalescent visit scheduled approximately 28 days (+7 days) after onset of hospitalization. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected (see Table 10).

7.4. Safety Definitions and Related Procedures

7.4.1. 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 AE unless complications arise.

An AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 7.4.9). 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 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 dose of injection and the 6 days after the day of dosing).

7.4.2. 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 one 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.

7.4.3. 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 7.1.1). 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 6 and Table 7, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs, whichever occurs first. Capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit. All solicited ARs (local and systemic) will be considered related to the IP.

Table 6: Solicited Adverse Reactions and Grades: Age 37 Months to < 12 Years[1]

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[2]
Injection site pain	None	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires emergency room visit[3] or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit[3] or hospitalization
Headache	None	No interference with activity	Some interference with activity	Significant; Prevents daily activity	Requires emergency room visit[3] or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit[3] or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit[3] or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit[3] or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity,	Requires emergency room visit[3] or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit[3] or hospitalization
Fever	< 38.0°C < 100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	> 40.0°C > 104.0°F

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[2]

[1] Age at time of enrollment determines the scale to be used.
[2] Grading for Grade 4 events per investigator assessment (with exception of fever).
[3] 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).

Table 7: Solicited Adverse Reactions and Grades: Age 6 to ≤ 36 Months[1]

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[2]
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[3] 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
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[3] 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
Irritability/crying	None	Lasting < 1 hour or easily consolable	Lasting 1-3 hours or requiring increased attention	Lasting > 3 hours or inconsolable	Requires emergency room visit[3] 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

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[2]
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[3] or hospitalization

[1] Age at time of enrollment determines the scale to be used.
[2] Grading for Grade 4 events per investigator assessment (with exception of fever).
[3] 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 a healthcare practitioner (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

7.4.4. 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 7.3.1]) 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 COVID-19 cases (Section 7.3.1) will be recorded as MAAEs and 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 7.4.11). 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 should be recorded as MAAEs and reported as an 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 7.4.11. 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

7.4.5. 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 in the form of a case narrative. Such events may require further investigation to characterize and understand them. Refer to Section 10.4, Appendix 4 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 7.4.11).

Acute Myocarditis and/or Pericarditis

All suspected cases of probable and confirmed myocarditis, pericarditis, or myopericarditis should be recorded as an AESI and reported as an SAE, if the event meets seriousness 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 7.4.11. The investigator will submit any updated myocarditis, pericarditis or myopericarditis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs/symptoms consistent with the CDC case definition as described below (Gargano et al, 2021), should be reported as a potential case of confirmed or probable myocarditis, pericarditis, or myopericarditis.

Acute Myocarditis Case Definition

Presence of ≥ 1 new or worsening of the following clinical symptoms (persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis [probable or confirmed]):

- Chest pain/pressure/discomfort
- Dyspnea/shortness of breath/pain with breathing
- Palpitations
- Syncope

OR

Infants and children aged < 12 years might instead have ≥ 2 of the following symptoms:

- Irritability
- Vomiting
- Poor feeding
- Tachypnea
- Lethargy

AND

For PROBABLE CASE:

Presence of ≥ 1 new finding of the following:

- Troponin level above upper limit of normal (any type of troponin)
- Abnormal electrocardiogram ECG or EKG or rhythm monitoring findings consistent with myocarditis

  - To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of the following:
    - ST segment or T-wave abnormalities
    - Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias
    - AV nodal conduction delays or intraventricular conduction defects

- Abnormal cardiac function or wall motion abnormalities on echocardiogram
- cMRI finding consistent with myocarditis (Ferreira et al, 2018)

AND

- No other identifiable cause of the symptoms and findings

For CONFIRMED CASE:

- Histopathologic confirmation of myocarditis (using Dallas criteria [Aretz, 1987])

OR

- cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)

AND

- No other identifiable cause of the symptoms and findings

Acute Pericarditis Case Definition

Presence of ≥ 2 new or worsening of the following clinical features (Adler, et al 2015):

- Acute chest pain (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 may occur)
- Pericardial rub on examination
- New ST-elevation or PR-depression on EKG
- New or worsening pericardial effusion on echocardiogram or MRI

Myopericarditis Case Definition

Participants who meet criteria for both myocarditis and pericarditis may be described under myopericarditis.

An independent Cardiac Event Adjudication Committee (CEAC) consisting of pediatric and adult cardiologists will review suspected cases of myocarditis, pericarditis, or myopericarditis to

determine if they meet CDC criteria of "probable" or "confirmed" event, and to assess severity and enable the DSMB to make recommendations to the Sponsor to continue vaccine dosing. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

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 2020d):

- An individual aged < 21 years presenting with fever, laboratory evidence of inflammation, 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

WITH OR WITHOUT

- 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:
    - Fever ≥ 38.0°C/≥ 100.4ºF for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours
    - 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

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.

7.4.6. Recording and Follow-up of Pregnancy

Female participants who have a positive pregnancy test at Screening should not be enrolled; participants who have a positive pregnancy test any time during the study should receive no further dosing with IP but should be asked to remain in the study and be monitored for safety.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancies occurring in participants after enrollment must be reported to the Sponsor or designee within 24 hours of the study site learning of its occurrence, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11). If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

7.4.7. Eliciting and Documenting Adverse Events

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 from Day 1 through 7 days after each dose (ie, the day of injection and 6 subsequent days). Other (unsolicited) AEs will be collected from Day 1 through 28 days after each dose.

Both MAAEs and SAEs will be collected from participants as specified in the SoA (Table 10) 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, participants or 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). Participants or 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 6.5).

7.4.8. 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 7.4.2), 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 children 37 months to < 12 years of age (Table 6) and 6 to ≤ 36 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 7.4.3.

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 or the 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.

7.4.9. 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.

7.4.10. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported at the times specified in Table 10, 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 Medical Dictionary for Regulatory Activities (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.

7.4.11. 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 7.4.2) 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 following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (United States and Canada): +1-866-599-1341

- SAE Fax line (United States and Canada): +1-866-599-1342

Regulatory reporting requirements for SAEs are described in Section 7.4.15.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, 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.

7.4.12. Time Period and Frequency for Collecting AE, AESI, 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 or participant's parent(s)/LAR(s)
- Questioning the participant or 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 (including AESIs) will be collected from the start of IP dosing until the last day of study participation.

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 7.4.11).

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). 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 end of the study participation. However, if the investigator learns of any SAE (including a death) at any time after a participant has withdrawn from or completed the study, and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

7.4.13. 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 and participant's parent(s)/LAR(s) is the preferred method to inquire about the occurrence of AE.

7.4.14. 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 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 6.5.

7.4.15. 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 adverse reactions 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.

7.5. Safety Monitoring

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

7.5.1. Internal Safety Team

An IST will review safety data throughout the study. For Part 1 dose-escalation and age de-escalation, based on the review of all available safety data through at least Day 8 (1 week after Dose 1 of mRNA-1273) for at least 75 participants at each dose level within the 6 to < 12 years and 2 to < 6 years age group, the IST will recommend whether dose-escalation and age de-escalation are appropriate. This process will then be repeated for all participants in the 25 and 50 µg dose levels within the lower age group of 6 months to < 2 years of age. An IST review of all available safety data through at least Day 36 (1 week after Dose 2 of mRNA-1273 at each dose level) of at least 75 participants will be required prior to the administration of the second injection of the next higher dose. 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.

7.5.2. 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 meet at pre-specified timepoints during the study to assess safety throughout study conduct. For the 6 to < 12 years age group, the DSMB will review cumulative safety data for approximately 300 participants enrolled at the selected dose level in Part 1 before enrollment begins in Part 2. For both the middle age group (2 to < 6 years) and the youngest age group (6 months to < 2 years) the DSMB will review cumulative safety data in both younger age groups (2 to < 6 years; 6 months to < 2 years) combined and at all dose levels administered in Part 1 before start of Part 2 (blinded phase) for each age group. 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, described in Section 6.4, 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.

The CEAC consisting of pediatric and adult cardiologists will review suspected cases of myocarditis, pericarditis, or myopericarditis to determine if they meet CDC criteria of "probable" or "confirmed" event, and to assess severity and enable the DSMB to make recommendations to the Sponsor to continue vaccine dosing. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

7.6. Treatment of Overdose

As the study treatment is to be administered by a healthcare professional, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 10.2.8).

7.7. Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

7.8. Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

7.9. Biomarkers

Immunogenicity assessments are presented in Section 7.2. Biomarkers will not be evaluated in this study.

7.10. Health Economics

Health economics will not be evaluated in this study.

8. 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 statistical analysis plan (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 clinical study report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

8.1. 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 participants, 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) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of IP to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- 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 unblinded statistical and programming team will perform the primary analyses in Part 2 (Section 8.6.2). Sponsor team members 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 dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the IP in a secure location that is not accessible or visible to other study staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different from those of placebo. Only delegated unblinded study site staff

will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

The planned study analyses are described in Section 8.6.

8.1.1. Breaking the Blind

A participant's treatment assignment may be unblinded (Part 2 of the study) in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved. If a COVID-19 vaccine is authorized or licensed for a specific age group before the end of the study, please refer to Section 3.3 for unblinding and/or cross-over plans.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for interim analyses as outlined in Section 8.6.1.

8.2. Statistical Hypothesis

If an accepted antibody threshold of protection against COVID-19 is established for the primary immunogenicity endpoint, the null hypothesis is that the percentage of participants on mRNA-1273 with serum antibody above the established threshold at Day 57 is $\leq 70\%$ (ie, H_0: percentage of participants on mRNA-1273 with serum antibody at Day 57 above the established threshold $\leq 70\%$).

For each age group, the study will be considered to meet the immunogenicity endpoint if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 70% (lower bound of the 95% CI is > 70%).

The null hypotheses may be updated when the information on an acceptable antibody threshold becomes available. In this case, the null hypothesis update will be provided in the SAP.

If an accepted serum antibody threshold of protection against COVID-19 is not available for the primary immunogenicity endpoint, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 antibody levels will be compared to Day 57 antibody levels

from young adults (18 to 25 years of age) in Study P301. Noninferiority tests of 2 null hypotheses based on 2 coprimary endpoints will be performed, respectively.

Coprimary endpoint 1: antibody GM value at Day 57

The null hypothesis H^1_0: immunogenicity response to mRNA-1273, as measured by antibody GM value at Day 57, is inferior in children (in age groups 6 months to < 2 years, 2 to < 6 years, and 6 to < 12 years) compared with that in young adults (18 to 25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in antibody GM value in an age group in children compared with that in young adults (18 to 25 years of age) is demonstrated by meeting both success criteria:

- The lower bound of the 95% CI of the geometric mean ratio (GMR) ruling out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, AND
- The GMR point estimate > 0.8 (minimum threshold).

The GMR is the ratio of the GM value of SARS-CoV-2-specific antibody in children in an age group receiving mRNA-1273 in this Study P204 compared with the GM value of young adults (18 to 25 years of age) receiving mRNA-1273 in Study P301 at Day 57.

Coprimary endpoint 2: antibody seroresponse rate at Day 57

A definition of seroresponse will be provided in the SAP based on forthcoming information about assay performance.

The null hypothesis H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in children compared with that in young adults (18 to 25 years of age) in Study P301.

The noninferiority in seroresponse rate in an age group in children compared with that in young adults (18 to 25 years of age) is demonstrated by meeting both success criteria:

- The lower bound of the 95% CI of the seroresponse rate difference ruling out -10% (ie, lower bound > -10%) using the noninferiority margin of 10%, AND
- The seroresponse rate difference point estimate > -5% (minimum threshold)

The seroresponse rate difference is defined as the seroresponse rate in children receiving mRNA-1273 minus the seroresponse rate in young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301.

The study would be considered to meet the primary immunogenicity endpoint in an age group if the noninferiority in the age group compared with the young adults (18 to 25 years of age) is demonstrated based on both coprimary endpoints.

8.3. Power and Sample Size

The initial age groups in Part 1 are for estimation purposes. With approximately 750 participants (approximately 375 participants at each dose level of mRNA-1273) in the initial 6 to < 12 years age group, there is at least a 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% for a given dose level. In each of the younger age groups (2 to < 6 years and 6 months to < 2 years), the safety assessment will occur during the conduct of Part 2 after approximately 375 participants have been exposed to mRNA-1273 at the dose level selected for Part 2. For further details, please refer to Section 7.5.2.

The sample size in the expansion (Part 2) is considered to be sufficient to support a safety database in the pediatric participants 6 months to < 12 years of age. With up to 3,000 participants each in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years of age groups exposed to mRNA-1273 at a given dose level in Part 2, the study has at least a 95% probability to observe at least 1 participant with an AE at a true 0.1% AE rate for a given dose level.

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group will be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset will be processed, and the analysis of primary immunogenicity endpoint will be based on the Immunogenicity PP Subset.

If a threshold of protection is available, for the primary immunogenicity endpoint, with approximately 289 participants on mRNA-1273 in the Immunogenicity PP Subset of an age group, there will be at least 90% power to rule out 70% with a 2-sided 95% CI (lower bound of the 95% CI > 70%) for the percentage of mRNA-1273 participants exceeding the accepted threshold if the true rate of participants exceeding the threshold is 80%.

If an acceptable antibody threshold of protection against COVID-19 is not available at the time of analysis for the primary immunogenicity endpoint, noninferiority tests of the 2 null hypotheses based on the 2 coprimary endpoints will be performed, respectively. The sample size calculation for each of the 2 noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be 90% power to demonstrate noninferiority of the immune response, as measured by the antibody GM value, in pediatric population at a 2-sided alpha of 0.05, compared with that in young adults (18 to 25 years of age) in Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1, a noninferiority margin of 0.67 (or 1.5), and a point estimate minimum threshold of 0.8. The standard deviation of the natural log-transformed levels is assumed to be 1.5.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in children at a 2-sided alpha of 0.05, compared with that in young adults 18 to 25 years of age in Study P301 receiving mRNA-1273, assuming seroresponse rate of 85% in young adults of 18 to 25 years of age from Study P301, true seroresponse rate of 85% in children (or true rate difference is 0 compared to young adults from Study P301), a noninferiority margin of 10% and a point estimate minimum threshold of -5% in seroresponse rate difference.

In the 1273-P203 interim analysis (data snapshot on 08 May 2021), the observed seroresponse rates at Day 57 were high in both 18 to 25 years of age group from Study P301 (98.6% with 95% CI: 96.6, 99.6) and 12 to17 years of age group (98.8% with 95% CI: 97.0, 99.7), based on pseudovirus nAb ID50 titers. For this Study P204, if the true seroresponse rates were assumed to be 95% or higher in both 18 to 25 years of age group from Study P301 and an age group in children, with between-group true difference within 4%, there will be a >90% power to demonstrate noninferiority by seroresponse rate in children compared with 18 to 25 years of age in Study P301, at a 2-sided alpha of 0.05.Assuming approximately 25% of participants in the Immunogenicity Subset will not meet the criteria to be included in the Immunogenicity PP Subset, approximately 528 participants in Part 2 (~396 receiving mRNA-1273 and ~132 receiving placebo) will be selected for the Immunogenicity Subset from which approximately 289 participants on mRNA-1273 will be suitable for the Immunogenicity PP Subset.

8.4. Analysis Sets

The analysis sets are defined in Table 8. The analysis sets may be defined for Part 1 and Part 2 separately.

Table 8: Analysis Sets

Analysis Set	Description
Randomization Set	Part 2: All participants who are randomly assigned, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	Part 1: All enrolled participants in Part 1 who receive at least 1 injection of IP. Part 2: All randomly assigned participants who receive at least 1 injection of IP.
Per-Protocol (PP) Set	All participants in the FAS who receive planned doses of IP per schedule, comply with the immunogenicity schedule, and have no major protocol deviations that impact key or critical data.

Analysis Set	Description
	Participants who are RT-PCR positive or seropositive at baseline will be excluded from the PP Set. The PP Set in Part 1 will be used for all analyses of immunogenicity in Part 1 unless specified otherwise.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity sampling and testing.
Per-Protocol Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset 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. Participants who are RT-PCR positive or seropositive at baseline will be excluded from the PP Immunogenicity Subset, in addition to participants with HIV who are receiving highly active anti-retroviral therapy (HAART). The PP Immunogenicity Subset will be used for all analyses of immunogenicity unless specified otherwise.
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	The Solicited Safety Set consists of participants in the Safety Set who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline.
Modified Intent-to-Treat-1 (mITT1) 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).

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; IP = investigational product; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

8.5. Statistical Methods

8.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, race, ethnicity) and baseline characteristics (eg, length/height, weight, and BMI) will be summarized by treatment group. Summary statistics (mean, standard deviation for continuous variables, and number and percentage for categorical variables) will be provided.

8.5.2. 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 and placebo) and by age group. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for safety analysis.

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, AEs leading to discontinuation, and physical examination findings.

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.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs 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 parameters. 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	—

Abbreviations: AE = adverse event; 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.

8.5.3. Immunogenicity Analyses

The primary analysis population for immunogenicity will be the Immunogenicity PP Subset, unless specified otherwise. The primary objective of this study is to use the immunogenicity response to infer efficacy in participants aged 6 months to < 12 years at the dose level selected for expansion. For this objective, analyses of immunogenicity will be performed for each pediatric age group separately at the selected dose level based on the participants in the Immunogenicity PP Subset. For each pediatric age group, participants in Part 2 in the Immunogenicity PP Subset may be used for immunogenicity primary analysis. Participants from Part 1 and Part 2 who receive the same mRNA-1273 dose level selected for expansion may be combined for immunogenicity analyses. If the same dose level is selected for expansion for more than one age group, these age groups may be combined for immunogenicity analyses.

An accepted antibody threshold of protection against COVID-19 may be available based on data from other mRNA-1273 studies or external data. If such a threshold of protection against COVID-19 is available, the number and percentage of participants with antibody greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. For an age group, if the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity endpoint of this study will be considered to be met for that age group.

The number and percentage of participants with serum antibody greater than or equal to the threshold with 2-sided 95% CI will be provided at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum antibody threshold of protection against COVID-19 is not established, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 antibody levels will be compared to that in young adults (18 to 25 years of age) using data from Study P301. An analysis of covariance model will be carried out with antibody at Day 57 as dependent variable and a group variable (a pediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable for each pediatric age group. The GM values of the pediatric age group at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI will be provided to assess the difference in immune response between the pediatric age group (Study P204) compared to the young adults (18 to 25 years of age) in Study P301 at Day 57. For each pediatric age group, the noninferiority of GM value will be considered demonstrated if:

- The lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5, AND
- The GMR point estimate > 0.8 (minimum threshold).

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 postbaseline time point with Day 57 being of the primary interest. The seroresponse rate difference with 95% CI at Day 57 will be provided between children receiving mRNA-1273 in Study P204 and young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301. For each pediatric age group, the noninferiority of seroresponse rate will be considered demonstrated if:

- The lower bound of the 95% CI of the seroresponse rate difference is > -10% based on the noninferiority margin of 10%, AND
- The seroresponse rate difference point estimate > -5% (minimum threshold).

In addition, the GM value of anti-SARS-CoV-2-specific antibody 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 values then back transformed to the original scale. For each age group, the geometric mean fold-rise of specific nAb and bAb with corresponding 95% CI at each postbaseline time point over preinjection baseline at Day 1 will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided.

Multiplicity Adjustment Between Age Groups:

A sequential hypothesis testing (fixed-sequence method) will be used to adjust multiplicity to preserve the family-wise Type I error rate (alpha = 0.05), starting with the oldest age group, followed by the middle age group, and then followed by the youngest age group. The

immunogenicity coprimary endpoint hypotheses for the oldest age group (6 to < 12 years of age) will be tested first at alpha level of 0.05. If the testing in the oldest age group is statistically significant (meeting the noninferiority success criteria of the coprimary endpoints), the alpha level of 0.05 will be passed to the testing of the coprimary endpoint hypotheses in the middle age group (2 to < 6 years of age). If the testing in the middle age group is statistically significant at alpha level of 0.05, then the alpha 0.05 is preserved for testing the coprimary endpoint hypotheses in the youngest age group (6 months to < 2 years of age). The testing will continue through the sequence only until an endpoint in an age group is not statistically significant (did not meet noninferiority success criteria of any primary endpoint), in which case the testing will stop.

8.5.4. Inferred Efficacy Analysis

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, dose level, and age group, calculated as the number of cases divided by the total person-time. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level (if applicable) may be combined in the analysis.

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

The secondary efficacy analyses will be performed on the PP Set, with sensitivity analyses in FAS, mITT Set, and mITT1 Set. Analyses of the efficacy endpoints in Part 2 will be performed for the randomized blinded phase. Additional exploratory analyses will be conducted in the blinded and unblinded phases for participants randomized to mRNA-1273 in Part 2, and in the unblinded phase for participants who are originally randomized to the placebo arm and cross-over to mRNA-1273 after use of any COVID-19 vaccine is authorized or licensed for the participant’s age group.

8.5.5. Exploratory Analyses

Exploratory analyses will be described in the SAP before database lock.

8.5.6. Subgroup Analyses

Subgroup analyses will be performed as described in the SAP.

8.6. Study Analyses

8.6.1. Interim Analyses

Part 1: Interim analyses may be performed after all or a subset of participants (with immunogenicity samples collected for D1 and D57) have completed Day 57 within an age group in Part 1 (one optional interim analysis for each age group, 3 interim analyses total for the 3 age

groups in Part 1). Analyses of safety and immunogenicity may be conducted at each interim analysis.

Part 2: An interim analysis of immunogenicity and safety will be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 1 or Part 2 within an age group. This interim analysis will be considered the primary analysis of immunogenicity for a given age group. Another interim analysis on safety may be performed after a different subset or all participants have completed Day 57 in an age group.

8.6.2. 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.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Schedule of Assessments

The SoA is presented in Table 10. The SoA for placebo recipient cross-over vaccination with mRNA-1273 if any COVID-19 vaccine is authorized or licensed for participant's age group is presented in Table 11.

If a participant cannot attend a study site visit (scheduled or unscheduled), with the exception of Screening, Day 1, and Day 29, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor (Section 7). If neither a participant visit to the study site nor a home visit to the participant is possible (with the aforementioned exceptions), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls.

The blood sampling schedule for exploratory serology and CMI in Part 2 of the study is presented in Table 12.

Table 10: Schedule of Assessments

Visit Number	0	1	2	3	3A	4	4S	5			6			7
Type of Visit	C	C	TMV	C	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1				M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D30	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+3	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	1	7	14	28	-	-	180	-	-	365
Informed consent/assent form, demographics, concomitant medications, medical history	X													
Review of inclusion and exclusion criteria	X	X												
Physical examination including body temperature, length/height, weight, and BMI[7]	X	X		X			X	X			X			X
Pregnancy test[8]	X	X		X										
Randomization		X												
Study injection (including 30-minute postdose observation period)		X		X										
Blood sample for vaccine immunogenicity (Part 1)[9]		X						X[19]			X[19]			X[19]
Blood sample for vaccine immunogenicity (Part 2)[10]		X		X				X			X			X
Blood sample for exploratory serology and cell-mediated immunity (Part 2)[3,10]		X					X				X			X
Blood sample for potential biomarker analysis (Part 2)[10,11]					X[11]									
Nasal swab sample for SARS-CoV-2[12]		X		X			X	X			X			X

Visit Number	0	1	2	3	3A	4	4S	5			6			7
Type of Visit	C	C	TMV	C	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1				M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D30	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+3	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	1	7	14	28	-	-	180	-	-	365
Surveillance for COVID-19/illness visit/ unscheduled visit[13]			X	X		X	X	X	X	X	X	X	X	X
Convalescent visit[14]						X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[15]		X		X										
Review of eDiary data			X			X								
Follow-up safety telephone calls[16]										X			X	
Recording of unsolicited AEs		X	X	X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[17]		X	X	X	X	X	X	X	X		X	X		X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[17,18]		X	X	X	X	X	X	X	X		X	X		X
Recording of AESIs (eg, MIS-C, myocarditis/pericarditis)[18]		X	X	X	X	X	X	X	X		X	X		X
Recording of concomitant medications and nonstudy vaccinations[17]		X	X	X	X	X	X	X						
Study completion														X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BMI = body mass index; 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; IP = investigational product; IRB = institutional review board; LAR = legally acceptable representative; M = month; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; 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; TMV = telemedicine visit; VTEU = Vaccine and Treatment Evaluation Units.

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, and Day 29) with the approval of the Sponsor.

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. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+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 29 + 21 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. Refer to Section 6.1.1 for individual participant criteria for delay of study vaccination.
3. To be conducted during Part 2 of the study in a cohort of participants at selected VTEU sites only.
4. 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 telemedicine visit should be conducted in place of the study site visit. The telemedicine visit 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).
5. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
6. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
7. A full physical examination, including body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]), length/height, and weight, will be performed at the Screening Visit or on Day 1. Symptom-directed physical examination will be performed on Day 1, Day 29, Day 43 (if the visit is applicable), Day 57, Day 209, and Day 394 and may be performed at other time points at the discretion of the investigator. Body mass index will be calculated only at Screening Visit. Body temperature (oral/tympanic) should be measured on each injection day prior to injection. 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 (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1 or Day 29 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.
8. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test and will be performed if deemed appropriate by the investigator. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time during the study.
9. On Day 1, sample must be collected prior to randomization and dosing. If a Day 1 (baseline) blood sample cannot be obtained in Part 1, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be scheduled for rescreening. Participants may be rescreened 1 time, either within the same screening period for Part 1 or for a new screening period for Part 2 later in the study. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3.
10. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing. In Part 2, participants in each age group will be assigned to 1 of 5 phlebotomy cohorts (Table 12). Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1, Day 57, and one of Day 29, Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the Cohort D (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and the first dose) and within 4 days of receiving Dose 2 at Day 30 (+3 days) for storage and potential future biomarker testing. A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on Day 1, Day 43, Day 209, and D394. Table 12 provides the blood sampling schedule in Part 2 of the study. If a Day 1 (baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be rescheduled for rescreening. Participants may be rescreened 1 time, either within the same screening period for Part 1 or Part 2 or in a new screening period of Part 2 if the initial screening was in Part 1. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3.
11. Part 2, Cohort D participants only, one ~4 mL blood draw. For participants already enrolled in Cohort D prior to protocol amendment 4, this blood draw will be optional and confirmed at time of re-consenting; for all participants newly enrolled into Cohort D under amendment 4, it is mandatory.
12. The nasal swab sample (collected before dosing on injection day) will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.

13. 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 (Section 7.1.5), 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.
14. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis of COVID-19. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.
15. 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. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolved or the next IP injection occurs, whichever occurs first. Capturing details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
16. 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.
17. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).
18. In addition to MIS-C and myocarditis and/or pericarditis, a list of AESIs pertinent to this study may be referenced in the list of AESIs that 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 (Section 7.4.11).
19. For Part 1, only the first approximately 75 participants in Arm 1 and Arm 2 will have postbaseline scheduled blood draws; the 300 participants in each of the expansion part of Arm 1 and Arm 2 may have an optional blood draw on Day 57. All participants in Arm 3, 4, 5, 6 and 7 will have postbaseline blood draws on Day 57, Day 209 and Day 394.

Table 11: Schedule of Assessments for Placebo Recipient Cross-Over Vaccination with mRNA-1273 if any COVID-19 Vaccine is Authorized or Licensed for Participant's Age Group[1]

Schedule of Assessments for Placebo Recipient Cross-Over Vaccination	Cross-Over D1	D29 (+ 7)[2]	D36 (+ 3)	D57 (+ 7)	Remainder of Study Visits
Study injection (including 30-minute postdose observation period)	X	X			
Safety follow-up call			X	X	
Recording of unsolicited AEs	X	X	X	X	
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE	X	X	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE	X	X	X	X	X
Recording of AESIs (eg, MIS-C and myocarditis and/or pericarditis)	X	X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; D = day; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. Authorized or licensed in participant's age group.
2. Refer to Section 6.1.1 for individual participant criteria for delay of study vaccination.

Table 12: Phlebotomy Schedule for Serology, Biomarker Sample, and Cell-Mediated Immunity for Part 2 (Expansion) of the Study

Cohort	Number of subjects		Study Visit Day					
		D1[1,2]	D29[1]	D30 (+3)[3]	D43	D57	D209	D394
Phlebotomy Schedule for Serology: To be Executed Within Age Group								
A	First 176 (132 mRNA-1273: 44 placebo)	X	X			X		
B	Next 176 (132 mRNA-1273: 44 placebo)	X				X	X	
C	Next 176 (132 mRNA-1273: 44 placebo)	X				X		X
D	Remainder of the age group	X		X[3]				
Phlebotomy Schedule for Cell-Mediated Immunity: To be Executed Within Each Age Group at Selected VTEU Sites only								
E (CMI with exploratory serology)	24 (18 mRNA-1273: 6 placebo)	X			X		X	X

Abbreviations: CMI = cell-mediated immunity; D = day; VTEU = Vaccine and Treatment Evaluation Units.

1. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing.
2. If a Day 1 (baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be scheduled for rescreening. Participants may be rescreened 1 time, either within same screening period for Part 1 or Part 2 or in a new screening period for Part 2 if the initial screening was in Part 1. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3.
3. Serum sample from ~4 ml of blood only, to be stored for potential future use for biomarker assessment.

