CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Trial to Evaluate the Safety and Immunogenicity of Cytomegalovirus Vaccine mRNA-1647 in Healthy Adults
Protocol Number:	mRNA-1647-P202
Sponsor Name:	ModernaTX, Inc.
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Sponsor Contact and Medical Monitor:	PPD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: PPD e-mail: PPD
Regulatory Agency Identifier Number:	Investigational New Drug (IND) number: 17725
Version of Protocol:	Amendment 5
Amendment 5 Date:	27 May 2021
Amendment 4 Date:	22 February 2021
Amendment 3 Date:	04 September 2020
Amendment 2 Date:	15 April 2020
Amendment 1 Date:	04 December 2019
Original Protocol Date:	09 September 2019

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title: A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Trial to Evaluate the Safety and Immunogenicity of Cytomegalovirus Vaccine mRNA-1647 in Healthy Adults

Protocol Number: mRNA-1647-P202

Amendment 5 Date: 27 May 2021

Protocol accepted and approved by:

Please see eSignature and Date in the last page of the document

PPD

Date

PPD

ModernaTX, Inc.

200 Technology Square

Cambridge, MA 02139

Telephone: PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "protocol" 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) Guidance for Industry, E6(R2) Good Clinical Practice (GCP): Consolidated Guidance,* and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without Independent Ethics Committee approval except to eliminate an immediate risk to participants. I agree to administer study vaccine only to participants under my personal supervision or the supervision of a sub-investigator.

I will not supply the study vaccine to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	27 May 2021
Amendment 4	22 February 2021
Amendment 3	04 September 2020
Amendment 2	15 April 2020
Amendment 1	04 December 2019
Original Protocol	09 September 2019

Amendment 5, 27 May 2021: Current Amendment

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts neither the safety or physical/mental integrity of participants nor the scientific value of the study.

Main Rationale for the Amendment:

The purpose of this amendment is to permit unblinding at the participant level after they complete all procedures in P202 to allow for screening for the extension study (mRNA-1647-P202-EXT).

The summary of changes table provided here describes the changes made in Amendment 5 relative to Amendment 4, including the sections modified and the corresponding rationales. The synopsis of Amendment 5 has been modified to correspond to changes in the body of the protocol. Minor editorial and grammatical corrections were also made.

Summary of Major Changes from Protocol Amendment 4 to Protocol Amendment 5:

Section # and Name	Description of Change	Brief Rationale
Title page, Protocol Approval page, page headers	Updated the protocol version and date.	To reflect the new version and date of the protocol.
Section 1.3 Schedule of Assessments and Appendix 2 Additional Schedule of Assessments	Added footnote for study completion to indicate that the participant may be unblinded via the IRT system upon completion of study procedures.	To allow for unblinding at the participant level following end of study procedures to allow for potential inclusion in an extension study (mRNA-1647-P202-EXT).
Section 2.1 Study Rationale	Updated text related to the status of Study mRNA-1647-P101.	To indicate that Study mRNA-1647-P101 has been completed.

Section # and Name	Description of Change	Brief Rationale
Section 2.2.2 Clinical Studies	Updated text related to Study mRNA-1647/mRNA-1443-P101 and added reference to the IB.	To provide details regarding completion of Study mRNA-1647/mRNA-1443-P101.
Section 4.1.3 Follow-up Period	Updated language for immunogenicity sampling timepoints.	To allow flexibility based on differences in schedule of events for participants completing the first 2 vaccinations only. Note: Month 8, defined as Day 252 and should have been labeled “Month 9” and Month 14, defined as Day 420 should have been labeled “Month 15.”
Section 4.6 End of Study Definition	Updated language for final visit.	To allow flexibility based on differences in schedule of events for participants completing the first 2 vaccinations only. Note: Month 8, defined as Day 252 and should have been labeled “Month 9” and Month 14, defined as Day 420 should have been labeled “Month 15.”
Section 6.3.2 Blinding	Added language to allow for participant level unblinding after the participant completes all procedures in this study and justification for unblinding.	To allow for unblinding at the participant level following end of study procedures to allow for potential inclusion in an extension study (mRNA-1647-P202-EXT).
Section 7.1 Discontinuation of Vaccination	Updated language for immunogenicity sampling timepoints.	To allow flexibility based on differences in schedule of events for participants completing the first 2 vaccinations only. Note: Month 8, defined as Day 252 and should have been labeled “Month 9” and Month 14, defined as Day 420 should have been labeled “Month 15.”
Section 8.9.2 Recording of Adverse Events, Serious Adverse Events, and Medically-attended Adverse Events	Added instruction for follow-up of all AEs and SAEs.	To provide instructions for following AEs and SAEs until resolution, stabilization, otherwise explained, or lost to follow-up.

Section # and Name	Description of Change	Brief Rationale
Section 8.11 Unblinding	Added language to allow for participant level unblinding after the participant completes all procedures in this study and provided instruction for unblinding.	To allow for unblinding at the participant level following end of study procedures to allow for potential inclusion in an extension study (mRNA-1647-P202-EXT).
Section 9.1 Responsibility of Analyses/Blinding	Added reference to Section 8.11.	To further reference the unblinding procedures.
Section 10.2 Study Monitoring	Added language to allow CRA unblinding after participant completes study procedures.	To allow for unblinding at the participant level following end of study procedures to allow for potential inclusion in an extension study (mRNA-1647-P202-EXT).

IRB and Regulatory Authority Approval

A copy of this amended protocol will be sent to the institutional review board (IRB) and regulatory authority.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit a revised informed consent for approval that incorporates the changes described in this amended protocol.

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1647

Protocol Title: A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Trial to Evaluate the Safety and Immunogenicity of Cytomegalovirus Vaccine mRNA-1647 in Healthy Adults

Protocol Number: mRNA-1647-P202

Phase of Development: Phase 2

Regimen and Dosing: A 0.5 mL volume of mRNA-1647 vaccine or 0.9% sodium chloride injection (USP) (normal saline) placebo will be administered by intramuscular (IM) injection in a 3-vaccination (0, 2, 6-month) schedule. Participants will be randomized in a sequential manner into one of 3 arms evaluating different dose levels CCI [redacted] in Part 1 and the CCI [redacted] dose level in Part 2.

Objectives	Endpoints
Primary	
• To evaluate the safety of different dose levels of mRNA-1647 vaccine administered in a 3-vaccination (0, 2, 6-month) schedule. • To evaluate neutralizing anti-cytomegalovirus (CMV) antibody responses against fibroblast and epithelial cell infection following vaccination with mRNA-1647 at different dose levels administered in a 3-vaccination (0, 2, 6-month) schedule.	• Solicited local and systemic adverse reactions (ARs) through 7 days after each vaccination. • Unsolicited adverse events (AEs) through 28 days after each vaccination. • Medically-attended adverse events (MAAEs) through 6 months after the last vaccination, and serious adverse events (SAEs) throughout the entire study period. • Geometric mean titer (GMT) of serum neutralizing anti-CMV antibodies against epithelial cell infection and against fibroblast infection and associated geometric mean ratio (GMR) of post-baseline/baseline titers at each timepoint.

	• Proportion of participants with ≥ 2-fold, 3-fold, and 4-fold increases in neutralizing antibody (nAb) over baseline against epithelial cell infection and against fibroblast infection at each timepoint.
Secondary	
• To evaluate antigen-specific antibody responses following vaccination with mRNA-1647 at different dose levels in a 3-vaccination schedule. • To evaluate the immunogenicity of mRNA-1647 by CMV serostatus at enrollment.	• GMT of anti-glycoprotein B (gB) specific immunoglobulin (Ig) G and anti-Pentamer specific IgG as measured by enzyme-linked immunosorbent assay (ELISA), and associated GMR of post-baseline/baseline titers at each timepoint. • GMT, GMR, and proportion of participants with ≥ 2-fold, 3-fold, and 4-fold increases over baseline of serum nAb against epithelial cell infection and against fibroblast infection at each timepoint, and GMT and GMR of antigen-specific IgG (ELISA) at each timepoint, in the CMV-seropositive group and in the CMV-seronegative group.
Exploratory	
• To evaluate cell-mediated immune responses following vaccination with mRNA-1647 at different dose levels. • In CMV-seropositive participants, to assess possible effects of immunologic response following vaccination with mRNA-1647 compared to placebo.	• gB- and Pentamer-specific interferon (IFN)-γ-secreting T-cell responses as measured by enzyme-linked immunospot (ELISpot) assay. • Exploratory assays to assess for anti-CMV immunologic response or for primary CMV infection may be performed at the discretion of the Sponsor.

Overall Design:

This is a Phase 2, randomized, placebo-controlled, observer-blind, dose-finding trial enrolling healthy participants 18-40 years of age. CMV-seronegative and CMV-seropositive groups will be enrolled at the same time. Randomization will be stratified by CMV serostatus (via an Interactive Response Technology [IRT]) in a sequential manner into the CCI dose levels in Part 1 and the CCI dose level in Part 2. At each dose level, participants will be randomized in 3:1 ratio to either mRNA-1647 vaccine or placebo, administered in a 3-vaccination (0, 2, 6-month) schedule.

As the appearance of vaccine and placebo differs, enrollment will be observer-blind as to treatment assignment.

Treatment Arms:

Part 1 CMV-seronegative Group (males and females aged 18-40 years)

- Approximately 60 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 60 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 60 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

Part 1 CMV-seropositive Group (males and females aged 18-40 years)

- Approximately 24 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 24 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 24 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

Part 2 CMV-seronegative Group (females aged 18-40 years)

- Approximately 80 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

Part 2 CMV-seropositive Group (females aged 18-40 years)

- Approximately 120 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

Number of Participants:

Approximately 452 participants will be enrolled, including 252 participants in Part 1 (approximately 180 CMV-seronegative participants and approximately 72 CMV-seropositive participants) and 200 participants in Part 2 (approximately 80 CMV-seronegative participants and approximately 120 CMV-seropositive participants).

The Sponsor may enroll up to 502 participants including 252 participants in Part 1 (approximately 180 CMV-seronegative participants and approximately 72 CMV-seropositive participants) and 250 participants in Part 2 (approximately 100 CMV-seronegative participants and approximately 150 CMV-seropositive participants).

Inclusion Criteria:

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

1. Age and sex
   - Part 1: Male or female 18-40 years of age at time of consent.
   - Part 2: Female 18-40 years of age at time of consent.
2. Understands and agrees to comply with the trial procedures and provides written informed consent.
3. According to the assessment of the Investigator, is in good general health and is capable of complying with trial procedures.
4. Body mass index (BMI) 18-35 kg/m^2.
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to Screening without an alternative medical cause). A follicle-stimulating hormone (FSH) level may be measured at the discretion of the Investigator to confirm postmenopausal status.
6. Female participants of childbearing potential may be enrolled in the study if the participant: 1) has a negative pregnancy test at Screening and on the day of the first vaccination, and 2) has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first vaccination, and 3) has agreed to continue adequate contraception through 3 months following the last vaccination, and 4) is not currently breastfeeding.

Adequate female contraception is defined as consistent and correct use of a US Food and Drug Administration (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 oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male participants engaging in activity that could result in pregnancy of sexual partners must agree to practice adequate contraception from the time of the first vaccination and through 3 months after the last vaccination.

Adequate contraception for male participants is defined as:

- Monogamous relationship with a female partner using an intrauterine device or hormonal contraception (described above)
- Use of barrier methods and spermicide
- History of surgical sterilization

Male participants with partners who have become pregnant prior to randomization are eligible to participate in the study.

Exclusion Criteria:

Participants eligible for this study must not meet any of the following criteria:

1. Acutely ill or febrile (temperature ≥ 38.0°C/100.4°F) on the day of the first vaccination. Participants meeting this criterion may be rescheduled within the enrollment window period. Afebrile participants with minor illnesses can be enrolled at the discretion of the Investigator.
2. Prior receipt of any CMV vaccine.
3. Positive for hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibody, or human immunodeficiency virus (HIV) type 1 or 2 antibodies at Screening.
4. Screening coagulation tests (prothrombin time [PT] or partial thromboplastin time [PTT]) with a toxicity grade of ≥ 1. Retesting of PT and/or PTT will be allowed once in an otherwise eligible participant.

5. Other than coagulation tests as described above, has a screening laboratory result with a toxicity score ≥ Grade 2. No repeat testing is allowed for these screening laboratory tests.
6. Diagnosis or condition that, in the judgment of Investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to trial procedures, including:
   - Congenital or acquired immunodeficiency (including HIV infection)
   - Diagnosed or suspected immunosuppressive condition or immune-mediated disease
   - Chronic hepatitis
   - Dermatologic conditions that could affect local solicited AR assessments
   - History of anaphylaxis, urticaria, or other significant reaction requiring medical intervention after receipt of a vaccine
   - History of bleeding disorder that is considered a contraindication to IM injection or phlebotomy
   - History of malignancy within the previous 10 years (excluding non-melanoma skin cancer)
   - Any psychiatric or occupational condition that, in the opinion of the Investigator, might pose an additional risk due to participation in the study or can interfere with the interpretation of study results
7. Has received or plans to receive a vaccine ≤ 28 days prior to the first vaccination or plans to receive a non-study vaccine within 28 days prior to or after any study vaccination, except for any licensed influenza vaccine, which can be administered >14 days before or after any study vaccination. COVID-19 vaccines (regardless of manufacturer) may be administered > 7 days but preferably > 14 days before or after any study vaccination, with the intention of prioritizing COVID-19 vaccination over all other considerations.
8. Received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the day of enrollment. Inhaled, nasal, and topical steroids are allowed.
9. Receipt of intravenous immunoglobulins or plasma products within 3 months prior to the day of the first study vaccination.
10. Part 1 participants only: Previous receipt of medications in lipid nanoparticle (LNP) formulation.
11. Has donated ≥ 450 mL of blood products within 28 days of the Screening visit. Participants engaging in blood sampling for cell-mediated immunogenicity should be advised to refrain from blood donation through the vaccination period (Day 1 through Month 7)
12. Participated in an interventional clinical trial within 28 days prior to the day of enrollment or plans to do so while enrolled in this trial.

13. Is an immediate family member or household member of trial personnel.
Investigational Product, Dosage, and Mode of Administration: mRNA-1647 vaccine consists of 6 messenger ribonucleic acid (mRNA) drug substances in an LNP formulation. The vaccine is provided as 520 µg of lyophilized product in glass vials and stored at -25°C to -15°C (-13°F to 5°F) until use. The lyophilized vaccine will be reconstituted with 0.6 mL of 0.9% sodium chloride injection (USP), then diluted with tris sucrose Diluent SD-0724 to a concentration for delivery of the specified dose level in a volume of 0.5 mL. Vaccines will be administered intramuscularly into the deltoid muscle.
Estimated Study Duration: Approximately 18 months for each participant.
Reference Therapy, Dosage, and Mode of Administration: Placebo consisting of a 0.9% sodium chloride injection (USP) will be administered intramuscularly in a volume of 0.5 mL.

Criteria for Evaluation:

Safety Assessments

1. Solicited local (injection site pain, erythema [redness], and swelling/induration [hardness]; and localized axillary swelling or tenderness ipsilateral to the vaccination arm) and systemic (headache, fatigue, myalgia [muscle aches all over the body], arthralgia [aching in several joints], nausea/vomiting, rash, fever, and chills) ARs occurring during the 7 days following each vaccination (ie, the day of vaccination and 6 subsequent days). Solicited ARs will be recorded daily using electronic diaries (eDiary).
2. Unsolicited AEs observed or reported during the 28 days following each vaccination (ie, the day of vaccination and 27 subsequent days). Unsolicited AEs are AEs that are not included as part of the protocol-defined solicited ARs. Unsolicited AEs will be collected during follow-up visits and follow-up safety calls.
3. Laboratory test abnormalities at Day 1, Day 8, Day 29, Day 56, Day 63, Day 84, Day 168, Day 175, and Day 196.
4. MAAEs from Day 1 through Day 336 (or through 6 months after last study vaccination).
5. SAEs from time of informed consent through the end of the study (Day 504).

Immunogenicity Assessments

6. Serum neutralizing anti-CMV antibody titers against epithelial cell infection on Day 1, Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504, and GMR of post-baseline/baseline titers.
7. Serum neutralizing anti-CMV antibody titers against fibroblast infection on Day 1, Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504, and GMR of post-baseline/baseline titers.
8. Proportion of participants with $\geq$ 2-fold, 3-fold, and 4-fold increases in nAb against epithelial cell infection on Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504, compared with Day 1.
9. Proportion of participants with $\geq$ 2-fold, 3-fold, and 4-fold increases in nAb against fibroblast infection on Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504, compared with Day 1.
10. Proportion of participants with nAb against epithelial cell infection above nAb titers associated with natural CMV infection at Day 1, Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504.

11. Proportion of participants with nAb against fibroblast infection above nAb titers associated with natural CMV infection at Day 1, Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504.
12. GMT of anti-gB IgG as measured by ELISA on Day 1, Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504, and GMR of post-baseline/baseline titers.
13. GMT of anti-Pentamer IgG as measured by ELISA on Day 1, Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504, and GMR of post-baseline/baseline titers.

Pharmacodynamic Assessments: Not applicable.

Pharmacokinetic Assessments: Not applicable.

Statistical Methods:

Analysis Populations

Analysis Set	Description
Randomized Set	All participants who are randomized in the study, regardless of the participant's treatment status in the study.
Solicited Safety Set	All randomized participants who received any study vaccination, and contribute any solicited AR data (ie, have at least one post-baseline solicited safety (eDiary) 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 vaccination they actually received.
Safety Set	All randomized participants who received any study vaccination. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the vaccination group corresponding to the study vaccination they actually received for the analysis of safety data using the Safety Set.
Full Analysis Set (FAS)	All randomized participants who a) receive any study vaccination, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least one post-vaccination assessment for the analysis endpoint. Participants will be included in the vaccination group to which they are randomized.
Per Protocol (PP) Set	All FAS participants who a) comply with the vaccination schedule, b) comply with the timings of immunogenicity blood sampling to have post-vaccination results available for at least one assay component corresponding to the immunogenicity analysis objective, and c) have no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective.

	The PP Set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the vaccination group to which they are randomized.

