ModernaTX, Inc.

Protocol mRNA-1647-P202, Amendment 5

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

Statistical Analysis Plan

SAP Version 5.0
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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Solicited AR	solicited adverse reaction
AST	alkaline phosphatase
BMI	body mass index
CBL	Moderna Clinical Biomarker Lab
CI	confidence interval
CMI	cell-mediated immunogenicity
CMV	cytomegalovirus
COVID	Coronavirus
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
eCRF	electronic case report form
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FSH	follicle-stimulating hormone
gB	glycoprotein B
GLSM	geometric least squares means
GMR	geometric mean ratio
GMT	geometric mean titer
HBsAg	hepatitis B virus surface antigen
HIV	human immunodeficiency virus
ICS	intracellular cytokine staining
IFN	interferon
IgG	immunoglobulin G
IRT	interactive response technology
LLOQ	lower limit of quantification
MAAEs	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
PBMC	peripheral blood mononuclear cell
Pentamer	pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex
PP	per-protocol
PT	preferred term

Abbreviation	Definition
PT	prothrombin time
PTT	partial thromboplastin time
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1647-P202, is based on the most recent approved clinical study protocol (CSP), Version Amendment 5, dated 27 May 2021 and the most recent approved electronic case report form (eCRF) Version 14.002, dated 02 Dec 2022.

This SAP version 5.0 is to update the planned analyses before the final database lock and full unblinding, after which the final analysis will be performed.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 9) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1647-P202 is a Phase 2, randomized, observer-blind, placebo-controlled, dose-finding study 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.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and immunogenicity data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the first interim analysis data extraction and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, subject and participant are used interchangeably; vaccination, injection, and dose are used interchangeably; vaccination group and treatment group are used interchangeably.

2. Study Objectives

2.1. Primary Objective

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.

2.2. 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.

2.3. 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. Study Endpoints

3.1. Primary Endpoints

The primary endpoints of the study are as follows:

- 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.

3.2. Secondary Endpoints

The second endpoints of the study are as follows:

- GMT of anti-glycoprotein B (gB) specific immunoglobulin G (IgG) and anti-pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex (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.

3.3. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

- 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.

* Reflects the description of this exploratory endpoint in the protocol; refer to Section 7 on the change of the assay for this endpoint from ELISpot to ICS.

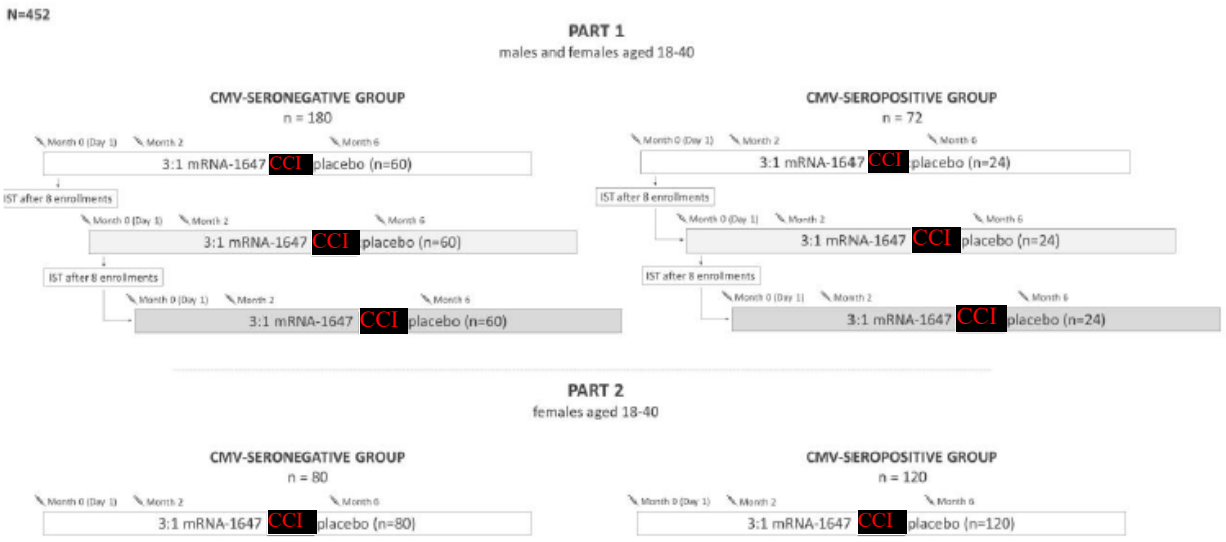
4. Study Design

4.1. Overall Study Design

This is a Phase 2, randomized, placebo-controlled, observer-blind, dose-finding trial enrolling healthy participants 18-40 years of age.