10.2. APPENDIX 2: Study Governance Considerations

10.2.1. 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.

10.2.2. 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 do the following:

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, the designated CRO, and the investigator.

According to ICH GCP guidelines, 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 the 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 that AEs and SAEs have been properly documented on eCRFs, that any SAEs have been forwarded to the SAE Hotline, and that those SAEs that meet criteria for reporting have been forwarded to the IRB.

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

10.2.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct study 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 study 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 E6(R2) GCP, 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 informed consent/assent forms and recruitment materials, must be maintained by the investigator and made available for inspection.

10.2.4. 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.

10.2.5. Recruitment Procedures

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.

10.2.6. Informed Consent/Assent Process

The informed consent and assent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, the Health Insurance Portability and Accountability Act, where applicable, and the IRB or study site. All consent/assent documents will be approved by the appropriate IRB. The actual ICF used at each study 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 willingness to continue participation 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 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 he/she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participants' 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.

10.2.7. 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 that may impact the conduct of the study or 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 an amendment will be released by the Sponsor, agreed to 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 to by the investigators, and notified to the IRB(s).

10.2.8. Protocol Deviations

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

It is the responsibility of the study 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 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.

10.2.9. 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 that 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 quality assurance (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 health care 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, the 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.

10.2.10. Sample Retention and Future Biomedical Research

The retention period of laboratory samples will be 20 years, or as permitted by local regulations, to address further scientific questions related to mRNA-1273 or anti-respiratory virus immune response. In addition, identifiable samples can be destroyed at any time at the request of the participant. 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 from Cohort D in Part 2. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1273, 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.

10.2.11. 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), and 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.

10.2.12. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the study site under the supervision of the study 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 study 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 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 less than 2 years. 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.

10.2.13. 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 WHO - Drug Dictionary.

10.2.14. 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.

10.2.15. 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.

10.2.16. 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 participants and should ensure 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 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.

10.2.17. 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.

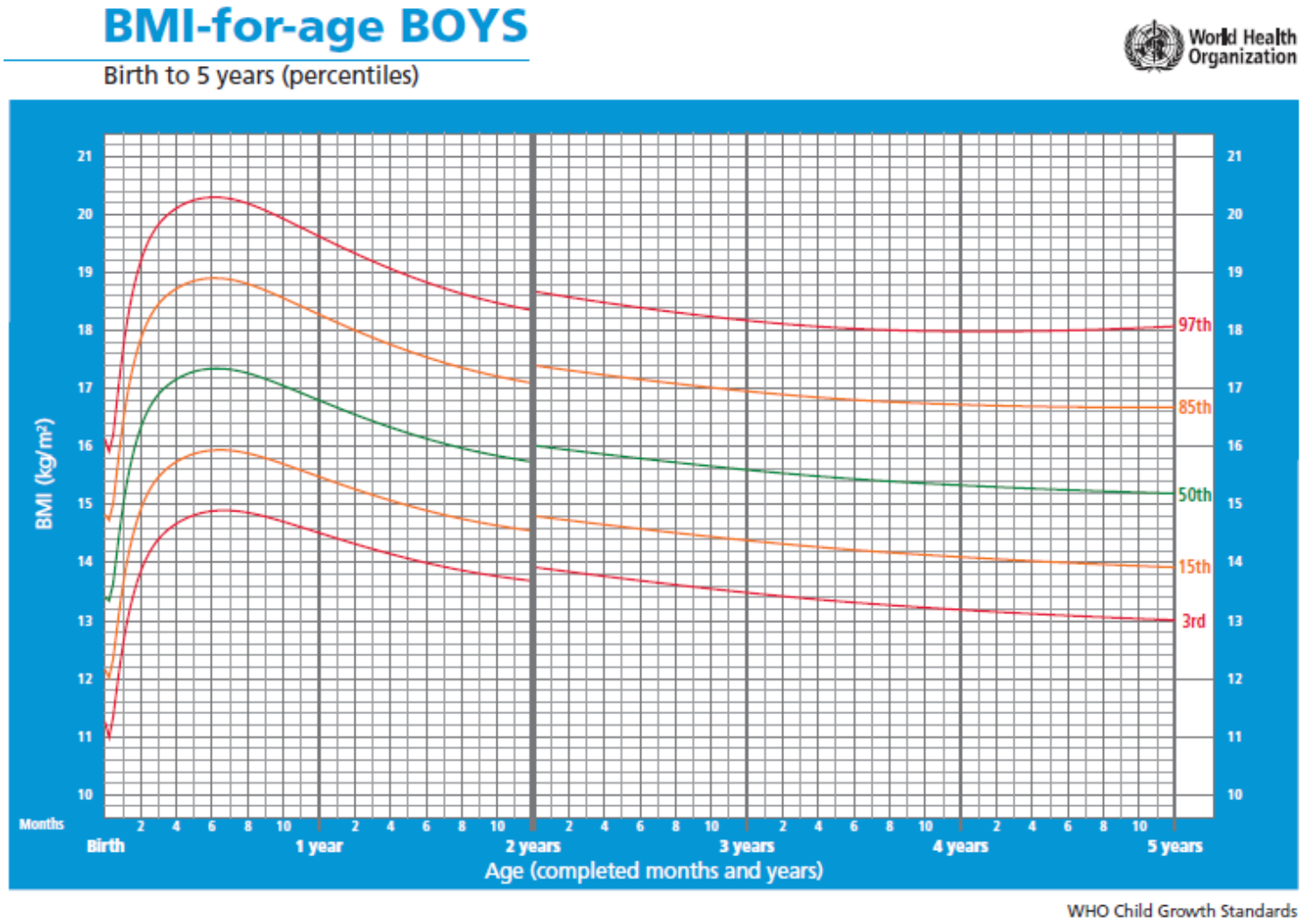
The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating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

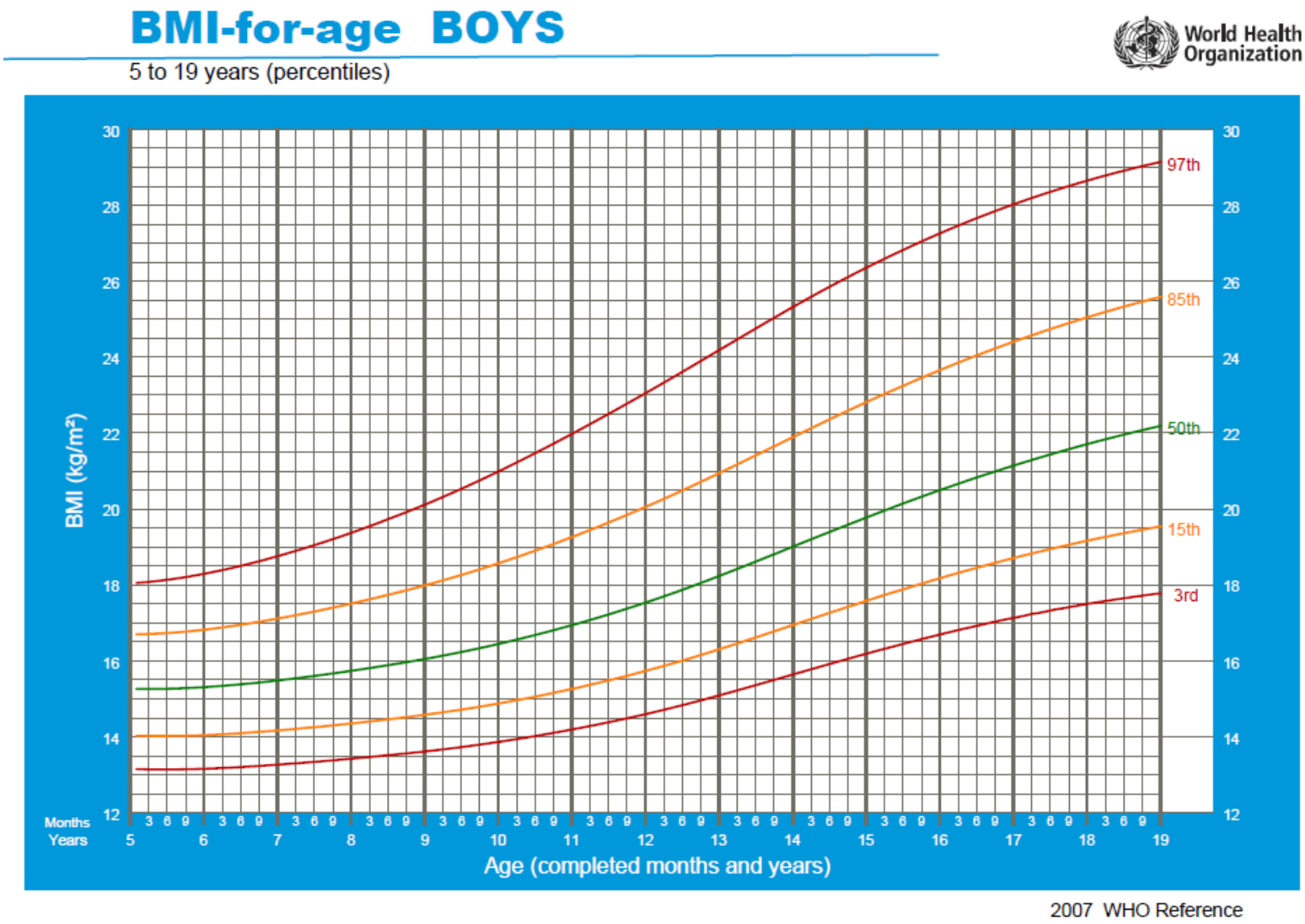
The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results and data from this study belong to the Sponsor.

10.2.18. Body Mass Index Charts for Boys and Girls

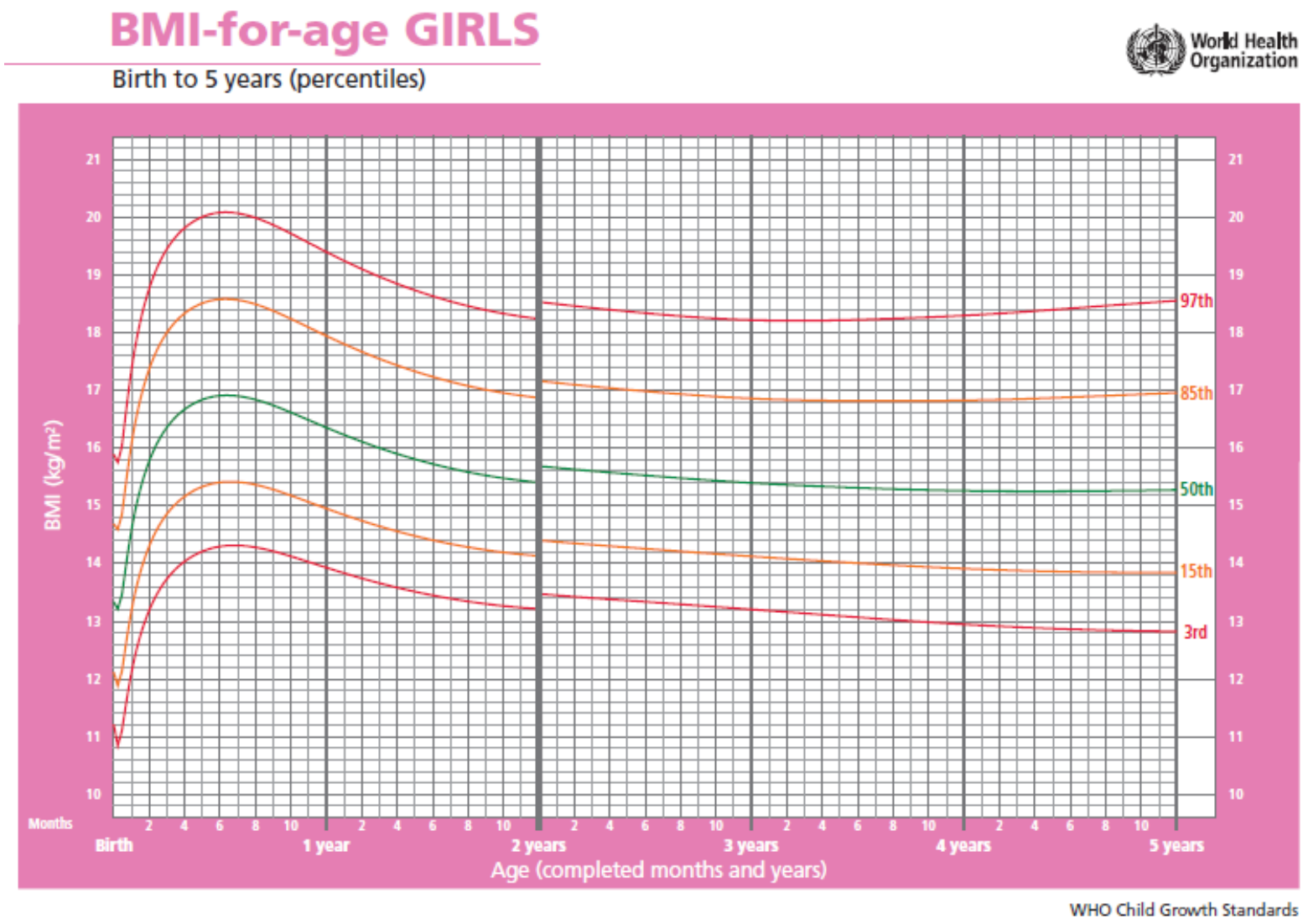
For boys from birth to 5 years:



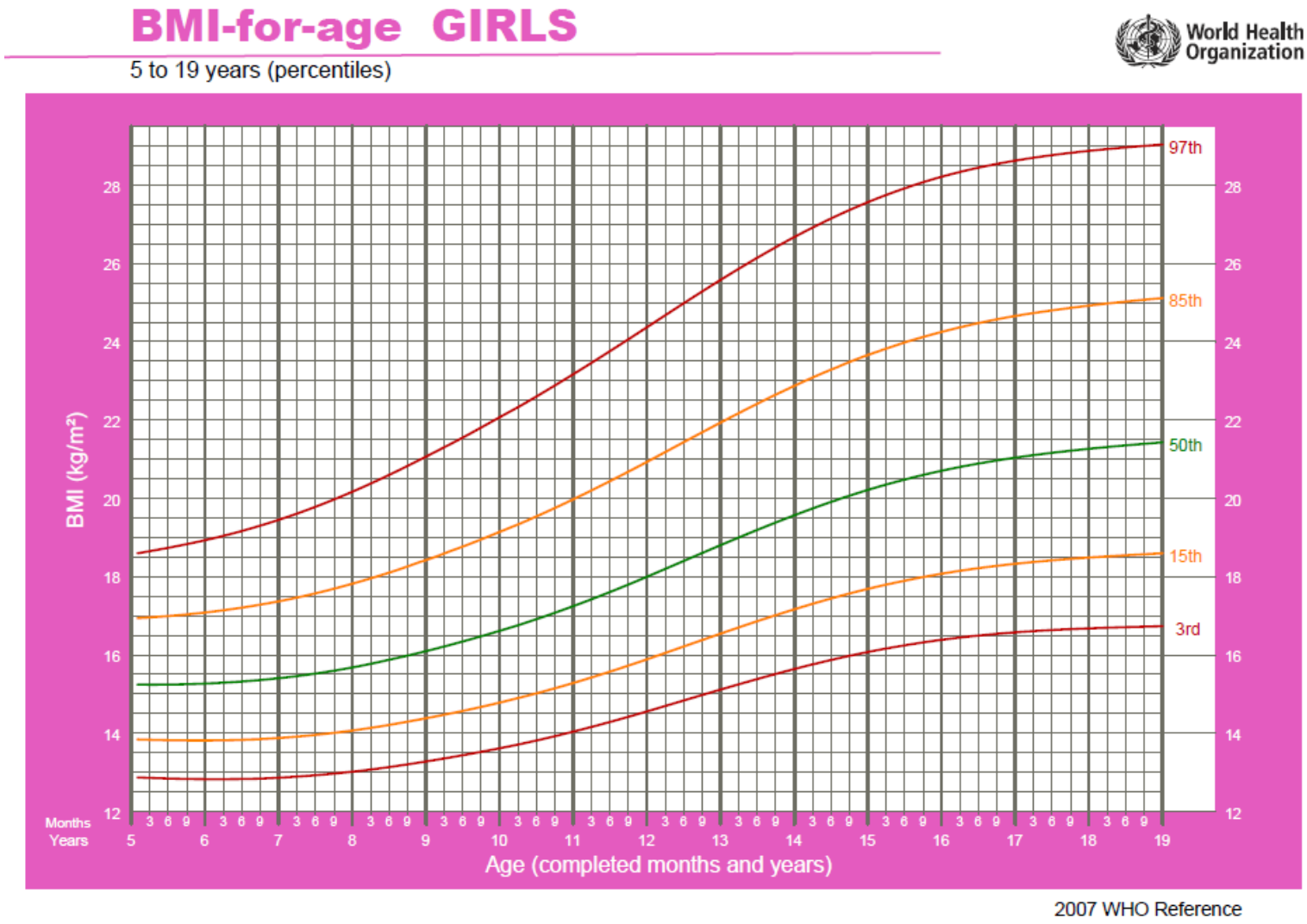
For boys aged 5 through 19 years:



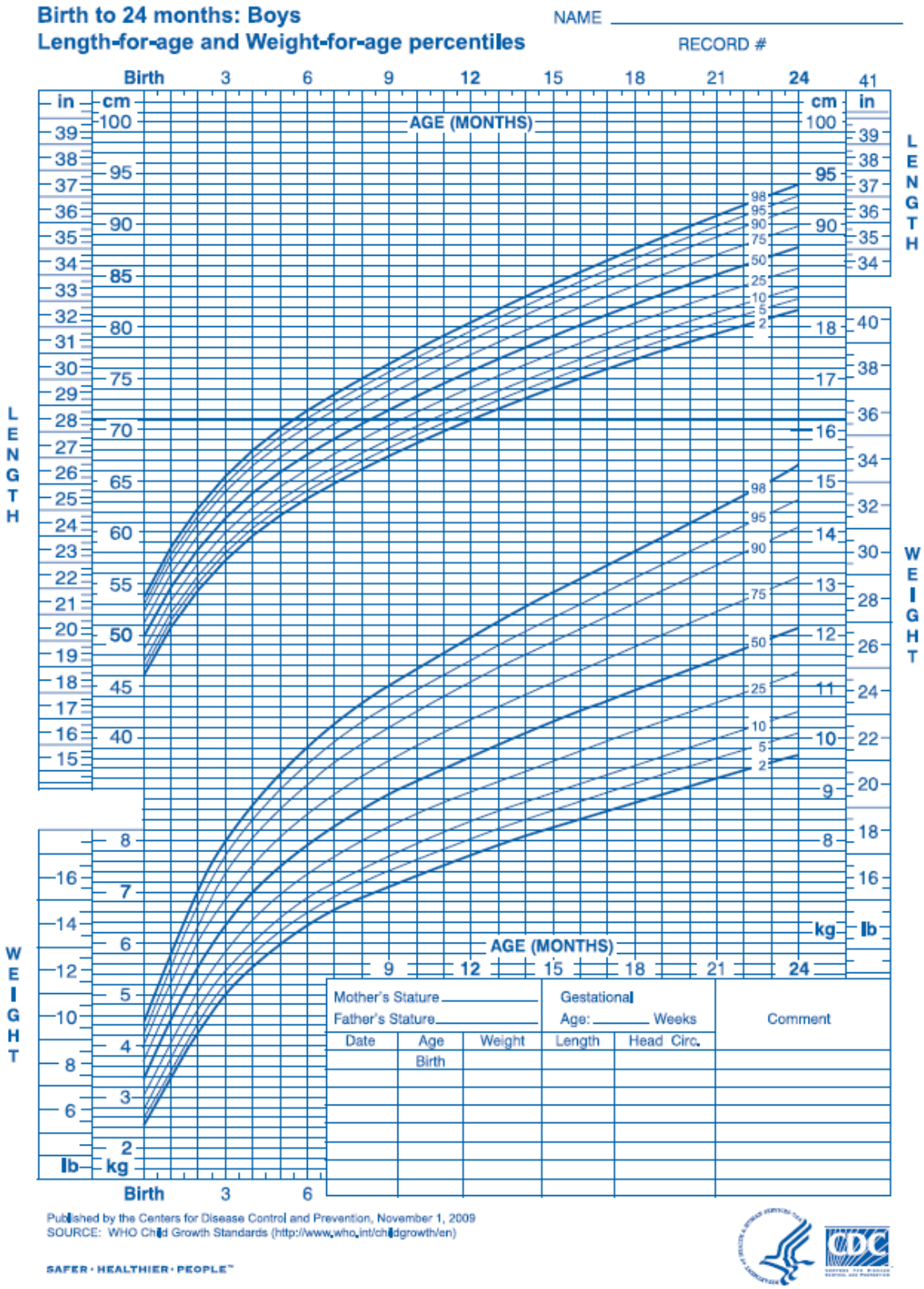
For girls from birth to 5 years:



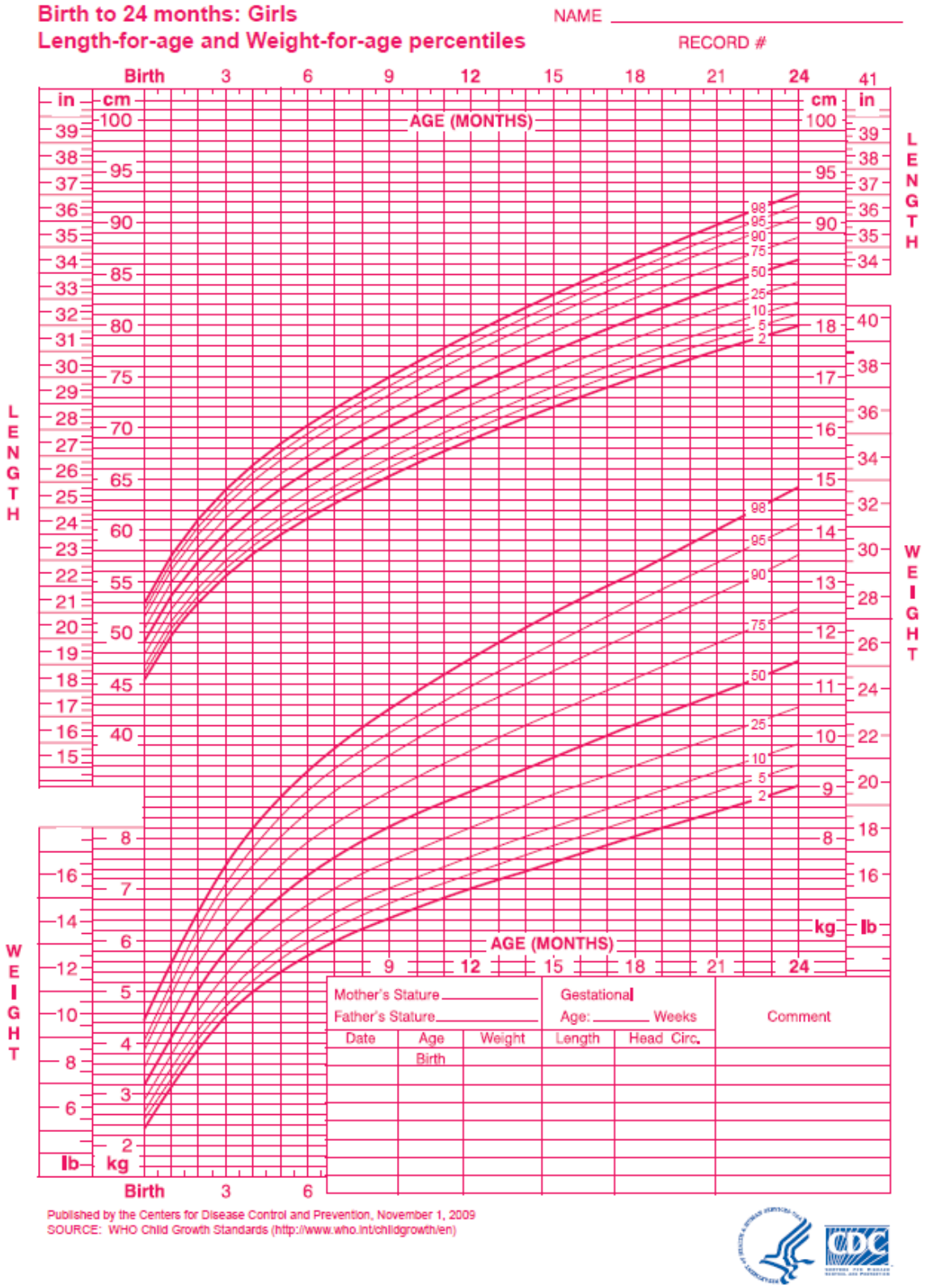
For girls aged 5 through 19 years:



For boys from 6 months to 2 years



For boys from 6 months to 2 years



10.3. APPENDIX 3: Contraceptive Guidance

Woman of Childbearing Potential (WOCBP)

Females of childbearing potential are those who are considered fertile following menarche and unless permanently sterile (see below). If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Surgically sterile female with one of the following:
    a. Documented complete hysterectomy
    b. Documented surgical sterilization

    For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study entry.

    Note: Documentation can come from the study site personnel's review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

Adequate female contraception is defined as consistent and correct use of an FDA-approved contraceptive method in accordance with the product label, for example:

Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide

Intrauterine device

Prescription hormonal contraceptive taken or administered via the oral (pill), transdermal (patch), subdermal, or IM route

Note: While **complete abstinence is accepted** as adequate female contraception in this age group, periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

10.4. APPENDIX 4: Adverse Event of Special Interest Terms

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in Section 7.4.5. The following AESIs are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if the events below occur in the setting of a COVID infection, the event should still be reported as an AESI if it is one of the medical concepts below.

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure.
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc) • Include all cases that meet the following criteria o Increase in serum creatinine by ≥ 0.3 mg/dl (≥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 OR ○ Urine volume ≤0.5 mL/ kg/ hour for 6 hours
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc) • Include all cases that meet the following criteria ○ 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 • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150 x10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (eg, gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to: ○ Guillain-Barre Syndrome ○ Acute disseminated encephalomyelitis (ADEM) ○ Peripheral facial nerve palsy (Bell's palsy) ○ Transverse myelitis ○ Encephalitis/Encephalomyelitis ○ Aseptic meningitis ○ Febrile seizures ○ Generalized seizures/convulsions ○ Stroke (Hemorrhagic and non-hemorrhagic)

	○ Narcolepsy
Anaphylaxis	• Anaphylaxis as defined per protocol. • Follow reporting procedures in protocol Section 7.4.5
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome) • Myasthenia gravis

10.5. APPENDIX 5: Protocol Amendment History

10.5.1. Amendment 4, 25 Aug 2021:

Main Rationale for the Amendment:

The main rationale for this amendment is to introduce an additional blood draw within 4 days after the second dose for participants in Cohort D in Part 2 in each age group. The samples will be stored for potential future analysis per a request from the FDA. For participants already enrolled in Cohort D prior to protocol amendment 4 implementation at the site, this blood draw will be optional and confirmed at time of re-consenting; for all participants newly enrolled into Cohort D under amendment 4, it will be mandatory.

Summary of Major Changes in Protocol Amendment 4:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature page, Synopsis, and Header	Updated the protocol version and date.	Updated to reflect the new version and date.
Global	Minor grammar and formatting corrections were made throughout the document.	Updates were made for clarity and readability.
Synopsis, Section 3.1.1.2 (Treatment and Follow-up period), and Section 10.1 (Appendix 1 Schedule of Assessments - Table 10)	Language was added to clarify that the 300 participants in the Arm 1 and 2 expansions will have a scheduled Day 1 blood draw and a voluntary blood draw on Day 57.	To clarify that only expansion portion of Arms 1 and 2 have a voluntary Day 57 blood draw, but that blood draws are mandatory for all other Arms in part 1 (as per Clarification Memo # 7)
Synopsis, Section 3.1 (General Design - Figure 1b), Section 3.1.1.2 (Treatment and Follow-up period), Section 7.2 (Blood Collections for Immunogenicity Assessments and Biomarker Samples), and Section 10.1	Day 30 (+3 days) blood draw was added to indicate that participants in Cohort D (remainder of the age group) will provide a blood sample at Day 1 and at Day 30 (+3 days) for storage and potential future biomarker testing.	Day 30 (+3 days) blood draw was added per the request from the FDA.