Power and Sample Size

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1647. Approximately 252 participants will be enrolled in Part 1 of the study with approximately 189 participants randomized to mRNA-1647 vaccine. With 189 participants, there is > 95% probability to observe at least one participant with an AE if the true incident of the AE is 2%. Approximately 200 participants will be enrolled in Part 2 of the study with approximately 150 participants randomized to CCI of mRNA-1647. With 150 participants who are randomized to receive CCI of mRNA-1647, there is > 90% probability to observe at least one participant with an AE if the true incident of the AE is 2%.

Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) for Adverse Reaction Terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for rash.

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 CMV serostatus (CMV-seropositive and CMV-seronegative) and vaccination group, unless otherwise specified.

Local and systemic solicited ARs will be tabulated by number and percentage of participants reporting ≥ 1 event. 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 vaccination will be provided with a two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method. Unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be reported by number and percentage of participants reporting ≥ 1 event, and number of events.

For all other safety parameters, descriptive statistics will be provided.

The number and percentage of participants who have chemistry, hematology, and coagulation results below or above the laboratory normal ranges will be tabulated at each timepoint.

Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP Set and will be by serostatus group. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the anti-CMV nAb titers, GMT with corresponding 95% CI at each timepoint and GMR with corresponding 95% CI at each post-baseline timepoint over pre-vaccination (eg, baseline) will be provided by serostatus and vaccination group. Descriptive summary statistics including median, minimum, and maximum will also be provided.

The number and percentage of participants with $\geq$ 2-fold, 3-fold, and 4-fold increases in serum anti-CMV nAb titers from baseline will be provided with two-sided 95% CI using Clopper-Pearson method at each post-baseline timepoint.

Planned Analyses

The following analyses will be conducted on cleaned data, and may be combined depending on study timelines.

1. An interim analysis of safety and immunogenicity data collected from Visit Day 1 through Day 84 (Month 3) was planned for Part 1. Due to the COVID-19 pandemic, this interim analysis was performed based on a subset of participants who have completed 3 months of safety and immunogenicity assessments as of 26 May 2020. This analysis will serve as the basis for selection of the mRNA-1647 dose level for implementation in Part 2 and in subsequent trials. Additional analyses of safety and immunogenicity data collected from Visit Day 1 through Day 84 (Month 3) may be performed for all participants in Part 1 and for all participants in Part 2 after all participants in Part 2 have completed 3 months of assessments, and available safety or immunogenicity data up to Day 196 (Month 7) may also be summarized as part of these interim analyses. Pre-identified Sponsor team members will be unblinded to group treatment level results. Participants, Investigators, and study sites will remain blinded.
2. The 7-month interim analyses of safety and immunogenicity data collected from Visit Day 1 through Day 196 (Month 7) may be performed for each dose level of Part 1 and for Part 2. Available safety or immunogenicity data up to Day 336 (Month 12) may also be summarized as part of these interim analyses. Pre-identified Sponsor team members will

be unblinded to group treatment level results and individual listings. Participants, Investigators, and study sites will remain blinded.

3. The final unblinded analysis of safety and immunogenicity data collected from Visit Day 1 through the end of the trial will be conducted when the database is cleaned and locked. Results of this analysis will be presented in a clinical study report (CSR), including individual listings.

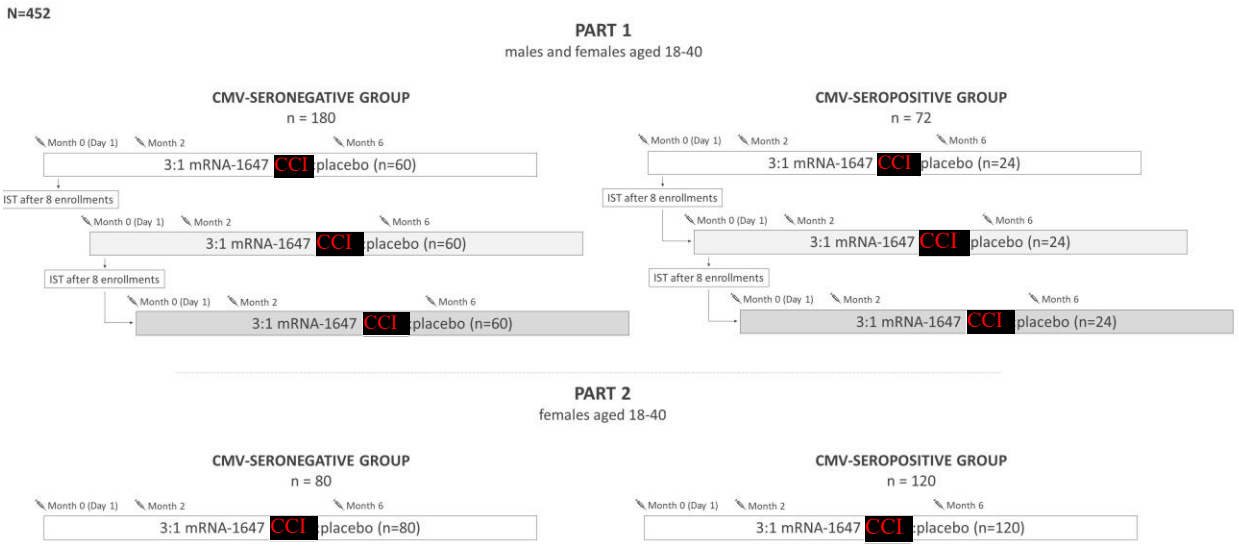
Study Safety Oversight

Participant safety will be primarily monitored by a blinded Internal Safety Team (IST) with ad hoc safety reviews by an unblinded independent Safety Monitoring Committee (SMC). Details regarding composition, responsibilities and procedures of the IST and the SMC will be presented in the respective charters. The IST will provide primary safety oversight at defined intervals through completion of enrollment and vaccine administration, including the review of available safety data to authorize initiation of Dose Level 2 CCI and Dose Level 3 CCI in Part 1.

In Part 1, scheduled IST reviews will be held for the CMV-seropositive and CMV-seronegative groups separately and will occur at each dose level after the first 8 participants in the respective group complete Day 8. In Part 2, the SMC will be convened on an ad hoc basis if a safety signal emerges.

1.2. Schema

Figure 1: Study Schema



Abbreviations: IST = internal safety team; mRNA = messenger ribonucleic acid.

1.3. Schedule of Assessments

Table 1: Schedule of Events for Participants Completing all Vaccinations[1,13]

Visit Number	0[2]		1	2	3	4[14]	5	6	7-8	9	10	11	12-15	16	17
Month Timepoint			M0		M1	M2		M3	M4-5	M6		M7	M8-11	M12	M18
Type of Visit	C		C	C	C	C	C	C	SC	C	C	C	SC	C	C
Study Visit Day	Part 1 D-27 to D0 (Screening)	Part 2 SN D-27 to D0 / SP D-41 to D0	D1 (Baseline)	D8	D29	D56	D63	D84	D112 D140	D168	D175	D196	D224 D252 D280 D308	D336	D504
Window Allowance (Days)			–	+3	± 7	± 7[14]	+3	-7 to +21	± 7	± 7	+3	± 7	± 7	± 7	± 7
Days Since Most Recent Vaccination (except M6/D168 visit should be based on D1)	-		0	7	28	55/0	7	28	56, 84	167/ 0	7	28	56, 84, 112, 140	168	336
ICF, demographics, inclusion/exclusion criteria, concomitant medications, non-study vaccinations, medical history[2]	X														
Physical examination[3]	X		X	X	X	X	X	X		X	X	X		X	
Vital signs[4]	X		X	X	X	X	X	X		X	X	X		X	
Pregnancy testing[5]	X		X			X				X					
Randomization			X												
Blood for Screening/safety labs[6,7,8]	X		X	X	X	X	X	X		X	X	X			
Blood for antibody-mediated immunogenicity[8]			X		X	X		X		X		X		X	X
Blood for cell-mediated immunogenicity[8, 12]			X	X		X	X			X	X			X	X

Visit Number	0[2]		1	2	3	4[14]	5	6	7-8	9	10	11	12-15	16	17
Month Timepoint			M0		M1	M2		M3	M4-5	M6		M7	M8-11	M12	M18
Type of Visit	C		C	C	C	C	C	C	SC	C	C	C	SC	C	C
Study Visit Day	Part 1 D-27 to D0 (Screening)	Part 2 SN D-27 to D0 / SP D-41 to D0	D1 (Baseline)	D8	D29	D56	D63	D84	D112 D140	D168	D175	D196	D224 D252 D280 D308	D336	D504
Window Allowance (Days)			–	+3	± 7	± 7[14]	+3	-7 to +21	± 7	± 7	+3	± 7	± 7	± 7	± 7
Days Since Most Recent Vaccination (except M6/D168 visit should be based on D1)	-		0	7	28	55/0	7	28	56, 84	167/ 0	7	28	56, 84, 112, 140	168	336
Study vaccination (including 60-minute post-dosing observation period)			X			X				X					
eDiary activation for recording solicited ARs (7 days)[9]			X			X				X					
Review of eDiary				X			X				X				
Follow-up safety calls[10]									X				X		
Recording of unsolicited AEs			X	X	X	X	X	X		X	X	X			
Recording of concomitant medications and non-study vaccinations[11]			X	X	X	X	X	X	X[15]	X	X	X	X[15]	X[15]	X[15]
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[11]			X	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[11]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion[16]															X

Abbreviations: AE = adverse event; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease-2019; D = day; eDiary = electronic diary; EUA = Emergency Use Authorization; FDA = US Food and Drug Administration; ICF = informed consent form; M = month; MAAE = medically-attended adverse event; SAE = serious adverse event; SC = safety (phone) call; SN = seronegative participants; SP = seropositive participants.

[1] Please refer to Section 7.1, Table 6 and Table 7 (Appendix 2) for participants not completing all vaccinations.

[2] Based on prior approval from the Sponsor, the Screening visit may be performed across 2 separate clinic visits. In Part 1, screening may occur up to 28 days prior to Visit Day 1. In Part 2, the screening window is 28 days (Days -27 to 0) for CMV-seronegative participants and 42 days (Days -41 to 0) for CMV-seropositive participants.

[3] Physical examination: a full physical examination, including height and weight, will be performed at Screening; symptom-directed physical examinations will be performed at all other scheduled timepoints. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified during a study visit should be reported as a MAAE.

[4] Vital signs to be collected pre and post-dosing on days of vaccination (Day 1, Day 56, and Day 168).

[5] Pregnancy test at Screening will be included in blood testing; pregnancy testing before each study vaccination (or at any time at the discretion of the Investigator) will be a point-of-care urine test.

[6] Screening laboratory tests:

- CMV IgG with reflex to IgM
- Serology: HBsAg, hepatitis C virus antibody, HIV type 1 and 2 antibodies
- Hematology: hemoglobin, platelet count, and total and differential white blood cell count
- Chemistry: alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, creatinine, random glucose
- Coagulation: PTT and PT
- FSH level may be measured to confirm menopausal status at the discretion of the Investigator.

[7] Safety laboratory tests:

- Hematology: hemoglobin, platelet count, total and differential white blood cell count
- Chemistry: AST, ALT, total bilirubin, creatinine
- Coagulation: PTT and PT

[8] Sample must be collected prior to dosing on days of vaccination (Day 1, Day 56, and Day 168).

[9] eDiary entries will be recorded by the participant at approximately 1 hour after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the diary each day after they leave the clinic, preferably in the evening, on the day of vaccination and for 6 days following vaccination. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit.

[10] Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, information on concomitant medications associated with those events, and any vaccinations.

[11] All non-study vaccinations administered during the period starting ≤ 28 days before the first dose of study vaccine, and all concomitant medications and non-study vaccinations through 28 days after each vaccination will be recorded;, COVID-19 vaccination (regardless of type of vaccine) will be recorded anytime from Day 1 through the End of the Study (Day 504); all concomitant medications relevant to or for the treatment of an SAE will be recorded from Screening through the End of Study (Day 504), and all concomitant medications relevant to or for the treatment of a MAAE will be recorded from Visit 1 (Day 1) through Day 336.

[12] Blood for exploratory cell-mediated immunogenicity will be collected for a subset of up to 16 participants (approximately 8 CMV-seropositive and 8 CMV-seronegative) for each dose level. The Sponsor will allocate clinical sites to enroll participants in this subset. Participants engaging in blood sampling for cell-mediated immunogenicity should be advised to refrain from blood donation through the vaccination period (Day 1 through Month 7).

[13] All scheduled study visits should be completed within the defined visit window. Timing of Dose 3 is calculated in relation to Dose 1 (Day 1) and should not shift later than 167 days (± 7 days) after Day 1; succeeding follow-up visits (Visits 10-17) are scheduled in relation to Dose 3. In the event the participant is not able to come on site for a clinic visit 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”), a safety call to the participant should be made in place of the clinic visit. The safety call 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 calls at Visits 12-15). Home visits will be permitted for all non-dosing visits in the event a participant cannot make it to the clinic as a result of the COVID-19 pandemic. Home visits must be permitted by the site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).

[14] In the event the visit for Dose 2 is disrupted and cannot be completed at Day 56 ± 7 days as a result of the COVID-19 pandemic (COVID-19 vaccination under the FDA EUA or FDA approval, 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 56 + 56 days (i.e., to 4 -months). When the extended window is utilized, the Day 84 visit is to be completed at 28 (-7 to +21) days after Dose 2 and monthly safety calls should occur every 28 days ± 7 days until the Month 6 visit (Day 168) for Dose 3. Dose 3 timing should continue to be based on Dose 1 and should not be adjusted if Dose 2 occurs in the extended dosing window (Dose 3 should not shift later than 167 days [± 7 days] after Day 1); succeeding follow-up visits (Visits 10-17) are scheduled in relation to Dose 3.

[15] Only documentation of COVID-19 vaccine is required.

[16] Upon completion of final study procedures, including the final assessment and recording of MAAEs and SAEs, the participant's treatment assignment may be unblinded via the IRT system.

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LIST OF ABBREVIATIONS

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

Abbreviation or Specialist Term	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate aminotransferase
BMI	Body mass index
cCMV	Congenital cytomegalovirus
CFR	Code of Federal Regulations
CI	Confidence interval
CMV	Cytomegalovirus
COVID-19	Coronavirus disease-2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical study report
eCRF	Electronic case report form
eDiary	Electronic diary
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	US Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
gB	Glycoprotein B
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Definition
GMR	Geometric mean ratio
GMT	Geometric mean titer
HBsAg	Hepatitis B virus surface antigen
HCP	Healthcare practitioner
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST	Internal Safety Team
LNP	Lipid nanoparticle
MAAE	Medically-attended adverse event
mRNA	Messenger ribonucleic acid
nAb	Neutralizing antibody
PP	Per-protocol
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious adverse event
SAP	Statistical analysis plan
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
US	United States

2. INTRODUCTION

2.1. Study Rationale

The purpose of this Phase 2 randomized, observer-blind, placebo-controlled, dose-finding study is to evaluate the safety and immunogenicity of messenger ribonucleic acid (mRNA)-1647 in healthy adults who are either cytomegalovirus (CMV)-seronegative or CMV-seropositive at enrollment. Results from this study will be used to inform the dose level for subsequent clinical development of mRNA-1647 (see Section 2.2.2).

This is the first study evaluating a vaccine using the Sponsor's technology platform in a lyophilized presentation. A Phase 1, first-in-human (FIH), randomized, observer-blind, placebo-controlled, dose-ranging study (Study mRNA-1647/mRNA-1443-P101) in CMV-seronegative and CMV-seropositive healthy adults to evaluate the safety and immunogenicity of different doses of mRNA-1647 injection in a liquid presentation has been completed.

Study mRNA-1647-P202 will assess safety and immunogenicity of the lyophilized presentation in CMV-seronegative and CMV-seropositive groups prior to a planned large-scale safety and clinical efficacy trial, as licensure will be sought for all women of childbearing potential regardless of CMV serostatus. Part 1 will evaluate the safety and immunogenicity of CCI mRNA-1647 vaccine or placebo in males and females. An interim analysis of safety and immunogenicity data collected at all dose levels through Month 3 (1 month after the second dose) for Part 1 will inform the selection of a dose level for further development. Part 2 will evaluate the safety and immunogenicity of the selected dose level in a larger female population, which is the target population for Phase 3 development.

2.2. Background and Overview

CMV is the most common congenital viral infection, affecting 30,000 to 40,000 infants (0.6%-2% of live births) in the United States (US) annually (Boppana et al 2013). Approximately 1/3 of infants born to mothers who acquire primary CMV infection during pregnancy will be born with congenital CMV (cCMV) infection; of these, 10%-15% will be symptomatic at birth, and 4%-10% will die in the first year of life (Boppana et al 1992, Lopez et al 2014, Manicklal et al 2013). The majority of children with cCMV will survive infancy, but their risk for lifelong complications is significant: approximately half of infants with symptomatic cCMV at birth suffer sensorineural hearing loss and developmental delay (Dollard et al 2007), and 10% of infants with cCMV but without symptoms at birth go on to develop sensorineural hearing loss (Goderis et al 2014, Boppana et al 2013).

A significant unmet medical need is a safe and effective method for the prevention of cCMV infection. A report from the National Institutes of Medicine identified the development of a prophylactic vaccine for the prevention of CMV infection as a high priority (Institute of Medicine 2000).

ModernaTX, Inc. has developed a proprietary mRNA-based vaccine platform for intramuscular (IM) delivery of mRNA encoding target antigens in a lipid nanoparticle (LNP) formulation. Endogenous translation of the mRNA within the cytoplasm produces structurally-intact viral antigens that mimic those of a natural infection. The mRNA-1647 vaccine against CMV infection consists of distinct mRNA sequences encoding the full-length CMV glycoprotein B (gB) and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex (Pentamer) in an LNP formulation and holds potential for preventing infections caused by CMV.

2.2.1. Non-clinical Studies

Non-clinical studies conducted in mice and non-human primates have demonstrated the immunogenicity of mRNA-1647 in the liquid form and the lyophilized form as measured by anti-gB and anti-Pentamer immunoglobulin (Ig) G titers, and titers of neutralizing antibody (nAb) against CMV infection in fibroblasts and in epithelial cells.