A schematic of the study design is shown in Figure 1.

Figure 1 Study Design Schematic



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

In protocol amendment version 3, Part 2 of the study was added to evaluate the safety and immunogenicity of the selected CCI mRNA-1647 dose level in a larger female population, which is the target population for Phase 3 development.

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.

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

4.2. Sample Size and Power

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%.

4.3. 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.

4.4. Blinding and Unblinding

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.

Except in the case of medical necessity, a participant's treatment should not be unblinded while participating in the study without the approval of the Sponsor. The treatment code should be broken only if the Investigator/physician in charge of the participant feels that the case cannot be treated without knowing the identity of the study vaccine. Instructions regarding emergency unblinding will be provided to the Investigator and is discussed in Section 8.11 of the protocol.

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 study procedures.

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.

5. Analysis Populations

The following analysis sets are defined: Randomized Set, Solicited Safety Set, Safety set, Full Analysis set (FAS), and Per-Protocol (PP) set.

5.1. 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. This set will be used for descriptive purposes.

5.2. 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.

In addition, a subset of the Solicited Safety Set is defined for each vaccination. The First (Second; Third) Vaccination Solicited Safety Set consists of all subjects in the Solicited Safety Set who have received the first (second; third) study vaccination and have contributed any solicited AR data (eDiary) from the time of first (second; third) study vaccination through the following 6 days.

Subjects will be analyzed according to the vaccination group a subject received, rather than the vaccination group to which the subject is randomized. Subjects who receive a vaccination/injection that is different from the vaccination/injection which the subject is randomized to will be summarized under the highest dose of vaccination group (i.e., mRNA-1647 CCI > mRNA-1647 CCI > mRNA-1647 CCI > Placebo).

5.3. 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.

Subjects will be analyzed according to the vaccination group a subject received, rather than the vaccination group to which the subject is randomized to. Subjects who receive a vaccination/injection that is different from the vaccination/injection which the subject is randomized to will be summarized under the highest dose of vaccination group (i.e., mRNA-1647 CCI > mRNA-1647 CCI > mRNA-1647 CCI > Placebo).

5.4. Full Analysis Set

Full Analysis Set (FAS) for Antibody-Mediated Immunogenicity

The FAS for antibody-mediated immunogenicity consists of all randomized participants who

a) receive any study vaccination,

b) have baseline (Day 1) antibody-mediated immunogenicity data available for those analyses that require baseline data, and

c) have at least one post-vaccination antibody-mediated immunogenicity assessment for the analysis endpoint.

FAS for Cell-Mediated Immunogenicity

The FAS for cell-mediated immunogenicity (CMI) consists of all randomized participants who

a) receive any study vaccination,

b) have baseline (Day 1) CMI data available for those analyses that require baseline data, and

c) have at least one post-vaccination CMI assessment for the analysis endpoint.

Participants will be included in the vaccination group to which they are randomized.

5.5. Per-Protocol Sets

The Per-Protocol (PP) Set for Antibody-Mediated Immunogenicity

PP Set for Antibody-Mediated Immunogenicity consist 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 (antibody-mediated immunogenicity endpoints), and

c) have no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective (antibody-mediated immunogenicity endpoints).

Subjects who were CMV seronegative at Screening and became CMV seropositive at baseline (before or on 1st dose of study vaccination) will be excluded from the PP Set for Antibody-Mediated Immunogenicity.

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

PP Set for CMI

PP Set for CMI consist of all FAS for Cell-Mediated participants who

a) comply with the 3-dose 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 (CMI endpoints), and

c) have no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective (CMI endpoints).