(Appendix 1 Schedule of Assessments - Table 10)		
Synopsis, Section 7.2 (Blood Collections for Immunogenicity Assessments and Biomarker Samples), Section 10.1 (Appendix 1 Schedule of Assessments) - Table 10 (Schedule of Assessments), and Table 12 (Phlebotomy Schedule for Serology, Biomarker Samples, and Cell-Mediated Immunity for Part 2 [Expansion] of the Study)	Header in Section 7.2 was updated from "Immunogenicity Assessments" to "Blood Collections for Immunogenicity Assessments and Biomarker Samples" A note was added to Section 7.2 indicating that if less than 8 mL of blood is drawn at baseline then the child cannot be enrolled. Table 12 title in Section 10.1 was updated to include "Biomarker Sample." Language and/or column was added to each section to indicate that there will be a Day 30 (+3 days) blood draw for storage and potential future biomarker testing for Cohort D in Part 2, and that the volume will be ~4 mL for all age groups.	Headings and titles were updated for clarity and consistency with content under heading. Blood volume was indicated as this is a pediatric study. Note language was added for clarity on enrollment procedure.
Synopsis and Section 7.4.5 (Adverse Events of Special interest)	The Cardiac Endpoint Adjudication Committee's name was updated to the officially recognized name as the "Cardiac Event Adjudication Committee"	This change was to align the committee language across all relevant Moderna studies.
Section 7.1.5 (Assessment for SARS-CoV-2 Infection)	Language was added to specify that exposure to an individual in the household confirmed to be infected with SARS-CoV-2 will require a study illness visit.	This clarification was made to capture highest risk exposure only.

Section 7.3.2 (Surveillance for COVID-19 Symptoms)	Language was added to specify when an illness visit would be required.	Clarification of circumstances that require an illness visit.
Section 10.2.10 (Sample Retention and Future Biomedical Research)	Language was added to indicate that the samples collected and stored from Cohort D in Part 2 may undergo additional exploratory analysis using Ab-based methodologies.	To reflect the addition of a Day 30 blood sample that will be stored but only analyzed if an appropriate biomarker is identified.

10.5.2. Amendment 3, 23 Jul 2021

Main Rationale for the Amendment:

The main rationale for this amendment is to add a case definition for myocarditis and pericarditis as well as guidance for reporting and assessing suspected cases for this study, given the recent emergence of a temporal association between mRNA vaccine administration and signs and symptoms of myocarditis/pericarditis.

In addition, the sample size for each age group in Part 2 (blinded part) is increased to allow for a 95% probability to detect a rare adverse event occurring at a rate of 1 in 1,000.

Summary of Major Changes in Protocol Amendment 3:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature page, Synopsis, and Header	Updated the protocol version and date.	Updated to reflect the new version and date.
Global	Minor grammar and formatting corrections were made throughout the document.	Updates were made for clarity and readability.
Synopsis, Section 3.1 (General Design), Section 5.2 (Randomization), and Section 8.3 (Power and Sample Size)	The overall sample size for Part 2 was updated to approximately 12,000 participants. The overall sample size for each age group was updated to up to 4,000 participants.	Samples sizes were increased to allow for a 95% probability to detect a rare adverse event occurring at a rate of 1 in 1,000.

	The sample size for Study Arms 8, 10, and 12 were each updated to up to 3,000 participants. The sample size for Study Arms 9, 11, and 13 were each updated to up to 1,000 participants.	
Synopsis, Section 2 (Objectives and Endpoints), Section 3.1 (General Design) - Study Progression, Section 6.2 (Discontinuing Study Vaccination), Section 7.1 (Safety Assessments and Procedures), and Section 10.1 (Appendix 1: Schedule of Assessments - Table 10 and Table 11)	AESIs of Myocarditis and/or pericarditis were added (in addition to MIS-C).	To reflect addition of case definition for myocarditis and pericarditis in AESI section.
Synopsis, Section 7.4.5 (Adverse Events of Special Interest), and Section 7.5.2 (Data Safety Monitoring Board)	Included language for the addition of an external clinical endpoint adjudication committee, that will adjudicate any suspected cases of myocarditis, pericarditis, or myopericarditis and make recommendations in consultation with the DSMB to the Sponsor.	To reflect the addition of an external clinical endpoint adjudication committee for cases of myocarditis/pericarditis to the safety oversight of the study.
Section 1.3.2 (Risks to Study Participation and Their Mitigation)	Added paragraph on very rare reports of myocarditis and pericarditis occurring after vaccination with Moderna COVID-19 Vaccine under Emergency Use Authorization in adults aged 18 years and older.	To reflect addendum made to Investigator's Brochure.

Section 7.4.4 (Medically Attended Adverse Events)	Language was updated to Unsolicited AEs will be captured on the AE page of the eCRF.	To reflect the correct method of collecting unsolicited AEs.
Section 7.4.5 (Adverse Events of Special Interest)	Added CDC case definitions for myocarditis and pericarditis.	To provide guidance to the investigators regarding assessing and reporting myocarditis and pericarditis for this study population.
Section 10.4 (Appendix 4: Adverse Event of Special Interest Terms)	Appendix 4 was added to the protocol.	To include AESI list in the protocol instead of a separate document.

10.5.3. Amendment 2, 17 Jun 2021

Main Rationale for the Amendment:

The main rationale for this amendment is to add an optional blood collection on Day 57 for participants in the expansion part of Arm 1 and Arm 2 to gather additional data on immunogenicity. The handling of potential unblinding requests in Part 2 is further clarified. In addition, the decision in Part 1 to not evaluate the 100-µg dose in participants less than 2 years old is integrated into this amendment by removing Arm 7 (6 months to < 2 years, 100 µg dose) from this age group. The change in dose level is based on moderate, increased reactogenicity observed in Arm 2 (6 to < 12 years of age, 100 µg), which led to the decision to not evaluate the 100-µg dose in the 2 to < 6 years age group. In order to maintain dose-ranging in the 2 to < 6 years age group, Arm 7 may instead enroll participants in this age group to evaluate the 25-µg dose if the 100-µg dose is eliminated at any point during the dose escalation process.

The Summary of Major Changes table describes the major changes made in Amendment 2, including the sections modified and the corresponding rationales. The synopsis of Amendment 2 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and Section 3.1 General Design	Clarified that preliminary safety and immunogenicity data of Arm 1 (6 to < 12 years of age, 50 µg) and Arm 2 (6 to < 12 years of age, 100 µg), as applicable, will aid in the selection of a dose level for Part 2.	Tolerability and safety data will be available from both doses (50 and 100 µg) and will be an essential metric for dose selection. Additionally, immunogenicity data from the 50-µg dose (a dose lower than the 100-µg dose assessed in the P301 adult efficacy trial) will allow for assessment of the likelihood of the 50-µg dose to meet noninferiority criteria. These data will allow an informed dose selection decision for Part 2.
Protocol Synopsis and Section 3.1 General Design	Revised the age group and dose level of Arm 7 (6 months to < 2 years of age, 100 µg) to 2 to < 6 years and 25 µg of mRNA-1273. Arm 7 was made optional, the 25-µg dose will be evaluated if 100-µg dose is eliminated at any point during the dose escalation process, to maintain dose ranging.	The 100-µg dose was not evaluated in participants aged < 2 years based on the internal safety team recommendation. The dose level and age group of Arm 7 was revised to maintain dose-ranging in the 2 to < 6 years age group by adding a lower dose than originally planned (25 µg).

Section 3.3 Justification for Dose, Control Product, and Choice of Study Population	Clarified that if a COVID-19 vaccine (mRNA-1273 or other) is authorized or licensed, eligible study participants will be offered the opportunity to unblind, and a nasal swab and a blood sample will be collected. Participants who received mRNA-1273 will continue in the study. If a participant previously received placebo and mRNA-1273 is authorized for use in the participant's age group, the participant will be offered unblinding followed by a cross-over vaccination with mRNA-1273. If mRNA-1273 is not yet authorized for the relevant age group, but an alternative vaccine is authorized, previous placebo recipients may seek the alternative vaccine and withdraw from study.	To clarify plans for unblinding requests.
Section 7.4.3 Solicited Adverse Reactions Table 7	Revised the temperature ranges for fever in Table 7: Solicited Adverse Reactions and Grades: Age 6 to ≤ 36 Months.	To correct the temperature cut-offs for consistency with internal Moderna standard for the 6 to ≤ 36 months age group.
Protocol Synopsis and Section 7.5.2 Data Safety Monitoring Board	Clarified that the DSMB will review safety data from a subset of approximately 300 participants at the selected dose level in the 6 to < 12 years age group rather than the full safety set for Arm 1 and Arm 2 from Part 1 (N = 750 participants) before allowing the start of enrollment in Part 2.	Dose selection will be based on safety data from approximately 300 participants. Approximately 300 participants will have reached Day 43. This will expedite expansion of the study. The safety review will still allow for detection of an AE occurring at a rate ~ 1% (N = ~ 375 participants per group remains the same).

Protocol Synopsis and Section 7.5.2 Data Safety Monitoring Board	For both the middle age group (2 to < 6 years) and the youngest age group (6 months to < 2 years) the DSMB will review cumulative safety data after approximately 400 participants have been exposed to mRNA-1273 at selected dose in each age group, combining participants from Part 1 and Part 2, before further expansion in each respective age group.	To reflect changes made to dose escalation for < 6 year olds in Part 1 (elimination of 100 µg group), and to moderately increase the subset of participants exposed at chosen dose level before final expansion in Part 2 (N= ~375 participants per group was updated to N= ~400 participants per group)
Protocol Synopsis and Section 8.6.1 Interim Analyses	Clarified that the interim analyses in Part 1 will be optional and will be performed after all or a subset of participants have completed Day 57. Clarified that the interim analysis in Part 2 will be performed after all or a subset of participants have completed Day 57.	To reflect changes made to dose selection plans that will expedite the expansion of the study.
Section 10.1 Appendix 1: Schedule of Assessments	Added an optional blood collection for immunogenicity on Day 57 for the expansion part of Arm 1 and Arm 2.	An optional blood collection was added for the expansion part of Arm 1 and Arm 2 to gather additional immunogenicity data in Part 1.

10.5.4. Amendment 1, 30 Apr 2021

Main Rationale for the Amendment:

The main purpose of this amendment is to allow a Data Safety Monitoring Board (DSMB) safety review when approximately 375 children have received mRNA-1273 in each age group, before expanding enrollment to each full age cohort. This review will allow assessment of less frequent adverse events (AEs), occurring at a rate of approximately 1 in 100. Per this amendment, this will be achieved in different ways for each of the 3 age groups:

1. For the 6 to < 12 years of age group: To expedite this formal safety review in school-aged children, an additional 300 participants will be enrolled to each dose level in Part 1 (ie, to have n = 375 per dose group), and the DSMB will review Day 57 safety data for all 375 participants in each dose group before advancing this age group to Part 2.
2. For the 2 to < 6 years and 6 months to < 2 years of age groups: DSMB safety review will occur within Part 2, at a time when it is anticipated that a total of approximately 375 participants (accounting for the 3:1 randomization to vaccine or placebo in the blinded Part 2) have been exposed to mRNA-1273 at the dose level selected for Part 2. DSMB will occur when Day 57 safety data from this subset is available for review.

The Summary of Changes table provided here describes the major changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. The synopsis of Amendment 1 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval Page, and Protocol Amendment Summary of Changes	Updated protocol version and date. Added Protocol Amendment Summary of Changes. Medical monitor/sponsor contact information was updated.	Updated to reflect new version, date of protocol, and new medical monitor/sponsor contact. Protocol Summary of Changes added to be in line with Moderna guidelines.
Global	Minor grammar and formatting corrections were made throughout the document.	Updates were made for clarity and readability.
Global	Primary endpoint language was updated to use 'antibody' rather than 'nAb.'	To reflect potential use of binding antibody at time of analysis, if available.
Protocol Synopsis and Section 2 (Objectives and Endpoints)	The Secondary Objective "to evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo" Endpoint language was updated.	To maintain consistency across all Moderna protocols.
Protocol Synopsis and Section 2 (Objectives and Endpoints)	The secondary objective "To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo" Endpoint language was updated.	To maintain consistency with other mRNA-1273 related protocols. Additionally, this language was updated to clarify that only participants without evidence of prior infection at baseline will be included in the analysis of the secondary objective of asymptomatic infection with SARS-CoV-2.

Protocol Synopsis and Section 2 (Objectives and Endpoints)	The following exploratory objective was added, "To explore asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline." The corresponding exploratory endpoint was added, "GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG)" New abbreviations were added to the footnote.	To explore serological evidence of asymptomatic infections in seropositive participants.
Synopsis and Section 2 (Objectives and Endpoints)	The definition of COVID-19 infection was updated to match the CDC guidelines and the details of this guideline was moved to the footer.	To reflect the generally milder and more varied presentation of SARS-CoV-2 infection in the pediatric population, matching the secondary case definition in adult study (P301/COVE study).
Section 3.1 (General Design) Figure 1 (Study Schema)	Study Schema was updated to correct typographical error.	Figure updated to ensure consistency throughout protocol.
Protocol Synopsis and Section 4.1 (Inclusion Criteria)	Language was added to clarify that the height and weight of children < 2 years of age must both meet or exceed the 3rd percentile according to WHO Child Growth Standard at the Screening Visit.	Height and weight are better measures of growth than BMI for children < 2 years of age.
Protocol Synopsis and Section 4.1 (Inclusion Criteria)	The heading before criterion 7, "Special inclusion criteria for children 6 months to < 2 years of age" was updated to "Special inclusion criteria for children 6 months to < 12 months of age"	Exclusion of prematurity is considered relevant only for children under 12 months of age in the context of mRNA vaccines (not live vaccines).

Protocol Synopsis and Section 4.2 (Exclusion Criteria)	A note was added to the exclusion of febrile seizures to indicate that a history of a simple, single febrile seizure is allowed for children 6 years and older in Part 2 of the study.	The risk of febrile seizures is most relevant for children up to 6 years of age. Once the safety data has been reviewed in Part 1, children 6 years of age and older can be included even with a history of a single, simple febrile seizures.
Protocol Synopsis, Section 3.1 (General Design), Section 5.2 (Randomization), and Section 8.3 (Power and Sample Size)	The sample size was increased from 750 to 1,350 participants in Part 1. Sample size in Part 2 was adjusted in the 6 to < 12 years of age group from 2,000 to 1,700 (mRNA-1273 arm ~1,275 participants; placebo arm ~425 participants).	To reflect changes per main rationale for Amendment.
Protocol Synopsis, Section 3.1 (General Design), Section 8.5.3 (Immunogenicity Analyses), and Section 8.6.1 (Interim Analyses)	Language was updated to reflect when the primary immunogenicity analysis will be done for Part 2.	To reflect adjustment in the safety oversight plan.
Synopsis and Section 7.5.2 (Data Safety Monitoring Board)	Language was added to update the plan for the review process.	To update and clarify the changes made to the process based on main reason for amendment.
Protocol Synopsis, Section 8.2 (Statistical Hypothesis), and Section 8.3 (Power and Sample Size)	Coprimary endpoint 1 and 2 language updated.	To reflect updates to the statistical plan.
Protocol Synopsis and Section 8.5.3 (Immunogenicity Analyses)	Language for multiplicity adjustment between age groups was added.	To reflect updates for the statistical plan.

Section 3.3 (Justification for Dose, Control Product, and Choice of Study Population)	Language was updated to indicate that if immunogenicity criteria are successfully met in P204 age cohorts, blinded placebo participants will be given the opportunity to receive the mRNA-1273 vaccine, and participants who received a lower dose than the dose receiving Emergency Use Authorization will be provided a booster with the 'optimal dose' for a given age group.	To describe the planned approach to dosing placebo recipients and lower dose recipients in case of Emergency Use Authorization of mRNA-1273 for each age group during the conduct of the trial.
Section 7.1.5 (Assessment for SARSCoV2 infection)	Language was updated to include further clarification on procedures to follow when participant is exposed to an individual with confirmed SARS-CoV-2 infection. A definition of last exposure was also added. Language was added to clarify that an initial assessment will be performed at a study illness visit to determine general appearance, and to provide details as to whom may perform the assessment.	To provide a clear definition of last exposure, and the processes and timing to follow when a participant is exposed to a confirmed SARS-CoV-2 infected person. Clarification of which providers can perform initial assessments for illness visits.
Section 7.3.1 (Vaccine Effectiveness Assessments) Table 5 (Age-Specific Cut-Offs for Vital Signs and Laboratory Variables	Removed irrelevant ages (rows). Systolic Blood pressure parameter updated to include hypotension parameters for pediatric population.	To ensure age-appropriate information is included in definition of Severe COVID-19.
Synopsis, Section 2 (Objectives and Endpoints), and Section 7.3.1 (Vaccine Effectiveness Assessments)	The definition of a SARS-CoV-2 infection was updated.	To reflect pediatric manifestations of SARS-CoV-2 infection and match CDC case definition.

Section 7.3.1 (Vaccine Effectiveness Assessments) Table 6 (Definition of renal-, liver-, and neurological dysfunction for Pediatric Population (< 12 years of age)	Table 6 was added to define renal, liver, and neurological dysfunction for this study.	To define severe COVID-19 with age-appropriate definitions and objective measures.
Section 7.3.2 (Surveillance for COVID-19 Symptoms:)	Language was added to provide guidance for omitting or conducting an illness visit for febrile children that have an alternative diagnosis identified.	To match the American Academy of Pediatrics guidance on COVID-19 testing in children.
Section 7.3.3 (Follow-up/Convalescent Period After Diagnosis with COVID-19)	Language was added to provide guidance for children hospitalized with possible or confirmed MIS-C.	Clarification of sample collection for suspected MIS-C.
Section 10.1 (APPENDIX 1: Schedule of Assessments); Table 10: Schedule of Assessments	A footnote was added to clarify the blood sample for vaccine immunogenicity in Part 1 and Part 2.	Clarification of subset of participants in each Arm that will have samples collected for immunogenicity postbaseline.
Section 10.2.18 (Body Mass Index Charts for Boys and Girls)	CDC charts based on WHO data for use in the US in children < 2 years old added for reference.	Height and weight charts were added for use in children < 2 years of age.

Signature Page for VV-CLIN-003244 v1.0

Approval	Rituparna Das Clinical 29-Sep-2021 23:51:06 GMT+0000

Approval	Deborah Manzo Clinical 30-Sep-2021 13:22:08 GMT+0000

Signature Page for VV-CLIN-003244 v1.0

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age
Protocol Number:	mRNA-1273-P204
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	Sabine Schnyder Ghamloush, MD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: 1-617-758-9453 e-mail: sabine.schnyder.ghamloush@modernatx.com
Regulatory Agency Identifier Number(s):	IND: 019745
Amendment Number:	5
Date of Amendment 5:	29 Sep 2021
Date of Amendment 4:	25 Aug 2021
Date of Amendment 3:	23 Jul 2021
Date of Amendment 2:	17 Jun 2021
Date of Amendment 1:	30 Apr 2021
Date of Original Protocol:	24 Feb 2021

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	29 Sep 2021
Amendment 4	25 Aug 2021
Amendment 3	23 Jul 2021
Amendment 2	17 Jun 2021
Amendment 1	30 Apr 2021
Original Protocol	24 Feb 2021

Amendment 5, (29 Sep 2021): Current Amendment

Main Rationale for the Amendment:

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/European Commission (EC) of the European Parliament and the Council of the European Union.

The main rationale for this amendment is to simplify the process for potential cross-over vaccination given the increased sample size of the study and to ensure retention in the study for safety follow-up, incorporate Clarification Memo #8, align with the Cardiac Event Adjudication Committee (CEAC) charter, and clarify the Data Safety Monitoring Board (DSMB) safety data review process for the younger age groups (2 to < 6 years; 6 months to < 2 years) to match the process in the older age group (6 to < 12 years) and allow DSMB review of Part 1 (open-label phase) data before start of Part 2 (blinded phase) for the younger age groups. Additional updates were made to clarify the statistical analysis plan, including the inferred efficacy analysis and interim analyses.

The summary of changes table provided below describes the major changes made to Amendment 5 relative to Amendment 4, including the sections modified and corresponding rationales. The synopsis of Amendment 5 has been modified to correspond to changes in the body of the protocol. Minor copy edits and administrative updates were made throughout the protocol to align with new content as well as for clarity, readability, and/or accuracy.

Summary of Major Changes in Protocol Amendment 5:

Section # and Name	Description of Change	Brief Rationale
Section 3.1 (General Design; Figure 1), Section 3.1.1.2	Made updates to explain that blood sample collection for participants	For clarification.

(Treatment and Follow-up Period), Section 7.2 (Blood Collections for Immunogenicity Assessments and Biomarker Samples), Appendix 1 (Schedule of Assessments; Table 10)	in Cohort D will be prior to randomization and the first dose at Day 1 and within 4 days of receiving Dose 2 at Day 30 (+ 3 days).	
Section 3.3 (Justification for Dose, Control Product, and Choice of Study Population), Appendix 1 (Schedule of Assessments)	Made updates to Section 3.3 to clarify the justification for the choice of study population, including unblinding of eligible study participants, placebo recipient cross-over vaccination, booster dose eligibility for participants who received a lower dose in Part 1 than was ultimately approved for their respective age group in Part 2, and study discontinuation for participants receiving an EUA vaccine outside the protocol. In accordance with changes made to Section 3.3, updated text and Table 11 in Appendix 1 to clarify placebo recipient cross-over vaccination.	Given the increase in sample size, unblinding via clinic visit is no longer feasible and will instead be performed over the phone, if desired by the family. To ensure retention in the study for safety follow-up, cross-over vaccination will be offered to all placebo recipients per their request if any COVID-19 vaccine (mRNA-1273 or other) becomes authorized or licensed for their age group.
Section 4.2 (Exclusion Criteria)	Added text to exclusion criteria #8 to provide context related to the influenza vaccine.	For incorporation of Clarification Memo #8.
Section 6.1.1 (Individual Participant Criteria for Delay of Study Vaccination)	Provided text in Section 6.1.1 to describe additional reasons to delay study vaccination for participants.	For incorporation of Clarification Memo #8.
Section 7.3.3 (Follow-up/Convalescent Period After Diagnosis with COVID-19)	Deleted text, "Study participants will be monitored by trained study site personnel for a 28 day period after diagnosis."	For accuracy.
Section 7.4.5 (Adverse Events of Special Interest), Section 7.5.2 (Data Safety Monitoring Board)	Clarified that the CEAC will review suspected cases of myocarditis/pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" event and to assess severity, but recommendations to	To align with CEAC charter.

	the Sponsor to continue vaccine dosing will be made by DSMB.	
Section 7.5.2 (Data Safety Monitoring Board)	Changed description of timing of DSMB review and scope for younger age groups (2 to < 6 years; 6 months to < 2 years) from separate reviews in each age group with data from Part 1 and Part 2 during the conduct of Part 2 to one review of all available Part 1 safety data for all doses used in < 6 years before start of Part 2 for each age group.	To allow the DSMB to review data from Part 1 (open-label phase) for all doses used in < 6 year old participants before starting Part 2 for 2 to < 6 years and 6 months to < 2 years age groups.
Section 8.5.4 (Inferred Efficacy Analysis)	Added text to explain the following: 1) analyses of efficacy endpoints in Part 2 will be performed for the randomized blinded phase, and 2) additional exploratory analyses will be conducted in the blinded and unblinded phases for participants randomized to mRNA-1273 in Part 2, and in the unblinded phase for participants who are originally randomized to the placebo arm and cross-over to mRNA-1273 after use of any COVID-19 vaccine is authorized or licensed for the participant's age group.	For clarification.
Section 8.6.1 (Interim Analyses)	Updated description of Part 2 to indicate that an interim analysis of immunogenicity and safety will be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 1 or Part 2 within an age group.	For clarification.
Appendix 1 (Schedule of Assessments; Table 10 and Table 11)	Updated footnote #2 in Table 10 and added footnote #2 to Table 11 to include cross-references for Section 6.1.1.	For alignment.

Abbreviations: CDC = Centers for Disease Control and Prevention; CEAC = Cardiac Event Adjudication Committee; COVID-19 = coronavirus disease 2019; DSMB = Data Safety Monitoring Board; EUA = Emergency Use Authorization; mRNA = messenger RNA; SoA = Schedule of Assessments.

Amendment 4, 25 Aug 2021:

Main Rationale for the Amendment:

The main rationale for this amendment is to introduce an additional blood draw within 4 days after the second dose for participants in Cohort D in Part 2 in each age group. The samples will be stored for potential future analysis per a request from the FDA. For participants already enrolled in Cohort D prior to protocol amendment 4 implementation at the site, this blood draw will be optional and confirmed at time of re-consenting; for all participants newly enrolled into Cohort D under amendment 4, it will be mandatory.

Summary of Major Changes in Protocol Amendment 4:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature page, Synopsis, and Header	Updated the protocol version and date.	Updated to reflect the new version and date.
Global	Minor grammar and formatting corrections were made throughout the document.	Updates were made for clarity and readability.
Synopsis, Section 3.1.1.2 (Treatment and Follow-up period), and Section 10.1 (Appendix 1 Schedule of Assessments - Table 10)	Language was added to clarify that the 300 participants in the Arm 1 and 2 expansions will have a scheduled Day 1 blood draw and a voluntary blood draw on Day 57.	To clarify that only expansion portion of Arms 1 and 2 have a voluntary Day 57 blood draw, but that blood draws are mandatory for all other Arms in part 1 (as per Clarification Memo # 7)
Synopsis, Section 3.1 (General Design - Figure 1b), Section 3.1.1.2 (Treatment and Follow-up period), Section 7.2 (Blood Collections for Immunogenicity Assessments and Biomarker Samples), and Section 10.1 (Appendix 1 Schedule of	Day 30 (+3 days) blood draw was added to indicate that participants in Cohort D (remainder of the age group) will provide a blood sample at Day 1 and at Day 30 (+3 days) for storage and potential future biomarker testing.	Day 30 (+3 days) blood draw was added per the request from the FDA.

Assessments - Table 10)		
Synopsis, Section 7.2 (Blood Collections for Immunogenicity Assessments and Biomarker Samples), Section 10.1 (Appendix 1 Schedule of Assessments) - Table 10 (Schedule of Assessments), and Table 12 (Phlebotomy Schedule for Serology, Biomarker Samples, and Cell-Mediated Immunity for Part 2 [Expansion] of the Study)	Header in Section 7.2 was updated from "Immunogenicity Assessments" to "Blood Collections for Immunogenicity Assessments and Biomarker Samples" A note was added to Section 7.2 indicating that if less than 8 mL of blood is drawn at baseline then the child cannot be enrolled. Table 12 title in Section 10.1 was updated to include "Biomarker Sample." Language and/or column was added to each section to indicate that there will be a Day 30 (+3 days) blood draw for storage and potential future biomarker testing for Cohort D in Part 2, and that the volume will be ~4 mL for all age groups.	Headings and titles were updated for clarity and consistency with content under heading. Blood volume was indicated as this is a pediatric study. Note language was added for clarity on enrollment procedure.
Synopsis and Section 7.4.5 (Adverse Events of Special interest)	The Cardiac Endpoint Adjudication Committee's name was updated to the officially recognized name as the "Cardiac Event Adjudication Committee"	This change was to align the committee language across all relevant Moderna studies.
Section 7.1.5 (Assessment for SARS-CoV-2 Infection)	Language was added to specify that exposure to an individual in the household confirmed to be infected with SARS-CoV-2 will require a study illness visit.	This clarification was made to capture highest risk exposure only.
Section 7.3.2 (Surveillance for COVID-19 Symptoms)	Language was added to specify when an illness visit would be required.	Clarification of circumstances that require an illness visit.

Section 10.2.10 (Sample Retention and Future Biomedical Research)	Language was added to indicate that the samples collected and stored from Cohort D in Part 2 may undergo additional exploratory analysis using Ab-based methodologies.	To reflect the addition of a Day 30 blood sample that will be stored but only analyzed if an appropriate biomarker is identified.

Amendment 3, 23 Jul 2021

Main Rationale for the Amendment:

The main rationale for this amendment is to add a case definition for myocarditis and pericarditis as well as guidance for reporting and assessing suspected cases for this study, given the recent emergence of a temporal association between mRNA vaccine administration and signs and symptoms of myocarditis/pericarditis.

In addition, the sample size for each age group in Part 2 (blinded part) is increased to allow for a 95% probability to detect a rare adverse event occurring at a rate of 1 in 1,000.

Summary of Major Changes in Protocol Amendment 3:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature page, Synopsis, and Header	Updated the protocol version and date.	Updated to reflect the new version and date.
Global	Minor grammar and formatting corrections were made throughout the document.	Updates were made for clarity and readability.
Synopsis, Section 3.1 (General Design), Section 5.2 (Randomization), and Section 8.3 (Power and Sample Size)	The overall sample size for Part 2 was updated to approximately 12,000 participants. The overall sample size for each age group was updated to up to 4,000 participants. The sample size for Study Arms 8, 10, and 12 were each updated to up to 3,000 participants.	Samples sizes were increased to allow for a 95% probability to detect a rare adverse event occurring at a rate of 1 in 1,000.