A study of mRNA-1647 vaccine in liquid form in Balb/c mice administered 2 IM vaccinations 21 days apart demonstrated robust anti-CMV nAb against fibroblast and epithelial cell infection. Similar dose-dependent nAb responses were observed in cynomolgus macaques administered 2 vaccinations 21 days apart, with nAb responses that remained above baseline through the 201-day duration of the study.

A study in Balb/c mice administered 2 IM vaccinations 21 days apart of either mRNA-1647 in liquid form or mRNA-1647 reconstituted from the lyophilized form showed similar dose-dependent increases in anti-gB and anti-Pentamer IgG titers. A study in rhesus macaques administered 3 IM vaccinations 28 days apart of either mRNA-1647 in liquid form or mRNA-1647 reconstituted from the lyophilized form showed increases in anti-gB and anti-Pentamer IgG titers after the second dose that were not appreciably enhanced after the third dose, with similar immune responses at all doses and all timepoints for the liquid and lyophilized forms of mRNA-1647 vaccine.

Repeat-dose toxicology studies of mRNA-1647 performed in Sprague-Dawley rats indicated that mRNA-1647 was clinically well-tolerated. Dose-dependent swelling and skin redness localized to the injection site with clinical pathology parameters consistent with a systemic inflammatory response to the injection site reaction.

An in vitro study of SM-102, the novel lipid used in mRNA-1647, showed no genotoxicity or increased mutation frequency. An in vivo micronucleus test using mRNA-1706, an mRNA-based vaccine encoding

the Zika virus pre-membrane and envelope (prME) polypeptide formulated in SM-102–containing LNPs and administered intravenously showed non-dose-dependent increases in events.

A biodistribution study showed only a relatively small fraction of mRNA-1647 administered IM distributed to distant tissues, and it did not persist past 1 to 3 days in tissues other than at the injection site, the spleen, and the lymph nodes.

A detailed review of non-clinical experience with the study vaccine is provided in the Investigator's Brochure (IB).

2.2.2. Clinical Studies

A Phase 1, FIH, randomized, observer-blind, placebo-controlled, dose-ranging study (Study mRNA-1647/mRNA-1443-P101) in healthy adults completed the final study visit in October 2020 (ClinicalTrials.gov Identifier: NCT03382405). The primary objective of this study was to evaluate the safety and reactogenicity of different dose levels of mRNA-1647 ranging from 30 μg to 300 μg, administered according to a 3-dose vaccination schedule. The secondary objectives were to evaluate longer-term safety and immunogenicity through 6 months following the last vaccination. Interim analyses to date demonstrate that the mRNA-1647 vaccine is generally well tolerated and immunogenic in both CMV-seronegative and CMV-seropositive adults. The final clinical study report (CSR) is pending.

A detailed description of the efficacy/immunogenicity and safety of mRNA-1647 is provided in the current IB.

2.3. Benefit/Risk Assessment

Approximately 339 participants will be exposed to mRNA-1647 vaccine in this study; approximately 113 participants will receive placebo.

A summary of the potential risks and benefits of mRNA-1647 vaccine is provided in the current IB.

2.3.1. Known Potential Benefits

Participants who receive mRNA-1647 may or may not directly benefit from vaccination as the efficacy of mRNA-1647 has yet to be established.

Participants can obtain medical advice about their general health status through the medical evaluations/assessments associated with this study (ie, physical examination, laboratory testing [hematology, chemistry, and coagulation data]).

Participants will be contributing to the process of developing a new potentially prophylactic measure in an area of unmet medical need.

2.3.2. Anticipated Risks

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. 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 precautionary measure, all participants will remain under observation at the study site for at least 60 minutes after vaccination.

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 will be followed to avoid injury from fainting.

IM vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This typically includes injection site pain, erythema (redness), or swelling/induration (hardness).

In the current, ongoing Phase 1 study of mRNA-1647, dose levels of 30 µg, 90 µg, 180 µg and 300 µg have been administered to healthy adults. A preliminary analysis of safety through one month after the final vaccination for all 4 dose levels was performed. The majority of local and systemic adverse reactions (ARs) within 7 days following vaccination were of mild or moderate severity and brief in duration. The most common local and systemic ARs observed have been injection site pain, myalgia, headache, chills, and fatigue. The majority of reported unsolicited adverse events (AEs) were not considered to be related to study vaccine by site Investigators.

A Phase 1 study with a similar mRNA-based vaccine, mRNA-1653, targeting human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) is ongoing in healthy adults with doses ranging from 25 µg to 300 µg administered as a 2-dose series. An interim analysis was performed through 1 month following the second vaccination. The study vaccine was generally well-tolerated. Within 7 days following vaccination, the most common local reactogenicity event was injection site pain and the most common systemic reactogenicity events were headache, fatigue and myalgia which appeared to increase with dose level after first vaccination.

Further details are provided in the current IB.

2.3.3. Overall Benefit/Risk Conclusion

mRNA-1647 is currently in a very early stage of investigation and no vaccine efficacy has been demonstrated thus far. Taking into account the measures taken to minimize the risk to individuals participating in this study, the potential risks to the participants are justified by the potential benefits linked to the development of mRNA-1647.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objectives

The primary objectives of the study are as follows:

- To evaluate the safety of different dose levels of mRNA-1647 vaccine administered in a 3-vaccination (0, 2, 6-month) schedule.
- To evaluate neutralizing anti-CMV antibody responses against fibroblast and epithelial cell infection following vaccination with mRNA-1647 at different dose levels administered in a 3-vaccination (0, 2, 6-month) schedule.

3.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate antigen-specific antibody responses following vaccination with mRNA-1647 at different dose levels in a 3-vaccination schedule.
- To evaluate the immunogenicity of mRNA-1647 by CMV serostatus at enrollment.

3.1.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- To evaluate cell-mediated immune responses following vaccination with mRNA-1647 at different dose levels.
- In CMV-seropositive participants, to assess possible effects of immunologic response following vaccination with mRNA-1647 compared to placebo.

3.2. Endpoints

3.2.1. Primary Endpoints

- Solicited local and systemic ARs through 7 days after each vaccination.
- Unsolicited AEs through 28 days after each vaccination.
- Medically-attended adverse events (MAAEs) through 6 months after the last vaccination, and serious adverse events (SAEs) throughout the entire study period.

- Geometric mean titer (GMT) of serum neutralizing anti-CMV antibodies against epithelial cell infection and against fibroblast infection, and associated geometric mean ratio (GMR) of post-baseline/baseline titers at each timepoint.
- Proportion of participants with ≥ 2-fold, 3-fold, and 4-fold increases in nAb over baseline against epithelial cell infection and against fibroblast infection at each timepoint.

3.2.2. Secondary Endpoints

- GMT of anti-gB specific IgG and anti-Pentamer specific IgG as measured by by enzyme-linked immunosorbent assay (ELISA), and associated GMR of post-baseline/baseline titers at each timepoint.
- GMT, GMR, and proportion of participants with ≥ 2-fold, 3-fold, and 4-fold increases over baseline of serum nAb against epithelial cell infection and against fibroblast infection at each timepoint, and GMT and GMR of antigen-specific IgG (ELISA) at each timepoint, in the CMV-seropositive group and in the CMV-seronegative group.

3.2.3. Exploratory Endpoints

- gB- and Pentamer-specific interferon (IFN)-γ-secreting T-cells as measured by enzyme-linked immunospot (ELISpot) assay.
- Exploratory assays to assess for anti-CMV immunologic response or for primary CMV infection may be performed at the discretion of the Sponsor.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, placebo-controlled, observer-blind, dose-finding trial enrolling healthy participants 18-40 years of age. The schematic of the study design is presented in Figure 1 in Section 1.2.

CMV-seronegative and CMV-seropositive groups will be enrolled at the same time. Randomization will be stratified by CMV serostatus (via an Interactive Response Technology [IRT]) in a sequential manner into 3 different dose levels CCI in Part 1 and the CCI dose level in Part 2. At each dose level, participants will be randomized in 3:1 ratio to either mRNA-1647 vaccine or placebo, administered in a 3-vaccination (0, 2, 6-month) schedule.

Treatment Arms

Part 1 CMV-seronegative Group (males and females aged 18-40 years)

- Approximately 60 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 60 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 60 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

Part 1 CMV-seropositive Group (males and females aged 18-40 years)

- Approximately 24 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 24 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule
- Approximately 24 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

Part 2 CMV-seronegative Group (females aged 18-40 years)

- Approximately 80 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

Part 2 CMV-seropositive Group (females aged 18-40 years)

- Approximately 120 participants randomized 3:1 to receive either CCI of mRNA-1647 vaccine or placebo in a 0, 2, 6-month schedule

4.1.1. Screening Period

The Screening of each participant will occur during the first visit at the clinic. In Part 1, screening may occur up to 28 days prior to Visit Day 1. For Part 2, screening may occur up to 28 days prior

to Visit Day 1 for CMV-seronegative participants and may occur up to 42 days for CMV-seropositive participants.

Based on prior approval from the Sponsor, the Screening visit may be performed across 2 separate clinic visits.

4.1.2. Treatment Period

All participants will receive vaccinations at Visits Day 1, Day 56, and Day 168.

4.1.3. Follow-up Period

All participants will be followed for safety for a minimum of 6 months after the last vaccination for MAAEs and up to 12 months after last vaccination for SAEs (refer to Table 1 and to Appendix 2).

Participants who withdraw from further vaccinations after either the first or second vaccination but do not withdraw consent will be followed for safety as noted above, and will provide blood samples for immunogenicity at specified timepoints (refer to Table 6 and Table 7 in Appendix 2).

4.2. Scientific Rationale for Study Design

The design and dose levels proposed for Study mRNA-1647-P202 Part 1 are based on accumulated safety and immunogenicity data from the Study mRNA-1647/mRNA-1443-P101. An interim analysis of safety and immunogenicity data across the 30 µg, 90 µg, and 180 µg dose level cohorts has shown mRNA-1647 to be generally well-tolerated in adults, CMV-seronegative and CMV-seropositive. No treatment-related SAEs or adverse events of special interest (AESIs) were reported. There was no pattern of clinically relevant laboratory abnormalities across treatment groups. In CMV-seronegative participants, nAbs against both epithelial cell infection and against fibroblast infection were observed at all dose levels of mRNA-1647. Additionally, nAbs against epithelial cell and against fibroblast infection were boosted in CMV-seropositive participants at all dose levels following the same vaccination schedule.

Study mRNA-1647-P202 will evaluate 3 dose levels of the mRNA-1647 vaccine for safety and immunogenicity in CMV-seronegative and CMV-seropositive adults 18 to 40 years of age. In Part 1, a dose escalation, sequential enrollment design is intended to allow selection of a dose level for further development. Part 2 will evaluate the safety and immunogenicity of the selected dose level in a larger female population, which is the target population for Phase 3 development.

In Part 1, an Internal Safety Team (IST) will review safety data for the CMV-seropositive and CMV-seronegative groups separately. For each serostatus group, after the first 8 participants have enrolled into the lowest dose level of CCI, the IST will review all available safety data through

7 days after the first vaccination. Favorable IST review will permit enrollment into the next dose level of CCI. Enrollment of participants into the highest dose level of CCI will proceed in the same manner, with IST review of all available safety data through 7 days after the first vaccination in the first 8 participants. A Safety Monitoring Committee (SMC) will convene on an ad hoc basis if any of the pause rules, described in Section 8.9.8, are met in order to provide recommendation regarding study continuation.

In Part 2, the SMC will be convened on an ad hoc basis if a safety signal emerges.

4.3. Justification for the Choice of Study Population

Immune response to investigational CMV vaccines in subjects who are seronegative may be different from responses in those who are seropositive. To explore the potential differences in safety and immunogenicity, this study will enroll healthy CMV-seronegative and CMV-seropositive participants.

4.4. Justification for Dose and Schedule

In Part 1 of the Study mRNA-1647-P202, the 3 dose levels of mRNA-1647 tested in participants will be CCI based on assessment of available safety and immunogenicity data from Study mRNA-1647/mRNA-1443-P101. In Part 2, the CCI dose level will be tested to collect additional safety and immunogenicity data at the dose level chosen for further development.

4.5. Justification for the Use of Placebo

Because there are currently no licensed CMV vaccines available, 0.9% sodium chloride injection (USP) (normal saline) placebo will be used as a control for the safety and immunogenicity assessments in each serostatus group.

4.6. End of Study Definition

The end of study is defined as completion of the last visit of the last participant in the study or last scheduled procedure as shown in the tables of Schedule of Assessments (Table 1, Table 6, and Table 7) for the last participant in the trial globally.

Participants are considered to have completed the study if they complete the final visit per Schedule of Assessments, independent of how many doses were administered.

5. STUDY POPULATION

5.1. Participant Recruitment

The study will enroll approximately 452 adult participants 18-40 years of age, including 252 participants in Part 1 (approximately 180 CMV-seronegative participants and approximately 72 CMV-seropositive participants) and 200 participants in Part 2 (approximately 80 CMV-seronegative participants and approximately 120 CMV-seropositive participants), who will receive mRNA-1647 vaccine or placebo.

The Sponsor may enroll up to 502 participants including 252 participants in Part 1 (approximately 180 CMV-seronegative participants and approximately 72 CMV-seropositive participants) and 250 participants in Part 2 (approximately 100 CMV-seronegative participants and approximately 150 CMV-seropositive participants).

Upon completion of all screening procedures (Section 8.1), the Investigator will review the inclusion/exclusion criteria for each participant to determine if the participant is eligible. Participants who meet all eligibility criteria will be enrolled in the study.

Their screening information will be recorded on the appropriate page of the electronic case report form (eCRF). Based on prior approval from the Sponsor, the Screening visit may be performed across 2 separate clinic visits.

5.2. Inclusion Criteria

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

1. Age and sex
   - Part 1: Male or female 18-40 years of age at time of consent.
   - Part 2: Female 18-40 years of age at time of consent.
2. Understands and agrees to comply with the trial procedures and provides written informed consent.
3. According to the assessment of the Investigator, is in good general health and is capable of complying with trial procedures.
4. Body mass index (BMI) 18-35 kg/m^2.
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for $\geq$ 12 consecutive months prior to Screening without an alternative medical cause). A follicle-

stimulating hormone (FSH) level may be measured at the discretion of the Investigator to confirm postmenopausal status.

6. Female participants of childbearing potential may be enrolled in the study if the participant: 1) has a negative pregnancy test at Screening and on the day of the first vaccination, and 2) has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first vaccination, and 3) has agreed to continue adequate contraception through 3 months following the last vaccination, and 4) is not currently breastfeeding.

   Adequate female contraception is defined as consistent and correct use of a US Food and Drug Administration (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 oral (pill), transdermal (patch), subdermal, or IM route
   - Sterilization of a female participant's monogamous male partner prior to entry into the study

   Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male participants engaging in activity that could result in pregnancy of sexual partners must agree to practice adequate contraception from the time of the first vaccination and through 3 months after the last vaccination.

   Adequate contraception for male participants is defined as:

   - Monogamous relationship with a female partner using an intrauterine device or hormonal contraception (described above)
   - Use of barrier methods and spermicide
   - History of surgical sterilization

   Male participants with partners who have become pregnant prior to randomization are eligible to participate in the study.

5.3. Exclusion Criteria

Participants eligible for this study must not meet any of the following criteria:

1. Acutely ill or febrile (temperature ≥ 38.0°C/100.4°F) on the day of the first vaccination. Participants meeting this criterion may be rescheduled within the enrollment window

period. Afebrile participants with minor illnesses can be enrolled at the discretion of the Investigator.

2. Prior receipt of any CMV vaccine.
3. Positive for hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibody, or human immunodeficiency virus (HIV) type 1 or 2 antibodies at Screening.
4. Screening coagulation tests (prothrombin time [PT] or partial thromboplastin time [PTT]) with a toxicity grade of ≥ 1. Retesting of PT and/or PTT will be allowed once in an otherwise eligible participant.
5. Other than coagulation tests as described above, has a screening laboratory result with a toxicity score ≥ Grade 2. No repeat testing is allowed for these screening laboratory tests.
6. Diagnosis or condition that, in the judgment of Investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to trial procedures, including:
    - Congenital or acquired immunodeficiency (including HIV infection)
    - Diagnosed or suspected immunosuppressive condition or immune-mediated disease
    - Chronic hepatitis
    - Dermatologic conditions that could affect local solicited AR assessments
    - History of anaphylaxis, urticaria, or other significant reaction requiring medical intervention after receipt of a vaccine
    - History of bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - History of malignancy within the previous 10 years (excluding non-melanoma skin cancer)
    - Any psychiatric or occupational condition that, in the opinion of the Investigator, might pose an additional risk due to participation in the study or can interfere with the interpretation of study results
7. Has received or plans to receive a vaccine ≤ 28 days prior to the first vaccination or plans to receive a non-study vaccine within 28 days prior to or after any study vaccination, except for any licensed influenza vaccine which can be administered >14 days before or after any study vaccination. COVID-19 vaccines (regardless of manufacturer) may be administered > 7 days but preferably > 14 days before or after any study vaccination, with the intention of prioritizing COVID-19 vaccination over all other considerations.
8. Received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the day of enrollment. Inhaled, nasal, and topical steroids are allowed.

9. Receipt of intravenous immunoglobulins or plasma products within 3 months prior to the day of the first study vaccination.
10. Part 1 participants only: Previous receipt of medications in LNP formulation.
11. Has donated ≥ 450 mL of blood products within 28 days of the Screening visit. Participants engaging in blood sampling for cell-mediated immunogenicity should be advised to refrain from blood donation through the vaccination period (Day 1 through Month 7).
12. Participated in an interventional clinical trial within 28 days prior to the day of enrollment or plans to do so while enrolled in this trial.
13. Is an immediate family member or household member of trial personnel.

5.4. Screen Failures

Screen failures are defined as participants who sign the consent form but who are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes informed consent data, eligibility criteria, demographic data, information on SAEs, and screen failure details.

Rescreening of an eligible participant is allowed if their originally intended dose level closes and their screening window will be surpassed before another dose level opens or if the Investigator believes there is a reason to do so (eg, an update to the medical history). The participant will be assigned a new screening number and all screening procedures will be repeated. Rescreening may not be repeated more than twice.