Subjects who were CMV seronegative at Screening and became CMV seropositive at baseline (before or on 1st dose of study vaccination) will be excluded from the PP Set for CMI.

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

6. Statistical Analysis

6.1. General Considerations

The Schedule of Assessments is provided in the protocol Table 1 for subjects completing all vaccinations, Table 6 for subjects completing the first 2 vaccinations only, and Table 7 for subjects who completing the first vaccination only.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study vaccination.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that vaccination group within the analysis set of interest, unless otherwise specified.

Study day relative to the first vaccination will be calculated as below:

a) study day prior to the first vaccination will be calculated as: date of assessment/event – date of the first vaccination;

b) study day on or after the date of the first vaccination will be calculated as: date of assessment/event – date of the first vaccination + 1;

Study day relative to the most recent vaccination will be calculated as below:

a) study day prior to the first vaccination will be calculated as: date of assessment/event – date of the first vaccination;

b) study day on or after the date of the first vaccination but before the second vaccination (if applicable) will be calculated as: date of assessment/event – date of the first vaccination + 1;

c) study day after the date of the second vaccination but before the third vaccination (if applicable) will be calculated as: date of assessment/event – date of the second vaccination + 1; if study day is on the same day as the second vaccination, date and time will be compared with the second vaccination date and time. If it is prior to the second vaccination, then study day is calculated as b); If it is after the second vaccination or the time is missing or not available, then study day is calculated as: date of assessment/event – date of the second vaccination + 1. If a subject did not receive the second vaccination, but received the third vaccination, study day after the second vaccination will be treated as missing, and only calculate in relative to the third vaccination.

d) study day after the date of the third vaccination will be calculated as: date of assessment/event – date of the third vaccination + 1; if study day is on the same day as the third vaccination, date and time will be compared with the third vaccination date and time. If it is prior to the third vaccination, then study day is calculated as: date of assessment/event – date of the second vaccination + 1; If it is after the third vaccination or the time is missing or not available then study day is calculated as: date of assessment/event – date of the third vaccination + 1.

For GMT calculation, antibody values reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

The following **stages** are used for reporting and analysis purposes:

- Vaccination stage:

  For assessments that will be collected throughout the study (eg, unsolicited AE), it consists first vaccination on Day 1 to the earliest date of (28 days after last vaccination [ie, the day of last vaccination and 27 subsequent days], discontinuation from the study, or death). If a subject receives three vaccinations, this stage starts at the first vaccination on Day 1 and continues through the earliest date of (28 days after 3rd vaccination, withdraw from study, or death).

  For assessments that will be collected at study visits (eg. laboratory and vital sign), if a subject receives three vaccinations, this stage starts at the first vaccination on Day 1 and continues through the earliest date of (Month 7 visit, withdraw from study, or death); If a subject receives first two vaccinations, this stage starts at the first vaccination on Day 1 and continues through the earliest date of (Month 3 visit, withdraw from study, or death); If a subject receives first vaccination only, this stage starts at the first vaccination on Day 1 and continues through the earliest date of (Month 1 visit, withdraw from study, or death).

- Follow up stage: For assessments that will be collected throughout the study (eg, unsolicited AE), this stage starts at 29 days after the last vaccination (ie, the day of last vaccination and 28 subsequent days, regardless of number of vaccinations received) and continue until the earliest date of (study completion, discontinuation from the study, or death).

There is no planned follow up stage for assessments that will be collected at study visits (eg. laboratory and vital sign).

- Overall stage: This stage starts at the first vaccination on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death).
- 28 days after each vaccination stage: This stage starts at the day of each vaccination and continue through the earliest date of (the day of each vaccination and 27 subsequent days, next vaccination (if applicable)).

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- For laboratory assessments, if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (eg, < 0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the ULOQ (eg, > 3000), the numeric values will be imputed by ULOQ in the summary.

Other incomplete/missing data will not be imputed, unless specified otherwise.

The following **vaccination groups** will be used for summary purposes:

- mRNA-1647 vaccine: CCI

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

Summary by study part and CMV serostatus:

All analyses and data summaries/displays will be provided by CMV serostatus (CMV-seropositive and CMV-seronegative) unless otherwise specified. Analyses and data summaries/displays may be provided by study part (Part 1, Part 2, and/or overall) when specified, please also refer to Section 6.5 Planned Analyses.