	The sample size for Study Arms 9, 11, and 13 were each updated to up to 1,000 participants.	
Synopsis, Section 2 (Objectives and Endpoints), Section 3.1 (General Design) - Study Progression, Section 6.2 (Discontinuing Study Vaccination), Section 7.1 (Safety Assessments and Procedures), and Section 10.1 (Appendix 1: Schedule of Assessments - Table 10 and Table 11)	AESIs of Myocarditis and/or pericarditis were added (in addition to MIS-C).	To reflect addition of case definition for myocarditis and pericarditis in AESI section.
Synopsis, Section 7.4.5 (Adverse Events of Special Interest), and Section 7.5.2 (Data Safety Monitoring Board)	Included language for the addition of an external clinical endpoint adjudication committee, that will adjudicate any suspected cases of myocarditis, pericarditis, or myopericarditis and make recommendations in consultation with the DSMB to the Sponsor.	To reflect the addition of an external clinical endpoint adjudication committee for cases of myocarditis/pericarditis to the safety oversight of the study.
Section 1.3.2 (Risks to Study Participation and Their Mitigation)	Added paragraph on very rare reports of myocarditis and pericarditis occurring after vaccination with Moderna COVID-19 Vaccine under Emergency Use Authorization in adults aged 18 years and older.	To reflect addendum made to Investigator's Brochure.
Section 7.4.4 (Medically Attended Adverse Events)	Language was updated to Unsolicited AEs will be captured on the AE page of the eCRF.	To reflect the correct method of collecting unsolicited AEs.

Section 7.4.5 (Adverse Events of Special Interest)	Added CDC case definitions for myocarditis and pericarditis.	To provide guidance to the investigators regarding assessing and reporting myocarditis and pericarditis for this study population.
Section 10.4 (Appendix 4: Adverse Event of Special Interest Terms)	Appendix 4 was added to the protocol.	To include AESI list in the protocol instead of a separate document.

Amendment 2, 17 Jun 2021

Main Rationale for the Amendment:

The main rationale for this amendment is to add an optional blood collection on Day 57 for participants in the expansion part of Arm 1 and Arm 2 to gather additional data on immunogenicity. The handling of potential unblinding requests in Part 2 is further clarified. In addition, the decision in Part 1 to not evaluate the 100-µg dose in participants less than 2 years old is integrated into this amendment by removing Arm 7 (6 months to < 2 years, 100 µg dose) from this age group. The change in dose level is based on moderate, increased reactogenicity observed in Arm 2 (6 to < 12 years of age, 100 µg), which led to the decision to not evaluate the 100-µg dose in the 2 to < 6 years age group. In order to maintain dose-ranging in the 2 to < 6 years age group, Arm 7 may instead enroll participants in this age group to evaluate the 25-µg dose if the 100-µg dose is eliminated at any point during the dose escalation process.

The Summary of Major Changes table describes the major changes made in Amendment 2, including the sections modified and the corresponding rationales. The synopsis of Amendment 2 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and Section 3.1 General Design	Clarified that preliminary safety and immunogenicity data of Arm 1 (6 to < 12 years of age, 50 µg) and Arm 2 (6 to < 12 years of age, 100 µg), as applicable, will aid in the selection of a dose level for Part 2.	Tolerability and safety data will be available from both doses (50 and 100 µg) and will be an essential metric for dose selection. Additionally, immunogenicity data from the 50-µg dose (a dose lower than the 100-µg dose assessed in the P301 adult efficacy trial) will allow for assessment of the likelihood of the 50-µg dose to meet noninferiority criteria. These data will allow an informed dose selection decision for Part 2.
Protocol Synopsis and Section 3.1 General Design	Revised the age group and dose level of Arm 7 (6 months to < 2 years of age, 100 µg) to 2 to < 6 years and 25 µg of mRNA-1273. Arm 7 was made optional, the 25-µg dose will be evaluated if 100-µg dose is eliminated at any point during the dose escalation process, to maintain dose ranging.	The 100-µg dose was not evaluated in participants aged < 2 years based on the internal safety team recommendation. The dose level and age group of Arm 7 was revised to maintain dose-ranging in the 2 to < 6 years age group by adding a lower dose than originally planned (25 µg).

Section 3.3 Justification for Dose, Control Product, and Choice of Study Population	Clarified that if a COVID-19 vaccine (mRNA-1273 or other) is authorized or licensed, eligible study participants will be offered the opportunity to unblind, and a nasal swab and a blood sample will be collected. Participants who received mRNA-1273 will continue in the study. If a participant previously received placebo and mRNA-1273 is authorized for use in the participant's age group, the participant will be offered unblinding followed by a cross-over vaccination with mRNA-1273. If mRNA-1273 is not yet authorized for the relevant age group, but an alternative vaccine is authorized, previous placebo recipients may seek the alternative vaccine and withdraw from study.	To clarify plans for unblinding requests.
Section 7.4.3 Solicited Adverse Reactions Table 7	Revised the temperature ranges for fever in Table 7: Solicited Adverse Reactions and Grades: Age 6 to ≤ 36 Months.	To correct the temperature cut-offs for consistency with internal Moderna standard for the 6 to ≤ 36 months age group.
Protocol Synopsis and Section 7.5.2 Data Safety Monitoring Board	Clarified that the DSMB will review safety data from a subset of approximately 300 participants at the selected dose level in the 6 to < 12 years age group rather than the full safety set for Arm 1 and Arm 2 from Part 1 (N = 750 participants) before allowing the start of enrollment in Part 2.	Dose selection will be based on safety data from approximately 300 participants. Approximately 300 participants will have reached Day 43. This will expedite expansion of the study. The safety review will still allow for detection of an AE occurring at a rate ~ 1% (N = ~ 375 participants per group remains the same).

Protocol Synopsis and Section 7.5.2 Data Safety Monitoring Board	For both the middle age group (2 to < 6 years) and the youngest age group (6 months to < 2 years) the DSMB will review cumulative safety data after approximately 400 participants have been exposed to mRNA-1273 at selected dose in each age group, combining participants from Part 1 and Part 2, before further expansion in each respective age group.	To reflect changes made to dose escalation for < 6 year olds in Part 1 (elimination of 100 µg group), and to moderately increase the subset of participants exposed at chosen dose level before final expansion in Part 2 (N= ~375 participants per group was updated to N= ~400 participants per group)
Protocol Synopsis and Section 8.6.1 Interim Analyses	Clarified that the interim analyses in Part 1 will be optional and will be performed after all or a subset of participants have completed Day 57. Clarified that the interim analysis in Part 2 will be performed after all or a subset of participants have completed Day 57.	To reflect changes made to dose selection plans that will expedite the expansion of the study.
Section 10.1 Appendix 1: Schedule of Assessments	Added an optional blood collection for immunogenicity on Day 57 for the expansion part of Arm 1 and Arm 2.	An optional blood collection was added for the expansion part of Arm 1 and Arm 2 to gather additional immunogenicity data in Part 1.

Amendment 1, 30 Apr 2021

Main Rationale for the Amendment:

The main purpose of this amendment is to allow a Data Safety Monitoring Board (DSMB) safety review when approximately 375 children have received mRNA-1273 in each age group, before expanding enrollment to each full age cohort. This review will allow assessment of less frequent adverse events (AEs), occurring at a rate of approximately 1 in 100. Per this amendment, this will be achieved in different ways for each of the 3 age groups:

1. For the 6 to < 12 years of age group: To expedite this formal safety review in school-aged children, an additional 300 participants will be enrolled to each dose level in Part 1 (ie, to have n = 375 per dose group), and the DSMB will review Day 57 safety data for all 375 participants in each dose group before advancing this age group to Part 2.
2. For the 2 to < 6 years and 6 months to < 2 years of age groups: DSMB safety review will occur within Part 2, at a time when it is anticipated that a total of approximately 375 participants (accounting for the 3:1 randomization to vaccine or placebo in the blinded Part 2) have been exposed to mRNA-1273 at the dose level selected for Part 2. DSMB will occur when Day 57 safety data from this subset is available for review.

The Summary of Changes table provided here describes the major changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. The synopsis of Amendment 1 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval Page, and Protocol Amendment Summary of Changes	Updated protocol version and date. Added Protocol Amendment Summary of Changes. Medical monitor/sponsor contact information was updated.	Updated to reflect new version, date of protocol, and new medical monitor/sponsor contact. Protocol Summary of Changes added to be in line with Moderna guidelines.
Global	Minor grammar and formatting corrections were made throughout the document.	Updates were made for clarity and readability.
Global	Primary endpoint language was updated to use 'antibody' rather than 'nAb.'	To reflect potential use of binding antibody at time of analysis, if available.
Protocol Synopsis and Section 2 (Objectives and Endpoints)	The Secondary Objective "to evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo" Endpoint language was updated.	To maintain consistency across all Moderna protocols.
Protocol Synopsis and Section 2 (Objectives and Endpoints)	The secondary objective "To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo" Endpoint language was updated.	To maintain consistency with other mRNA-1273 related protocols. Additionally, this language was updated to clarify that only participants without evidence of prior infection at baseline will be included in the analysis of the secondary objective of asymptomatic infection with SARS-CoV-2.

Protocol Synopsis and Section 2 (Objectives and Endpoints)	The following exploratory objective was added, "To explore asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline." The corresponding exploratory endpoint was added, "GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG)" New abbreviations were added to the footnote.	To explore serological evidence of asymptomatic infections in seropositive participants.
Synopsis and Section 2 (Objectives and Endpoints)	The definition of COVID-19 infection was updated to match the CDC guidelines and the details of this guideline was moved to the footer.	To reflect the generally milder and more varied presentation of SARS-CoV-2 infection in the pediatric population, matching the secondary case definition in adult study (P301/COVE study).
Section 3.1 (General Design) Figure 1 (Study Schema)	Study Schema was updated to correct typographical error.	Figure updated to ensure consistency throughout protocol.
Protocol Synopsis and Section 4.1 (Inclusion Criteria)	Language was added to clarify that the height and weight of children < 2 years of age must both meet or exceed the 3rd percentile according to WHO Child Growth Standard at the Screening Visit.	Height and weight are better measures of growth than BMI for children < 2 years of age.
Protocol Synopsis and Section 4.1 (Inclusion Criteria)	The heading before criterion 7, "Special inclusion criteria for children 6 months to < 2 years of age" was updated to "Special inclusion criteria for children 6 months to < 12 months of age"	Exclusion of prematurity is considered relevant only for children under 12 months of age in the context of mRNA vaccines (not live vaccines).

Protocol Synopsis and Section 4.2 (Exclusion Criteria)	A note was added to the exclusion of febrile seizures to indicate that a history of a simple, single febrile seizure is allowed for children 6 years and older in Part 2 of the study.	The risk of febrile seizures is most relevant for children up to 6 years of age. Once the safety data has been reviewed in Part 1, children 6 years of age and older can be included even with a history of a single, simple febrile seizures.
Protocol Synopsis, Section 3.1 (General Design), Section 5.2 (Randomization), and Section 8.3 (Power and Sample Size)	The sample size was increased from 750 to 1,350 participants in Part 1. Sample size in Part 2 was adjusted in the 6 to < 12 years of age group from 2,000 to 1,700 (mRNA-1273 arm ~1,275 participants; placebo arm ~425 participants).	To reflect changes per main rationale for Amendment.
Protocol Synopsis, Section 3.1 (General Design), Section 8.5.3 (Immunogenicity Analyses), and Section 8.6.1 (Interim Analyses)	Language was updated to reflect when the primary immunogenicity analysis will be done for Part 2.	To reflect adjustment in the safety oversight plan.
Synopsis and Section 7.5.2 (Data Safety Monitoring Board)	Language was added to update the plan for the review process.	To update and clarify the changes made to the process based on main reason for amendment.
Protocol Synopsis, Section 8.2 (Statistical Hypothesis), and Section 8.3 (Power and Sample Size)	Coprimary endpoint 1 and 2 language updated.	To reflect updates to the statistical plan.
Protocol Synopsis and Section 8.5.3 (Immunogenicity Analyses)	Language for multiplicity adjustment between age groups was added.	To reflect updates for the statistical plan.

Section 3.3 (Justification for Dose, Control Product, and Choice of Study Population)	Language was updated to indicate that if immunogenicity criteria are successfully met in P204 age cohorts, blinded placebo participants will be given the opportunity to receive the mRNA-1273 vaccine, and participants who received a lower dose than the dose receiving Emergency Use Authorization will be provided a booster with the 'optimal dose' for a given age group.	To describe the planned approach to dosing placebo recipients and lower dose recipients in case of Emergency Use Authorization of mRNA-1273 for each age group during the conduct of the trial.
Section 7.1.5 (Assessment for SARSCoV2 infection)	Language was updated to include further clarification on procedures to follow when participant is exposed to an individual with confirmed SARS-CoV-2 infection. A definition of last exposure was also added. Language was added to clarify that an initial assessment will be performed at a study illness visit to determine general appearance, and to provide details as to whom may perform the assessment.	To provide a clear definition of last exposure, and the processes and timing to follow when a participant is exposed to a confirmed SARS-CoV-2 infected person. Clarification of which providers can perform initial assessments for illness visits.
Section 7.3.1 (Vaccine Effectiveness Assessments) Table 5 (Age-Specific Cut-Offs for Vital Signs and Laboratory Variables	Removed irrelevant ages (rows). Systolic Blood pressure parameter updated to include hypotension parameters for pediatric population.	To ensure age-appropriate information is included in definition of Severe COVID-19.
Synopsis, Section 2 (Objectives and Endpoints), and Section 7.3.1 (Vaccine Effectiveness Assessments)	The definition of a SARS-CoV-2 infection was updated.	To reflect pediatric manifestations of SARS-CoV-2 infection and match CDC case definition.
Section 7.3.1 (Vaccine Effectiveness Assessments) Table 6 (Definition of renal-, liver-, and neurological dysfunction for Pediatric Population (< 12 years of age)	Table 6 was added to define renal, liver, and neurological dysfunction for this study.	To define severe COVID-19 with age-appropriate definitions and objective measures.

Section 7.3.2 (Surveillance for COVID-19 Symptoms:)	Language was added to provide guidance for omitting or conducting an illness visit for febrile children that have an alternative diagnosis identified.	To match the American Academy of Pediatrics guidance on COVID-19 testing in children.
Section 7.3.3 (Follow-up/Convalescent Period After Diagnosis with COVID-19)	Language was added to provide guidance for children hospitalized with possible or confirmed MIS-C.	Clarification of sample collection for suspected MIS-C.
Section 10.1 (APPENDIX 1: Schedule of Assessments); Table 10: Schedule of Assessments	A footnote was added to clarify the blood sample for vaccine immunogenicity in Part 1 and Part 2.	Clarification of subset of participants in each Arm that will have samples collected for immunogenicity postbaseline.
Section 10.2.18 (Body Mass Index Charts for Boys and Girls)	CDC charts based on WHO data for use in the US in children < 2 years old added for reference.	Height and weight charts were added for use in children < 2 years of age.

ModernaTX, Inc.

Protocol mRNA-1273-P204

A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age

Statistical Analysis Plan

SAP Version 1.0
Version Date of SAP: 01 July 2021

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List of Abbreviations

Abbreviation	Definition
AB	antibody
AE	adverse event
AR	adverse reaction
AESI	AEs of special interest
BMI	body mass index
bAb	binding antibody
CI	confidence interval
CMI	Cell-Mediated Immunity
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data Safety and Monitoring Committee
eCRF	electronic case report form
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
GMR	geometric mean ratio
IgG	immunoglobulin G
IP	investigational product
IRT	interactive response technology
IST	internal safety team
LOD	limit of detection
LLOQ	lower limit of quantification
MAAEs	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
PP	per-protocol
PT	preferred term
RT-PCR	reverse transcriptase polymersa chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

Abbreviation	Definition
AB	antibody
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P204, is based on the most recent approved clinical study protocol (CSP), Version Amendment 2, dated 17-Jun-2021 and the most recent approved electronic case report form (eCRF) Version 2.002, dated 12-May-2021.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 8) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1273-P204 is a phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy children 6 months to less than 12 years of age.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, tolerability, reactogenicity, and effectiveness data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the primary analysis clinical database lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, subject and participant are used interchangeably; injection of IP, injection, and dose are used interchangeably; vaccination group and treatment group are used interchangeably.

2. Study Objectives

2.1. Primary Objective

The primary objectives are the following:

- To evaluate the safety and reactogenicity of up to 3 dose levels (25, 50, and 100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart in 3 age groups
- To infer the efficacy of mRNA-1273 (25, 50, and 100 μg, administered as 2 doses 28 days apart) based on immunogenicity in 3 age groups

2.2. Secondary Objectives

The secondary objectives are the following:

- To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 µg) administered as 2 doses 28 days apart
- To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo
- To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with COVID-19 AND positive RT-PCR for SARS-CoV-2

2.3. Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence
- To describe the ratio or profile of specific S protein bAb relative to nAb in serum
- To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection
- To assess, in a subset of participants, the SARS-CoV-2 S protein-specific T-cell responses
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline

3. Study Endpoints

3.1. Primary Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after each injection

- Unsolicited adverse events (AEs) through 28 days after each injection
- Medically-attended AEs (MAAEs) through the entire study period
- Serious AEs (SAEs) through the entire study period
- AEs of special interest (AESIs), including multisystem inflammatory syndrome in children (MIS-C) through the entire study period

The primary immunogenicity objective will be evaluated by either:

- The proportion of participants with a serum antibody level at Day 57 ≥ antibody threshold of protection. If an accepted serum antibody threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy.
- The GM value of serum antibody level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301). If a threshold is not available, efficacy will be inferred based on establishing noninferiority for each age group (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years in Study P204) compared to 18- to 25-year old participants (Study P301) by both GM value of serum antibody levels and seroresponse rate.

  Seroresponse due to vaccination at a subject level may be defined as a change from below the LLOQ to equal to or above LLOQ, or a z-fold rise if baseline is equal to or above LLOQ. The definition of seroresponse may depend on assay-specific performance characteristics, and the table below lists the assay-specific definition of seroresponse for each assay/test of interest.

Assay Name	**Category**	**Test Name/ Description**	**Definition of Seroresponse**
Pseudovirus (PsVNT)	nAb	PsVNT50 (ID 50)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 3.3-foldrise
		PsVNT80 (ID 80)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 2.3-foldrise

Anti-Spike ELISA	bAb	Anti-Spike VAC65 Spike IgG Antibody	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 4.6-foldrise
MSD multiplex	bAb	Anti-Spike	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 1.9-foldrise

Among the two Pseudovirus tests, PsVNT50 and PsVNT80, PsVNT50 is considered the most appropriate measure of subject response because it falls in the middle of the dynamic range of the dilution response curve while PsVNT80 is close to the plateau and thus subject to restriction.

The GM and seroresponse rate comparisons between children in P204 and young adults (18-25 years of age) in P301 will be compared for the bAb and nAb measures listed in the table above, with pseudovirus nAb PsVNT50 (ID50) considered as the primary assay test for the immunobridging.

3.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- The GM values of SARS-CoV-2 S protein-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2).
- The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2).
- The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or RT-PCR), starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:
    - bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by Roche Elecsys) post baseline, OR
    - Positive RT-PCR post baseline.

- The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) post baseline in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms, starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP
- The incidence of the first occurrence of COVID-19 post baseline, starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP.COVID-19 is defined as symptomatic disease based on the following criteria according to CDC case definition:
    - The participant must have a positive test for SARS-CoV-2 by RT-PCR; AND
    - Either
        - The participant must have experienced at least ONE of the following systemic symptoms: Fever (temperature $\geq 38^{o}$ C/$\geq 100.4^{o}$ F) or chills (of any duration, including $\leq$ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding; OR
        - The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough (of any duration, including $\leq$ 48 hours), shortness of breath or difficulty breathing (of any duration, including $\leq$ 48 hours)
- The incidence of the first occurrence of the alternative definition of COVID-19 case post baseline, starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP.

  The alternative case definition of COVID-19 is defined by the following criteria:
    - The participant must have experienced at least TWO of the following systemic symptoms: Fever ($\geq 38^{o}$ C/$\geq 100.4^{o}$ F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR

- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- At least one positive RT-PCR test for SARS-CoV-2

3.3. Exploratory Endpoints

The exploratory endpoints are the following:

- Alignment of genetic sequence of viral isolates with that of the vaccine sequence
- Relative amounts or profiles of S protein-specific bAb and specific nAb titers in serum
- Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)
- Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points after vaccination relative to baseline
- GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x, and 4x rise of bAb relative to baseline

4. Study Design

4.1. Overall Study Design

This is a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation, randomized, observer-blind, placebo-controlled, expansion study intended to infer the effectiveness of mRNA-1273 in children aged 6 months to < 12 years. The study population will be divided into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years) and up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 will be evaluated.

The study will be conducted in 2 parts. Part 1 of the study will be open label and consist of dose-escalation, age de-escalation in 1,275 participants (see Table1 below for the number of participants in each age group) to select the dose for each age group. Part 2 of the study will be placebo-controlled, observer-blind evaluation of the selected dose in approximately 5,700 participants (approximately 1,700 participants in the 6 to < 12 years of age group and

approximately 2,000 participants in both the 2 to < 6 years and the 6 months to < 2 years age group). No participants in Part 1 will participate in Part 2 of the study.

Table 1: Planned Age Groups and mRNA-1273 Dose Levels in Part 1 and Part 2 of the Study

	Part 1			Part 2	
Age Group	**mRNA-1273 25 µg**	**mRNA-1273 50 µg**	**mRNA-1273 100 µg**	**Selected Dose Level of mRNA-1273 From Part 1**	**Placebo**
6 to < 12 years		Study Arm 1 (n=375)	Study Arm 2 (n=375)	Study Arm 8 (n=1,275)	Study Arm 9 (n=425)
2 to < 6 years	Study Arm 7 (Optional) (n=75)	Study Arm 3 (n=75)	Study Arm 4 (n=75)	Study Arm 10 (n=1,500)	Study Arm 11 (n=500)
6 months to < 2 years	Study Arm 5 (n=150)	Study Arm 6 (n=150)		Study Arm 12 (n=1,500)	Study Arm 13 (n=500)

The study will begin with the oldest age group (6 to < 12 year) and age de-escalate. Each age group will begin with Part 1 and advance to Part 2 independently. The mRNA-1273 investigational vaccine or placebo will be administered as 2 intramuscular (IM) injections, approximately 28 days apart.

4.1.1. Part 1, the Open-Label Phase

Part 1 of the study will be open label, dose-escalation and age de-escalation. The study schematic is presented in Figure 1.

The study will include 3 age groups: Group 1 with 750 participants (≥ 6 to < 12 years old) and Group 2 with approximately 225 participants (≥ 2 to < 6 years old) and Group 3 with 300 participants (≥ 6 months to < 2 years old). Up to three dose levels (25 µg , 50 µg and 100 µg) will be evaluated in each age group in Part 1. Each age group will begin dosing with the lowest dose planned for that group. Dose escalation and age de-escalation will progress only after confirming the safety of a dose level in each group after each IP injection.

The study will be initiated with enrollment of 375 participants in the 6 to < 12-years age group (Study Arm 1), and dosing with 50 µg of mRNA-1273.

After at least 75 participants in Study Arm 1 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an internal safety team (IST) will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 6 to < 12 years age group (Study Arm 2; n = 375) and independently whether to begin dosing at the 50 µg dose

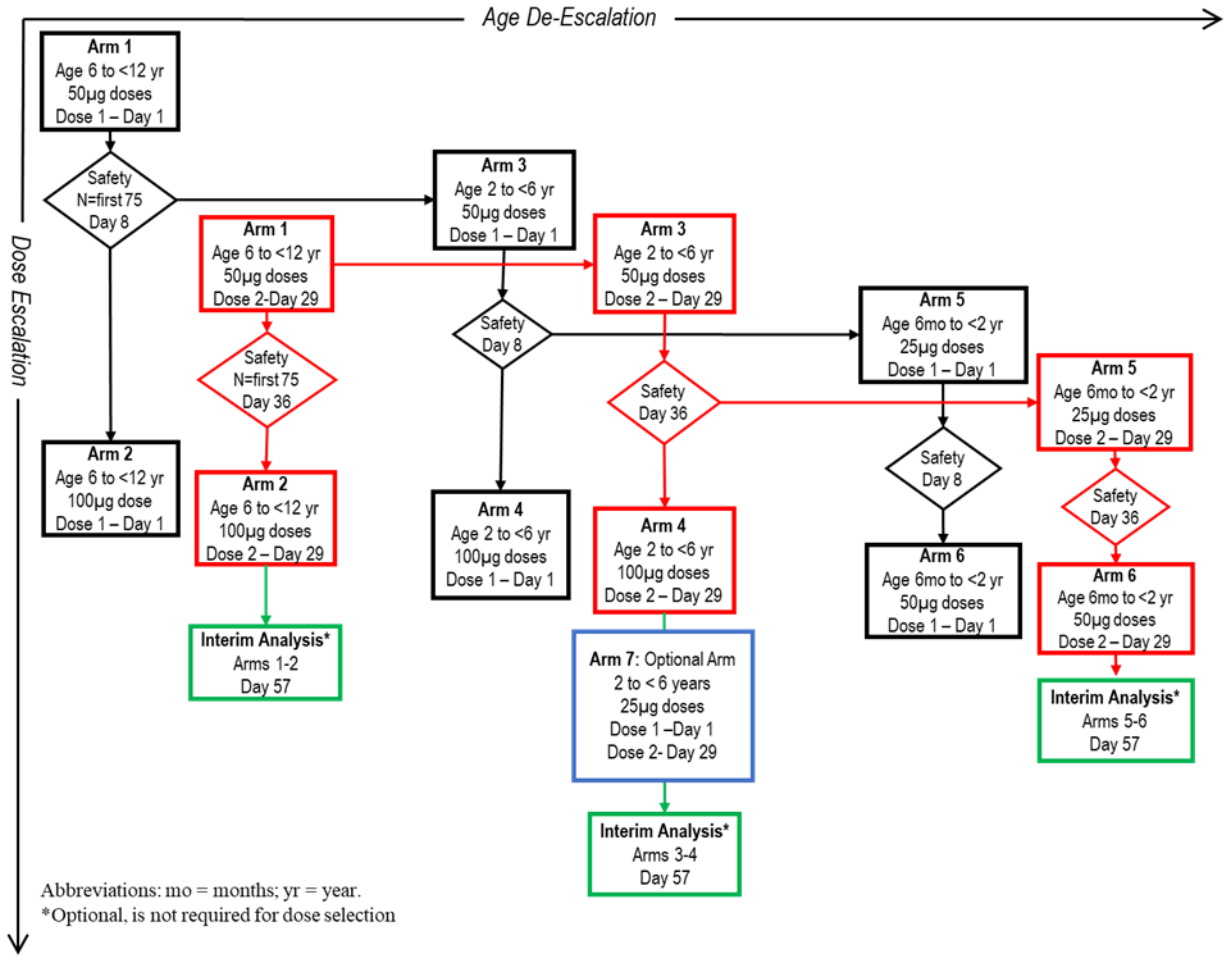
level in the 2 to < 6 years age group (Study Arm 3; n = 75). After at least 75 participants in Study Arm 1 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will again review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 2 and whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 3. Simultaneously, the enrollment of the remaining 300 planned participants for Arms 1 and 2 will be ongoing. A preliminary safety and immunogenicity data review of Arm 1, and Arm 2 as applicable, will aid in the selection of a dose level for Part 2. Once all or a subset of participants from each of Study Arms 1 and 2 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the safety and immunogenicity data. Cumulative safety data for approximately 300 participants at the selected dose level will be reviewed by the Data Safety Monitoring Board (DSMB) before enrollment in Part 2, and the DSMB safety review recommendation will enable the expansion of the 6 to < 12 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 8; n = 1,275) or placebo (Study Arm 9; n = 425).

Similar analysis as above will apply to other age groups in part 1, details can be found in protocol section 3.1. An optional Arm 7 may be enrolled in middle age group (2 to < 6 years, approximately 75 participants) at the 25 µg dose if the 100 µg dose is eliminated at any point during dose escalation, to maintain dose ranging for this age group. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2. Once all or a subset of participants in all applicable Arms reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review safety and immunogenicity data. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2 and for expansion of the 2 to < 6 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 10; n = 1,500) or placebo (Study Arm 11; n = 500).

Once all participants in Study Arms 5 and 6 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the tolerability and immunogenicity data at each dose level. A preliminary safety and immunogenicity data review of Arm 5 and Arm 6, as applicable, will aid in the selection of a dose level for Part 2 and allow for expansion of the 6 months to < 2 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 12; n = 1,500) or placebo (Study Arm 13; n = 500). Detail schematic of study arms and process can be found in Section 3.1 from protocol and Figure 1 below.

In general, if a decision is made not to proceed with administration of the higher dose and/or the second injection at a given dose level (eg, due to safety concerns), the participants scheduled to receive the higher dose may receive a lower dose, and the participants who had received the higher dose level as their first injection will likely be given the next lower dose level that was tolerated for their second injection. The dose level not tolerated in the older age group will not be administered in any of the younger age groups. Within an age group, if one of the dose levels is found to have an unacceptable tolerability profile, the age group may progress to Part 2 at a lower dose level.