Exclusion 4 permits retesting of PT and/or PTT once in an otherwise eligible participant; however, subjects who screen fail under Exclusion 4 are not permitted to rescreen at any time. Subjects who screen failed under Exclusion 5 are not permitted to rescreen at any time.

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of Study Vaccine

The mRNA-1647 vaccine against CMV infection consists of 6 distinct mRNA sequences encoding important targets of nAb response to human CMV infection (full length CMV gB and pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex [Pentamer]) in an LNP formulation.

The LNP formulation includes 4 lipid excipients: heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6(undecyloxy)hexyl)amino)octanoate (SM-102), a proprietary ionizable amino lipid, and the commercially-available lipids cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and 1,2-dimyristoyl-sn-glycerol, methoxypolyethyleneglycol (PEG2000-DMG) (Mui et al 2013).

mRNA-1647 injection is provided as 520 µg of lyophilized product in glass vials and stored at -25°C to -15°C (-13°F to 5°F) until use. Following appropriate dose preparation, mRNA-1647 injection will be administered intramuscularly into the deltoid muscle in a volume of 0.5 mL.

The lyophilized vaccine will be reconstituted with 0.6 mL of 0.9% sodium chloride injection (USP), then diluted with tris sucrose Diluent SD-0724 to a concentration for delivery of the specified dose level in a volume of 0.5 mL.

A 0.9% sodium chloride injection (USP) (normal saline) placebo will be administered in a volume of 0.5 mL.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Clinical Trial Material

The Sponsor or designee is responsible for the following:

- Supplying the clinical trial material
- Confirming the appropriate labeling of mRNA-1647 injection, such that it complies with the legal requirements of each country where the study is to be performed

The Investigator is responsible for the following:

- Acknowledgment of the receipt of the clinical trial material by a designated staff member at the site, including the following:
  - Confirming that the clinical trial material were received in good condition
  - Confirmation to the Sponsor that the temperature during shipment from the Sponsor to the Investigator's designated storage location was appropriate
  - Confirming whether the Sponsor has authorized the clinical trial material for use
  - Ensuring the appropriate dose level of mRNA-1647 injection is prepared using aseptic technique (lyophilized vaccine reconstituted with 0.9% sodium chloride injection [USP],

then diluted with Diluent SD-0724 to a concentration for delivery of the specified dose level in a volume of 0.5 mL)

Further description of the clinical trial material and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the clinical trial material are described in the mRNA-1647-P202 Pharmacy Manual.

6.2.2. Clinical Trial Material Administration

The mRNA-1647 injection is formulated for IM administration. mRNA-1647 injection is to be used for single-dose preparation for Part 1 study participants. mRNA-1647 injection may be used for multiple-dose preparation for Part 2 study participants.

Following appropriate dose preparation, mRNA-1647 injection will be administered intramuscularly into the deltoid muscle in a volume of 0.5 mL.

A 0.9% sodium chloride injection (USP) (normal saline) placebo will be administered intramuscularly into the deltoid muscle in a volume of 0.5 mL.

Further instructions for the preparation (reconstitution and dilution) and administration of mRNA-1647 injection are described in the mRNA-1647-P202 Pharmacy Manual.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE

Prior to vaccination, participants must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the Investigator to vaccinate the participant. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the study entry criteria outlined in protocol Section 5.2 (Inclusion Criteria) and Section 5.3 (Exclusion Criteria).

Study vaccine should not be administered to participants with known hypersensitivity to any component of the vaccine.

Standard vaccination practices are to be observed and care should be taken to administer the IM injection. Before administering the vaccine, the vaccination site must be disinfected with a skin disinfectant (eg, 70% isopropyl alcohol or ethanol) and allowed to dry. The vaccine should NOT be injected intravascularly.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.2.3. Clinical Trial Material Packaging and Labeling

All investigational products used in this study (mRNA-1647 injection and Diluent SD-0724) will be prepared, packaged, and labeled in accordance with the Standard Operating Procedures (SOPs) of ModernaTX, Inc. or those of its designee, Code of Federal Regulations Title 21 (CFR), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, guidelines for Quality System Regulations (QSR), and applicable regulations.

A 0.9% sodium chloride injection (USP) (normal saline) for use as placebo and study vaccine preparation contains a commercial label and does not contain study-specific identification.

6.2.4. Clinical Trial Material Storage

The mRNA-1647 injection should be stored at -25°C to -15°C (-13°F to 5°F). Diluent SD-0724 should be stored at 15°C to 30°C (59°F to 86°F).

The 0.9% sodium chloride injection (USP) should be stored at 20°C to 25°C (68°F to 77°F).

Clinical trial material must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the designated unblinded site personnel have access. Upon receipt, the study vaccine, Diluent SD-0724, and 0.9% sodium chloride injection (USP) should be stored at the appropriate temperature condition as specified on the study vaccine labels and in the mRNA-1647-P202 Pharmacy Manual.

6.2.5. Clinical Trial Material Accountability

The Investigator or designee must maintain an accurate record of the shipment receipt, the inventory at the site, dispensation of study vaccine, and the return to the Sponsor or alternative disposition of used/unused products in a vaccine accountability log. The clinical trial material accountability will be noted by the unblinded Clinical Research Associate (CRA) during site visits and at the completion of the study. For further direction, refer to the mRNA-1647-P202 Pharmacy Manual.

6.2.6. Clinical Trial Material Handling and Disposal

The designated unblinded CRA will reconcile the clinical trial material during the conduct and at the end of the trial for compliance. Once fully reconciled at the site, the clinical trial material can be destroyed at the investigational site or Sponsor-selected third party, as appropriate.

Clinical trial material may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A document for destruction (ie, Certificate of Destruction) must be

obtained and sent to the Sponsor or designee. For further direction refer to mRNA-1647-P202 Pharmacy Manual.

6.3. Randomization and Blinding

6.3.1. Randomization

In Part 1, randomization will be stratified by CMV serostatus group (via IRT) in a sequential manner into one of 3 arms evaluating different dose levels of mRNA-1647 administered in a 3-vaccination (0, 2, 6-month) schedule. In Part 2, randomization will be stratified by CMV serostatus group (via IRT) and participants will be randomized in 3:1 ratio to receive CCI of mRNA-1647 or placebo in a 3-vaccination (0, 2, 6-month) schedule.

6.3.2. Blinding

As the appearance of vaccine and placebo differs, this study will be conducted as an observer-blind study. Clinical site staff with the responsibility of safety assessments including the Investigators, participants, and Sponsor personnel (or its designees) are blinded to treatment assignment. Only designated unblinded personnel qualified to prepare and/or administer vaccine are aware of the treatment assignment.

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

Dose preparation, administration and accountability will be performed by designated unblinded site personnel who will not participate in any of the clinical study evaluations. The unblinded site personnel will prepare the dose out of view of the participant and the blinded site personnel, and will administer the vaccine in a separate room, or at minimum, using a curtain to shield view of the injection syringe and injected arm from blinded personnel.

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

A participant's treatment should not be unblinded, during the study without the approval of the Sponsor. The treatment code should be broken only as outlined in Section 8.11 (ie, if the Investigator/physician in charge of the participant feels that the case cannot be treated without knowing the identity of the study vaccine or after of the participant's study assessments are completed). Instructions regarding unblinding will be provided to the Investigator and are outlined in Section 8.11.

The Sponsor will remain blinded to individual treatment assignment up until the 7-month interim analyses. At the 3--month and 7-month interim analyses, 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. Participants, Investigators, and study sites will remain blinded to individual treatment assignments until the end of the participant's study participation. After final study visit procedures are completed, including the recording of any MAAEs and SAEs, the Investigator may unblind the participant's treatment. The primary purpose of End of Study unblinding is to allow the Investigator to assess eligibility of seropositive participants for enrollment into the extension study (mRNA-1647-P202-EXT); however, any participant's treatment may be unblinded upon completion of the study including seronegative participants and participants who do not wish to enroll into the Extension trial.

6.4. Criteria for Delay of Vaccine Administration

Oral temperature should be measured prior to any study vaccine administration. If the participant has a temperature ≥ 38.0°C/100.4°F on the day of vaccination, the vaccination visit should be rescheduled within the allowed interval for that visit.

If the Investigator determines that the participant's health on the day of administration temporarily precludes vaccine administration, the visit should be rescheduled within the allowed interval for that visit.

6.5. Concomitant Therapy

At each study visit, the site personnel should question the participant regarding any medications taken and vaccinations received by the participant and record the information as specified in Section 6.5.1.

6.5.1. Recording of Concomitant Medications and Non-study Vaccinations

The following concomitant medication(s) and vaccine(s) must be recorded in the eCRF:

- All non-study vaccinations administered during the period starting ≤ 28 days before the first dose of study vaccine.
- COVID-19 vaccination (regardless of type of vaccine) will be recorded anytime from Day 1 through the End of the Study (Day 504)
- All concomitant medications and non-study vaccinations taken through 28 days after each vaccination. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of a vaccination reaction) will be recorded as such.
- Any concomitant medications relevant to or for the treatment of an SAE or a MAAE.

- Prophylactic medications (ie, medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination) from Day 1 through 28 days after each dose. For example, an antipyretic or analgesic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring.
- Participant will be asked if they have taken any antipyretic or analgesic to treat or prevent fever or pain in the electronic diary (eDiary) within 7 days post vaccination, including day of vaccination. Reported antipyretic or analgesic medications should be recorded in the source document by the site staff during the post vaccination study visits or via other participant interactions (eg, phone calls).

6.5.2. Concomitant Medications and Non-study Vaccinations that May Lead to the Elimination of a Participant from Per-Protocol Analyses

The use of the following concomitant medications and non-study vaccinations will not require withdrawal of the participant from the study but may determine a participant's inclusion in Per-protocol (PP) analyses. Analysis sets are described in Section 9.4.

- Any investigational or nonregistered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs taken or administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs taken or administered at any time during the study period (eg, infliximab).
- A non-study vaccine administered within 28 days prior to or after any study vaccination, except for any licensed influenza vaccine, which can be administered >14 days before or after any study vaccination. COVID-19 vaccines (regardless of manufacturer) may be administered > 7 days but preferably > 14 days before or after any study vaccination, with the intention of prioritizing COVID-19 vaccination over all other considerations.
- Immunoglobulins and/or any blood products administered during the study period.

6.6. Intervention After the End of the Study

Any AE occurring at any time outside the observation period or after the end of the study and considered to be caused by the study vaccine must be reported to the Sponsor.

7. DISCONTINUATION OF VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Vaccination

A "withdrawal" from the study vaccine refers to any participant who does not receive all study vaccinations from the date of withdrawal due to either participant request or Investigator recommendation. A participant who withdraws from further study vaccination but does not withdraw consent will be followed for safety and immunogenicity as outlined in Appendix 2. The Investigator should make all efforts to ensure that the participants remain in the study to ensure a proper safety follow-up. The reason for participant withdrawal from study vaccination must be documented in the appropriate source documentation.

Information relative to premature discontinuation of the study vaccine will be documented in the eCRF. The Investigator will document which of the following reasons was responsible for withdrawal:

- SAE
- AE (non-SAE)
- Dosing error
- Other (specify)

Participants who withdraw from further vaccinations after either the first or second vaccination but do not withdraw consent will be followed for safety as noted above, and will provide blood samples for immunogenicity at specified timepoints after their last vaccination (refer to Table 6 and Table 7 in Appendix 2).

Participants who miss the second vaccination for any reason will still be able to receive the third vaccination, at the discretion of the Investigator. These participants will have safety calls every 28 ± 7 days until Visit 9 (Month 6), and complete all study procedures from Visit 9 through End of Study as outlined in Table 1.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants who are withdrawn will not be replaced.

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit foreseen in the protocol.

All data collected until the date of withdrawal or last contact of the participant will be used for the analysis, including collected specimens.

A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for that participant from the date of withdrawal or last contact.

Information relative 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 responsible for withdrawal:

- AE (specify)
- Death
- Lost to follow-up
- Physician decision (specify)
- Pregnancy
- Protocol violation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Participant has received another investigational drug or vaccine other than the study vaccine at any point from Visit 1 (Month 0)
- Other (specify)

Participants who are withdrawn from the study because of SAEs/AEs 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.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the

assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, 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 study source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- A participant should not be considered lost to follow-up until due diligence has been completed. Date of withdrawal/lost to follow-up should be the date of last contact with the participant where safety status of the participant was assessed (eg, clinic visit, phone call).

8. STUDY ASSESSMENTS AND PROCEDURES

The study Schedule of Assessments can be found in Table 1 in Section 1.3.

Two additional Schedule of Assessments tables to instruct how to complete study procedures if the participant receives only the first 2 doses (Month 0 and Month 2) or the first dose (Month 0) are presented in Table 6 and Table 7, respectively, in Appendix 2.

8.1. Screening

At Visit Day 1, all screening requirements, including reason for screen failure if a participant is not randomized, must be completed. The Enrollment Page in the eCRF must also be completed.

Based on prior approval from the Sponsor, the Screening visit may be performed across 2 separate clinic visits.

8.2. Confirm Inclusion and Exclusion Criteria

All inclusion and exclusion criteria described in Section 5.2 and Section 5.3 must be met before enrollment (Visit Day 1).

8.3. Collect Demographic and Baseline Data

Demographic and baseline data such as age, month and year of birth, sex, race, ethnicity, weight, and height (BMI will be calculated) will be recorded in the participant's eCRF.

8.4. Medical History

The participant medical history will be obtained during the screening period by interviewing the participant or by reviewing the participant's medical records. Any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study vaccination should be recorded in the eCRF.

8.5. Physical Examination and Vital Signs

A full physical examination will be performed during the screening period according to standard medical practice, including assessment of vital signs, height, and weight. Vital sign measurements include the assessment of body temperature, systolic and diastolic blood pressures, heart rate, and respiratory rate. The information collected will be recorded in the eCRF.

On days of dosing, vital signs will be collected prior to dosing and approximately 60 minutes after dosing, prior to discharge of the participant.

Symptom-directed physical examinations will be performed at all other scheduled timepoints. Interim physical examinations will be performed at the discretion of the Investigator.

Treatment of any abnormality observed during physical examination should be performed according to local medical practice outside the study or by referral to an appropriate healthcare provider at the discretion of the Investigator.

8.6. Randomization

Study group and treatment assignment allocation will be performed on Visit Day 1 as described in Section 6.3.1. The confirmation for study vaccine administration must be recorded on the Exposure page of the eCRF.

8.7. Study Vaccine Administration

A 3-vaccination, 0, 2, 6-month schedule will be administered to all participants at all dose levels.

After completing all prerequisite procedures prior to vaccination, the first dose of study vaccine will be administered via IM injection into the deltoid muscle. A detailed description of the vaccine administration procedure is provided in Section 6.2.2.

In Part 1, scheduled IST reviews will be held for the CMV-seropositive and CMV-seronegative groups separately, and will occur at each dose level after the first 8 participants in the respective group complete Day 8. Favorable IST review will allow escalation to the next highest dose level.

The participants will be observed closely (via clinical assessment including measurement of vital signs) for at least 60 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis or other hypersensitivity reactions.

8.8. Sampling for Safety and Immunogenicity Assessments

Detailed instructions for the collection, handling, and processing of samples are provided in the Laboratory Manual and Collection Flow Chart. The approximate blood volumes to be collected from each participant during the study are provided in Table 2.

Participants will have 12 blood draws over the course of the trial to assess for eligibility, safety, and immunogenicity to mRNA-1647 vaccine.

Blood samples for screening laboratory testing will be collected at the Screening visit. Blood samples for safety laboratory assessments will be collected at Day 1, Day 8, Day 29, Day 56, Day 63, Day 84, Day 168, Day 175, and Day 196. Blood samples for antibody-mediated immunogenicity will be collected at Day 1, Day 29, Day 56, Day 84, Day 168, Day 196, Day 336, and Day 504. Blood samples for cell-mediated immunogenicity will be collected at Day 1, Day 8, Day 56, Day 63, Day 168, Day 175, Day 336, and Day 504. Blood for cell-mediated immunogenicity will be collected for a subset of up to 16 participants (approximately 8 CMV-

seropositive and 8 CMV-seronegative) for each dose level. The Sponsor will allocate clinical sites to enroll participants in this subset.

Table 2: Total Blood Volume

Assessment	Approximate Blood Volume per Sample	Scheduled Number of Collections[1]	Approximate Total Amount of Scheduled Blood
Clinical Laboratory Assessments			
Hematology	2 mL	10	20 mL
Chemistry	4 mL	10	40 mL
Coagulation	2.7 mL	10	27 mL
Screening serology (HBV, HCV, HIV) CMV (IgG/IgM)	5 mL 4 mL	1 1	5 mL 4 mL
Immunogenicity Assessments			
Anti-CMV nAb titers	10 mL	8	80 mL
Cell-mediated immunogenicity[2]	48 mL	8	384 mL
Participant Total			**560 mL**

Abbreviations: CMV = cytomegalovirus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; nAb = neutralizing antibody.

[1] Additional blood collections may be required at the discretion of the Investigator to follow-up on abnormal results.

[2] Only collected for subjects enrolled into cell-mediated immunogenicity subset.

The retention period of laboratory samples will be 15 years, or as permitted by local regulations, to address further scientific questions related to mRNA-1647 vaccine.

During the study, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted in the CMV-seropositive group, using other antibody-based methodologies on any remaining blood or serum samples, including participants who provide samples for screening, but are not subsequently enrolled. These analyses would extend the search for other potential relevant biomarkers to investigate the effect of mRNA-1647 vaccine, as well as to determine how changes in the markers 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.

8.8.1. Blood Sampling for Screening Laboratory Testing

Screening laboratory testing will include CMV IgG with reflex to IgM, screening serology (HBsAg, hepatitis C virus antibody, HIV type 1 and 2 antibodies), hematology (hemoglobin, platelet count, and total and differential white blood cell count), chemistry (liver function tests including alanine aminotransferase [ALT], alkaline phosphatase [ALP], aspartate aminotransferase [AST], total bilirubin, creatinine, and random glucose), coagulation (PTT and PT), and FSH level (may be measured to confirm menopausal status at the discretion of the Investigator). A serum pregnancy test will be performed on all female participants of childbearing potential at Screening. Pregnancy testing before each study vaccination (or at any time at the discretion of the Investigator) will be a point-of-care urine test.