For those subjects who were CMV seronegative at Screening and became CMV seropositive at Baseline (before or on the day of 1st vaccination), the subjects will be:

- included in the Randomized Set under the CMV status group the subjects were randomized under, ie, CMV seronegative
- included in the Solicited Safety Set and Safety Set, under CMV seropositive group
- included in the FAS, under CMV seropositive group
- excluded from the PP Set for Antibody-Mediated Immunogenicity data and CMI data

All analyses will be conducted using SAS Version 9.4 or higher.

6.2. Background Characteristics

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories will be summarized by CMV serostatus (CMV-seropositive, CMV-seronegative, and overall) and vaccination group as defined in Section 6.1 based on Randomized Set:

- Randomized Set
- Solicited Safety Set
- Safety Set
- Full Analysis Set

- PP Set

The percentage will be based on subjects in that vaccination group within the Randomized Set. A separate table based on the Safety Set reporting the number and percentage of subjects in the Solicited Safety Set will be provided.

The number of subjects in the following categories will be summarized based on subjects screened:

- Number of subjects screened
- Number and percentage of screen failure subjects and the reason for screen failure

The percentage of subjects who screen failed will be based on the number of subjects screened. The reason for screen failure will be based on the number of subjects who screen failed.

The number and percentage of subjects in each of the following disposition categories will be summarized by CMV serostatus and vaccination group based on the Randomized Set:

- Received each study vaccine
- Prematurely discontinued study vaccine and the reason for discontinuation
- Completed study
- Willing to enroll in Study P202-EXT
- Prematurely discontinued the study and the reason for discontinuation

The denominator for all percentages will be the number of subjects in that vaccination group within the Randomized Set.

A subject disposition listing will be provided including informed consent, subjects who completed study, subjects who were willing to enroll in Study P202-EXT, subjects who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure subjects with reasons for screen failure.

Study duration will be summarized since randomization, since first vaccination, since second vaccination, and since third vaccination. Study duration since randomization (first vaccination, second vaccination, third vaccination) will be calculated as the earliest date of (study completion, discontinuation from the study, data cutoff, or death) – date of randomization (date of first vaccination, second vaccination, third vaccination) + 1. If the

date of randomization (date of first vaccination, second vaccination, third vaccination) is not available, the corresponding duration will be zero. The summaries will be provided separately for the Safety Set, FAS for Antibody-Mediated Immunogenicity, and PP Set for Antibody-Mediated Immunogenicity.

A subject is considered to have completed the study if they complete the final visit per the protocol Schedule of Assessments, independent of how many doses were administered.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of subjects will be provided for categorical variables such as gender, race, ethnicity, CMV serostatus at screening, and baseline CMV serology. Positive baseline CMV serology will be defined as either nAb titer against epithelial cell infection or the nAb titer against fibroblast infection above the LLOQ at baseline. The summaries will be presented by CMV serostatus (CMV-seropositive, CMV-seronegative and overall) and vaccination group as defined in Section 6.1 based on the Safety Set. If the Safety Set differs from the Randomized Set (eg, subjects randomized but not treated; subjects received wrong treatment), the analysis will also be conducted using the Randomized Set.

For screened failure subjects, age (years), gender, race, ethnicity will be presented in a listing.

In addition, subjects with any inclusion and exclusion criteria violation will also be provided in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending frequency in the total mRNA-1647 group, and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD).

The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (ie, on the day of vaccination and the 6 subsequent days) and during the 28-day follow-up period after each vaccination (ie, on the day of vaccination and the 27 subsequent days) will be summarized by CMV serostatus (CMV-seropositive, CMV-seronegative, and overall) and vaccination groups as defined in Section 6.1 as follows:

- Any concomitant medications and non-study vaccination within 7 Days Post Vaccination
- Any concomitant medications and non-study vaccination within 28 Days Post Vaccination
- Prophylactic antipyretics or analgesics medication within 28 Days Post Vaccination
- Antipyretic or analgesic medication within 28 Days Post Vaccination

A summary table of concomitant medications and non-study vaccination that continued or newly received at or after the first vaccination through 28 days after the last vaccination will be provided by PT in descending frequency in the mRNA-1647 group with all dose level combined.