Figure 1 Study Design Schematic, Part 1: Dose-escalation, age de-escalation

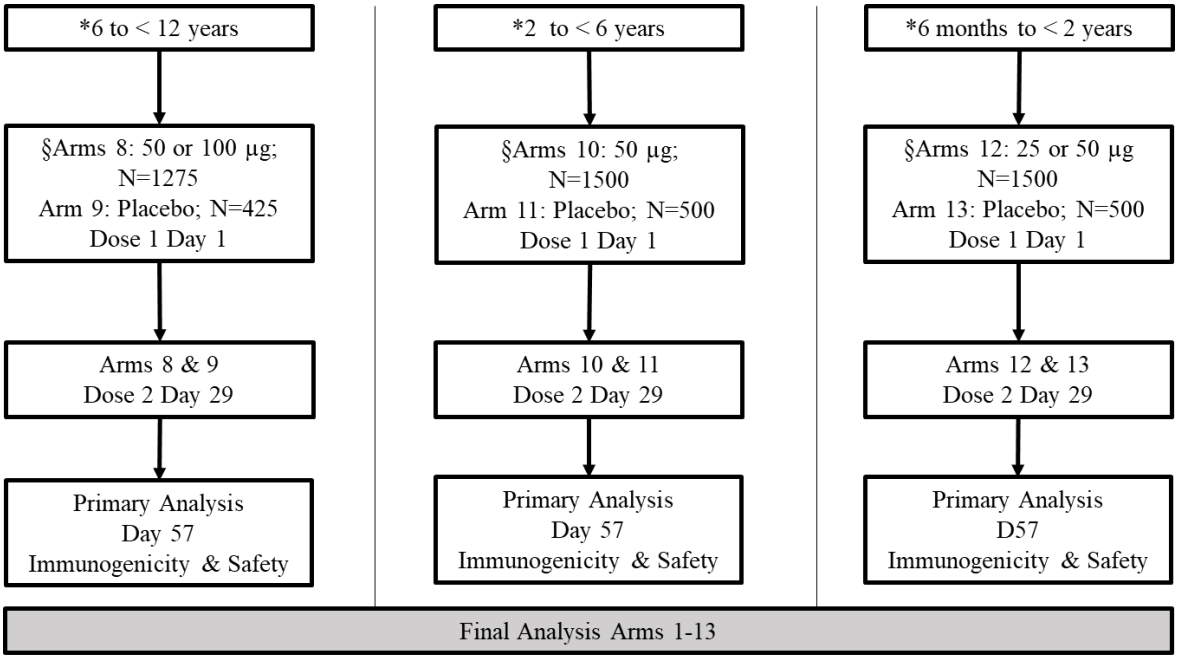


4.1.2. Part 2, the Blinded Phase

The blinded phase of the study will be a placebo-controlled observer-blind evaluation of the selected dose in approximately 5,700 participants (approximately 1,700 participants in the 6 to < 12 years of age group and approximately 2,000 participants in both the 2 to < 6 years and the 6 months to < 2 years age group). No participants in Part 1 will participate in Part 2 of the study. Each age group will begin with Part 1 and advance to Part 2 independently.

For each age group, the primary analysis immunogenicity in part 2 will be conducted after the pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis will be conducted after a subset or all participants reach Day 57.

Figure 2 Study Design Schematic, Part 2: Expansion



Abbreviations: CMI = cell-mediated immunity; D = Day; S = spike; VTEU = Vaccine and Treatment Evaluation Units.
*Expansion and primary analysis for each age group may occur at different times.
§Participants in each age group will be assigned to one of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity on D1 (prior to randomization and first dose), D57, and one of D29 (prior to the second dose), D209, or D394 (such that each participant provides a total of 3 blood samples only). Participants in the fourth cohort (remainder of the age group) will provide a blood sample on D1 (prior to randomization and before the first dose). A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on D1 (prior to randomization and before the first dose), D43, D209, and D394.

4.2. Sample Size and Power

The initial age groups in Part 1 are for estimation purposes. With approximately 750 participants (approximately 375 participants at each dose level of mRNA-1273) in the initial

6 to < 12 years age group, there is at least a 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% for a given dose level. In each of the younger age groups (2 to < 6 years and 6 months to < 2 years), the safety assessment will occur during the conduct of Part 2 after approximately 400 participants have been exposed to mRNA-1273 at the dose level selected for Part 2. For further details, please refer to protocol section 7.5.2.

The sample size in the expansion (Part 2) is considered to be sufficient to support a safety database in the pediatric participants 6 months to < 12 years of age. With approximately 1,275 participants in the 6 to < 12 years of age group (or 1,500 participants in each of the younger age groups, 2 to < 6 years and 6 months to < 2 years) exposed to mRNA-1273 at a given dose level in Part 2, the study has at least a 90% probability to observe at least 1 participant with an AE at a true 0.2% AE rate for a given dose level.

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group will be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset will be processed, and the analysis of primary immunogenicity endpoint will be based on the Immunogenicity PP Subset.

If a threshold of protection is available, for the primary immunogenicity endpoint, with approximately 289 participants on mRNA-1273 in the Immunogenicity PP Subset of an age group, there will be at least 90% power to rule out 70% with a 2-sided 95% CI (lower bound of the 95% CI > 70%) for the percentage of mRNA-1273 participants exceeding the accepted threshold if the true rate of participants exceeding the threshold is 80%.

If an acceptable antibody threshold of protection against COVID-19 is not available at the time of analysis for the primary immunogenicity endpoint, noninferiority tests of the 2 null hypotheses based on the 2 coprimary endpoints will be performed, respectively. The sample size calculation for each of the 2 noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be 90% power to demonstrate noninferiority of the immune response, as measured by the antibody GM value, in pediatric population at a 2-sided alpha of 0.05, compared with that in young adults (18 to 25 years of age) in Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1, a noninferiority margin of 0.67 (or 1.5), and a point estimate minimum threshold

of 0.8. The standard deviation of the natural log-transformed levels is assumed to be 1.5.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in children at a 2-sided alpha of 0.05, compared with that in young adults 18 to 25 years of age in Study P301 receiving mRNA-1273, assuming seroresponse rate of 85% in young adults of 18 to 25 years of age from Study P301, true seroresponse rate of 85% in children (or true rate difference is 0 compared to young adults from Study P301), a noninferiority margin of 10% and a point estimate minimum threshold of -5% in seroresponse rate difference.
- In the 1273-P203 interim analysis (data snapshot on 08 May 2021), the observed seroresponse rates at Day 57 were high in both 18 to 25 years of age group from Study P301 (98.6% with 95% CI: 96.6, 99.6) and 12 to17 years of age group (98.8% with 95% CI: 97.0, 99.7), based on pseudovirus nAb ID50 titers . For this Study P204, if the true seroresponse rates were assumed to be 95% or higher in both 18 to 25 years of age group from Study P301 and an age group in children, with between-group true difference within 4%, there will be a >90% power to demonstrate noninferiority by seroresponse rate in children compared with 18 to 25 years of age in Study P301, at a 2-sided alpha of 0.05.

Assuming approximately 25% of participants in the Immunogenicity Subset will not meet the criteria to be included in the Immunogenicity PP subset, approximately 528 participants in Part 2 (~396 receiving mRNA-1273 and ~132 receiving placebo) will be selected for the Immunogenicity Subset from which approximately 289 participants on mRNA-1273 will be suitable for the Immunogenicity PP subset.

4.3. Randomization

Random assignment of participants in Part 2 of the study will use a centralized interactive response technology, in accordance with pregenerated randomization schedules. Approximately 1,700 participants in the 6 to < 12 years of age group and approximately 2,000 participants in both the 2 to < 6 years and the 6 months to < 2 years age group approximately will be randomized in a 3:1 ratio to the mRNA1273 arm (n = ~1,275, ~1,500,

and ~1,500 participants, respectively) or placebo arm (n = ~425, ~500, and ~500 participants, respectively).

4.4. Blinding and Unblinding

This study is conducted in two parts, 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 participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end, with certain exceptions, please refer to Section 8.1 of the protocol for details.

The final analysis of all endpoints will be performed after all participants (Arm1-13) have completed all planned study procedures.

At the time of interim analysis, only pre-identified Sponsor and unblinded Contract Research Organization (CRO) team members as specified in the study Data Blinding Plan will be unblinded to review treatment level results and individual listings. Please also refer to Section 6.7. Study sites will remain blinded to individual treatment assignments until the end of the study.

If a COVID-19 vaccine is authorized or licensed for a specific age group before the end of the study, please refer to protocol section 3.3 for unblinding and/or cross-over plans.

5. Analysis Populations

The following analysis sets are defined: Randomization Set, Full Analysis Set (FAS), Per-Protocol (PP) Set for Efficacy, Immunogenicity Subset, Per-Protocol (PP) Immunogenicity Subset, Safety Set, Solicited Safety Set, Modified Intent-to-Treat (mITT) Set, Modified Intent-to-Treat-1 (mITT1) Set.

5.1. Randomization Set

The Randomization Set consists of all participants who are randomized in the Part 2 of study, regardless of the participant's treatment status in the study. Participants will be analyzed according to the treatment group to which they were randomized.

5.2. Full Analysis Set

The Full Analysis Set (FAS) for Part 1 consists of all enrolled participants who receive at least 1 injection of IP, and the FAS for Part 2 consists of all randomly assigned participants

who receive at least 1 injection of IP. Participants will be analyzed according to the treatment group for the treatment they actually received in Part 1 and will be analyzed according to the treatment group to which they were randomized in Part 2.

5.3. Per-Protocol (PP) Set for Efficacy

The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who meet all the following criteria:

a) Received planned doses of IP per schedule

b) Complied with the 2nd dose injection timing

c) Had no major protocol deviations that impact key or critical efficacy data

d) Had a negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline

The PP Set for Efficacy in both parts will be used as the primary analysis population in the efficacy analyses unless otherwise specified. Participants will be analyzed according to the treatment group for the treatment they actually received in Part 1 and to which they were randomized in Part 2.

5.4. Immunogenicity Subset

A subset of participants in the FAS will be selected for immunogenicity sampling and testing. Participants in Part 1 and 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for analysis.

Immunogenicity Subset consists of

a) a subset of participants in the FAS, and

b) have baseline (Day 1) SARS-CoV-2 status available, and

c) have baseline and at least one post-injection antibody assessment for the analysis endpoint.

Immunogenicity Subset will be used for sensitivity analyses or supportive analysis. Participants will be analyzed according to the treatment group to which they were randomized.

Table 2: Phlebotomy Schedule for Serology and CMI for Part 2 (Expansion) of the Study

Cohort	Number of subjects	Study Visit Day					
		D1[1,2]	D29[1]	D43	D57	D209	D394
Phlebotomy Schedule for Serology: To be Executed Within Age Group							
A	First 176 (132 mRNA-1273: 44 placebo)	X	X		X		
B	Next 176 (132 mRNA-1273: 44 placebo)	X			X	X	
C	Next 176 (132 mRNA-1273: 44 placebo)	X			X		X
D	Remainder of the age group	X					
Phlebotomy Schedule for Cell-Mediated Immunity: To be Executed Within Each Age Group at Selected VTEU Sites only							
E (CMI with exploratory serology)	24 (18 mRNA-1273: 6 placebo)	X		X		X	X

Abbreviations: CMI = cell-mediated immunity; D = day; VTEU = Vaccine and Treatment Evaluation Units.
1. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing.
2. If a Day 1 (baseline) blood sample cannot be obtained, the participant will be considered either a screen failure due to inability to satisfy inclusion criteria 3 or could be scheduled for rescreening either within same screening period for Part 1, or for a new screening period for Part 2 later in the study. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3.

5.5. Per-Protocol (PP) Immunogenicity Subset

Per-Protocol (PP) Immunogenicity Subset consists of all participants in Immunogenicity Subset who meet all the following criteria:

a) Received planned doses of IP per schedule

b) Complied with the immunogenicity window based on 2nd dose injection timing

c) Had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline

d) If participants have a diagnosis of HIV, they are not receiving highly active anti-retroviral therapy (HAART)

e) Had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint

f) Had no major protocol deviations that impact key or critical data

The PP Immunogenicity Subset will serve as the primary population for the analysis of immunogenicity data in this study unless specified otherwise. Participants will be analyzed

according to the treatment group for the treatment which they actually received in Part 1 and to which they were randomized in Part 2.

5.6. Safety Set

The Safety Set of Part 1 consists of all enrolled participants and of Part 2 consists of all randomized participants who received any study injection. The Safety Set will be used for analysis of safety except for the solicited ARs. In addition, the following Safety Set is defined for each injection separately. The First (Second) Injection Safety Set consists of all subjects in the Safety Set who have received the first (second) study injection. Participants will be included in the vaccination group corresponding to the vaccination they actually received. For a participant who was randomized to placebo in Part 2 but received any dose of mRNA-1273 at any injection, the participant will be included in the mRNA-1273 group in the Safety Set.

5.7. Solicited Safety Set

The Solicited Safety Set consists of all participants in the safety set who contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the study injection they actually received. In addition, the following Solicited Safety Set is defined for each injection separately.

The First (Second) Injection Solicited Safety Set consists of all subjects in the Solicited Safety Set who have received the first (second) study injection and have contributed any solicited AR data from the time of first (second) study injection through the following 6 days.

Participants will be analyzed according to the vaccination group a participant received, rather than the vaccination group to which the subject was randomized. A participant who was randomized to placebo but received any dose of mRNA-1273 at any injection will be included in the mRNA-1273 group in the Solicited Safety Set.

5.8. Modified Intent-to-Treat (mITT) Set

The Modified Intent-to-Treat (mITT) Set consists of all participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2

nucleocapsid) at baseline, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline.

Participants will be analyzed according to the treatment group to which they were randomized.

5.9. Modified Intent-to-Treat-1 (mITT1) Set

The Modified Intent-to-Treat-1 (mITT1) Set consists of all participants in the mITT Set excluding those who received wrong treatment (i.e., at least one dose received that is not as randomized).

Participants will be analyzed according to the treatment group to which they were randomized.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Assessments is provided in Appendix E.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of IP. For immunogenicity tests and nasal swab tests, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of first dose of IP (Day 1).

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that age group and vaccination group within the analysis set of interest, unless otherwise specified.

Baseline SARS-CoV-2 status is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1.

Positive SARS-CoV-2 status at Baseline is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Negative status at Baseline is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid at Day 1.

Study day relative to the first injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection will be calculated as: date of assessment/event – date of the first injection + 1

Study day relative to the most recent injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection but before the second injection (if applicable) will be calculated as: date of assessment/event – date of the first injection + 1;

c) study day on or after the date of the second injection will be calculated as: date of assessment/event – date of the second injection + 1; if study day is on the same day as the second injection, date and time will be compared with the second injection date and time.

For calculation regarding antibody levels/titers, antibody values reported as LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ if actual values are not available, and actual values will be used if available. Missing results will not be imputed.

The following **analysis periods or stages for safety analyses** will be used in this study:

- Up to 28 days after any vaccination: this stage starts at the day of each vaccination and continue through the earliest date of (the day of each vaccination and 27 subsequent days, next vaccination [if applicable]). This analysis period will be used

as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

- Follow-up analysis period:

  For unsolicited AE or assessments that will be collected throughout the study, this analysis period starts from 28 days after the last injection date (i.e. the day of last injection + 28 days, regardless of number of injections received) and continues until the earliest date of (study completion, discontinuation from the study, or death).

  For assessments that will be collected at study visits, if a subject receives two injections, this stage starts from the day after Day 57 visit and continues until the earliest date of (study completion, discontinuation from the study, or death); if a subject receives first injection only, this stage starts from the day after Day 29 visit and continues until the earliest date of (study completion, discontinuation from the study, or death).

- Overall period: this analysis period starts at the first injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death).

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- For laboratory assessments, if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (e.g., <0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the ULOQ (e.g., >3000), the numeric values will be imputed by ULOQ in the summary.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups:

The following vaccination groups will be used for summary purposes:

- Part 1, Open-Label Phase:
    - mRNA-1273 vaccine 25 µg
    - mRNA-1273 vaccine 50 µg
    - mRNA-1273 vaccine 100 µg
    - mRNA-1273 vaccine Total
- Part 2, Blinded Phase:

  Treatment in Part 2 will be the selected dose level in each of the age groups from Part 1 or Placebo

    - mRNA-1273 vaccine 25 µg, or
    - mRNA-1273 vaccine 50 µg, or
    - mRNA-1273 vaccine 100 µg

  And

    - Placebo

If a subject received any study vaccination injection that is at a non-protocol dose level, the subject will be assigned to a protocol dose (mRNA-1273 vaccine 25 µg ,mRNA-1273 vaccine 50 µg, or mRNA-1273 vaccine 100 µg) for that injection according to the following rule:

- mRNA-1273 25 µg if the received dose > 0 µg and <= 25 µg, or
- mRNA-1273 50 µg if the received dose > 25 µg and <= 75 µg, or
- mRNA-1273 100 µg if the received dose > 75 µg

For subjects who receive a second injection that is different from the first injection will be summarized under the higher dose of vaccination group (eg, Placebo < mRNA-1273 25 µg < mRNA-1273 50 µg < mRNA-1273 100 µg) as the actual treatment group received for safety analyses.

Summary by age group:

All analyses and data summaries/displays will be provided by vaccination group for each age cohort (6 months to < 2 years, 2 to < 6 years, and 6 to < 12 years), unless otherwise specified. Participants in Part 1 and 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for safety analysis.

Summary by study part:

Separate shells will be provided for Part 1 and Part 2 of the study. In Part 1, all analyses and data summaries/ displays will be provided by age and vaccination group. In Part 2, all analyses and data summaries/ displays will be provided by age and vaccination group.

All analyses will be conducted using SAS Version 9.4 or higher.

6.2. Background Characteristics

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories will be summarized by age and vaccination group as defined in Section 6.1 based on the Full analysis for Part 1 and Randomization Set for Part 2:

- Randomization Set (Part 2)
- Full Analysis Set (Part 1 and Part 2)
- Per-Protocol (PP) Set for Efficacy (Part 1 and Part 2)
- Immunogenicity Subset (Part 1 and Part 2)
- Per-Protocol (PP) Immunogenicity Subset (Part 1 and Part 2)
- Safety Set (Part 1 and Part 2)

- Solicited Safety Set (Part 1 and Part 2)
- mITT Set (Part 1 and Part 2)
- mITT1 Set (Part 1 and Part 2)

The percentage will be based on subjects in that age and vaccination group within the Full Analysis Set for Part 1 and in that age and vaccination group within the Randomization Set (as randomized) for Part 2, except the Solicited Safety Set and Safety Set for which the percentages will be based on the age and vaccination group in the Safety Set (as treated).

The number of subjects in the following categories will be summarized based on subjects screened:

- Number of subjects screened
- Number and percentage of screen failure subjects and the reason for screen failure

The percentage of subjects who screen failed will be based on the number of subjects screened. The reason for screen failure will be based on the number of subjects who screen failed.

The number and percentage of subjects in each of the following disposition categories will be summarized by age and vaccination group based on Full Analysis Set for Part 1 and summarized by age and vaccination group based on the Randomization Set for Part 2:

- Received each dose of IP
- Prematurely discontinued before receiving the second dose of IP and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

A subject disposition listing will be provided, including informed consent, subjects who completed the study injection schedule, subjects who completed study, subjects who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure subjects with reasons for screen failure.

A subject who completed 12 months of follow up after the last injection received is considered to have completed the study.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (months or years), weight (kg, z-score), height (cm, z-score), and body mass index (BMI) (kg/m^2, z-score). Number and percentage of subjects will be provided for categorical variables such as gender, race, ethnicity. The summaries will be presented separately by age and vaccination group as defined in Section 6.1, based on the FAS, Randomization Set (Part 2), Per-Protocol (PP) Set for Efficacy, Immunogenicity Subset, Per-Protocol (PP) Immunogenicity Subset, Safety Set, mITT Set and mITT1 Set.

Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined. If the Safety Set differs from the Randomization Set in Part 2 (e.g., subjects randomized but not received any study injection; subjects received study vaccination other than the vaccination group they were randomized to), the analysis will also be conducted using the Randomization Set.

For screened failure subjects, age (months or years), as well as gender, race, ethnicity will be presented in a listing.

In addition, subjects with any inclusion and exclusion criteria violation will also be provided in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the oldest age group's total mRNA-1273 group with all dose level combined in Part 1 and the oldest age group's total mRNA-1273 group in Part 2 and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of

concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications is summarized in Appendix C Table 4.

The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after each injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by vaccination groups as defined in Section 6.1 as follows:

- Any concomitant medications and non-study vaccination within 7 Days Post Injection
- Any concomitant medications and non-study vaccination within 28 Days Post Injection
- Seasonal influenza vaccine within 28 Days Post Injection
- Antipyretic or analgesic medication within 28 Days Post Injection

A summary table of non-study vaccination that continued or newly received at or after the first injection through 14 days after the last injection will be provided by PT in descending frequency in the mRNA-1273 group with all dose level combined.

A summary table of concomitant medications that continued or newly received at or after the first injection through 28 days after the last injection will be provided by PT in descending frequency of oldest age group's total mRNA-1273 group with all dose level combined in Part 1 and the oldest age group's total mRNA-1273 group in Part 2 .

Prior, concomitant and post medications and non-study vaccination will be presented in a listing.

Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study IP administration data will be presented in a listing.

Study duration will be summarized since randomization, since the first injection, and since the second injection.

6.2.6. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the subjects with each major protocol deviation type will be provided by age and vaccination group as defined in Section 6.1 based on the Full Analysis Set for Part 1 and will be provided by age and vaccination group based on the Randomization Set for Part 2.

Major protocol deviations will be presented in a listing.

6.2.7. COVID-19 Impact

A listing will be provided for COVID-19 impact.

6.3. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to withdrawal from study vaccine and/or study participation, and physical examination findings. Solicited ARs and unsolicited AEs will be coded by SOC and PT according to the MedDRA. Two modified versions of The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) are used in this study for solicited ARs as presented in protocol section 7.4.3's Table 6 and 7 from protocol; Table 6 is the pediatric toxicity scale used for children older than 36 months, and Table 7 is the infant/toddler toxicity scale used for children 6 to 36 months of age, inclusive

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 age and vaccination group unless otherwise specified.

6.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study not before exposure to study vaccine or any event already present that worsens after exposure to study vaccine. [Note: worsening of a pre-existing condition after vaccination will be reported as a new AE.]

Adverse events will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by age and vaccination group, and stage (up to 28 days after any vaccination for Part 1 and Part 2 separately, follow-up analysis period and overall stage; see Section 6.1 for definitions of vaccination group and stage).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT for TEAEs with counts of subjects included. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of oldest age group's total mRNA-1273 group with all dose level combined in Part 1 and oldest age group's total mRNA-1273 group in Part 2 and then alphabetically within SOC. When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Subjects will be presented according to the highest severity (the strongest relationship) in the summaries by severity (of related AEs), if subjects reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of subjects in the Safety Set within each age and vaccination group for Part 1 and Part 2 separately.

6.3.1.1. Incidence of Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of subjects who experience the following will be presented:

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited medically-attended TEAEs
- Any unsolicited TEAEs leading to discontinuation from study vaccine
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs
- Any AESI of MIS-C

- Any AESI other than MIS-C

The table will also include number and percentage of subjects with unsolicited TEAEs that are treatment-related in each of the above categories.

In addition, separate listings containing individual subject adverse event data for unsolicited AEs, unsolicited TEAEs leading to discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, serious AEs, unsolicited medically-attended AEs, AESI other than MIS-C and AESI of MIS-C will be provided separately.

6.3.1.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event):

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from study vaccine
- All unsolicited TEAEs leading to discontinuation from participation in the study
- All unsolicited Severe TEAEs
- All unsolicited Severe TEAEs that are treatment-related
- All unsolicited medically-attended TEAEs
- All unsolicited medically-attended TEAEs that are treatment-related
- All AESI of MIS-C
- All AESI other than MIS-C

6.3.1.3.TEAEs and AESI other than MIS-C by Preferred Term

A summary table of all unsolicited TEAEs and AESI other than MIS-C will be provided. PTs will be sorted in a descending order according to the frequency in oldest age group's total mRNA-1273 group.

6.3.1.4.TEAEs by System Organ Class, Preferred Term and Severity

The following summary tables of TEAEs will be provided by SOC, PT, and maximum severity (mild < moderate < severe) using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related

6.3.2. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term "Solicited Adverse Reactions" refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the subject in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist (i.e., solicited ARs).

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, localized axillary swelling or tenderness ipsilateral to the injection arm, and groin or underarm swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, fever, chills, irritability/crying, sleepiness, and loss of appetite.

The AR categories are different for younger population between Age 37 months to <12 years and Age 6 months to ≤ 36 months. Details presented in Table 6 and 7 in the protocol.

The solicited ARs will be graded based on the grading scales presented in Table 6 and 7 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). Investigator will assess Grade 4 events (with exception of fever).

If a solicited local or systemic AR continues beyond 7 days post injection, the participant's parent(s)/ LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs, whichever occurs first.

All solicited ARs (local and systemic) will be considered causally related to injection.

Analyses of solicited ARs will be provided by age and treatment group for each injection (first or second) based on the associated subset of Solicited Safety Set, i.e. First (Second) Injection Solicited Safety Set; and for any injection based on the Solicited Safety Set, unless otherwise specified.

The number and percentage of subjects who reported each individual solicited local AR (has a toxicity grade of Grade 1 or greater) and solicited systemic AR (has a toxicity grade of Grade 1 or greater) during the 7-day follow-up period after each injection will be tabulated by age group, vaccination group, toxicity grade, and injection. The number and percentage of subjects who reported each individual solicited AR will also be summarized by age group, vaccination group, toxicity grade, days of reporting and injection.

The number and percentage of subjects experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral, axillary, or tympanic route) by toxicity grade will be provided.

A two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of subjects who reported any solicited local AR, solicited systemic AR, or any solicited AR.

The onset of individual solicited AR is defined as the time point after each injection at which the respective solicited AR first occurred. The number and percentage of subjects with onset of individual solicited AR will be summarized by age group, vaccination group, study day relative to the corresponding injection (Day 1 through Day 7), and injection.

The number of days will be calculated as the days of the solicited AR is reported within the 7 days of injection including the day of injection, no matter it is intermittent or continued. If the solicited AR continues beyond 7 days, the consecutive days a solicited AR is reported after 7 days will be included (e.g., an event that lasted 5 days in the first 7 days post injection and 3 consecutive days beyond 7 days post injection, the duration will be reported as 8 (5+3) days.)

Solicited ARs collected on eDiary and those collected on reactogenicity aCRF will be provided in a listing, and the maximum grade from eDiary and aCRF will be presented. All solicited ARs that continue beyond 7 days post injection will be presented in separate data listings.

6.3.3. Pregnancy Tests

A point-of-care urine pregnancy test will be performed, if deemed appropriate by the investigator, at the Screening Visit and before each vaccine dose in female participants of childbearing potential. At any time during the study, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator. A by-subject listing will be provided for pregnancy tests.

6.3.4. Physical Examinations

A full physical examination, including body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]), length/height, weight and BMI will be presented in a listing.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Immunogenicity Subset for both parts and will be performed for each pediatric age group separately at the selected dose level in Part 1 and Part 2 based on the participants in the PP Immunogenicity Subset. The PP Immunogenicity Subset is the primary analysis population used in the immunogenicity analyses, unless otherwise specified. For each pediatric age group, participants from Part 1 and Part 2 in the PP Immunogenicity Subset who receive the same mRNA-1273 dose level selected for expansion may be combined for immunogenicity analyses. If the same dose level is selected for expansion for more than one age group, these age groups may be combined for immunogenicity analyses.

The GMT and geometric mean (GM) level will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers or levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity titers or levels within subjects. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers or levels for subject i at time points j and k, $j \neq k$,where j represent pre-injection baseline at Day 1.

6.4.1. Immunogenicity Assessments

Immunogenicity assessments for both Part 1 and Part 2:

- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays.
- Serum bAb titer as measured by enzyme-linked immunosorbent assay specific to the SARS-CoV-2 S protein.

Immunogenicity assessment for SARS-CoV-2 infection and CMI in Part 2:

- For Part 2, participants in each age group will be assigned to one of 5 phlebotomy cohorts (Table 2). Blood sampling will be performed in 3 of these 5 cohorts for immunogenicity at 3 of the following time points: Day 1 (prior to randomization and the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, and Day 394. Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1 only (prior to randomization and the first dose). A fifth cohort of participants at selected VTEU sites only, will provide blood samples for assessment of exploratory serology and CMI on Day 1 (prior to randomization and the first dose), Day 43, Day 209, and Day 394.

6.4.2. Primary Analysis of Antibody-Mediated Immunogenicity Endpoints

If an accepted serum Antibody (Ab) threshold of protection against COVID-19 is available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity objective of this study will be considered to be met for that age group.

The number and percentage of participants with serum Ab greater than or equal to the threshold with 2-sided 95% CI will be provided by age and vaccination group as defined in Section 6.1 at each post baseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum Ab threshold of protection against COVID-19 is not established, immune response as measured by GM value and seroresponse rate in each age group based

on Day 57 Ab levels will be compared to that in young adults (18 to 25 years of age) using data from Study P301. An analysis of covariance model will be carried out with Ab at Day 57 as dependent variable and a group variable (a pediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable for each pediatric age group. The GM values of the pediatric age group at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI will be provided to assess the difference in immune response between the pediatric age group (Study P204) compared to the young adults (18 to 25 years of age) in Study P301 at Day 57. For each pediatric age group, the noninferiority of GM value will be considered demonstrated if the lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5 and the GMR point estimate > 0.8 (minimum threshold). In addition, GMR with 95% CI calculated using t-distribution will be provided to assess if the two methods are consistent in the analysis results.