8.8.2. Blood Sampling for Safety Laboratory Testing

On vaccination days (Day 1, Day 56, and Day 168), blood samples for safety laboratory testing will be collected before administration of vaccination.

Safety laboratory testing performed on Day 1, Day 8, Day 29, Day 56, Day 63, Day 84, Day 168, Day 175, and Day 196 will include hematology (hemoglobin, platelet count, and total and differential white blood cell count), chemistry (liver function tests including ALT, AST, total bilirubin, and creatinine) and coagulation (PTT and PT).

8.8.3. Blood Sampling for Antibody-mediated Immunogenicity

Blood samples for antibody-mediated immunogenicity will be collected during certain study visits as specified in Section 8.8. On vaccination days (Day 1, Day 56, and Day 168), blood samples for antibody-mediated immunogenicity testing will be collected before administration of vaccination.

Antibody-mediated immunogenicity includes serum anti-CMV nAbs, anti-gB IgG, and anti-Pentamer IgG.

Serological assessments for anti-CMV nAb, anti-gB IgG, and anti-Pentamer IgG titers will be performed in a laboratory designated by the Sponsor.

8.8.4. Blood Sampling for Cell-mediated Immunogenicity

Blood samples for cell-mediated immunogenicity will be collected during certain study visits as specified in Section 8.8. On vaccination days (Day 1, Day 56, and Day 168), blood samples for cell-mediated immunogenicity testing will be collected before administration of vaccination. Blood samples for cell-mediated immunogenicity will be collected on a subset of up to 16 participants (approximately 8 CMV-seropositive and 8 CMV-seronegative participants) for each dose level. The Sponsor will allocate clinical sites to enroll participants into this subset.

Participants engaging in blood sampling for cell-mediated immunogenicity should be advised to refrain from blood donation through the vaccination period (Day 1 through Month 7).

Cell-mediated immunogenicity includes gB-specific and Pentamer-specific CD4 and CD8 IFN-γ-secreting T-cells as measured by ELISpot.

Cell-mediated immunogenicity samples for T-cell ELISpot will be centrally processed for separation of peripheral blood mononuclear cells (PBMCs). Samples must be shipped out on the day of collection for overnight priority (next day delivery).

8.9. Safety Assessments

8.9.1. Safety Definitions

8.9.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of mRNA-1647 vaccine, whether or not considered related to the mRNA-1647 vaccine.

NOTE: An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) whether or not related to the medicinal (investigational) product.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator.
- 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 mRNA-1647 vaccine administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

8.9.1.2. Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes (21 CFR 312.32[a]).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in 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 study vaccine.

- 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.

- Requires 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 observation and/or 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 an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.

- Results in persistent disability/incapacity

  The term disability means a substantial disruption of a person's 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Medically important event

  Medical or scientific 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 may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Hospitalization or prolongation of hospitalization in the absence of a precipitating event is not in itself an SAE. Examples include:

- Elective treatments or surgical procedures; documentation of the pre-planned nature of these treatments/procedures should be recorded in the participant's baseline study documentation.
- Diagnostic or therapeutic procedures should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported as an AE if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to the Sponsor.

8.9.1.3. Solicited Adverse Reaction

The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-vaccination follow-up period (day of vaccination and 6 subsequent days), using a predefined checklist in the eDiary (ie, solicited ARs).

The following local ARs will be solicited: pain at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the vaccination arm.

The following systemic ARs will be solicited: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, rash, fever, and chills.

The study site staff will contact the participant within 24 hours of becoming aware of the event if any of the following occurs within 7 days after study vaccination:

- severe (Grade 3) local or systemic ARs,
- presence of any rash, or
- presence of any underarm swelling or tenderness on the same side as the vaccination arm.

The purpose of the contact is to assess the nature of AR, including assessment of potential pause rules. In the event that rash or underarm swelling or tenderness on the same side as the vaccination arm is reported, the participant will be asked to return to the study clinic for assessment by the Investigator.

Grading scales are presented in Table 3, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Table 3: Solicited Adverse Reactions and Grading Scales

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit 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 vaccination*	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit 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 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 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 outpatient intravenous hydration	Requires emergency room visit 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 or hospitalization
Fever (oral)	< 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
Rash*	No rash	Localized rash, without associated symptoms	Maculopapular rash, covering < 50% body surface area	Generalized urticarial, covering > 50% body surface area	Generalized exfoliative, ulcerative or bullous dermatitis, eg, Stevens-Johnson syndrome or erythema multiforme

* Grading for rash and Grade 4 events per Investigator assessment (with exception of fever)

Grade of solicited local and systemic ARs are defined based on CBER guidance (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days post vaccination, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit.

All solicited ARs (local and systemic) will be considered causally related to vaccination.

Note: Any solicited AR that meets any of the following criteria must be entered into the participants' source document and also be recorded as an AE on the Adverse Event eCRF:

- Solicited local or systemic AR that results in a visit to a healthcare provider (MAAE)
- Solicited local or systemic AR that leads to the participant withdrawing from the study or the study vaccination (AE leading to withdrawal)
- Solicited local or systemic AR that otherwise meets the definition of an SAE

At the time of consent, the participants must confirm they will be willing to complete an eDiary via an application downloaded to their smartphone or via a device that is provided at the time of enrollment. Prior to enrollment on Day 1, the participant will be instructed to download the eDiary application, or will be provided an eDiary device to record solicited ARs on Day 1.

At each vaccination visit, participants will be instructed (Visit Day 1) or reminded (Visit Day 56 and Day 168) on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness ipsilateral to the vaccination arm. Participants will record body temperature, any solicited local (injection site) and systemic ARs, and whether any medications were taken to prevent or treat pain or fever starting on the day of each vaccination visit, at approximately 1 hour post vaccination under supervision of the clinical site staff to ensure successful entry of assessments. The site staff will perform any re-training as necessary. Thereafter, the participant will be instructed to complete the eDiary later that day, preferably in the evening and at the same time each day on the 6 subsequent days post vaccination. If any solicited ARs are ongoing at 7 days post vaccination, the participant will be prompted to capture the ongoing solicited ARs in the eDiary until it is no longer reported. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit.

Site personnel will review completed eDiary assessments during discussion with the participants on Day 8, Day 29, Day 56, Day 63, Day 84, Day 175, and Day 196, as applicable.

Additionally, delegated site staff will interview the participant to assess the occurrence of any unsolicited AEs, SAEs and medications taken. Unsolicited AEs will be captured from Day 1 through 28 days after each dose, and MAAEs from Day 1 to Day 336. SAEs will be captured from time of informed consent to the end of the study. The Investigator or designated site staff will transcribe the collected information into the eCRF.

The only source documents allowed for solicited systemic and local ARs (including body temperature measurements) will be the eDiary. The following additional rules apply to documentation of safety information collected using eDiary:

1. Participants will be instructed to complete eDiary entries daily. If assessments are not recorded for a given day, the participant will have a limited window on the following day to complete assessments for the previous day; quantitative temperature recording and measurement of any injection site erythema or swelling/induration (hardness) reported on the following day may be excluded from the analyses of solicited AR.
2. Any new safety information reported during safety calls or at the site visit (including a solicited reaction) not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be described as an unsolicited event and therefore entered on the AE eCRF.

8.9.1.4. Medically-attended Adverse Event

A MAAE is an AE that leads to a visit to a healthcare practitioner (HCP). This would include visits to study clinic for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, etc.), and visits to HCPs external to the clinical site (eg, urgent care, primary care physician, etc.).

8.9.1.5. Treatment Emergent Adverse Event

A treatment emergent adverse event (TEAE) is any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.

8.9.2. Recording of Adverse Events, Serious Adverse Events, and Medically-attended Adverse Events

The participants will be instructed to contact the Investigator immediately should they develop any untoward signs or symptoms or any medical condition that leads to hospitalization or an emergency room visit. In addition, the study site staff will contact the participant within 24 hours of becoming aware of the event if any of the following is reported via eDiary within 7 days after study vaccination: severe (Grade 3) local or systemic ARs, rash, or underarm swelling or tenderness on the same side as the vaccination arm. In the event that rash or underarm swelling or tenderness on the same side as the vaccination arm is reported, the participant will be asked to return to the study clinic for assessment by the Investigator.

Laboratory test results or vital sign measurements with a toxicity score of Grade 3 or greater should be entered as an AE in the eCRF. The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor.

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the eCRF in standard medical terminology, along with the date and time of onset and the date and time of resolution.

It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE eCRF page.

There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.

The Investigator will attempt to establish a single diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to mRNA-1647 vaccine. During the study period, all AEs and SAEs (as defined in Section 8.9.1) will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is considered lost to follow-up (as defined in Section 7.3). SAEs ongoing after study completion will also be followed until resolution, stabilization, or until the event is otherwise explained.

Pregnancies occurring in subjects after enrollment must be reported to Sponsor or designee within 72 hours of the site learning of its occurrence. If the subject 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 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.

8.9.3. Safety Phone Calls

A safety phone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. The participant will be interviewed according to the script, and information relating to MAAEs, SAEs, and concomitant medications associated with these events; receipt of non-study vaccinations and AEs leading to study withdrawal will be collected.

Participants will have 6 safety phone calls on Day 112, Day 140, Day 224, Day 252, Day 280, and Day 308 to collect MAAEs, SAEs, concomitant medications associated with these events, receipt of non-study vaccinations, and AEs leading to withdrawal.

Participants who miss the second vaccination for any reason and are expected to receive the third vaccination will have safety calls at Visit 6 (Month 3), Visit 7 (Month 4), and Visit 8 (Month 5). They should follow the same script as the other safety calls performed during the study.

All scheduled study visits should be completed within the defined visit window. In the event the participant is not able to come on site for a clinic visit 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"), a safety call to the subject should be made in place of the clinic visit. The safety call 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 calls at Visits 12-15). Home visits will be permitted for all non-dosing visits in the event a participant cannot make it to the clinic as a result of the COVID-19 pandemic. Home visits must be permitted by the site IRB and the subject via informed consent and have prior approval from the Sponsor (or its designee).

All safety information described by the participant must be written down in a designated location within the source documents and not written on the script used for the telephone call.

8.9.4. Assessment of Intensity

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 8.9.1.2), 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) will be used to categorize local and systemic solicited ARs (per Table 3), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for clinical and laboratory abnormalities are presented in Appendix 3 and will be graded if outside of the reference range for the laboratory utilized.

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.

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 duration of each episode. An

AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

8.9.5. Assessment of Causality

The causality assessment between the AE and study vaccine exposure is one of the criteria used when determining regulatory reporting requirements. For each AE, the Investigator determines whether there is a reasonable possibility that the AE may have been caused by the study vaccine according to the categories below:

Not Related: There is no suspicion of a causal relationship between study vaccine exposure and the AE.

Related: There is reasonable possibility that there is a causal relationship between study vaccine exposure and the AE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The Investigator is obligated and will use clinical judgment to assess the relationship between mRNA-1647 vaccine and each occurrence of each AE, even if there is only limited information at the time.
- Alternative causes, such as underlying disease(s), concomitant medications or therapy, temporal relationship of the event to study vaccine administration, and other risk factors, will be considered and investigated.
- The Investigator can reference the IB in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- All solicited ARs (local and systemic) will be considered causally related to vaccination.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.9.6. Reporting of Serious Adverse Events

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the Investigator or designee is responsible for reporting the SAE to the Sponsor, regardless of relationship, within 24 hours of becoming aware of the event via the EDC system.

It is the Principal Investigator's responsibility to notify the IRB of all SAEs that occur at his or her site. Investigators will be notified of all unexpected, serious, vaccine-related events (7- and 15-day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB of these additional SAEs.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events in accordance with the regulations for each country.

The Sponsor will provide the SMC and the IST with data of all SAEs on an ongoing basis.

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to the Sponsor will be the EDC.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours of becoming aware of the event.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form.

SAE Reporting to the Sponsor via Paper CRF

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 (US and Canada): +1-866-599-1341

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

8.9.7. Follow-up of Adverse Events and Serious Adverse Events

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature

and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF. Supplemental eCRF pages should be current at the time of SAE reporting: medical history, concomitant medications associated with these events, demographics, mRNA-1647 vaccine administration, and death as applicable.

Unavailable details of the event should not delay submission of the known information. As additional details (eg, laboratory data, concomitant medication, participant's status) become available, the SAE report form should be updated and re-submitted via the EDC system.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

8.9.8. Pause Rules

Safety precautions including dose-escalation, sequential enrollment, limited vaccination, and continuous safety evaluation by the IST will be taken.

The pause rules are presented in Table 4.

Table 4: Pause rules

Pause Rule	Event	Threshold for Triggering Study Pause
1	SAE that cannot be reasonably attributed to a cause other than vaccination	≥ 1 participant
2	Grade 4 AE (including safety laboratory abnormality) that cannot be reasonably attributed to a cause other than vaccination	≥ 1 participant
3	Systemic hypersensitivity reaction[1] within 60 minutes after vaccination	≥ 1 participant
4	Grade 3 solicited **local** AR lasting > 24 hours in a mRNA-1647 vaccine cohort beginning within 7 days following each vaccination	≥ 20% and ≥ 2 participants within a dose level

5	Grade 3 solicited **systemic** AR lasting > 24 hours in a mRNA-1647 vaccine cohort beginning within 7 days following each vaccination	≥ 20% and ≥ 2 participants within a dose level
6	Grade 3 unsolicited AE in a mRNA-1647 vaccine cohort that cannot be reasonably attributed to a cause other than vaccination -or- Grade 3 safety laboratory abnormality in a mRNA-1647 vaccine cohort that cannot reasonably be attributed to a cause other than vaccination	≥ 10% and ≥ 2 participants within a dose level

Abbreviations: AE = adverse event; AR = adverse reaction; SAE = serious adverse event.

[1]Systemic hypersensitivity reaction is defined as acute onset of illness involving skin and/or mucosa (eg, generalized hives, pruritis or flushing; swollen lips/tongue/uvula) plus one of the following: a) respiratory compromise (eg, shortness of breath, wheezing) b) reduced blood pressure or symptoms consistent with reduced blood pressure (eg, syncope, orthostasis).

Pause rules will be applied separately by serostatus group. The 7-day post-vaccination period refers to the time from study vaccination through the following 6 days. The percentage and participant numbers for triggering unblinded assessment for study pause will be computed based on the number of exposed participants within a dose level who have provided safety data at any point during the 7-day post-vaccination period. Part 2 participants will be combined with Part 1 participants at the same dose level and considered as a single cohort. Unblinded assessment for study pause will be performed by the SMC. Grading of laboratory parameters was based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (DHHS 2007).

The Investigators, CRA, Sponsor Medical Lead and IST will monitor for events contributing to Pause Rules throughout the entire duration of the study. When a study pause occurs, the IST will request an ad hoc SMC meeting to review all relevant safety data in a blinded and unblinded manner in order to recommend study continuation, modification, or discontinuation as outlined in the SMC Charter.

If a study pause occurs, enrollment and vaccinations will be immediately suspended within the affected dose level and higher dose levels in the affected serostatus group (ie, CMV-seronegative group or CMV-seropositive group), and all safety and immunogenicity assessments will continue per protocol. The SMC will convene to review all available data and will issue a recommendation to the Sponsor for continuation without modification, continuation with modification, or study termination. 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, the window allowance for vaccination visits may be extended by an additional 7 days (ie, +14 days) for affected participants at the discretion of the Sponsor.

8.10. Study Completion

At the last study visit (Day 504), the Investigator will:

- Review data collected to ensure accuracy and completeness; and
- Complete the Study Completion Page in the eCRF.

Further information regarding study completion and early withdrawal is provided in Section 7.

8.11. Unblinding

Except in the case of medical necessity, a participant's treatment assignment should not be unblinded while participating in the study without the approval of the Sponsor. If a participant becomes seriously ill or pregnant while participating in the study, the blind will be broken only if knowledge of the treatment assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual treatment assignment, the Investigator will make every attempt to contact the CRO CRA to explain the need for unblinding within 24 hours of opening the code. The Investigator will be responsible for documenting the time, date, reason for unblinding, and the names of the personnel involved. The Investigator (or designee) will have access to unblind participants within IRT. All instances of treatment unblinding will be tracked in IRT and documented in the final study report.

If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the study, the Investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms.

Upon completion of final study procedures, including the final assessment and recording of MAAEs and SAEs, the participant's treatment assignment may be unblinded, using the IRT system, to the Investigator, participant, Sponsor, and Sponsor representatives/delegates. The primary purpose for unblinding the participant's treatment assignment upon completion of the final procedures is to allow the Investigator to assess the eligibility of seropositive participants for enrollment into the extension study (mRNA-1647-P202-EXT). However, the treatment assignment may also be unblinded upon completion of final study procedures for seronegative participants and participants who do not wish to enroll in Study mRNA-1647-P202-EXT. The Investigator is responsible for documenting the treatment unblinding for each participant.

8.12. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.13. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.14. Genetics

Genetics are not evaluated in this study.

8.15. Biomarkers

Biomarkers are not evaluated in this study.

8.16. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the Statistical Analysis Plan (SAP), which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

9.1. Responsibility of Analyses/Blinding

This trial is being conducted as an observer-blind study. The Sponsor Biostatistics department or designee will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented via an IRT.

Planned interim analyses and unblinded independent SMC review are described in Section 9.7. At each 3-month interim analysis, pre-identified Sponsor members will be unblinded to review treatment level results as defined in the study Data Blinding Plan. Sponsor personnel who have access to review unblinded results will be documented. Participants, Investigators, and study sites will remain blinded according to the blinding/unblinding procedures outlined in Section 8.11. The results of interim analyses will not be shared with the Investigators prior to the completion of the study.

9.2. Hypotheses/Estimation

Study objectives are presented in Section 3.1.

There is no hypothesis testing in this study.

9.3. Analysis Endpoints

9.3.1. Primary Endpoints

The primary endpoints for the study are presented in Section 3.2.1.