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 57 being of the primary interest. The seroresponse rate difference with 95% CI using the Miettinen-Nurminen (score) confidence limits at Day 57 will be provided between children receiving mRNA-1273 in Study P204 and young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301. For each pediatric age group, the noninferiority of seroresponse rate will be considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is > -10% based on the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

6.4.3. Secondary Analysis of Antibody-Mediated Immunogenicity Endpoints

For each group, the following evaluations will be performed at each time point at which blood samples are collected for immunogenicity (unless otherwise specified).

- GM level of anti-SARS-CoV-2-specific bAb 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 values then back transformed to the original scale for presentation. GM level and corresponding 95% CI will be plotted at each timepoint. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

- GM fold-rise (GMFR) of SARS-CoV-2-specific bAb levels with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1. 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. GM fold-rise and corresponding 95% CI will be plotted at each timepoint. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

  Proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2 specific bAb levels from Visit Day 1 (baseline) at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs

- GMT of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each time point using the same method mentioned above.

- GMFR of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1 using the same method mentioned above.

  Proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum nAb from Visit Day 1 (baseline) at each post-injection time points will be tabulated with 2-sided 95% Clopper-Pearson CIs.

- Proportion of subjects with seroresponse due to vaccination will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint. Seroresponse due to vaccination at a participant level is defined as a change from below the LLOQ to equal to or above LLOQ, or a z-fold rise if baseline is equal to or above LLOQ. The definition of seroresponse may depend on assay-specific performance characteristics, and the details definition of seroresponse for each assay/test of interest can be found in section 3.1.

- Per the study protocol, if the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+7 days) as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), the window may be extended to Day 29 + 21 days. More rigid visit window will be used in the Per-Protocol Immunogenicity Subset, -7/+14 for Day 29 visit, as appropriate.

Multiplicity adjustment between age groups:

A sequential hypothesis testing (fixed-sequence method) will be used to adjust multiplicity to preserve the family-wise Type I error rate (alpha = 0.05), starting with the oldest age group, followed by the middle age group, and then followed by the youngest age group. The immunogenicity coprimary endpoint hypotheses for the oldest age group (6 to < 12 years of age) will be tested first at alpha level of 0.05. If the testing in the oldest age group is statistically significant, the alpha level of 0.05 will be passed to the testing of the coprimary endpoint hypotheses in the middle age group (2 to < 6 years of age). If the testing in the middle age group is statistically significant at alpha level of 0.05, then the alpha 0.05 is preserved for testing the coprimary endpoint hypotheses in the youngest age group (6 months to < 2 years of age). The testing will continue through the sequence only until an endpoint in an age group is not statistically significant, in which case the testing will stop.

6.5. Efficacy Analysis

Efficacy analyses will be performed using the FAS, mITT, mITT1 and PP Set for Efficacy. The mITT1 Set will be the primary analysis set used for efficacy analysis of efficacy endpoints starting from 14 days after first dose, and PP Set for Efficacy will be the primary analysis set used in the efficacy analyses for efficacy endpoints starting 14 days after second dose, unless otherwise specified. Subjects will be included in the treatment group to which they were randomized.

Baseline SARS-CoV-2 status is described in Section 6.1. Baseline SARS-CoV-2 status, the serology test results at baseline, the RT-PCR test results at baseline will be summarized by age group and treatment group.

Participants with baseline positive or missing SARS-CoV-2 status will be excluded from the PP Set for Efficacy Analysis.

In this study, the serology test results and the RT-PCR test results will be summarized by visit.

6.5.1. Endpoint Definition/Derivation

6.5.1.1. Derivation of SARS-CoV-2 Infection

This is a secondary efficacy endpoint, which is a combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: the incidence of SARS-CoV-2 infection counted starting 14 days after the second

dose of IP will be summarized by treatment group. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:

- bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) post-baseline, OR
- Positive RT-PCR post-baseline.

Derivation of this secondary efficacy endpoint is summarized in Table 3 below.

Table 3. Derivation for SARS-CoV-2 Infection

	Post-baseline assessments		
Baseline SARS-CoV-2 Status	PCR test post baseline	bAb levels against SARS-CoV-2 Nucleocapsid	**Endpoint**: SARS-CoV-2 infection
Negative at Baseline	**Positive** (either at scheduled nasal swab test, or at symptom-prompt nasal swab test)		Case
Negative at Baseline		**Positive** (at scheduled Post baseline visit or later) as measured by *Roche Elecsys*	Case

The date of documented infection will be the earlier of:

- Date of positive post-baseline RT-PCR result, or
- Date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid

The time to the first SARS-CoV-2 infection will be calculated as:

Time to the 1st SARS-CoV-2 infection = Date of the 1st documented infection – Date of randomization + 1. (For Part 1, switch date of randomization to date of 1st injection)

Cases will be counted starting 14 days after the second injection, i.e. date of documented infection – Date of the 2nd injection ≥ 14.

SARS-CoV-2 infection cases will also be summarized based on tests performed at least 14 days after first dose.

6.5.1.2. Derivation of Asymptomatic SARS-CoV-2 Infection

This is a secondary efficacy endpoint: the incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or serology tests obtained post-baseline visits counted starting 14 days after the second injection in participants with negative SARS-COV-2 status at baseline.

Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Specifically:

- Absent of COVID-19 symptoms
- AND at least one from below:
    - bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) post-baseline, OR
    - Positive RT-PCR test post-baseline (at scheduled or unscheduled/illness visits)

The date of documented asymptomatic infection is the earlier date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid due to infection, or positive RT-PCR at scheduled visits, with absence of symptoms.

The time to the asymptomatic SARS-CoV-2 infection will be calculated as:

Time to the asymptomatic SARS-CoV-2 infection = Date of asymptomatic SARS-CoV-2 infection test – Date of randomization + 1. (For Part 1, switch date of randomization to date of first injection)

6.5.1.3 Derivation of COVID-19

This is a secondary efficacy endpoint: the incidence of the first occurrence of COVID-19 starting 14 days after the first or second dose of IP. COVID-19 is defined as symptomatic disease based on the criteria specified in Section 3.2. Cases are defined as participants meeting clinical criteria based on both symptoms for COVID-19 and positive RT-PCR test results.

Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary. Subjects reporting COVID-19 symptoms, as defined in Section 7.3.2 of the protocol, will be arranged an unscheduled visit to collect a nasal swab for SARS-CoV-2.

For this efficacy endpoint, a COVID-19 case will be identified as a positive post-baseline RT-PCR test result that is prompted by symptom(s), together with eligible symptoms, i.e. a positive PCR result of the eligible symptoms summarized below in Table 4.

Table 4. Derivation for COVID-19

	COVID-19
Post-baseline PCR results at unscheduled visits prompted by symptom(s)	Positive, **AND**
Systemic Symptoms	at least **ONE** of the following systemic symptoms: Fever (temperature ≥ 38° C/≥ 100.4° F) or chills (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/vomiting, poor appetite/poor feeding; OR
Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours).

The date of documented COVID-19 (case) will be the later date of ([1 systemic symptom reported, or respiratory symptom reported] and, [date of positive PCR test]). Specifically, the date of documented COVID-19 will be the later date of the following two dates (date of positive PCR test, and the date of eligible symptom(s)), and the two dates should be within 14 days of each other.

- Date of positive PCR test,

- Date of eligible symptom(s), defined as earliest of
    - Respiratory symptom: earliest date of an eligible respiratory symptom is reported
    - Systemic symptoms: earliest date of the eligible systemic symptom is reported

The time to the first occurrence of COVID-19 will be calculated as:

Time to the 1st occurrence of COVID-19 = Date of documented COVID-19 – Date of randomization + 1. (For Part 1, switch date of randomization to date of first injection).

Cases will be counted start 14 days after the 2nd injection, i.e. date of documented COVID-19 ‑ Date of the 2nd injection ≥ 14.

6.5.1.4 Derivation of Alternative Definition of COVID-19

This is a secondary efficacy endpoint: the incidence of the first occurrence of COVID-19 cases meeting the alternative case definition, starting 14 days after the first dose of IP, and COVID-19 cases starting 14 days after the second dose of IP.

The alternative case definition of COVID-19 is defined by the following criteria:

- At least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- At least one positive RT-PCR test for SARS CoV-2

Date of the documented secondary definition of COVID-19 will be later date of:

- Date of the positive RT-PCR test (prompt by symptom)
- Date of eligible symptom(s), defined as earliest of
    - Respiratory symptom: earliest date of an eligible respiratory symptom is reported

- Systemic symptoms: earliest date of the 2nd eligible systemic symptom is reported

and the two dates should be within 14 days of each other.

Secondary case definition of COVID-19 cases will also be summarized based on tests performed after randomization (For Part 1, switch date of randomization to date of first injection).

6.5.2. Analysis Method

The number and percentage of subjects who had an event (i.e. the first asymptomatic SARS-CoV-2 infection) will be summarized in the PP set for Efficacy.

The incidence rate will be provided by age and vaccination group, calculated as the number of cases divided by the total person-time. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

Person-time is defined in Part 2 as the total time from randomization date to the date of event, last date of study participation, censoring time, or efficacy data cutoff date, whichever is earlier. For Part 1, switch randomization date to enrollment date.

6.5.3 Sensitivity and Subgroup Analysis

Sensitivity analysis for these efficacy endpoints will be performed with the same methods described above based on the FAS, mITT Set and mITT1 Set, with cases counted starting from enrollment in Part 1 and starting from randomization in Part 2. A sensitivity analysis will be performed to include subjects with positive SARS-CoV-2 status at baseline.

Subgroup analysis in Part 1 is not needed and it may be done for Part 2 (or Part 1 +Part 2).

6.6. Exploratory Analysis

6.6.1. Exploratory Analysis of Immunogenicity

The below exploratory analyses of immunogenicity may be performed:

- The genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.

- Descriptive summaries of the ratio or profile of specific S protein bAb relative to nAb in serum during the study. The analysis may not be included in the Clinical Study Report (CSR).
- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study.
- Assess the SARS-CoV-2 S protein-specific T-cell responses in a subset of participants.
- Descriptive summaries of GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x and 4x rise of bAb relative to baseline)

6.6.2. SARS-CoV-2 Exposure and Symptoms

SARS-CoV-2 reported exposure history and symptoms assessment will be assessed during the study.

The number and percentage of subjects who had close contact with a person with SARS-CoV-2 infection or COVID-19, reasons for exposure, subjects with any symptoms of potential COVID-19, and subjects with each symptoms will be presented by visit, age and vaccination group as defined in Section 6.1. Descriptive statistics will be provided for length of exposure in days by vaccination group.

In addition, the following listings will be provided for subjects infected by SARS-CoV-2:

- Serum bAb level against SARS-CoV-2
- Serum nAb titer against SARS-CoV-2
- Solicited ARs
- Unsolicited AEs

6.7. Interim Analyses

Part 1: Interim analyses may be performed after all or a subset of participants (with immunogenicity samples collected for D1 and D57) have completed Day 57 within an age group in Part 1 (one optional interim analysis for each age group, 3 interim analyses total for the 3 age groups in Part 1). Analyses of safety and immunogenicity may be conducted at each interim analysis.

Part 2: An interim analysis of immunogenicity and safety will be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 2 within an age group. This interim analysis will be considered the primary analysis of immunogenicity for a given age group. Another interim analysis on safety may be performed after a different subset or all participants have completed Day 57 in an age group.

The final analysis of all endpoints will be performed after all participants have completed all planned study procedures and after the database is cleaned and locked. Results of this analysis will be presented in an end of study CSR, including individual listings.

6.8. 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 meet at pre-specified timepoints during the study to assess safety throughout study conduct. For the 6 to < 12 years age group, the DSMB will review cumulative safety data for approximately 300 participants enrolled at the selected dose level in Part 1 before enrollment begins in Part 2. For both the middle age group (2 to < 6 years) and the youngest age group (6 months to < 2 years) the DSMB will review cumulative safety data after approximately 400 participants have been exposed to mRNA-1273 at selected dose in each age group, combining participants from Part 1 and Part 2, before further expansion in each respective age group. Enrollment will be paused during the DSMB review period. 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, described in protocol section **Error! Reference source not found.**, 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.

7. References

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. September2007[cited2019 Apr 10][10 screens].Availablefrom: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

8. List of Appendices

8.1. Appendix A Standards for Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place.

8.2. Appendix B Analysis Visit Windows for Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, i.e. nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 5 below.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 5. Visit Window

Visit	Target Study Day	Visit Window in Study Day
Nasal Swabs for SARS-CoV-2		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43]

Day 57 (Month 2)	57	[44,133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302
Immunogenicity		
Part 1		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 57 (Month 2)	57	[44,133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302
Part 2 where Day 29 is selected		
Day 1	1 (Date of First Injection)	1, Pre-first-dose and prior to the randomization
Day 29	29	[2,43], Pre-second-dose
Day 57	57	[44,133]
Part 2 where Day 209 is selected		
Day 1	1 (Date of First Injection)	1, Pre-first-dose and prior to the randomization
Day 57	57	[44,133]
Day 209	209	[134,301]
Part 2 where Day 394 is selected		
Day 1	1 (Date of First Injection)	1, Pre-first-dose and prior to the randomization
Day 57	57	[44,133]
Day 394	394	≥302

8.3. Appendix A Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless:
     - The medication end date is after the date of first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first injection. In this case, use the date of first injection
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first injection. In this case, use the date of first injection
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication stop date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in Table 4 below.

Table 4. Prior, Concomitant, and Post Categorization of Medications and Non-study Vaccinations

	Medication Stop Date		
Medication Start Date	**< First Injection Date of IP**	**≥ First Injection Date and ≤ 28 Days After Last Injection**	**> 28 Days After Last Injection [2]**
< First injection date of IP [1]	P	P, C	P, C, A
≥ First injection date and ≤ 28 days after last injection	-	C	C, A
> 28 days after last injection [3]	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date
[3] on the day of last injection and the 27 subsequent days

8.4. Appendix B Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:

   - If only Day is missing, use the first day of the month, unless:
     - The AE end date is after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if time is collected.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The AE end date is after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date of first injection

- If Day, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

2. Missing or partial AE end dates will not be imputed.

8.5. Appendix E: Schedule of Events

Visit Number	0	1	2	3	4	4S	5			6			7
Type of Visit	C	C	TMV	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	7	-	28	-	-	180	-	-	365
Informed consent/assent form, demographics, concomitant medications, medical history	X												
Review of inclusion and exclusion criteria	X	X											
Physical examination including body temperature, length/height, weight, and BMI[7]	X	X		X		X	X			X			X
Pregnancy test[8]	X	X		X									
Randomization		X											
Study injection (including 30-minute postdose observation period)		X		X									
Blood sample for vaccine immunogenicity (Part 1)[9]		X					X[18]			X[18]			X[18]

Visit Number	0	1	2	3	4	4S	5			6			7
Type of Visit	C	C	TMV	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	7	-	28	-	-	180	-	-	365
Blood sample for vaccine immunogenicity (Part 2)[10]		X		X			X[18]			X[18]			X[18]
Blood sample for exploratory serology and cell-mediated immunity (Part 2)[3,10]		X				X				X			X
Nasal swab sample for SARS-CoV-2[11]		X		X		X	X			X			X
Surveillance for COVID-19/illness visit/ unscheduled visit[12]			X	X	X	X	X	X	X	X	X	X	X
Convalescent visit[13]					X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[14]		X		X									
Review of eDiary data			X		X								
Follow-up safety telephone calls[15]									X			X	
Recording of unsolicited AEs		X	X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[16]		X	X	X	X	X	X	X		X	X		X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[16,17]		X	X	X	X	X	X	X		X	X		X
Recording of AESIs (eg, MIS-C)[17]		X	X	X	X	X	X	X		X	X		X
Recording of concomitant medications and nonstudy vaccinations[16]		X	X	X	X	X	X						
Study completion													X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BMI = body mass index; 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; IP = investigational product; IRB = institutional review board; LAR = legally acceptable representative; M = month; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; 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; TMV = telemedicine visit; VTEU = Vaccine and Treatment Evaluation Units.

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, and Day 29) with the approval of the Sponsor.

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. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+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 29 + 21 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.
3. To be conducted during Part 2 of the study in a cohort of participants at selected VTEU sites only.
4. 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 telemedicine visit should be conducted in place of the study site visit. The telemedicine visit 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).
5. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
6. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
7. A full physical examination, including body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]), length/height, and weight, will be performed at the Screening Visit or on Day 1. Symptom-directed physical examination will be performed on Day 1, Day 29, Day 43 (if the visit is applicable), Day 57, Day 209, and Day 394 and may be performed at other time points at the discretion of the investigator. Body mass index will be calculated only at Screening Visit. Body temperature (oral/tympanic) should be measured on each injection day prior to injection. 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 (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1 or Day 29 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.
8. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test and will be performed if deemed appropriate by the investigator. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time during the study.
9. On Day 1, sample must be collected prior to randomization and dosing. If a Day 1 (Baseline) blood sample cannot be obtained, the participant will be considered either a screen failure due to inability to satisfy inclusion criteria 3 or could be scheduled for rescreening (allowed once) within the Screening Period. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3.

10. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing. Participants in each age group will be assigned to 1 of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1, Day 57, and one of Day 29, Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1. A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on Day 1, Day 43, Day 209, and D394. Table provides the blood sampling schedule in Part 2 of the study. If a Day 1 (Baseline) blood sample cannot be obtained, the participant will be considered either a screen failure due to inability to satisfy inclusion criteria 3 or could be scheduled for rescreening (allowed once) within the Screening Period. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criteria 3.
11. The nasal swab sample (collected before dosing on injection day) will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.
12. 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 prespecified 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.
13. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis of COVID-19. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.
14. 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. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolved or the next IP injection occurs, whichever occurs first. Capturing details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
15. Trained study site personnel will call all participants to collect information relating to any AEs, 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.
16. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).
17. In addition to MIS-C, a list of AESIs pertinent to this study may be referenced in the list of AESIs that 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.
18. For Part 1, only the first approximately 75 participants will have post-baseline scheduled blood draws. Additionally, the 300 participants of the expansion part of Arm 1 and Arm 2 may have an optional blood draw on Day 57. For Part 2 see Table 2.

ModernaTX, Inc.

Protocol mRNA-1273-P204

A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age

Statistical Analysis Plan

SAP Version 3.0
Version Date of SAP: 16 Dec 2021

Prepared by:

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Summary of Major Changes in SAP Version

SAP Version	Section # and Name	Description of Change
V2.0 Based on Protocol Amendment 3	3.1 Primary Endpoints 6.3 Safety Analysis	AESIs of myocarditis and/or pericarditis were added (in addition to MIS-C).
V2.0 Based on Protocol Amendment 3	3.1 Primary Endpoints	Seroresponse definition updated to as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ.
V2.0 Based on Protocol Amendment 3	4.1 Overall Study Design	1.The overall sample size for Part 2 was updated to approximately 12,000 participants. 2.The sample size for Study Arms 8, 10, and 12 were each updated to up to 3,000 participants. 3. The sample size for Study Arms 9, 11, and 13 were each updated to up to 1,000 participants.
V2.0 Based on Protocol Amendment 3	4.2 Sample size and Power 4.3 Randomization	The overall sample size for each age group was updated to up to 4,000 participants.
V2.0 Based on Protocol Amendment 3	6.6.1 Assay Specific Definition of Seroresponse	Definition of assay specific seroesponse is included and updated based on a more conservative approach
V2.0 Based on Protocol Amendment 4	6.8 Data Safety Monitoring Board	Included language for the addition of an independent Cardiac Event Adjudication Committee that will adjudicate any suspected cases of myocarditis, pericarditis, or myopericarditis and enable the DSMB to make recommendations to the Sponsor.
V2.0 Based on Protocol Amendment 4	5.4 Immunogenicity Subset 8.5 Appendix E: Schedule of Events	Day 30 (+3 days) blood draw was added to indicate that participants in Cohort D

		(remainder of the age group) will provide a blood sample at Day 1 and at Day 30 (+3 days)
V3.0 Based on Protocol Amendment 5	4.1.2 Part 2, the Blinded Phase	Made updates in figure 2 footnotes to explain that blood sample collection for participants in Cohort D will be prior to randomization and the first dose at Day 1 and within 4 days of receiving Dose 2 at Day 30 (+ 3 days).
V3.0 Based on Protocol Amendment 5	6.1 General Considerations	Analysis Period for blinded phase for safety and efficacy analysis
V3.0 Based on Protocol Amendment 5	8.5 Appendix E: Schedule of Events	Updated footnote #2 in appendix E

List of Abbreviations

Abbreviation	Definition
AB	antibody
AE	adverse event
AR	adverse reaction
AESI	AEs of special interest
BMI	body mass index
bAb	binding antibody
CI	confidence interval
CEAC	Cardiac Event Adjudication Committee
CMI	Cell-Mediated Immunity
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
GMR	geometric mean ratio
IgG	immunoglobulin G
IP	investigational product
IRT	interactive response technology
IST	internal safety team
LOD	limit of detection
LLOQ	lower limit of quantification
MAAEs	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
PP	per-protocol
PT	preferred term
RT-PCR	reverse transcriptase polymersa chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class

Abbreviation	Definition
AB	antibody
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P204, is based on the most recent approved clinical study protocol (CSP), Version Amendment 5, dated 29-Sep-2021 and the most recent approved electronic case report form (eCRF) Version 5.005, dated 29-Oct-2021.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 8) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1273-P204 is a phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy children 6 months to less than 12 years of age.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, tolerability, reactogenicity, and effectiveness data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the primary analysis clinical database lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, subject and participant are used interchangeably; injection of IP, injection, and dose are used interchangeably; vaccination group and treatment group are used interchangeably.

A separate SAP will provide more details for part 2 open-label or cross-over phase.

2. Study Objectives

2.1. Primary Objective

The primary objectives are the following:

- To evaluate the safety and reactogenicity of up to 3 dose levels (25, 50, and 100 μg) of mRNA-1273 vaccine administered as 2 doses 28 days apart in 3 age groups

- To infer the efficacy of mRNA-1273 (25, 50, and 100 µg, administered as 2 doses 28 days apart) based on immunogenicity in 3 age groups

2.2. Secondary Objectives

The secondary objectives are the following:

- To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 µg) administered as 2 doses 28 days apart
- To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo
- To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with COVID-19 AND positive RT-PCR for SARS-CoV-2

2.3. Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence
- To describe the ratio or profile of specific S protein bAb relative to nAb in serum
- To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection
- To assess, in a subset of participants, the SARS-CoV-2 S protein-specific T-cell responses
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline

3. Study Endpoints

3.1. Primary Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after each injection
- Unsolicited adverse events (AEs) through 28 days after each injection
- Medically-attended AEs (MAAEs) through the entire study period
- Serious AEs (SAEs) through the entire study period
- AEs of special interest (AESIs), including multisystem inflammatory syndrome in children (MIS-C) and myocarditis and/or pericarditis, through the entire study period

The primary immunogenicity objective will be evaluated by either:

- The proportion of participants with a serum antibody level at Day 57 ≥ antibody threshold of protection. If an accepted serum antibody threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy.
- The GM value of serum antibody level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301). If a threshold of protection is not available, efficacy will be inferred based on establishing noninferiority for each age group (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years in Study P204) compared to 18- to 25-year old participants (Study P301) by both GM value of serum antibody levels and seroresponse rate.

  Seroresponse due to vaccination at a subject level is defined as a change from baseline below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ.

  Among the two Pseudovirus tests, PsVNT50 and PsVNT80, PsVNT50 is considered the most appropriate measure of subject response because it falls in the middle of the dynamic range of the dilution response curve while PsVNT80 is close to the plateau and thus subject to restriction.

  The GM and seroresponse rate comparisons between children in P204 and young adults (18-25 years of age) in P301 will be compared for the bAb and nAb

measures, with pseudovirus nAb PsVNT50 (ID50) considered as the primary assay test for the immunobridging.

3.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- The GM values of SARS-CoV-2 S protein-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2).
- The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2).
- The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or RT-PCR), starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:
    - bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by Roche Elecsys) post baseline, OR
    - Positive RT-PCR post baseline.
- The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) post baseline in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms, starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP
- The incidence of the first occurrence of CDC Case Definition of COVID-19 post baseline, starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP. COVID-19 is defined as symptomatic disease based on the following criteria according to CDC case definition:
    - The participant must have a positive test for SARS-CoV-2 by RT-PCR; AND
    - Either
        - The participant must have experienced at least ONE of the following systemic symptoms: Fever (temperature $\geq 38^{o}$ C/$\geq 100.4^{o}$ F) or chills

(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/vomiting, poor appetite/poor feeding; OR

- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours)

- The incidence of the first occurrence of the P301 primary definition of COVID-19 case post baseline, starting 14 days after the second dose of IP, and starting 14 days after the first dose of IP.

  The alternative case definition of COVID-19 is defined by the following criteria:

  - The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38° C/≥ 100.4° F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
  - The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
  - At least one positive RT-PCR test for SARS-CoV-2

3.3. Exploratory Endpoints

The exploratory endpoints are the following:

- Alignment of genetic sequence of viral isolates with that of the vaccine sequence
- Relative amounts or profiles of S protein-specific bAb and specific nAb titers in serum
- Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)
- Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points after vaccination relative to baseline

- GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x, and 4x rise of bAb relative to baseline

4. Study Design

4.1. Overall Study Design

This is a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation, randomized, observer-blind, placebo-controlled, expansion study intended to infer the effectiveness of mRNA-1273 in children aged 6 months to < 12 years. The study population will be divided into 3 age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years) and up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 will be evaluated.

The study will be conducted in 2 parts. Part 1 of the study will be open label and consist of dose-escalation, age de-escalation in 1,275 participants (see Table1 below for the number of participants in each age group) to select the dose for each age group. Part 2 of the study will be placebo-controlled, observer-blind evaluation of the selected dose in up to 12,000 participants (up to 4,000 participants each in the 6 to < 12 years, 2 to < 6 years, and the

6 months to < 2 years of age groups).). No participants in Part 1 will participate in Part 2 of the study.

Table 1: Planned Age Groups and mRNA-1273 Dose Levels in Part 1 and Part 2 of the Study

	Part 1			Part 2	
Age Group	**mRNA-1273 25 µg**	**mRNA-1273 50 µg**	**mRNA-1273 100 µg**	**Selected Dose Level of mRNA-1273 From Part 1**	**Placebo**
6 to < 12 years		Study Arm 1 (n=375)	Study Arm 2 (n=375)	Study Arm 8 (n=3,000)	Study Arm 9 (n=1,000)
2 to < 6 years	Study Arm 7 (Optional) (n=75)	Study Arm 3 (n=75)	Study Arm 4 (n=75)	Study Arm 10 (n=up to 3,000)	Study Arm 11 (n=up to 1,000)
6 months to < 2 years	Study Arm 5 (n=150)	Study Arm 6 (n=150)		Study Arm 12 (n=up to 3,000)	Study Arm 13 (n=up to 1,000)

After assessing part 1 data in 6 to <12 years old group, 50 ug is used in arm 4 instead of 100 ug

The study will begin with the oldest age group (6 to < 12 year) and age de-escalate. Each age group will begin with Part 1 and advance to Part 2 independently. The mRNA-1273

investigational vaccine or placebo will be administered as 2 intramuscular (IM) injections, approximately 28 days apart.

4.1.1. Part 1, the Open-Label Phase

Part 1 of the study will be open label, dose-escalation and age de-escalation. The study schematic is presented in Figure 1.

The study will include 3 age groups: Group 1 with 750 participants (≥ 6 to < 12 years old) and Group 2 with approximately 225 participants (≥ 2 to < 6 years old) and Group 3 with 300 participants (≥ 6 months to < 2 years old). Up to three dose levels (25 µg , 50 µg and 100µg) will be evaluated in each age group in Part 1. Each age group will begin dosing with the lowest dose planned for that group. Dose escalation and age de-escalation will progress only after confirming the safety of a dose level in each group after each IP injection.

The study will be initiated with enrollment of 375 participants in the 6 to < 12-years age group (Study Arm 1), and dosing with 50 µg of mRNA-1273.