9.3.2. Secondary Endpoints

The secondary endpoints for the study are presented in Section 3.2.2.

9.3.3. Exploratory Endpoints

The exploratory endpoints for the study are presented in Section 3.2.3.

9.4. Analysis Populations

9.4.1. Randomized Set

The Randomized Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study.

9.4.2. Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomized and received any study vaccination, and contribute any solicited AR data, ie, have at least one post-baseline solicited safety (eDiary) 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 vaccination they actually received.

9.4.3. Safety Set

The Safety Set consists of all randomized participants who received any study vaccination. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the vaccination group corresponding to the study vaccination they actually received for the analysis of safety data using the Safety Set.

9.4.4. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized participants who a) receive any study vaccination, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least one post-vaccination assessment for the analysis endpoint. Participants will be included in the vaccination group to which they are randomized.

9.4.5. Per-Protocol Set

The PP Set consists of all FAS participants who a) comply with the vaccination schedule, b) comply with the timings of immunogenicity blood sampling to have post-vaccination results available for at least one assay component corresponding to the immunogenicity analysis objective, and c) have no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective.

The PP Set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the vaccination group to which they are randomized.

9.5. Sample Size Determination

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1647.

Approximately 252 participants will be enrolled in Part 1 of the study with approximately 189 participants randomized to mRNA-1647 vaccine. With 189 participants, there is > 95% probability to observe at least one participant with an AE if the true incident of the AE is 2%. Approximately 200 participants will be enrolled in Part 2 of the study with approximately 150 participants randomized to CCI of mRNA-1647. With 150 participants who are randomized to receive CCI of mRNA-1647, there is > 90% probability to observe at least one participant with an AE if the true incident of the AE is 2%.

9.6. Statistical Methods

9.6.1. Summary of Baseline Characteristics and Demographics

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by serostatus and vaccination group by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

The vaccination groups are:

- mRNA-1647 vaccine: CCI
- mRNA-1647 vaccine: CCI
- mRNA-1647 vaccine: CCI
- Placebo

9.6.2. Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) for Adverse Reaction Terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for rash.

Rash will be graded as:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

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 CMV serostatus (CMV-seropositive and CMV-seronegative) and vaccination group, unless otherwise specified.

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 vaccination will be provided with a two-sided 95% exact CI using the Clopper-Pearson method.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

For all other safety parameters, descriptive summary statistics will be provided and Table 5 summarizes analysis strategy for safety parameters.

Table 5: Analysis strategy for safety parameters

Safety Endpoint	Descriptive Statistics (Number and Percentage of participants)	95% CI
Any Solicited AR	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 Grade 3 and above AE	X	

95% CI using the Clopper-Pearson method
X=results will be provided

For treatment emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by serostatus, vaccination group and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, and coagulation results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the SAP.

9.6.3. Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP Set and will be by serostatus group. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the anti-CMV nAb titers, GMT with corresponding 95% CI at each timepoint and GMR with corresponding 95% CI at each post-baseline timepoint over pre-vaccination (eg, baseline) will be provided by serostatus and vaccination group. Descriptive summary statistics including median, minimum, and maximum will also be provided.

The number and percentage of participants with ≥ 2-fold, 3-fold, and 4-fold increases in serum anti-CMV nAb titers from baseline will be provided with two-sided 95% CI using Clopper-Pearson method at each post-baseline timepoint. The definition of sero-response will be provided in the SAP.

9.7. Interim Analyses and Data Monitoring Committee Analyses

The following analyses will be conducted on cleaned data and may be combined depending on study timelines.

1. An interim analysis of safety and immunogenicity data collected from Visit Day 1 through Day 84 (Month 3) was planned for Part 1. Due to the COVID-19 pandemic, this interim analysis was performed based on a subset of participants who have completed 3 months of safety and immunogenicity assessments as of 26 May 2020. This analysis will serve as the basis for selection of the mRNA-1647 dose level for implementation in Part 2 and in subsequent trials. Additional of safety and immunogenicity data collected from Visit Day 1 through Day 84 (Month 3) may be performed after all participants in Part 1 and for all participants in Part 2 after all participants in Part 2 have completed 3 months of assessments, and available safety or immunogenicity data up to Day 196 (Month 7) may also be summarized as part of these interim analyses. Pre-identified Sponsor team members will be unblinded to group treatment level results. Participants, Investigators, and study sites will remain blinded.
2. The 7-month interim analyses of safety and immunogenicity data collected from Visit Day 1 through Day 196 (Month 7) may be performed for each dose level of Part 1 and for

Part 2. Available safety or immunogenicity data up to Day 336 (Month 12) may also be summarized as part of these interim analyses. Pre-identified Sponsor team members will be unblinded to group treatment level results and individual listings. Participants, Investigators, and study sites will remain blinded.

3. The final unblinded analysis of safety and immunogenicity data collected from Visit Day 1 through the end of the trial will be conducted when the database is cleaned and locked. Results of this analysis will be presented in a CSR, including individual listings.

9.7.1. Study Safety Oversight

Participant safety will be primarily monitored by a blinded IST with ad hoc safety reviews by an unblinded independent SMC. Details regarding composition, responsibilities and procedures of the IST and the SMC will be presented in the respective charters. The IST will provide primary safety oversight at defined intervals through completion of enrollment and vaccine administration, including the review of available safety data to authorize initiation of Dose Level 2 CCI and Dose Level 3 CCI The IST will also review all available safety data through 7 days after the first vaccination at the highest dose level in Part 1.

In Part 1, scheduled IST reviews will be held for the CMV-seropositive and CMV-seronegative groups separately and will occur at each dose level after the first 8 participants in the respective group complete Day 8. In Part 2, the SMC will be convened on an ad hoc basis if a safety signal emerges.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with ICH Guideline for GCP, all applicable regulatory requirements, applicable participant privacy requirements, and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH harmonized tripartite guideline E6(R2): GCP and current SOPs.

Conduct of the study includes, but is not limited to, the following:

- IRB review and favorable opinion/approval of study protocol and any subsequent amendments
- Participant's informed consent process
- Investigator reporting requirements as stated in the protocol

Federal regulations and the ICH E6(R2) guidelines require that approval be obtained from an IRB before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study's participants, and any other written information regarding this study to be provided to the participant must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2) guidelines will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the name and address of the IRB, the clinical protocol by title or protocol number or both and the date on which the approval or a favorable opinion was granted.

10.2. Study Monitoring

The CRA, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the CRA will visit the Investigator and study facility at periodic intervals in addition to maintaining necessary telephone and letter contact. The CRA will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. The CRA will be blinded to treatment assignment during the participant's study participation but may become unblinded when the participant completes the study (see Section 8.11). A separate unblinded CRA will be responsible for treatment accountability.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

10.3. Audits and Inspections

The Investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

10.4. 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.

10.5. Informed Consent Process

Written informed consent in compliance with the US Title 21 CFR Part 50 will be obtained from each participant before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the participant is performed. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent form should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the Investigator should submit the informed consent form (ICF) to the IRB for review and approval before the start of the study. If the ICF is revised during the study, all active participants must sign the revised form.

Before enrollment, each prospective participant will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give his or her consent to participate in the study by signing the ICF.

The ICF will also explain that excess samples from immunogenicity testing may be used for future research which may be performed at the discretion of the Sponsor to further the understanding of the immunobiology that underlies the human immune response to mRNA-1647, and to CMV and/or other diseases. Any future research done with left over specimens from this study may help to develop new products or laboratory tests in the future that could be sold by Moderna. There will be no human genetic testing (eg, whole genome sequencing, cell line creation) performed on these samples.

Participant consent for use of samples for future testing is a part of the overall informed consent document and does not require a separate consent or signature. Participants may withdraw the use of their samples from future research at any time by informing the site. Participants who withdraw consent (whether from all study activities or just from future use of samples) will be documented by site staff in the participant's source documentation and reported to the Sponsor (or its designated CRO) -- their leftover study samples will not be used for any additional future testing outside the scope of the protocol endpoints. All data (including samples for protocol-specified endpoints) collected until the date that the participant withdraws study consent may be used for analysis.

All study samples collected will be centrally stored at PPD Labs in Highland Heights, Kentucky. Samples left over from protocol-specified assays will remain securely stored at PPD Labs until transfer to a qualified 3rd party laboratory for future research or long-term storage under the direction of the Sponsor. After 15 years from completion of the study any leftover samples will be destroyed.

The results of any future testing will not be communicated to Investigators or study participants and will not be stored in the participant's medical record. All samples collected and stored for this study (including future research) will be de-identified. Any link connecting the samples to the participant will remain at the individual clinical study sites in adherence to Good Clinical Practices. No study participant identifiers (ie, Protected Health Information "PHI") will be maintained at any time by the Sponsor or any of its storage / testing laboratories. Samples for future testing may retain the de-identified codes to link the data with the original study results and ensure chain of custody and traceability. Data generated from future testing will not identify the study participants and will not be shared with public databases (eg, dbGaP).

The Investigator or designee will provide a copy of the ICF to the participant. The original form will be maintained in the participant's medical records at the study site.

10.6. Protocol Amendments

Protocol amendments must be approved by the Sponsor, health authorities where required, and the IRB. In cases when the amendment is required in order to protect the participant safety, the

amendment can be implemented prior to IRB approval. Notwithstanding the need for formal approval of a protocol amendment, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action; the IRB at the study site; and, if required by local regulations, the relevant health authority should be informed within 10 working days.

10.7. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Major protocol deviations are defined as exclusionary from the analysis according to the protocol objectives and endpoints. In some cases, exclusion of data may be due to a reason other than a protocol deviation (eg, early termination).

10.8. Data Protection

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, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

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

10.9. Study Safety Oversight by Internal Safety Team and Safety Monitoring Committee

Two safety monitoring boards, an IST and an independent SMC, will be organized to oversee safety of the study. Details regarding composition, responsibilities, and procedures of the IST and the SMC are presented in the respective charters.

Internal Safety Team

The IST will include a coordinating Investigator, the CRO CRA and Sponsor representatives. In Part 1, the IST will review blinded safety data at 7 days after each study vaccination at each dose level as specified in Figure 1. For the 2 lower dose levels, the IST will provide authorization for

enrollment into the next dose level. The IST will also review all available safety data through 7 days after the first vaccination at the highest dose level.

If the IST determines that a pre-specified pause rule (see Section 8.9.8) is met or any safety concern is identified, the SMC will be notified. In such cases, study enrollment and study vaccination of the respective dose cohort(s) will be paused. The IST will be notified within 24 hours of the Investigator reporting any event listed in Table 4. In addition, the IST will receive the following blinded reports:

- Summary listings of accumulated solicited ARs, unsolicited AEs, SAEs, and results of laboratory testing
- New information that may adversely affect the safety of the participant or the conduct of the study
- All protocol amendments and informed consent modifications

Safety Monitoring Committee

This study will be overseen by an unblinded SMC which will be called to convene on an ad hoc basis if any of the pause rules are met or if other safety concerns emerge throughout the study. Overall, the role of the SMC includes the review and protection of data integrity and rights and safety of study participants throughout the study period. It will provide initial, regular, and closing advice to the Sponsor on medical, ethical, scientific, and safety-related issues. The SMC's advice will be based on the interpretation of study data with reference to the study protocol.

The SMC will review the protocol and ICF. Meetings will be documented and minutes of open sessions of the SMC meetings made available to the Sponsor. The SMC may, if deemed necessary, convene a meeting with, or request further information from the Principal Investigator and the Sponsor's representatives at any stage of the study.

The SMC may recommend to the Sponsor to suspend the enrollment of participants to the study and/or suspend the enrollment of certain study group(s) based on their review of safety data arising in this study.

Closed sessions of the SMC safety reviews will be conducted using unblinded data. The SMC will review all available safety data while taking into account any other findings that could have an impact on the safety of the participants.

The SMC members will determine whether any of the predefined study pause rules are met or if there are any other safety concerns. If no safety concern is observed, the favorable outcome of the safety evaluation will be documented and provided in writing.

The SMC will receive the following safety data within 48 hours of the Sponsor becoming aware of the event:

- Fatal SAEs
- Life-threatening SAEs
- SAEs assessed as related to study vaccination
- Any SAEs occurring within 30 days of vaccination

10.10. Dissemination of Clinical Study Data

The Sponsor will ensure that the key design elements of this protocol are posted in a publicly accessible database such as clinicaltrials.gov in compliance with current regulations. The Sponsor will also ensure that key results of this clinical study are posted in a publicly accessible database within the required time-frame from the end of study.

10.11. Data Collection and Management

This study will be conducted in compliance with the current version of the ICH document "Guidance for Industry-E6 Good Clinical Practice: Consolidated Guidance". This study will also be conducted in accordance with the Declaration of Helsinki (2013).

This study will use electronic data collection (to collect data directly from the investigational 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. CRAs 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.

10.12. Source Documents

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for participants who are treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and similar sources.

10.13. Retention of Records

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study vaccination. However, these documents should

be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the Investigator/institution as to when these documents no longer need to be retained.

10.14. Publication Policy

The data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

The data are the property of the Sponsor and cannot be published without their prior authorization, but data and publication thereof will not be unduly withheld.

APPENDIX 2. ADDITIONAL SCHEDULE OF ASSESSMENTS

Table 6: Schedule of Events for Participants Completing the First 2 Vaccinations Only[12]

Visit Number	0[1]	1	2	3	4[13]	5	6	7-10	11	12
Month Timepoint		M0		M1	M2[13]		M3	M4-7	M8	M14
Type of Visit	C	C	C	C	C	C	C	SC	C	C
Study Visit Day	Part 1 D-27 to D0 (Screening) Part 2 SN D-27 to D0 SP D-41 to D0	D1 (Baseline)	D8	D29	D56	D63	D84	D112 D140 D169	D252	D420
Window Allowance (Days)		−28	+3	± 7	± 7[13]	+3	- 7 to +21	± 7	± 7	± 7
Days Since Most Recent Vaccination (except M6/D168 visit should be based on D1)	-	0	7	28	55/0	7	28	56, 84, 167, 140	196	364
ICF, demographics, inclusion/exclusion criteria, concomitant medications, non-study vaccinations, medical history[1]	X									
Physical examination[2]	X	X	X	X	X	X	X		X	
Vital signs[3]	X	X	X	X	X	X	X		X	
Pregnancy testing[4]	X	X			X					
Randomization		X								
Blood for Screening/safety labs[5,6,7]	X	X	X	X	X	X	X			
Blood for antibody-mediated immunogenicity[7]		X		X	X		X		X	X
Blood for cell-mediated immunogenicity[7, 11]		X	X		X	X			X	X
Study vaccination (including 60-minute post-dosing observation period)		X			X					
eDiary activation for recording solicited ARs (7 days)[8]		X			X					
Review of eDiary			X			X				
Follow-up safety calls[9]								X		
Recording of unsolicited AEs		X	X	X	X	X	X			

Visit Number	0[1]		1	2	3	4[13]	5	6	7-10	11	12
Month Timepoint			M0		M1	M2[13]		M3	M4-7	M8	M14
Type of Visit	C		C	C	C	C	C	C	SC	C	C
Study Visit Day	Part 1 D-27 to D0 (Screening)	Part 2 SN D-27 to D0 SP D-41 to D0	D1 (Baseline)	D8	D29	D56	D63	D84	D112 D140 D168	D252	D420
Window Allowance (Days)			−28	+3	± 7	± 7[13]	+3	- 7 to +21	± 7	± 7	± 7
Days Since Most Recent Vaccination (except M6/D168 visit should be based on D1)	-		0	7	28	55/0	7	28	56, 84, 167, 140	196	364
Recording of concomitant medications and non-study vaccinations[10]			X	X	X	X	X	X	X[14]	X[14]	X[14]
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[10]			X	X	X	X	X	X	X	X	
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[10]	X		X	X	X	X	X	X	X	X	X
Study completion[15]											X

Abbreviations: AE = adverse event; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease-2019; D = day; eDiary = electronic diary; EUA = Emergency Use Authorization; FDA = US Food and Drug Administration; ICF = informed consent form; M = month; MAAE = medically-attended adverse event; SAE = serious adverse event; SC = safety (phone) call; SN = seronegative participants; SP = seropositive participants.

1 Based on prior approval from the Sponsor, the Screening visit may be performed across 2 separate clinic visits. In Part 1, screening may occur up to 28 days prior to Visit Day 1. In Part 2, the screening window is 28 days (Days -27 to 0) for CMV-seronegative participants and 42 days (Days -41 to 0) for CMV-seropositive participants.

2 Physical examination: a full physical examination, including height and weight, will be performed at Screening; symptom-directed physical examinations will be performed at all other scheduled timepoints. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified during a study visit should be reported as a MAAE.

3 Vital signs to be collected pre and post-dosing on days of vaccination (Day 1 and Day 56).

4 Pregnancy test at Screening will be included in blood testing; pregnancy testing before each study vaccination (or at any time at the discretion of the Investigator) will be a point-of-care urine test.

5 Screening laboratory tests:

- CMV IgG with reflex to IgM
- Serology: HBsAg, hepatitis C virus antibody, HIV type 1 and 2 antibodies
- Hematology: hemoglobin, platelet count, and total and differential white blood cell count
- Chemistry: ALT, ALP, AST, total bilirubin, creatinine, random glucose
- Coagulation: PTT and PT
- FSH level may be measured to confirm menopausal status at the discretion of the Investigator.

[6] Safety laboratory tests:

- Hematology: hemoglobin, platelet count, total and differential white blood cell count
- Chemistry: AST, ALT, total bilirubin, creatinine
- Coagulation: PTT and PT

[7] Sample must be collected prior to dosing on days of vaccination (Day 1 and Day 56).

[8] eDiary entries will be recorded by the participant at approximately 1 hour after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the diary each day after they leave the clinic, preferably in the evening, on the day of vaccination and for 6 days following vaccination. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit.

[9] Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, information on concomitant medications associated with those events, and any vaccinations.

[10] All non-study vaccinations administered during the period starting ≤ 28 days before the first dose of study vaccine and all concomitant medications and non-study vaccinations through 28 days after each vaccination will be recorded; COVID-19 vaccination (regardless of type of vaccine) will be recorded anytime from Day 1 through the End of the Study (Day 420); all concomitant medications relevant to or for the treatment of an SAE will be recorded from Screening through the End of Study (Day 420), and all concomitant medications relevant to or for the treatment of a MAAE will be recorded from Visit 1 (Day 1) through Day 252.