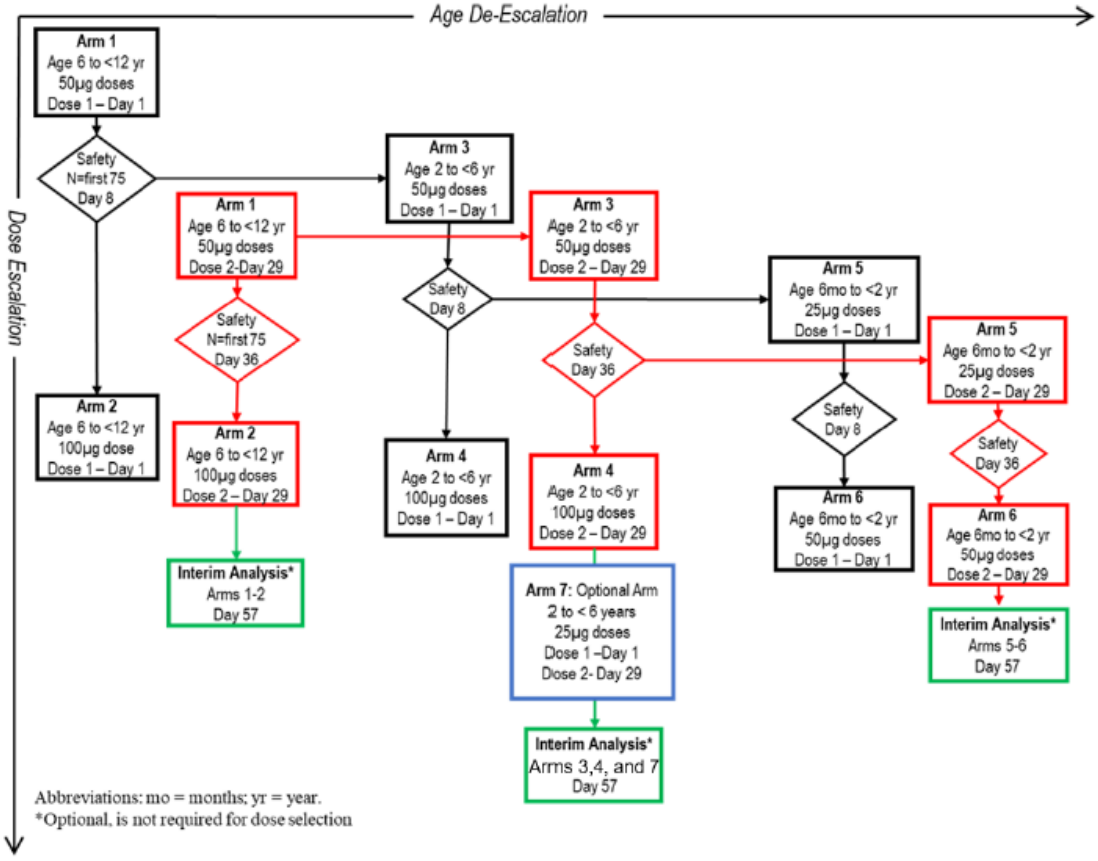
After at least 75 participants in Study Arm 1 have completed Day 8 (1 week after Dose 1 of mRNA-1273 50 µg), an internal safety team (IST) will review the available safety data and provide a recommendation whether to escalate the dose to 100 µg in the 6 to < 12 years age group (Study Arm 2; n = 375) and independently whether to begin dosing at the 50 µg dose level in the 2 to < 6 years age group (Study Arm 3; n = 75). After at least 75 participants in Study Arm 1 reach Day 36 (1 week after Dose 2 of mRNA-1273 50 µg), the IST will again review the available safety data and provide a recommendation whether to administer Dose 2 of mRNA-1273 100 µg in Study Arm 2 and whether to administer Dose 2 of mRNA-1273 50 µg in Study Arm 3. Simultaneously, the enrollment of the remaining 300 planned participants for both Arms 1 and 2 will be ongoing. A preliminary safety and immunogenicity data review of Arm 1, and Arm 2 as applicable, will aid in the selection of a dose level for Part 2. Once all or a subset of participants from each of Study Arms 1 and 2 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the safety and immunogenicity data. Cumulative safety data for approximately 300 participants at the selected dose level will be reviewed by the Data Safety Monitoring Board (DSMB) before enrollment in Part 2, and the DSMB safety review recommendation will enable the expansion of the 6 to < 12 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 8; n = 3,000) or placebo (Study Arm 9; n = 1,000).

Similar analysis as above will apply to other age groups in part 1, details can be found in protocol section 3.1. An optional Arm 7 may be enrolled in middle age group (2 to < 6 years, approximately 75 participants) at the 25 µg dose if the 100 µg dose is eliminated at any point during dose escalation process, to maintain dose ranging for this age group. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2. Once all or a subset of participants in all applicable Arms reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review safety and immunogenicity data. A preliminary safety and immunogenicity data review of all applicable Arms will aid in the selection of a dose level for Part 2 and for expansion of the 2 to < 6 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 10; n = up to 3,000) or placebo (Study Arm 11; n = up to 1,000).

Once all participants in Study Arms 5 and 6 reach Day 57 (1 month after Dose 2 of mRNA-1273), an interim analysis may be conducted to review the tolerability and immunogenicity data at each dose level. A preliminary safety and immunogenicity data review of Arm 5 and Arm 6, as applicable, will aid in the selection of a dose level for Part 2 and allow for expansion of the 6 months to < 2 years age group (Part 2) to receive either mRNA-1273 at the selected dose level (Study Arm 12; n = up to 3,000) or placebo (Study Arm 13; n = up to 1,000). Detail schematic of study arms and process can be found in Section 3.1 from protocol and Figure 1 below.

In general, if a decision is made not to proceed with administration of the higher dose and/or the second injection at a given dose level (eg, due to safety concerns), the participants scheduled to receive the higher dose may receive a lower dose, and the participants who had received the higher dose level as their first injection will likely be given the next lower dose level that was tolerated for their second injection. The dose level not tolerated in the older age group will not be administered in any of the younger age groups. Within an age group, if one of the dose levels is found to have an unacceptable tolerability profile, the age group may progress to Part 2 at a lower dose level.

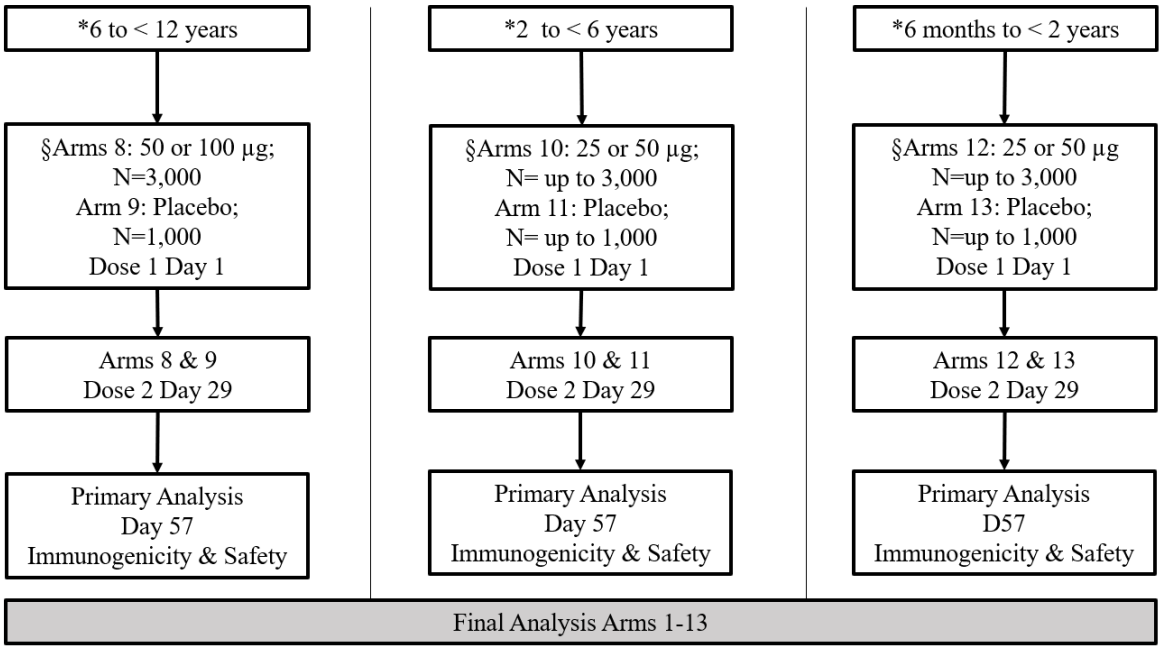
Figure 1 Study Design Schematic, Part 1: Dose-escalation, age de-escalation



4.1.2. Part 2, the Blinded Phase

The blinded phase of the study will be a placebo-controlled observer-blind evaluation of the selected dose in up to 12,000 participants (up to 4,000 participants each in the 6 to < 12 years, 2 to < 6 years, and the 6 months to < 2 years of age groups). No participants in Part 1 will participate in Part 2 of the study. Each age group will begin with Part 1 and advance to Part 2 independently. For each age group, the primary analysis immunogenicity in part 2 will be conducted after the pre-specified Immunogenicity Subset of participants reaches Day 57, and safety analysis will be conducted after a subset or all participants reach Day 57.

Figure 2 Study Design Schematic, Part 2: Expansion



Abbreviations: CMI = cell-mediated immunity; D = Day; S = spike; VTEU = Vaccine and Treatment Evaluation Units.
*Expansion and primary analysis for each age group may occur at different times.
§Participants in each age group will be assigned to one of 5 phlebotomy cohorts. Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity on D1 (prior to randomization and first dose), D57, and one of D29 (prior to the second dose), D209, or D394 (such that each participant provides a total of 3 blood samples only). Participants in the Cohort D (remainder of the age group) will provide a blood sample on D1 (prior to randomization and before the first dose) and within 4 days of receiving Dose 2 at D30 (+3 days) for storage and potential future biomarker testing. A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on D1 (prior to randomization and before the first dose), D43, D209, and D394.

4.2. Sample Size and Power

The initial age groups in Part 1 are for estimation purposes. With approximately 750 participants (approximately 375 participants at each dose level of mRNA-1273) in the initial 6 to < 12 years age group, there is at least a 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% for a given dose level. In each of the younger age groups (2 to < 6 years and 6 months to < 2 years), the safety assessment will occur during the conduct of Part 2 after approximately 400 participants have been exposed to mRNA-1273 at the dose level selected for Part 2. For further details, please refer to protocol section 7.5.2.

The sample size in the expansion (Part 2) is considered to be sufficient to support a safety database in the pediatric participants 6 months to < 12 years of age. With up to 3,000 participants each in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years of age groups exposed to mRNA-1273 at a given dose level in Part 2, the study has at least a 95%

probability to observe at least 1 participant with an AE at a true 0.1% AE rate for a given dose level.

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group will be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset will be processed, and the analysis of primary immunogenicity endpoint will be based on the Immunogenicity PP Subset.

If a threshold of protection is available, for the primary immunogenicity endpoint, with approximately 289 participants on mRNA-1273 in the Immunogenicity PP Subset of an age group, there will be at least 90% power to rule out 70% with a 2-sided 95% CI (lower bound of the 95% CI > 70%) for the percentage of mRNA-1273 participants exceeding the accepted threshold if the true rate of participants exceeding the threshold is 80%.

If an acceptable antibody threshold of protection against COVID-19 is not available at the time of analysis for the primary immunogenicity endpoint, noninferiority tests of the 2 null hypotheses based on the 2 coprimary endpoints will be performed, respectively. The sample size calculation for each of the 2 noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be 90% power to demonstrate noninferiority of the immune response, as measured by the antibody GM value, in pediatric population at a 2-sided alpha of 0.05, compared with that in young adults (18 to 25 years of age) in Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1, a noninferiority margin of 0.67 (or 1.5), and a point estimate minimum threshold of 0.8. The standard deviation of the natural log-transformed levels is assumed to be 1.5.
- With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and young adults (18 to 25 years of age) in Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in children at a 2-sided alpha of 0.05, compared with that in young adults 18 to 25 years of age in Study P301 receiving mRNA-1273, assuming seroresponse rate of 85% in young adults of 18 to 25 years of age from Study P301, true seroresponse rate of 85% in children (or true rate difference is 0 compared to young adults from Study P301), a

noninferiority margin of 10% and a point estimate minimum threshold of -5% in seroresponse rate difference.

- In the 1273-P203 interim analysis (data snapshot on 08 May 2021), the observed seroresponse rates at Day 57 were high in both 18 to 25 years of age group from Study P301 (98.6% with 95% CI: 96.6, 99.6) and 12 to17 years of age group (98.8% with 95% CI: 97.0, 99.7), based on pseudovirus nAb ID50 titers . For this Study P204, if the true seroresponse rates were assumed to be 95% or higher in both 18 to 25 years of age group from Study P301 and an age group in children, with between-group true difference within 4%, there will be a >90% power to demonstrate noninferiority by seroresponse rate in children compared with 18 to 25 years of age in Study P301, at a 2-sided alpha of 0.05.

Assuming approximately 25% of participants in the Immunogenicity Subset will not meet the criteria to be included in the Immunogenicity PP Subset, approximately 528 participants in Part 2 (~396 receiving mRNA-1273 and ~132 receiving placebo) will be selected for the Immunogenicity Subset from which approximately 289 participants on mRNA-1273 will be suitable for the Immunogenicity PP Subset.

4.3. Randomization

Random assignment of participants in Part 2 of the study will use a centralized interactive response technology, in accordance with pregenerated randomization schedules. Up to 4,000 participants each in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years age groups will be randomized in a 3:1 ratio to the mRNA-1273 arm (n = up to 3,000 participants in each group) or placebo arm (n = up to 1,000 participants in each group).

4.4. Blinding and Unblinding

This study is conducted in two parts, 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 participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end, with certain exceptions, please refer to Section 8.1 of the protocol for details.

The final analysis of all endpoints will be performed after all participants (Arm1-13) have completed all planned study procedures.

At the time of interim analysis, only pre-identified Sponsor and unblinded Contract Research Organization (CRO) team members as specified in the study Data Blinding Plan will be unblinded to review treatment level results and individual listings. Please also refer to Section 6.7. Study sites will remain blinded to individual treatment assignments until the end of the study.

If a COVID-19 vaccine is authorized or licensed for a specific age group before the end of the study, please refer to protocol section 3.3 for unblinding and/or cross-over plans.

5. Analysis Populations

The following analysis sets are defined: Randomization Set, Full Analysis Set (FAS), Per-Protocol (PP) Set for Efficacy, Immunogenicity Subset, Per-Protocol (PP) Immunogenicity Subset, Safety Set, Solicited Safety Set, Modified Intent-to-Treat (mITT) Set, Modified Intent-to-Treat-1 (mITT1) Set.

5.1. Randomization Set

The Randomization Set consists of all participants who are randomized in the Part 2 of study, regardless of the participant's treatment status in the study. Participants will be analyzed according to the treatment group to which they were randomized.

5.2. Full Analysis Set

The Full Analysis Set (FAS) for Part 1 consists of all enrolled participants who receive at least 1 injection of IP, and the FAS for Part 2 consists of all randomly assigned participants who receive at least 1 injection of IP. Participants will be analyzed according to the treatment group for the treatment they actually received in Part 1 and will be analyzed according to the treatment group to which they were randomized in Part 2.

5.3. Per-Protocol (PP) Set for Efficacy

The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who meet all the following criteria:

a) Received planned doses of IP per schedule

b) Complied with the 2nd dose injection timing

c) Had no major protocol deviations that impact key or critical efficacy data

d) Had a negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline

The PP Set for Efficacy in both parts will be used as the primary analysis population in the efficacy analyses unless otherwise specified. Participants will be analyzed according to the treatment group for the treatment they actually received in Part 1 and to which they were randomized in Part 2.

5.4. Immunogenicity Subset

A subset of participants in the FAS will be selected for immunogenicity sampling and testing. Participants in Part 1 and 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for analysis.

Immunogenicity Subset consists of

a) a subset of participants in the FAS, and

b) have baseline (Day 1) SARS-CoV-2 status available, and

c) have baseline and at least one post-injection antibody assessment for the analysis endpoint.

Immunogenicity Subset will be used for sensitivity analyses or supportive analysis. Participants will be analyzed according to the treatment group to which they were randomized.

Table 2: Phlebotomy Schedule for Serology, Biomarker Sample, and CMI for Part 2 (Expansion) of the Study

Cohort	Number of subjects		Study Visit Day					
		D1[1,2]	**D29[1]**	**D30 (+3)[3]**	**D43**	**D57**	**D209**	**D394**
Phlebotomy Schedule for Serology: To be Executed Within Age Group								
A	First 176 (132 mRNA-1273: 44 placebo)	X	X			X		
B	Next 176 (132 mRNA-1273: 44 placebo)	X				X	X	
C	Next 176 (132 mRNA-1273: 44 placebo)	X				X		X
D	Remainder of the age group	X		X[3]				
Phlebotomy Schedule for Cell-Mediated Immunity: To be Executed Within Each Age Group at Selected VTEU Sites only								

E (CMI with exploratory serology)	24 (18 mRNA-1273: 6 placebo)	X			X		X	X

Abbreviations: CMI = cell-mediated immunity; D = day; VTEU = Vaccine and Treatment Evaluation Units.
1. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing.
2. If a Day 1 (baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be scheduled for rescreening. Participants may be rescreened 1 time, either within same screening period for Part 1 or Part 2 or in a new screening period for Part 2 if the initial screening was in Part 1. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3.
3. Serum sample from ~4 ml of blood only, to be stored for potential future use for biomarker assessment

5.5. Per-Protocol (PP) Immunogenicity Subset

Per-Protocol (PP) Immunogenicity Subset consists of all participants in Immunogenicity Subset who meet all the following criteria:

a) Received planned doses of IP per schedule

b) Complied with the immunogenicity window based on 2nd dose injection timing

c) Had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline

d) If participants have a diagnosis of HIV, they are not receiving highly active anti-retroviral therapy (HAART)

e) Had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint

f) Had no major protocol deviations that impact key or critical data

The PP Immunogenicity Subset will serve as the primary population for the analysis of immunogenicity data in this study unless specified otherwise. Participants will be analyzed according to the treatment group for the treatment which they actually received in Part 1 and to which they were randomized in Part 2.

5.6. Safety Set

The Safety Set of Part 1 consists of all enrolled participants and of Part 2 consists of all randomized participants who received any study injection. The Safety Set will be used for analysis of safety except for the solicited ARs. In addition, the following Safety Set is defined for each injection separately. The First (Second) Injection Safety Set consists of all subjects in the Safety Set who have received the first (second) study injection. Participants will be included in the vaccination group corresponding to the vaccination they actually

received. For a participant who was randomized to placebo in Part 2 but received any dose of mRNA-1273 at any injection, the participant will be included in the mRNA-1273 group in the Safety Set.

5.7. Solicited Safety Set

The Solicited Safety Set consists of all participants in the safety set who contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the study injection they actually received. In addition, the following Solicited Safety Set is defined for each injection separately.

The First (Second) Injection Solicited Safety Set consists of all subjects in the Solicited Safety Set who have received the first (second) study injection and have contributed any solicited AR data from the time of first (second) study injection through the following 6 days.

Participants will be analyzed according to the vaccination group a participant received, rather than the vaccination group to which the subject was randomized. A participant who was randomized to placebo but received any dose of mRNA-1273 at any injection will be included in the mRNA-1273 group in the Solicited Safety Set.

5.8. Modified Intent-to-Treat (mITT) Set

The Modified Intent-to-Treat (mITT) Set consists of all participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline.

Participants will be analyzed according to the treatment group to which they were randomized.

5.9. Modified Intent-to-Treat-1 (mITT1) Set

The Modified Intent-to-Treat-1 (mITT1) Set consists of all participants in the mITT Set excluding those who received wrong treatment (i.e., at least one dose received that is not as randomized).

Participants will be analyzed according to the treatment group to which they were randomized.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Assessments is provided in Appendix E.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of IP. For immunogenicity tests and nasal swab tests, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of first dose of IP (Day 1).

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that age group and vaccination group within the analysis set of interest, unless otherwise specified.

Baseline SARS-CoV-2 status is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1.

Positive SARS-CoV-2 status at Baseline is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Negative status at Baseline is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid at Day 1.

Study day relative to the first injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection will be calculated as: date of assessment/event – date of the first injection + 1

Study day relative to the most recent injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection but before the second injection (if applicable) will be calculated as: date of assessment/event – date of the first injection + 1;

c) study day on or after the date of the second injection will be calculated as: date of assessment/event – date of the second injection + 1; if study day is on the same day as the second injection, date and time will be compared with the second injection date and time.

For calculation regarding antibody levels/titers, antibody values reported as LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ if actual values are not available, and actual values will be used if available. Missing results will not be imputed.

The following **analysis periods or stages for safety analyses** will be used in this study:

- Up to 28 days after any vaccination: this stage starts at the day of each vaccination and continue through the earliest date of (the day of each vaccination and 27 subsequent days, next vaccination [if applicable]). This analysis period will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

- Follow-up analysis period:

  For unsolicited AE or assessments that will be collected throughout the study, this analysis period starts from 28 days after the last injection date (i.e. the day of last injection + 28 days, regardless of number of injections received) and continues

until the earliest date of (study completion, discontinuation from the study, or death).

For assessments that will be collected at study visits, if a subject receives two injections, this stage starts from the day after Day 57 visit and continues until the earliest date of (study completion, discontinuation from the study, or death); if a subject receives first injection only, this stage starts from the day after Day 29 visit and continues until the earliest date of (study completion, discontinuation from the study, or death).

- Overall period (throughout the study): this analysis period starts at the first injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death).

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- For laboratory assessments, if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (e.g., <0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If

the laboratory results are reported as greater than the ULOQ (e.g., >3000), the numeric values will be imputed by ULOQ in the summary.

- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups:

The following vaccination groups will be used for summary purposes:

- Part 1, Open-Label Phase:
  - mRNA-1273 vaccine 25 μg
  - mRNA-1273 vaccine 50 μg
  - mRNA-1273 vaccine 100 μg
  - mRNA-1273 vaccine Total
- Part 2, Blinded Phase:

  Treatment in Part 2 will be the selected dose level in each of the age groups from Part 1 or Placebo
  - mRNA-1273 vaccine 25 μg, or
  - mRNA-1273 vaccine 50 μg, or
  - mRNA-1273 vaccine 100 μg

  And
  - Placebo

Subjects in an age group who received at least one dose of mRNA-1273 in Part 2 will be included in the mRNA-1273 selected dose level group (as actual treatment) for that age group in Part 2 in the safety analyses.

Summary by age group:

All analyses and data summaries/displays will be provided by vaccination group for each age cohort (6 months to < 2 years, 2 to < 6 years, and 6 to < 12 years), unless otherwise specified. Participants in Part 1 and 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for safety analysis.

Summary by study part:

Separate shells will be provided for Part 1 and Part 2 of the study. In Part 1, all analyses and data summaries/ displays will be provided by age and vaccination group. In Part 2, all analyses and data summaries/ displays will be provided by age and vaccination group.

Analysis Periods

The following analysis periods and treatment groups will be used for efficacy or immunogenicity analyses for Part 2, the blinded phase:

Part 2 Group	Description	Part 2 Blinded Phase Analysis Period for Efficacy or Immunogenicity
mRNA-1273	Participants randomized to mRNA-1273 in the Blinded Phase	From randomization to earliest date of unblinding (date on Participant Decision Visit / Crossover Day 1 or unblinding day inclusive), study discontinuation, study completion, death, and data cutoff date
Placebo	Participants randomized to Placebo in the Blinded Phase	

The following analysis period and treatment groups will be used for safety analysis for Part 2, the blinded phase:

Part 2 Group	Description	Part 2 Blinded Phase Analysis Period for Safety
mRNA-1273	Participants received at least one dose of mRNA-1273 in the Blinded Phase	From the date of 1st injection to the earliest date of unblinding (date on Participant Decision Visit / Crossover Day 1 or unblinding day exclusive), study discontinuation, study completion, death, and data cutoff date
Placebo	Participants only received Placebo in the Blinded Phase	

All analyses will be conducted using SAS Version 9.4 or higher.

6.2. Background Characteristics

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories will be summarized by age and vaccination group as defined in Section 6.1 based on the Full analysis for Part 1 and Randomization Set for Part 2:

- Randomization Set (Part 2)

- Full Analysis Set (Part 1 and Part 2)
- Per-Protocol (PP) Set for Efficacy (Part 1 and Part 2)
- Immunogenicity Subset (Part 1 and Part 2)
- Per-Protocol (PP) Immunogenicity Subset (Part 1 and Part 2)
- Safety Set (Part 1 and Part 2)
- Solicited Safety Set (Part 1 and Part 2)
- mITT Set (Part 1 and Part 2)
- mITT1 Set (Part 1 and Part 2)

The percentage will be based on subjects in that age and vaccination group within the Full Analysis Set for Part 1 and in that age and vaccination group within the Randomization Set (as randomized) for Part 2, except the Solicited Safety Set and Safety Set for which the percentages will be based on the age and vaccination group in the Safety Set (as treated).

The number of subjects in the following categories will be summarized based on subjects screened:

- Number of subjects screened
- Number and percentage of screen failure subjects and the reason for screen failure

The percentage of subjects who screen failed will be based on the number of subjects screened. The reason for screen failure will be based on the number of subjects who screen failed.

The number and percentage of subjects in each of the following disposition categories will be summarized by age and vaccination group based on Full Analysis Set for Part 1 and summarized by age and vaccination group based on the Randomization Set for Part 2:

- Received each dose of IP
- Prematurely discontinued before receiving the second dose of IP and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

A subject disposition listing will be provided, including informed consent, subjects who completed the study injection schedule, subjects who completed study, subjects who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure subjects with reasons for screen failure.

A subject who completed 12 months of follow up after the last injection received is considered to have completed the study.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (months or years), weight (kg, z-score), height (cm, z-score), and body mass index (BMI) (kg/m^2, z-score). Number and percentage of subjects will be provided for categorical variables such as gender, race, ethnicity. The summaries will be presented separately by age and vaccination group as defined in Section 6.1, based on the FAS, Randomization Set (Part 2), Per-Protocol (PP) Set for Efficacy, Immunogenicity Subset, Per-Protocol (PP) Immunogenicity Subset, Safety Set, mITT Set and mITT1 Set.

Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined. If the Safety Set differs from the Randomization Set in Part 2 (e.g., subjects randomized but not received any study injection; subjects received study vaccination other than the vaccination group they were randomized to), the analysis will also be conducted using the Randomization Set.

For screened failure subjects, age (months or years), as well as gender, race, ethnicity will be presented in a listing.

In addition, subjects with any inclusion and exclusion criteria violation will also be provided in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the oldest age group's total mRNA-

1273 group with all dose level combined in Part 1 and the oldest age group's total mRNA-1273 group in Part 2 and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications is summarized in Appendix C Table 4.

The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after each injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by vaccination groups as defined in Section 6.1 as follows:

- Any concomitant medications and non-study vaccination within 7 Days Post Injection
- Any concomitant medications and non-study vaccination within 28 Days Post Injection
- Seasonal influenza vaccine within 28 Days Post Injection
- Antipyretic or analgesic medication within 28 Days Post Injection

A summary table of non-study vaccination that continued or newly received at or after the first injection through 14 days after the last injection will be provided by PT in descending frequency in the mRNA-1273 group with all dose level combined.

A summary table of concomitant medications that continued or newly received at or after the first injection through 28 days after the last injection will be provided by PT in descending frequency of oldest age group's total mRNA-1273 group with all dose level combined in Part 1 and the oldest age group's total mRNA-1273 group in Part 2 .

Prior, concomitant and post medications and non-study vaccination will be presented in a listing.

Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study IP administration data will be presented in a listing.

Study duration will be summarized since randomization, since the first injection, and since the second injection.

6.2.6. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the subjects with each major protocol deviation type will be provided by age and vaccination group as defined in Section 6.1 based on the Full Analysis Set for Part 1 and will be provided by age and vaccination group based on the Randomization Set for Part 2.

Major protocol deviations will be presented in a listing.

6.2.7. COVID-19 Impact

A listing will be provided for COVID-19 impact.

6.3. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to withdrawal from study vaccine and/or study participation, and physical examination findings. Solicited ARs and unsolicited AEs will be coded by SOC and PT according to the MedDRA. Two modified versions of The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) are used in this study for solicited ARs as presented in protocol section 7.4.3's Table 6 and 7 from protocol; Table 6 is the pediatric toxicity scale used for children older than 36 months, and Table 7 is the infant/toddler toxicity scale used for children 6 to 36 months of age, inclusive

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 age and vaccination group unless otherwise specified.

6.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study not before exposure to study vaccine or any event already present that worsens after exposure to study vaccine. [Note: worsening of a pre-existing condition after vaccination will be reported as a new AE.]

Adverse events will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by age and vaccination group, and stage (up to 28 days after any vaccination for Part 1 and Part 2 separately, follow-up analysis period and overall stage (throughout the study); see Section 6.1 for definitions of vaccination group and stage).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT for TEAEs with counts of subjects included. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of oldest age group's total mRNA-1273 group with all dose level combined in Part 1 and oldest age group's total mRNA-1273 group in Part 2 and then alphabetically within SOC. When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Subjects will be presented according to the highest severity (the strongest relationship) in the summaries by severity (of related AEs), if subjects reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of subjects in the Safety Set within each age and vaccination group for Part 1 and Part 2 separately.

6.3.1.1. Incidence of Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of subjects who experience the following will be presented:

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited medically-attended TEAEs

- Any unsolicited TEAEs leading to discontinuation from study vaccine
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited Grade 3/Severe TEAEs
- Any unsolicited Grade 3 or higher TEAEs
- Any unsolicitd Non-serious TEAEs
- Any unsolicited Non-serious and Grade 3/Severe TEAEs
- Any unsolicited Non-serious and Grade 3 or higher TEAEs
- Any AESI of MIS-C
- Any AESI of myocarditis and/or pericarditis
- Any AESI other than MIS-C and myocarditis and/or pericarditis

The table will also include number and percentage of subjects with unsolicited TEAEs that are treatment-related in each of the above categories.