[11] Blood for exploratory cell-mediated immunogenicity will be collected for a subset of up to 16 participants (approximately 8 CMV-seropositive and 8 CMV-seronegative) for each dose level. The Sponsor will allocate clinical sites to enroll participants in this subset. Participants engaging in blood sampling for cell-mediated immunogenicity should be advised to refrain from blood donation through the vaccination period (Day 1 through Month 7).

[12] All scheduled study visits should be completed within the defined visit window. In the event the participant is not able to come on site for a clinic visit as a result of the COVID-19 pandemic (COVID-19 vaccination under the FDA EUA or FDA approval, 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”), a safety call to the participant should be made in place of the clinic visit. The safety

call 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 calls at Visits 12-15). Home visits will be permitted for all non-dosing visits in the event a participant cannot make it to the clinic as a result of the COVID-19 pandemic. Home visits must be permitted by the site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).

[13] In the event the visit for Dose 2 is disrupted and cannot be completed at Day 56 ±7 days as a result of the COVID-19 pandemic (COVID19 vaccination under the FDA EUA or FDA approval, 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 56 + 56 days (ie, to 4 months). When the extended window is utilized, the Day 84 visit is to be completed at 28 (-7 to +21) days after Dose 2 and monthly safety calls should occur every 28 days ± 7 days until the Month 6 visit (Day 168).

[14] Only documentation of the COVID-19 vaccine is required for Visit 7 (Day 110) through Visit 12 (Day 420).

[15] Upon completion of final study procedures, including the final assessment and recording of MAAEs and SAEs, the participant's treatment assignment may be unblinded via the IRT system.

Table 7: Schedule of Events for Participants Completing the First Vaccination Only[12]

Visit Number	0[1]		1	2	3	4-7	8	9
Month Timepoint			M0		M1	M2-5	M6	M12
Type of Visit	C		C	C	C	SC	C	C
Study Visit Day	Part 1 D-27 to D0 (Screening)	Part 2 SN D-27 to D0 SP D-41 to D0 (Screening)	D1 (Baseline)	D8	D29	D56 D84 D112 D140	D168	D336
Window Allowance (Days)			−28	+3	± 7	± 7	± 7	± 7
Days Since Most Recent Vaccination	-		0	7	28	55, 83, 111, 139	167	335
ICF, demographics, inclusion/exclusion criteria, concomitant medications, non-study vaccinations, medical history[1]	X							
Physical examination[2]	X		X	X	X		X	
Vital signs[3]	X		X	X	X		X	
Pregnancy testing[4]	X		X					
Randomization			X					
Blood for Screening/safety labs[5,6,7]	X		X	X	X			
Blood for antibody-mediated immunogenicity[7]			X		X		X	X
Blood for cell-mediated immunogenicity[7,11]			X	X			X	X
Study vaccination (including 60-minute post-dosing observation period)			X					
eDiary activation for recording solicited ARs (7 days)[8]			X					
Review of eDiary				X				
Follow-up safety calls[9]						X		
Recording of unsolicited AEs			X	X	X			
Recording of concomitant medications and non-study vaccinations[10]			X	X	X	X[13]	X[13]	X[13]

Visit Number	0[1]		1	2	3	4-7	8	9
Month Timepoint			M0		M1	M2-5	M6	M12
Type of Visit	C		C	C	C	SC	C	C
Study Visit Day	Part 1 D-27 to D0 (Screening)	Part 2 SN D-27 to D0 SP D-41 to D0 (Screening)	D1 (Baseline)	D8	D29	D56 D84 D112 D140	D168	D336
Window Allowance (Days)			−28	+3	± 7	± 7	± 7	± 7
Days Since Most Recent Vaccination	-		0	7	28	55, 83, 111, 139	167	335
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[10]			X	X	X	X	X	
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[10]	X		X	X	X	X	X	X
Study completion[14]								X

Abbreviations: AE = adverse event; AR = adverse reaction; C = clinic visit; COVID 19 = coronavirus disease-2019; D = day; eDiary = electronic diary; EUA = Emergency Use Authorization; FDA = US Food and Drug Administration; ICF = informed consent form; M = month; MAAE = medically-attended adverse event; SAE = serious adverse event; SC = safety (phone) call; SN = seronegative participants; SP = seropositive participants.

[1] Based on prior approval from the Sponsor, the Screening visit may be performed across 2 separate clinic visits. In Part 1, screening may occur up to 28 days prior to Visit Day 1. In Part 2, the screening window is 28 days (Days -27 to 0) for CMV-seronegative participants and 42 days (Days -41 to 0) for CMV-seropositive participants.

[2] Physical examination: a full physical examination, including height and weight, will be performed at Screening; symptom-directed physical examinations will be performed at all other scheduled timepoints. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified during a study visit should be reported as a MAAE.

[3] Vital signs to be collected pre and post-dosing on the day of vaccination (Day 1).

[4] Pregnancy test at Screening will be included in blood testing; pregnancy testing before each study vaccination (or at any time at the discretion of the Investigator) will be a point-of-care urine test.

[5] Screening laboratory tests:

- CMV IgG with reflex to IgM
- Serology: HBsAg, hepatitis C virus antibody, HIV type 1 and 2 antibodies

- Hematology: hemoglobin, platelet count, and total and differential white blood cell count
- Chemistry: ALT, ALP, AST, total bilirubin, creatinine, random glucose
- Coagulation: PTT and PT
- FSH level may be measured to confirm menopausal status at the discretion of the Investigator.

[6] Safety laboratory tests:

- Hematology: hemoglobin, platelet count, total and differential white blood cell count
- Chemistry: AST, ALT, total bilirubin, creatinine
- Coagulation: PTT and PT

[7] Sample must be collected prior to dosing on the day of vaccination (Day 1).

[8] eDiary entries will be recorded by the participant at approximately 1 hour after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the diary each day after they leave the clinic, preferably in the evening, on the day of vaccination and for 6 days following vaccination. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit.

[9] Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, information on concomitant medications associated with those events, and the vaccination.

[10] All non-study vaccinations administered during the period starting ≤ 28 days before the first dose of study vaccine and all concomitant medications and non-study vaccinations through 28 days after vaccination will be recorded; COVID-19 vaccination (regardless of type of vaccine) will be recorded anytime from Day 1 through the End of the Study (Day 336); all concomitant medications relevant to or for the treatment of an SAE will be recorded from Screening through the End of Study (Day 336), and all concomitant medications relevant to or for the treatment of a MAAE will be recorded from Visit 1 (Day 1) through Day 168.

[11] Blood for exploratory cell-mediated immunogenicity will be collected for a subset of up to 16 participants (approximately 8 CMV-seropositive and 8 CMV-seronegative) for each dose level. The Sponsor will allocate clinical sites to enroll participants in this subset. Participants engaging in blood sampling for cell-mediated immunogenicity should be advised to refrain from blood donation through the vaccination period (Day 1 through Month 7).

[12] All scheduled study visits should be completed within the defined visit window. In the event the participant is not able to come on site for a clinic visit as a result of the COVID-19 pandemic (COVID-19 vaccination under the FDA EUA or FDA approval, 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”), a safety call to the participant should be made in place of the clinic visit. The safety call 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 calls at Visits 12-15). Home visits will be permitted for all non-dosing visits in the event a participant cannot

make it to the clinic as a result of the COVID-19 pandemic. Home visits must be permitted by the site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).

[13] Only documentation of the COVID-19 vaccine is required for Visit 4 (Day 56) through Visit 9 (Day 336).

[14] Upon completion of final study procedures, including the final assessment and recording of MAAEs and SAEs, the participant's treatment assignment may be unblinded via the IRT system.

APPENDIX 3. TOXICITY GRADING SCALE TABLES

The toxicity grading scales for clinical and laboratory abnormalities are presented in Table 8 and Table 9, respectively.

Note that for laboratory abnormalities, grading only occurs if the values are outside of the normal values established by the clinical laboratory.

For Solicited ARs, grading is assessed based on the modified 2007 CBER toxicity grading scale found in Section 8.1.3.

Table 8: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Swelling/Induration (hardness)**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Swelling/induration should be evaluated and graded using the functional scale as well as the actual measurement.

Source: DHHS 2007

Vital Signs †	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130	Emergency room visit or hospitalization for arrhythmia
Bradycardia (beats per minute)‡	50 – 54	45 – 49	< 45	Emergency room visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	Emergency room visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	Emergency room visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	Emergency room visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Note that fever is classified under systemic reactions for grading purposes.

† Participant should be at rest for all vital sign measurements.

‡ When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Source: DHHS 2007

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Fever (°C) [§] (°F) [§]	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Nausea/ Vomiting	No interference with activity or 1 to 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 h ours	Prevents daily activity, requires outpatient IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/24 hours	4 – 5 stools or 400 – 800 g/24 hours	6 or more watery stools or > 800 g/24 hours or requires outpatient IV hydration	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Emergency room visit or hospitalization

Abbreviations: IV = intravenous

§ Oral temperature; no recent hot or cold beverages or smoking.

Source: DHHS 2007 and DHHS 2014

Table 9: Tables for Laboratory Abnormalities

Serum Chemistry*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)****
Glucose – hypoglycemia (mg/dL)	65 – 69	55 – 64	45 – 54	< 45
Glucose – hyperglycemia Random (mg/dL)	---	139 – 200	> 200	Insulin requirements or hyperosmolar coma
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphatase; increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	> 10 × ULN
Liver function tests – ALT and AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
Bilirubin – when accompanied by any increase in liver function test; increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	> 1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN

Abbreviations: CPK = creatine phosphokinase; ULN = upper limit of normal

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125 – 129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Source: DHHS 2007

Hematology †	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Hemoglobin (female) (g/dL)	---	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (female) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) (g/dL)	---	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase (cell/mm3)	11,001– 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC decrease (cell/mm3)	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease (cell/mm3)	750 –899	500 – 749	250 – 499	< 250
Neutrophils decrease (cell/mm3)	1,500 – 1,699	1,000 – 1,499	500 – 999	< 500
Eosinophils (cell/mm3)	801 – 1,500	1,501 – 5,000	> 5,000	Hypereosinophilic
Platelets decreased (cell/mm3)	125,000 – 162,999	100,000 – 124,000	25,000 – 99,000	< 25,000
PT; increase by factor	> 1.0 – 1.10 × ULN	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 × ULN
PTT; increase by factor	> 1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN

Abbreviations: WBC = white blood cell

† The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Source: DHHS 2007

Urine ‡	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field	1 – 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells transfusion

‡ The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Source: DHHS 2007

APPENDIX 4. PROTOCOL AMENDMENT HISTORY

The document history table for this protocol and the Protocol Amendment Summary of Changes Table for the current Amendment 5 is located directly before the Table of Contents.

A description of Amendment 4, Amendment 3, Amendment 2, and Amendment 1 is presented in this appendix.

Amendment 4, 22 February 2021

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Main Rationale for the Amendment:

The purpose of this amendment is to include the use of the COVID-19 vaccine, which can be administered at least 14 days before or after any study vaccination.

The summary of changes table provided here describes the major changes made in Amendment 4 relative to Amendment 3, including the sections modified and the corresponding rationales. The synopsis of Amendment 4 has been modified to correspond to changes in the body of the protocol. Minor editorial and grammatical corrections were also made.

Summary of Major Changes from Protocol Amendment 3 to Protocol Amendment 4:

Section # and Name	Description of Change	Brief Rationale
Title page, Protocol Approval page, page headers	Updated the protocol version and date	To reflect the new version and date of the protocol.
Protocol Amendment Summary of Changes	Added the summary of changes section	For consistency with Moderna's latest protocol template.
IRB and Regulatory Authority Approval	Added section related to IRB and Regulatory Authority approval	For consistency with Moderna's latest protocol template.
Section 1.3 Schedule of Assessments	Updated footnote 14	To include the use of the COVID-19 vaccine.
Section 1.3 Schedule of Assessments	Added additional data collection days for concomitant medications and non-study vaccinations in Table 1 Added footnote 15 to clarify only COVID-19 vaccination data would be collected.	To include additional data collection time points at Days 7-8 and 12-17 for COVD-19 vaccination.

Section # and Name	Description of Change	Brief Rationale
Section 5.3 Exclusion Criteria	Added language on COVID-19 vaccines in exclusion criterion #7 Clarified exclusion criteria #10 is specific to participants in Part 1 of the study	To include the use of the COVID-19 vaccine > 7 days but preferably > 14 days before or after any study vaccination. To clarify that exclusion criterion #10 is specific to participants in Part 1 of the study only.
5.4 Screen Failures	Added language allowing Investigator discretion for rescreening and clarified participants who cannot be rescreened	To include rescreening at the Investigator's discretion. To clarify that participants who screen failed under exclusion criterion #4 and #5 cannot be rescreened.
Section 6.5.1	Added language on recording receipt of COVID-19 vaccine	To clarify that the COVID-19 vaccination (regardless of type of vaccine) will be recorded anytime from Day 1 through the End of the Study (Day 504).
Section 6.5.2. Concomitant Medications and Non-study Vaccinations that May Lead to the Elimination of a Participant from Per-Protocol Analyses	Added language on COVID-19 vaccines	To include the use of the COVID-19 vaccine.
Appendix 2	Updated footnote 13 in Table 6 and footnote 12 in Table 7	To include the use of the COVID-19 vaccine.
Appendix 2	Added additional data collection days for concomitant medications and non-study vaccinations in Table 6 Updated footnotes 10, 12, and 13 to include collection of COVID-19 vaccination data Added footnote 14 to clarify COVID-19 vaccination data collection	To include additional data collection time points from Visit 7 through Visit 12 for COVD-19 vaccination.

Section # and Name	Description of Change	Brief Rationale
Appendix 2	Added additional data collection days for concomitant medications and non-study vaccinations in Table 7 Updated footnotes 10 and 12 to include collection of COVID-19 vaccination data Added footnote 13 to clarify COVID-19 vaccination data collection	To include additional data collection time points from Visit 4 through Visit 9 for COVD-19 vaccination.
Appendix 4 Protocol Amendment History	Added protocol amendment history section	For consistency with Moderna's latest protocol template.

Amendment 3, 04 September 2020

Main Rationale for the Amendment:

The purpose of this amendment was to enroll additional female CMV-seronegative and CMV-seropositive participants in the CCI mRNA-1647 vs. placebo treatment group under "Part 2" of the protocol and allow for interim analyses of safety and immunogenicity for Part 2 participants.

The summary of changes table provided here describes the major changes made in Amendment 3 relative to Amendment 2, including the sections modified and the corresponding rationale. The synopsis of Amendment 3 has been modified to correspond to changes in the body of the protocol. Minor editorial and grammatical corrections were also made.

Summary of Major Changes from Protocol Amendment 2 to Protocol Amendment 3:

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval Page, Headers	Updated the protocol version and date.	To reflect the new version and date of the protocol.
Section 1.2 Schema	Replaced previous Schema figure with a new Schema figure that included Part 2 of the study.	To present the study schema for both Part 1 and Part 2 of the study.
Section 1.3 Schedule of Assessments	Updated header rows for Visit Number, Study Visit Day, Window Allowance (Days), and Days Since Most Recent Vaccination and updated footnotes for Table 1	To add study visit days for Part 2 of the study and to distinguish study visit days from Part 1 of the study.

Section # and Name	Description of Change	Brief Rationale
Section 2.1 Study Rationale	Added rationale for Part 1 and Part 2 of the protocol.	To include female CMV-seronegative and CMV-seropositive participants in the CCI mRNA-1647 vs. placebo treatment group under Part 2 of the protocol. To distinguish between Part 1 and Part 2 of the protocol.
Section 2.3 Benefit/Risk Assessment	Updated numbers of participants.	To include female CMV-seronegative and CMV-seropositive participants under Part 2 of the study.
Section 2.3.2 Anticipated Risks	Clarified when analysis of safety would occur.	To include female CMV-seronegative and CMV-seropositive participants under Part 2 of the study.
Section 4.1 Overall Design	Clarified dose levels, added sex and age ranges for each group for Part 1 and Part 2, and added numbers of participants per group for Part 2	To include additional female participants in the CCI mRNA-1647 vs. placebo treatment group under Part 2 of the protocol and to distinguish between Part 1 and Part 2 of the study.
Section 4.1.1 Screening Period	Added language about screening for Part 1 and Part 2 of the study.	To include additional female participants in the CCI mRNA-1647 vs. placebo treatment group under Part 2 of the study and to distinguish between Part 1 and Part 2 of the study.
Section 4.2 Scientific Rationale for Study Design	Added additional language about Part 1 and Part 2 of the study.	To include additional female participants under Part 2 of the study and to distinguish between Part 1 and Part 2 of the protocol.
Section 4.4 Justification for Dose and Schedule	Added language about the CCI dose for Part 2 of the study.	To include additional female participants under Part 2 of the study and to distinguish between Part 1 and Part 2 of the protocol.
Section 5.1 Participant Recruitment	Updated number of participants to be enrolled.	To include additional female participants under Part 2 of the study and to distinguish between Part 1 and Part 2 of the protocol.
Section 5.2 Inclusion Criteria	Added the age and sex of participants for Part 2 of the study to inclusion criterion #1.	To include additional female participants under Part 2 of the study and to distinguish between Part 1 and Part 2 of the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 6.2.2 Clinical Trial Material Administration	Added injection use for Part 2 of the study.	To clarify that mRNA-1647 injection can be used for multiple dose preparation for Part 2 of the study.
Section 6.3.1 Randomization	Added randomization details for Part 2 of the study.	To specify stratification and randomization ratio for Part 2 of the study.
Section 6.3.2 Blinding	Updated list of who will be blinded to treatment assignments.	To clarify that participants and Investigators will also be blinded to individual treatment assignments.
Section 8.4 Medical History	Removed days for screening period.	To broaden the definition of the screening period due to differences between Part 1 and Part 2 of the study.
Section 8.5 Physical Examination and Vital Signs	Removed days for screening period.	To broaden the definition of the screening period due to differences between Part 1 and Part 2 of the study.
Section 8.7 Study Vaccine Administration	Added “Part 1”.	To clarify description of study vaccine administration referred to Part 1 of the study.
Section 8.9.1.3 Solicited Adverse Reaction	Clarified temperature recording and measurement reporting for injection site erythema or swelling/induration.	To clarify temperature is recorded quantitatively and that measurement of injection site erythema or swelling/induration on the following day may be excluded from solicited AR analysis.
Section 8.9.8 Pause Rules	Updated Table 4 footnotes.	To include additional female participants under Part 2 of the study and to distinguish between Part 1 and Part 2 of the study.
Section 9.1 Responsibility of Analyses/Blinding	Updated text that participants and Investigators will also remain blinded to treatment assignments.	To clarify that participants and Investigators will also be blinded to individual treatment assignments.
Section 9.5 Sample Size Determination	Added the number of participants and sample size calculations for Part 2 of the study.	To include additional female participants under Part 2 of the study.