In addition, separate listings containing individual subject adverse event data for unsolicited AEs, unsolicited TEAEs leading to discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, serious AEs, unsolicited medically-attended AEs, AESI other than MIS-C and myocarditis and/or pericarditis, AESI of MIS-C and AESI of myocarditis and/or pericarditis will be provided separately.

6.3.1.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event):

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from study vaccine
- All unsolicited TEAEs leading to discontinuation from participation in the study

- All unsolicited Severe TEAEs
- All unsolicited Severe TEAEs that are treatment-related
- All unsolicited medically-attended TEAEs
- All unsolicited medically-attended TEAEs that are treatment-related
- All AESI of MIS-C
- All AESI of myocarditis and/or pericarditis
- All AESI other than MIS-C and myocarditis and/or pericarditis

6.3.1.3.TEAEs by System Organ Class, Preferred Term and Severity

The following summary tables of TEAEs will be provided by SOC, PT, and maximum severity (mild < moderate < severe) using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related

6.3.2. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term “Solicited Adverse Reactions” refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the subject in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist (i.e., solicited ARs).

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, localized axillary swelling or tenderness ipsilateral to the injection arm, and groin or underarm swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, fever, chills, irritability/crying, sleepiness, and loss of appetite.

The AR categories are different for younger population between Age 37 months to <12 years and Age 6 months to ≤ 36 months. Details presented in Table 6 and 7 in the protocol.

The solicited ARs will be graded based on the grading scales presented in Table 6 and 7 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). Investigator will assess Grade 4 events (with exception of fever).

If a solicited local or systemic AR continues beyond 7 days post injection, the participant's parent(s)/ LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs, whichever occurs first.

All solicited ARs (local and systemic) will be considered causally related to injection.

Analyses of solicited ARs will be provided by age and treatment group for each injection (first or second) based on the associated subset of Solicited Safety Set, i.e. First (Second) Injection Solicited Safety Set; and for any injection based on the Solicited Safety Set, unless otherwise specified.

The number and percentage of subjects who reported each individual solicited local AR (has a toxicity grade of Grade 1 or greater) and solicited systemic AR (has a toxicity grade of Grade 1 or greater) during the 7-day follow-up period after each injection will be tabulated by age group, vaccination group, toxicity grade, and injection. The number and percentage of subjects who reported each individual solicited AR will also be summarized by age group, vaccination group, toxicity grade, days of reporting and injection.

The number and percentage of subjects experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral, axillary, or tympanic route) by toxicity grade will be provided.

A two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of subjects who reported any solicited local AR, solicited systemic AR, or any solicited AR.

The onset of individual solicited AR is defined as the time point after each injection at which the respective solicited AR first occurred. The number and percentage of subjects with onset of individual solicited AR will be summarized by age group, vaccination group, study day relative to the corresponding injection (Day 1 through Day 7), and injection.

The number of days will be calculated as the days of the solicited AR is reported within the 7 days of injection including the day of injection, no matter it is intermittent or continued. If the solicited AR continues beyond 7 days, the consecutive days a solicited AR is reported after 7 days will be included (e.g., an event that lasted 5 days in the first 7 days

post injection and 3 consecutive days beyond 7 days post injection, the duration will be reported as 8 (5+3) days.)

Solicited ARs collected on eDiary and those collected on reactogenicity aCRF will be provided in a listing, and the maximum grade from eDiary and aCRF will be presented. All solicited ARs that continue beyond 7 days post injection will be presented in separate data listings.

6.3.3. Pregnancy Tests

A point-of-care urine pregnancy test will be performed, if deemed appropriate by the investigator, at the Screening Visit and before each vaccine dose in female participants of childbearing potential. At any time during the study, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator. A by-subject listing will be provided for pregnancy tests.

6.3.4. Physical Examinations

A full physical examination, including body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]), length/height, weight and BMI will be presented in a listing.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Immunogenicity Subset for both parts and will be performed for each pediatric age group separately at the selected dose level in Part 1 and Part 2 based on the participants in the PP Immunogenicity Subset. The PP Immunogenicity Subset is the primary analysis population used in the immunogenicity analyses, unless otherwise specified. For each pediatric age group, participants from Part 1 and Part 2 in the PP Immunogenicity Subset who receive the same mRNA-1273 dose level selected for expansion may be combined for immunogenicity analyses. If the same dose level is selected for expansion for more than one age group, these age groups may be combined for immunogenicity analyses.

The GMT and geometric mean (GM) level will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are *n* observed immunogenicity titers or levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity titers or levels within subjects. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for *n* subjects, v_{ij} and v_{ik} are observed immunogenicity titers or levels for subject *i* at time points *j* and *k*, $j \neq k$,where j represent pre-injection baseline at Day 1.

6.4.1. Immunogenicity Assessments

Immunogenicity assessments for both Part 1 and Part 2:

- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays.
- Serum bAb specific to the SARS-CoV-2 S protein.

Immunogenicity assessment for SARS-CoV-2 infection and CMI in Part 2:

- For Part 2, participants in each age group will be assigned to one of 5 phlebotomy cohorts (Table 2). Blood sampling will be performed in 3 of these 5 cohorts for immunogenicity at 3 of the following time points: Day 1 (prior to randomization and the first dose), Day 57, and one of Day 29 (prior to the second dose), Day 209, and Day 394. Participants in the fourth cohort (remainder of the age group) will provide a blood sample at Day 1 only (prior to randomization and the first dose). A fifth cohort of participants at selected VTEU sites only, will provide blood samples for assessment of exploratory serology and CMI on Day 1 (prior to randomization and the first dose), Day 43, Day 209, and Day 394.

6.4.2. Primary Analysis of Antibody-Mediated Immunogenicity Endpoints

If an accepted serum Antibody (Ab) threshold of protection against COVID-19 is available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity objective of this study will be considered to be met for that age group.

The number and percentage of participants with serum Ab greater than or equal to the threshold with 2-sided 95% CI will be provided by age and vaccination group as defined in Section 6.1 at each post baseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum Ab threshold of protection against COVID-19 is not established, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 Ab levels will be compared to that in young adults (18 to 25 years of age) using data from Study P301. An analysis of covariance model will be carried out with Ab at Day 57 as dependent variable and a group variable (a pediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable for each pediatric age group. The GM values of the pediatric age group at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI will be provided to assess the difference in immune response between the pediatric age group (Study P204) compared to the young adults (18 to 25 years of age) in Study P301 at Day 57. For each pediatric age group, the noninferiority of GM value will be considered demonstrated if the lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5 and the GMR point estimate > 0.8 (minimum threshold). In addition, GMR with 95% CI calculated using t-distribution will be provided to assess if the two methods are consistent in the analysis results.

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 57 being of the primary interest. The seroresponse rate difference with 95% CI using the Miettinen-Nurminen (score) confidence limits at Day 57 will be provided between children receiving mRNA-1273 in Study P204 and young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301. For each pediatric age group, the noninferiority of seroresponse rate will be considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is > -10% based on the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

Multiplicity adjustment between age groups:

A sequential hypothesis testing (fixed-sequence method) will be used to adjust multiplicity to preserve the family-wise Type I error rate (alpha = 0.05), starting with the oldest age group, followed by the middle age group, and then followed by the youngest age group. The

immunogenicity coprimary endpoint hypotheses for the oldest age group (6 to < 12 years of age) will be tested first at alpha level of 0.05. If the testing in the oldest age group is statistically significant, the alpha level of 0.05 will be passed to the testing of the coprimary endpoint hypotheses in the middle age group (2 to < 6 years of age). If the testing in the middle age group is statistically significant at alpha level of 0.05, then the alpha 0.05 is preserved for testing the coprimary endpoint hypotheses in the youngest age group (6 months to < 2 years of age). The testing will continue through the sequence only until an endpoint in an age group is not statistically significant, in which case the testing will stop.

6.4.3. Secondary Analysis of Antibody-Mediated Immunogenicity Endpoints

For each group, the following evaluations will be performed at each time point at which blood samples are collected for immunogenicity (unless otherwise specified).

- GM level of anti-SARS-CoV-2-specific bAb 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 values then back transformed to the original scale for presentation. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.
- GM fold-rise (GMFR) of SARS-CoV-2-specific bAb levels with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1. 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 following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

  Proportion of subjects with fold-rise ≥ 2, and fold-rise ≥ 4 of serum SARS-CoV-2 specific bAb levels from Visit Day 1 (baseline) at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs
- GMT of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each time point using the same method mentioned above.
- GMFR of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1 using the same method mentioned above.

Proportion of subjects with fold-rise ≥ 2, and fold-rise ≥ 4 of serum nAb from Visit Day 1 (baseline) at each post-injection time points will be tabulated with 2-sided 95% Clopper-Pearson CIs.

- Proportion of subjects with seroresponse due to vaccination will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint. The definition of seroresponse can be found in section 3.1.
- Per the study protocol, if the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+7 days) as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the window may be extended to Day 29 + 21 days. More rigid visit window will be used in the Per-Protocol Immunogenicity Subset, -7/+14 for Day 29 visit, as appropriate.

6.5. Efficacy Analysis

Efficacy analyses will be performed using the FAS, mITT, mITT1 and PP Set for Efficacy. The mITT1 Set will be the primary analysis set used for efficacy analysis of efficacy endpoints starting from 14 days after first dose, and PP Set for Efficacy will be the primary analysis set used in the efficacy analyses for efficacy endpoints starting 14 days after second dose, unless otherwise specified. Subjects will be included in the treatment group to which they were randomized.

Baseline SARS-CoV-2 status is described in Section 6.1. Baseline SARS-CoV-2 status, the serology test results at baseline, the RT-PCR test results at baseline will be summarized by age group and treatment group.

Participants with baseline positive or missing SARS-CoV-2 status will be excluded from the PP Set for Efficacy Analysis.

In this study, the serology test results and the RT-PCR test results will be summarized by visit.

6.5.1. Endpoint Definition/Derivation

6.5.1.1. Derivation of SARS-CoV-2 Infection

This is a secondary efficacy endpoint, which is a combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at

baseline: the incidence of SARS-CoV-2 infection counted starting 14 days after the second dose of IP will be summarized by treatment group. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:

- bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) post-baseline, OR
- Positive RT-PCR post-baseline.

Derivation of this secondary efficacy endpoint is summarized in Table 3 below.

Table 3. Derivation for SARS-CoV-2 Infection

	Post-baseline assessments		
Baseline SARS-CoV-2 Status	PCR test post baseline	bAb levels against SARS-CoV-2 Nucleocapsid	**Endpoint**: SARS-CoV-2 infection
Negative at Baseline	**Positive** (either at scheduled nasal swab test, or at symptom-prompt nasal swab test)		Case
Negative at Baseline		**Positive** (at scheduled Post baseline visit or later) as measured by *Roche Elecsys*	Case

The date of documented infection will be the earlier of:

- Date of positive post-baseline RT-PCR result, or
- Date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid

The time to the first SARS-CoV-2 infection will be calculated as:

Time to the 1st SARS-CoV-2 infection = Date of the 1st documented infection – Date of randomization + 1. (For Part 1, switch date of randomization to date of 1st injection)

Cases will be counted starting 14 days after the second injection, i.e. date of documented infection – Date of the 2nd injection ≥ 14.

SARS-CoV-2 infection cases will also be summarized based on tests performed at least 14 days after first dose.

6.5.1.2. Derivation of Asymptomatic SARS-CoV-2 Infection

This is a secondary efficacy endpoint: the incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or serology tests obtained post-baseline visits counted starting 14 days after the second injection in participants with negative SARS-COV-2 status at baseline.

Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Specifically:

- Absent of COVID-19 symptoms
- AND at least one from below:
    - bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) post-baseline, OR
    - Positive RT-PCR test post-baseline (at scheduled or unscheduled/illness visits)

The date of documented asymptomatic infection is the earlier date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid due to infection, or positive RT-PCR at scheduled visits, with absence of symptoms.

The time to the asymptomatic SARS-CoV-2 infection will be calculated as:

Time to the asymptomatic SARS-CoV-2 infection = Date of asymptomatic SARS-CoV-2 infection test – Date of randomization + 1. (For Part 1, switch date of randomization to date of first injection)

6.5.1.3 Derivation of CDC Case Definition of COVID-19

This is a secondary efficacy endpoint: the incidence of the first occurrence of cases (CDC Case Definition of COVID-19) starting 14 days after the first dose of IP, and cases starting 14 days after the second dose of IP. CDC Case Definition of COVID-19 is defined as symptomatic disease based on the criteria specified in Section 3.2. Cases are defined as participants meeting clinical criteria based on both symptoms for COVID-19 and positive RT-PCR test results.

Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary. Subjects reporting CDC Case Definition of COVID-19 symptoms, as defined in

Section 7.3.2 of the protocol, will be arranged an unscheduled visit to collect a nasal swab for SARS-CoV-2.

For this efficacy endpoint, a CDC Case Definition of COVID-19 case will be identified as a positive post-baseline RT-PCR test result that is prompted by symptom(s), together with eligible symptoms, i.e. a positive PCR result of the eligible symptoms summarized below in Table 4.

Table 4. Derivation for CDC Case Definition of COVID-19

	COVID-19
Post-baseline PCR results at unscheduled visits prompted by symptom(s)	Positive, **AND**
Systemic Symptoms	at least **ONE** of the following systemic symptoms: Fever (temperature ≥ 38° C/≥ 100.4° F) or chills (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/vomiting, poor appetite/poor feeding; OR
Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours).

The date of documented CDC Case Definition of COVID-19 (case) will be the later date of ([1 systemic symptom reported, or respiratory symptom reported] and, [date of positive PCR test]). Specifically, the date of documented CDC Case Definition of COVID-19 will

be the later date of the following two dates (date of positive PCR test, and the date of eligible symptom(s)), and the two dates should be within 14 days of each other.

- Date of positive PCR test,
- Date of eligible symptom(s), defined as earliest of
    - Respiratory symptom: earliest date of an eligible respiratory symptom is reported
    - Systemic symptoms: earliest date of the eligible systemic symptom is reported

The time to the first occurrence of CDC Case Definition of COVID-19 will be calculated as:

Time to the 1st occurrence of CDC Case Definition of COVID-19 = Date of documented CDC Case Definition of COVID-19 – Date of randomization + 1. (For Part 1, switch date of randomization to date of first injection).

Cases will be counted start 14 days after the 2nd injection, i.e. date of documented CDC Case Definition of COVID-19 - Date of the 2nd injection ≥ 14.

6.5.1.4 Derivation of COVID-19 (P301 Primary Definition)

This is a secondary efficacy endpoint: the incidence of the first occurrence of COVID-19 cases meeting the P301 primary definition, starting 14 days after the first dose of IP, and COVID-19 cases starting 14 days after the second dose of IP.

The P301 primary definition of COVID-19 is defined by the following criteria:

- At least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- At least one positive RT-PCR test for SARS CoV-2

Date of the documented definition of COVID-19 (P301 Primary Definition) will be later date of:

- Date of the positive RT-PCR test (prompt by symptom)
- Date of eligible symptom(s), defined as earliest of
    - Respiratory symptom: earliest date of an eligible respiratory symptom is reported
    - Systemic symptoms: earliest date of the 2nd eligible systemic symptom is reported

and the two dates should be within 14 days of each other.

COVID-19 (P301 Primary Definition) cases will also be summarized based on tests performed after randomization (For Part 1, switch date of randomization to date of first injection).

6.5.2. Analysis Method

The number and percentage of subjects who had an event (i.e. the first asymptomatic SARS-CoV-2 infection) will be summarized in the PP set for Efficacy.

The incidence rate will be provided by age and vaccination group, calculated as the number of cases divided by the total person-time. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

Person-time is defined in Part 2 as the total time from randomization date to the date of event, last date of study participation, censoring time, or efficacy data cutoff date, whichever is earlier. For Part 1, switch randomization date to date of first injection.

6.5.3 Sensitivity and Subgroup Analysis

Sensitivity analysis for these efficacy endpoints will be performed with the same methods described above based on the FAS, mITT Set and mITT1 Set, with cases counted starting from date of first injection in Part 1 and starting from randomization in Part 2. A sensitivity analysis will be performed to include subjects with positive SARS-CoV-2 status at baseline.

Subgroup analysis in Part 1 is not needed and it may be done for Part 2 (or Part 1 +Part 2).

6.6. Exploratory Analysis

6.6.1. Exploratory Analysis of Immunogenicity

The below exploratory analyses of immunogenicity may be performed:

- The genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.
- Descriptive summaries of the ratio or profile of specific S protein bAb relative to nAb in serum during the study. The analysis may not be included in the Clinical Study Report (CSR).
- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study.
- Assess the SARS-CoV-2 S protein-specific T-cell responses in a subset of participants.
- Descriptive summaries of GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x and 4x rise of bAb relative to baseline)
- The seroresponse rate comparisons between children in P204 and young adults (18-25 years of age) in P301 may be performed using the bAb and nAb measures based on assay-specific seroresponse definitions listed in the table below.

The definition of assay-specific seroresponse may depend on assay-specific performance characteristics and may defined as a change from below the LLOQ to equal to or above LLOQ, or a z-fold rise if baseline is equal to or above LLOQ. The table below lists the assay-specific definition of seroresponse for select assay/test with established assay-specific seroresponse definition.

Assay Name	**Category**	**Test Name/ Description**	**Definition of Seroresponse**
Pseudovirus (PsVNT)	nAb	PsVNT50 (ID 50)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 3.3-foldrise

		PsVNT80 (ID 80)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 2.3-foldrise
Anti-Spike ELISA	bAb	Anti-Spike VAC65 Spike IgG Antibody	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 4.6-foldrise
MSD multiplex	bAb	Anti-Spike	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 1.9-foldrise established based on MSD multiplex anti-S by VRC

6.6.2. SARS-CoV-2 Exposure and Symptoms

SARS-CoV-2 reported exposure history and symptoms assessment will be assessed during the study.

The number and percentage of subjects who had close contact with a person with SARS-CoV-2 infection or COVID-19, reasons for exposure, subjects with any symptoms of potential COVID-19, and subjects with each symptoms will be presented by visit, age and vaccination group as defined in Section 6.1. Descriptive statistics will be provided for length of exposure in days by vaccination group.

In addition, the following listings will be provided for subjects infected by SARS-CoV-2:

- Serum bAb level against SARS-CoV-2
- Serum nAb titer against SARS-CoV-2
- Solicited ARs
- Unsolicited AEs

6.7. Interim Analyses

Part 1: Interim analyses may be performed after all or a subset of participants (with immunogenicity samples collected for D1 and D57) have completed Day 57 within an age group in Part 1 (one optional interim analysis for each age group, 3 interim analyses total for the 3 age groups in Part 1). Analyses of safety and immunogenicity may be conducted at each interim analysis.

Part 2: An interim analysis of immunogenicity and safety will be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 1 or

Part 2 within an age group. This interim analysis will be considered the primary analysis of immunogenicity for a given age group. Another interim analysis on safety may be performed after a different subset or all participants have completed Day 57 in an age group.

The final analysis of all endpoints will be performed after all participants have completed all planned study procedures and after the database is cleaned and locked. Results of this analysis will be presented in an end of study CSR, including individual listings.

6.8. 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 meet at pre-specified timepoints during the study to assess safety throughout study conduct. For the 6 to < 12 years age group, the DSMB will review cumulative safety data for approximately 300 participants enrolled at the selected dose level in Part 1 before enrollment begins in Part 2. For both the middle age group (2 to < 6 years) and the youngest age group (6 months to < 2 years) the DSMB will review cumulative safety data in both younger age groups (2 to < 6 years; 6 months to < 2 years) combined and at all dose levels administered in Part 1 before start of Part 2 (blinded phase) for each age group. 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, described in protocol section **Error! Reference source not found.**, 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.

The Cardiac Event Adjudication Committee (CEAC) consisting of pediatric and adult cardiologists will review suspected cases of myocarditis, pericarditis, or myopericarditis to determine if they meet CDC criteria of “probable” or “confirmed” event, and to assess severity and enable the DSMB to make recommendations to the Sponsor to continue vaccine

dosing. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

7. References

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. September2007[cited2019 Apr 10][10 screens].Availablefrom: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

8. List of Appendices

8.1. Appendix A Standards for Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place.

8.2. Appendix B Analysis Visit Windows for Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, i.e. nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 5 below.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 5. Visit Window

Visit	Target Study Day	Visit Window in Study Day
Nasal Swabs for SARS-CoV-2		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43]

Day 57 (Month 2)	57	[44,133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302
Immunogenicity		
Part 1		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 57 (Month 2)	57	[44,133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302
Part 2 where Day 29 is selected		
Day 1	1 (Date of First Injection)	1, Pre-first-dose and prior to the randomization
Day 29	29	[2,43], Pre-second-dose
Day 57	57	[44,133]
Part 2 where Day 209 is selected		
Day 1	1 (Date of First Injection)	1, Pre-first-dose and prior to the randomization
Day 57	57	[44,133]
Day 209	209	[134,301]
Part 2 where Day 394 is selected		
Day 1	1 (Date of First Injection)	1, Pre-first-dose and prior to the randomization
Day 57	57	[44,133]
Day 394	394	≥302

8.3. Appendix A Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless:
     - The medication end date is after the date of first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first injection. In this case, use the date of first injection
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first injection. In this case, use the date of first injection
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication stop date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in Table 4 below.

Table 4. Prior, Concomitant, and Post Categorization of Medications and Non-study Vaccinations

	Medication Stop Date		
Medication Start Date	**< First Injection Date of IP**	**≥ First Injection Date and ≤ 28 Days After Last Injection**	**> 28 Days After Last Injection [2]**
< First injection date of IP [1]	P	P, C	P, C, A
≥ First injection date and ≤ 28 days after last injection	-	C	C, A
> 28 days after last injection [3]	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date
[3] on the day of last injection and the 27 subsequent days

8.4. Appendix B Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:

   - If only Day is missing, use the first day of the month, unless:
     - The AE end date is after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if time is collected.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The AE end date is after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date of first injection

- If Day, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

2. Missing or partial AE end dates will not be imputed.

8.5. Appendix E: Schedule of Events

Visit Number	0	1	2	3	3A	4	4S	5			6			7
Type of Visit	C	C	TMV	C	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1				M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D30	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+3	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	1	7	14	28	-	-	180	-	-	365
Informed consent/assent form, demographics, concomitant medications, medical history	X													
Review of inclusion and exclusion criteria	X	X												
Physical examination including body temperature, length/height, weight, and BMI[7]	X	X		X			X	X			X			X
Pregnancy test[8]	X	X		X										
Randomization		X												
Study injection (including 30-minute postdose observation period)		X		X										

Visit Number	0	1	2	3	3A	4	4S	5			6			7
Type of Visit	C	C	TMV	C	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1				M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D30	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+3	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	1	7	14	28	-	-	180	-	-	365
Blood sample for vaccine immunogenicity (Part 1)[9]		X						X[19]			X[19]			X[19]
Blood sample for vaccine immunogenicity (Part 2)[10]		X		X				X			X			X
Blood sample for exploratory serology and cell-mediated immunity (Part 2)[3,10]		X					X				X			X
Blood sample for potential biomarker analysis (Part 2)[10,11]					X[11]									
Nasal swab sample for SARS-CoV-2[12]		X		X			X	X			X			X
Surveillance for COVID-19/illness visit/ unscheduled visit[13]			X	X		X	X	X	X	X	X	X	X	X
Convalescent visit[14]						X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[15]		X		X										
Review of eDiary data			X			X								
Follow-up safety telephone calls[16]										X			X	
Recording of unsolicited AEs		X	X	X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[17]		X	X	X	X	X	X	X	X		X	X		X

Visit Number	0	1	2	3	3A	4	4S	5			6			7
Type of Visit	C	C	TMV	C	C	TMV	C	C	SFU		C	SFU		C
Month Time Point		M0		M1				M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D-28 to D-1 (Screening)[1]	D1 (Baseline)	D8	D29[2]	D30	D36[2]	D43[2,3]	D57[2, 4]	Every 4 weeks D71 – D183[2, 5]	Every 4 weeks D85– D197[2, 6]	D209[2, 4]	Every 4 weeks D223– D363[2, 5]	Every 4 weeks D237– D377[2, 6]	D394[2, 4]
Window Allowance (Days)	-	-	+ 3	+ 7	+3	+ 3	± 2	+ 7	± 3	± 3	± 14	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28	1	7	14	28	-	-	180	-	-	365
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[17,18]		X	X	X	X	X	X	X	X		X	X		X
Recording of AESIs (eg, MIS-C, myocarditis/pericarditis)[18]		X	X	X	X	X	X	X	X		X	X		X
Recording of concomitant medications and nonstudy vaccinations[17]		X	X	X	X	X	X	X						
Study completion														X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BMI = body mass index; 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; IP = investigational product; IRB = institutional review board; LAR = legally acceptable representative; M = month; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; 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; TMV = telemedicine visit; VTEU = Vaccine and Treatment Evaluation Units.

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, and Day 29) with the approval of the Sponsor.

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. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+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 29 + 21 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. Refer to protocol section **Error! Reference source not found.** for individual participant criteria for delay of study vaccination.
3. To be conducted during Part 2 of the study in a cohort of participants at selected VTEU sites only.

4. 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 telemedicine visit should be conducted in place of the study site visit. The telemedicine visit 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).
5. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
6. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
7. A full physical examination, including body temperature (oral [for participants > 4 years of age] or tympanic [for participants ≤ 4 years of age]), length/height, and weight, will be performed at the Screening Visit or on Day 1. Symptom-directed physical examination will be performed on Day 1, Day 29, Day 43 (if the visit is applicable), Day 57, Day 209, and Day 394 and may be performed at other time points at the discretion of the investigator. Body mass index will be calculated only at Screening Visit. Body temperature (oral/tympanic) should be measured on each injection day prior to injection. 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 (body temperature ≥ 38.0°C/≥ 100.4°F) before injection on Day 1 or Day 29 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.
8. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test and will be performed if deemed appropriate by the investigator. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time during the study.
9. On Day 1, sample must be collected prior to randomization and dosing. If a Day 1 (baseline) blood sample cannot be obtained in Part 1, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be scheduled for rescreening. Participants may be rescreened 1 time, either within the same screening period for Part 1 or for a new screening period for Part 2 later in the study. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3.
10. On Day 1, sample must be collected prior to randomization and dosing. On Day 29, sample must be collected prior to dosing. In Part 2, participants in each age group will be assigned to 1 of 5 phlebotomy cohorts (**Error! Reference source not found.**). Participants in 3 of these 5 cohorts will provide blood specimens for immunogenicity at the following time points: Day 1, Day 57, and one of Day 29, Day 209, or Day 394 (such that each participant provides a total of 3 blood samples only). Participants in the Cohort D (remainder of the age group) will provide a blood sample at Day 1 (prior to randomization and the first dose) and within 4 days of receiving Dose 2 at Day 30 (+3 days) for storage and potential future biomarker testing. A fifth cohort of participants (selected VTEU sites only) will provide blood samples for assessment of exploratory serology and CMI (S protein-specific T-cell responses) on Day 1, Day 43, Day 209, and D394. **Error! Reference source not found.** 2 provides the blood sampling schedule in Part 2 of the study. If a Day 1 (baseline) blood sample cannot be obtained in either Part 1 or Part 2, the participant will be considered either a screen failure due to inability to satisfy inclusion criterion 3 or could be rescheduled for rescreening. Participants may be rescreened 1 time, either within the same screening period for Part 1 or Part 2 or in a new screening period of Part 2 if the initial screening was in Part 1. If the participant is rescreened and a blood sample still cannot be obtained, then he/she will be considered a screen failure due to inability to satisfy inclusion criterion 3.
11. Part 2, Cohort D participants only, one ~4 mL blood draw. For participants already enrolled in Cohort D prior to protocol amendment 4, this blood draw will be optional and confirmed at time of re-consenting; for all participants newly enrolled into Cohort D under amendment 4, it is mandatory.
12. The nasal swab sample (collected before dosing on injection day) will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.
13. 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 (Protocol Section **Error! Reference source not found.**), 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.

14. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis of COVID-19. At this visit, a nasal swab sample for viral RT-PCR and a blood sample for potential immunologic assessment of SARS-CoV-2 infection will be collected.
15. 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. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant's parent(s)/LAR(s) will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolved or the next IP injection occurs, whichever occurs first. Capturing details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
16. 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.
17. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).
18. In addition to MIS-C and myocarditis and/or pericarditis, a list of AESIs pertinent to this study may be referenced in the list of AESIs that 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 (Protocol Section **Error! Reference source not found.**).
19. For Part 1, only the first approximately 75 participants in Arm 1 and Arm 2 will have postbaseline scheduled blood draws;the 300 participants in each of the expansion part of Arm 1 and Arm 2 may have an optional blood draw on Day 57. All participants in Arm 3, 4, 5, 6 and 7 will have postbaseline blood draws on Day 57, Day 209 and Day 394.