Section # and Name	Description of Change	Brief Rationale
Section 9.7 Interim Analyses and Data Monitoring Committee Analyses	Updated Month 3 IA to include additional data collection for Part 2 of the study Updated Month 7 IA to include Part 2 of the study and add participants and Investigators will also remain blinded to treatment assignments.	To include data collection and SMC oversight for female participants under Part 2 of the study. To clarify that blinding refers to participants and Investigators, in addition to study sites.
Section 9.7.1 Study Safety Oversight	Added SMC oversight for Part 2 of the study.	To include SMC oversight for female participants under Part 2 of the study.
Section 10.9 Study Safety Oversight by Internal Safety Team and Safety Monitoring Committee	Updated frequency of SMC meetings.	To clarify ad hoc SMC meetings would occur if pause rules are met or safety concerns emerge.
Appendix 2 Additional Schedule of Assessments	Updated header rows for Visit Number, Study Visit Day, Window Allowance (Days), and Days Since Most Recent Vaccination and footnotes for Table 6 and Table 7	To add study visit days for Part 2 of the protocol and to distinguish study visit days from Part 1 of the study.

Amendment 2, 15 April 2020

Main Rationale for the Amendment:

The purpose of this amendment was to incorporate revisions that maintain the safety of participants and site personnel and to manage the breadth of changes necessitated by the response to the COVID-19 pandemic.

The summary of changes table provided here describes the major changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationale. The synopsis of Amendment 2 has been modified to correspond to changes in the body of the protocol. Minor editorial and grammatical corrections were also made.

Summary of Major Changes from Protocol Amendment 1 to Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Title page, Protocol Approval page, page headers	Updated the protocol version and date	To reflect the new version and date of the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments	Updated the header rows for Study Visit Day and Window Allowance (Days) and footnotes for Table 1. The window allowance for Day 84 was adjusted in the header row of Table 1 Added language that participants who have blood sampling for cell-mediated immunogenicity were to refrain from blood donation	To increase the Day 56 window so that participants may receive the second vaccination in the event that the visit cannot be completed within ±7 days of Day 56 due to local, state, or study site restrictions implemented in response to the COVID-19 pandemic. To reflect changes to exclusion criterion #11.
Section 5.2 Inclusion Criteria	Corrected study period in inclusion criterion #7	To clarify that male participants with partners who have become pregnant prior to randomization, not screening, are eligible to participate in the study.
Section 5.3 Exclusion Criteria	Added text on blood donation in exclusion criterion #11	To add guidance regarding participants having cell-mediated immunogenicity blood draws to be advised to refrain from blood donation through the vaccination period.
Section 6.5.1 Recording of Concomitant Medications and Non-study Vaccinations	Corrected the day of enrollment	To correct the day of enrollment from Day 0 to Day 1.
Section 7.1 Discontinuation of Vaccination	Clarified timing of safety calls	To add guidance on procedures to be followed for participants who miss the second vaccination and receive the third vaccination.
Section 8.1 Screening	Corrected the day of enrollment	To correct the day of enrollment from Day 0 to Day 1.
Section 8.4 Medical History	Corrected the visit window for the screening period	To correct the visit window for the screening period.
Section 8.5 Physical Examination and Vital Signs	Corrected the visit window for the screening period	To correct the visit window for the screening period.
Section 8.8 Sampling for Safety and Immunogenicity Assessments	Removed day of screening visit	To correct screening visit.

Section # and Name	Description of Change	Brief Rationale
Section 8.8.4. Blood Sampling for Cell-mediated Immunogenicity	Added text related to blood donations	To reflect changes to exclusion criterion #11 regarding participants having cell-mediated immunogenicity blood draws to be advised to refrain from blood donation through the vaccination period.
Section 8.9.2 Recording of Adverse Events, Serious Adverse Events, and Medically-Attended Adverse Events	Added text on supplemental measurements	To clarify guidance regarding follow-up of Grade 3 laboratory test results or vital sign measurements.
Section 8.9.3 Safety Phone Calls	Added text for safety calls and possibility of home visits for blood draws	To substitute clinic visit safety assessments with safety calls in the event the participant is not able to come on site for a clinic visit due to changes implemented in response to the COVID-19 pandemic. To add the possibility of home visits for blood draws contingent on IRB approval, subject informed consent, site capacity, and Sponsor approval for non-vaccination clinic visits.
Appendix 2 Additional Schedule of Assessments	Updated the header rows for Study Visit Day and Window Allowance (Days) and footnotes for Table 1. The window allowance for Day 84 was adjusted in the header row of Table 1 Added language that participants who have blood sampling for cell-mediated immunogenicity were to refrain from blood donation	To increase the Day 56 window so that participants may receive the second vaccination in the event that the visit cannot be completed within ±7 days of Day 56 due to local, state, or study site restrictions implemented in response to the COVID-19 pandemic. To reflect changes to exclusion criterion #11.
Appendix 3 Toxicity Grading Scale Tables	Updated normal laboratory ranges and removed non-study specific parameters in Table 9	To align the central laboratory normal ranges with the CBER toxicity grade ranges ensuring clear interpretation and grading of study-specific laboratory test results, and to mirror the grading parameters of the CMV-mRNA-P101 trial.

Amendment 1, 04 December 2019

Main Rationale for the Amendment:

The purpose of this amendment was to add the IST review of safety data through 7 days after the first vaccination at the CCI dose level and to include localized axillary swelling or tenderness ipsilateral to the vaccination arm as a solicited local adverse reaction (AR).

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. Minor editorial and grammatical corrections were also made.

Summary of Major Changes from the Original Protocol to Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title page, Protocol Approval page, page headers	Updated the protocol version and date	To reflect the new version and date of the protocol.
Section 1.2 Schema	Added IST review for mRNA-1647 CCI groups	To add the IST review of safety data through 7 days after the first vaccination at the mRNA-1647 CCI dose level.
Section 1.3 Schedule of Assessments	Added header row for Days Since Most Recent Vaccination to Table 1 Updated the header row for Study Visit Day and updated footnotes to include review of ARs and add blood collection for cell-mediated immunity for Table 1	To add "Days Since Most Recent Vaccination" to the table. To add blood collection for cell-mediated immunity.
Section 3.2.3 Exploratory Endpoints	Removed endpoints for plasmablasts and circulating T, B, and NK cells	To remove the exploratory endpoints of total and/or antigen-specific plasmablasts and circulating T, B, and NK cells.
Section 4.2 Scientific Rationale for Study Design	Added IST review through 7 days after the first vaccination	To add the IST review of safety data through 7 days after the first vaccination at the CCI dose level.
Section 5.2 Inclusion Criteria	Added text for male participants with partners who become pregnant before screening in inclusion criterion #7	To add that male participants with partners who have become pregnant prior to the participant's screening visit are eligible to participate in the study.

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Description of Study Vaccine	Updated storage temperature	To correct and clarify investigational product storage temperature ranges (ºC and ºF).
Section 6.2.4 Clinical Trial Material Storage	Added storage temperature	To correct and clarify investigational product storage temperature ranges (ºC and ºF).
Section 8.3 Collect Demographic and Baseline Data	Added age and replaced date of birth with month and year of birth	To correct parameters collected for baseline and demographic data.
Section 8.8 Sampling for Safety and Immunogenicity Assessments	Updated timing of laboratory assessment sample collection, added text for collection of blood for cell-mediated immunity, updated blood volumes for chemistry and coagulation (Table 1)	To reduce the scope of cell-mediated immunogenicity testing from testing all participants to testing a subset of participants and to correct study days listed for sample collection.
Section 8.8.2 Blood Sampling for Safety Laboratory Testing	Updated timing of laboratory assessment sample collection	To correct study days listed for sample collection.
Section 8.8.4 Blood Sampling for Cell-mediated Immunogenicity	Added text for collection of blood for cell-mediated immunity Removed IgG-memory B-cell responses, Pentamer-specific IgG memory B-cell responses, and gB-specific CD4 and CD8 T-cells secreting interleukin (IL)-2 and/or tumor necrosis factor (TNF)-α form the list of cell-mediated immunogenicity parameters Clarified the cell-mediated immunogenicity parameters included gB-specific and Pentamer-specific CD4 and CD8 IFN-γ-secreting T-cells as measured by ELISpot	To reduce the scope of cell-mediated immunogenicity testing and reflect changes to the exploratory endpoints.

Section # and Name	Description of Change	Brief Rationale
Section 8.9.1.3 Solicited Adverse Reaction	Added text for localized axillary swelling or tenderness ipsilateral to the vaccination arm and updated Table 2 accordingly Clarified guidance for follow-up of ARs within 7 days after study vaccination and ARs recorded in eDiaries beyond Day 7 Updated timing of review of completed eDiaries	To include localized axillary swelling or tenderness ipsilateral to the vaccination arm as a solicited local AR. To clarify that ARs recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit. To update guidance for ARs within 7 days after study vaccination. To adjust days when review of completed eDiaries takes place.
Section 8.9.2 Recording of Adverse Events, Serious Adverse Events, and Medically-Attended Adverse Events	Clarified guidance for follow-up of ARs within 7 days after study vaccination Added text to clarify when the study site staff will contact the participant and added text on reporting pregnancies	To clarify that the study site staff will contact the participant within 24 hours of becoming aware of any reports of Grade 3 ARs, presence of any rash, or presence of any underarm swelling or tenderness. To add the description of pregnancy reporting procedures.
Section 8.9.5 Assessment of Causality	Added that all solicited ARs will be considered causally related	To clarify that all solicited ARs (local and systemic) will be considered causally related to vaccination.
Section 8.9.8 Pause Rules	Updated Table 4 footnote to include text on IST requested ad hoc SMC meetings	To correct the description of the ad hoc SMC review of Pause Rules.
Section 9.7 Interim Analyses and Data Monitoring Committee Analyses	Updated timings for safety and immunogenicity data collection	To reduce the scope of cell-mediated immunogenicity testing from testing all participants to testing a subset of participants and to correct study days listed.
Section 9.7.1 Study Safety Oversight	Added text about IST review	To add the IST review of safety data through 7 days after the first vaccination at the CCI dose level.
Section 10.5 Informed Consent Process	Added text for future testing of samples	To clarify process for future testing and communication of results of future testing.
Section 10.9 Study Safety Oversight by Internal Safety Team and Safety Monitoring Committee	Added text for IST review	To add the IST review of safety data through 7 days after the first vaccination at the CCI dose level.

Section # and Name	Description of Change	Brief Rationale
Appendix 2 Schedule of Events for Participants Completing the First 2 Vaccinations Only	Added header row for Days Since Most Recent Vaccination, updated the header row for Study Visit Day, and updated footnotes to include review of ARs and add blood collection for cell-mediated immunity for Table 6 and Table 7	To add "Days Since Most Recent Vaccination" to the tables.
Appendix 3 Toxicity Grading Scale Tables	Updated solicited AR grading	To clarify grading of solicited ARs is assessed based on the modified 2007 CBER toxicity grading scale.

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Signature Page for VV-CLIN-000477 v10.0

Approval	PPD 07-Jun-2021 15:03:55 GMT+0000
Approval	PPD 07-Jun-2021 15:08:53 GMT+0000
Approval	PPD 07-Jun-2021 15:09:11 GMT+0000
Approval	PPD 07-Jun-2021 16:20:51 GMT+0000
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Approval	PPD 08-Jun-2021 01:57:28 GMT+0000

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Administrative Change Letter 1 to Protocol Amendment 5

Protocol Title:	A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Trial to Evaluate the Safety and Immunogenicity of Cytomegalovirus Vaccine mRNA-1647 in Healthy Adults
Protocol Number:	mRNA-1647-P202
Date of Memorandum:	31May2022
Memorandum Rationale:	Safety Case Processing Update

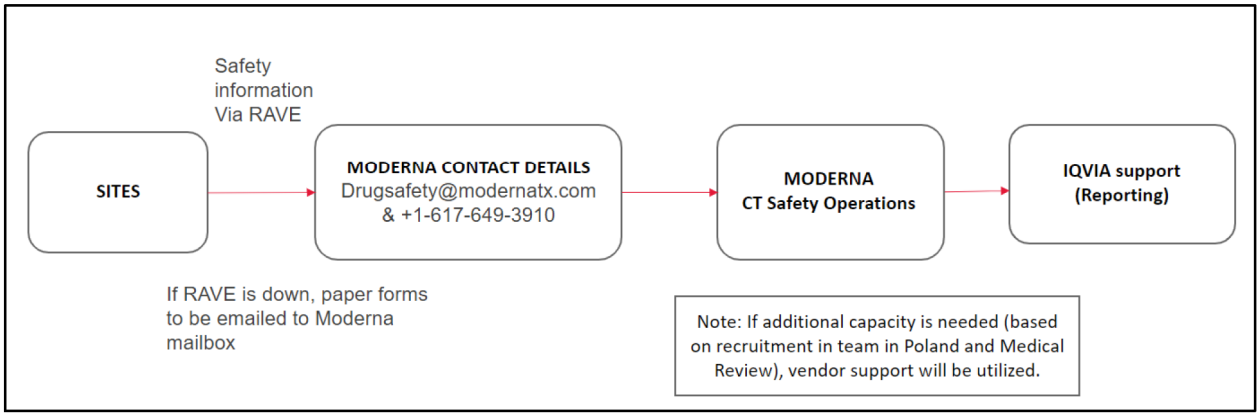
Please be advised that CT Safety Case processing and medical review will now be managed in-house at Moderna effective 6 Jun 2022. IQVIA will continue providing expedited reporting. As such the following changes will apply:

1.Safety Reporting contact details need to be updated to Moderna contact details:

Email address: Drugsafety@modernatx.com
Fax number: +1-617-649-3910
Please remove IQVIA contact details and any hotline numbers for safety reporting

2. In the event RAVE is down, please use the Moderna SAE/AESI/Pregnancy paper templates provided

3. You will receive communication from Moderna mailbox (drugsafety@modernatx.com) when the Safety team needs to follow up with you to answer queries raised in RAVE.



Please submit this letter to your Ethics Committee and file in your Investigator Site File. For sites utilizing Central IRB, Advarra, this letter will be submitted on your behalf.

Sponsor Approval of Administrative Change Letter to Protocol mRNA-1647-P202 Amendment 5, 27May2021 (dated 31-May-2022):

I approve the above-named administrative changes:

PPD

02-Jun-2022 | 14:54 EDT

PPD

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Date

Investigator Acknowledgement of Administrative Change Letter to Protocol mRNA-1647-P202 Amendment 5, 27May2021 (dated 31-May-2022):

I acknowledge receipt of the above-named administrative changes:

Signature: _____ _____

Principal Investigator Date

_____

Title

Printed Name: _____

Principal Investigator

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Administrative Change Letter

Protocol Title:	A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Trial to Evaluate the Safety and Immunogenicity of Cytomegalovirus Vaccine mRNA-1647 in Healthy Adults
Protocol Number:	mRNA-1647-P202
Amendment Number:	5
Date of Amendment #:	27-May-2021
Date of Memorandum:	12-Oct-2022
Memorandum Rationale:	To clarify intention for/further define future research.

This letter is to clarify that the sponsor may perform future testing on excess samples from immunogenicity testing as defined in the protocol (see reference below) while the study is ongoing or after all data is collected.

Although not described in the main sections, the following language in Section 10.5 under Appendix 1 of the Clinical Protocol describes future research/testing:

"The ICF will also explain that excess samples from immunogenicity testing may be used for future research which may be performed at the discretion of the Sponsor to further the understanding of the immunobiology that underlies the human immune response to mRNA-1647, and to CMV and/or other diseases. Any future research done with left over specimens from this study may help to develop new products or laboratory tests in the future that could be sold by Moderna. There will be no human genetic testing (eg, whole genome sequencing, cell line creation) performed on these samples."

Any future testing performed by Moderna will align with the language already present in the Main ICF:

WILL MY SAMPLES BE USED FOR ANYTHING ELSE?

Additional laboratory tests may be performed in the future with left over samples to further understand immune responses to the study vaccine or for further research related to CMV and/or other diseases and for other future research and development purposes. The blood samples will be stored until the tests analyzing your immune response to the study vaccine are performed. The blood samples may be stored for up to approximately 15 years by the sponsor or designee. The future use of your blood samples may result in new discoveries that are important to our understanding of the study

vaccine or of immune responses. The results of the study of your samples will be used for research purposes only and you will not be told the results of the tests.

PPD will submit to your Institutional Review Board. Please file in your Investigator Site File.

Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact:	PPD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: PPD e-mail: PPD
Regulatory Authority Identifier Number(s):	IND: 17725

Sponsor Approval of Administrative Change Letter to Protocol mRNA-1647-P202 Amendment 5, 27May2021 (dated 31-May-2022): I approve the above-named administrative changes:

See eSignature on last page

_____

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Investigator Acknowledgement of Administrative Change Letter to Protocol mRNA-1647-P202 Amendment 5, 27May2021 (dated 31-May-2022):

I approve the above-named administrative changes:

Principal Investigator Printed Name: _____

Principal Investigator Signature: _____

Date: _____

Signature Page for VV-CLIN-008022 v1.0

Approval	PPD 14-Oct-2022 17:26:51 GMT+0000

Approval	PPD 14-Oct-2022 18:24:38 GMT+0000

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