The summary tables will be based on the Safety Set.

Prior, concomitant and post medications and non-study vaccination will be presented in a listing.

Medications taken to treat or prevent pain or fever will be collected in the electronic diary (eDiary) within 7 days after vaccination and beyond 7 days after vaccination (if any solicited AR continues beyond 7 days). Summaries will be provided up to 28 days after vaccination based on the Solicited Safety Set by CMV serostatus (CMV-seropositive, CMV-seronegative, and overall) and vaccination group as defined in Section 6.1 for each vaccination (first, second, third). Medications to treat or prevent pain or fever as collected in the eDiary will also be presented in a separate listing.

Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study vaccine administration data will be presented in a listing.

6.2.6. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the subjects with each major protocol deviation type will be provided by CMV serostatus (CMV-seropositive, CMV-seronegative, and overall) and treatment group as defined in Section 6.1 based on the Randomized Set.

Major protocol deviations will be presented in a listing.

6.2.7. COVID-19 Impact

A listing of COVID-19 impact will be provided.

6.3. Safety Analysis

Safety and reactogenicity assessments will include monitoring and recording of solicited (local and systemic reactogenicity events) ARs and unsolicited AEs, medically-attended AEs, SAEs, AEs leading to discontinuation from study vaccine or participation in the study, clinical laboratory test results including hematology, serum chemistry, and coagulation; vital sign measurements; and physical examination findings. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [DHHS 2007] will be used 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, CMV-seronegative and overall) and vaccination group, unless otherwise specified.

6.3.1. Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject who is administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with the treatment.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study vaccine or any event already present that worsens in intensity or frequency after exposure. Adverse events will also be evaluated by the investigator for the coexistence of medically-attended AE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Unsolicited adverse events will be coded by PT and SOC using MedDRA and summarized by CMV serostatus (CMV-seropositive, CMV-seronegative and overall), vaccination group and stage (Vaccination Stage, Follow-up Stage, Overall Stage, and 28 days after each vaccination stage [including an overall summary, i.e., after any vaccination]; see Section 6.1 for definitions of vaccination group and stage).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will present SOC and PT, will include counts of subjects, and will be based on TEAEs. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of total mRNA-1647 and then alphabetically within SOC.

Percentages will be based upon the number of subjects in the Safety Set within each vaccination group.

6.3.1.1. Incidence of Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of subjects who experience the following will be presented:

- Any unsolicited TEAEs
- Any serious TEAEs
- Any unsolicited TEAEs that are medically-attended
- Any unsolicited TEAEs leading to discontinuation from study vaccine
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited TEAEs of Grade 3 or higher
- Any unsolicited TEAEs that are fatal
- Any non-serious unsolicited TEAEs
- Any non-serious unsolicited TEAEs Grade 3 or higher

The table will also include number and percentage of subjects with unsolicited TEAEs that are treatment-related in each of the above categories.

In addition, separate listings containing individual subject adverse event data for all unsolicited TEAEs, TEAEs leading to discontinuation from study vaccine, TEAEs leading to discontinuation from participation in the study, serious TEAEs, and medically-attended TEAEs will be provided separately.

6.3.1.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by MedDRA SOC and PT using frequency counts and percentages (ie, number and percentage of subjects with an event). SOC will be displayed in internationally agreed order. Within SOC, PT will be displayed in descending frequency of total mRNA-1647 and then alphabetically. When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from study vaccine
- All unsolicited TEAEs leading to discontinuation from participation in the study
- All unsolicited TEAEs of Grade 3 or higher
- All unsolicited TEAEs of Grade 3 or higher that are treatment-related
- All unsolicited TEAEs that are medically-attended

Summary tables of unsolicited TEAEs will also be provided by SOC, PT, and severity/toxicity grade (ie, Any Grade, Grade 3, Grade 4, Grade 3 or Higher).

In addition, summary tables of selected unsolicited TEAEs of clinical interest as identified by Standardized MedDRA Query (SMQ) will be provided by PT. The following SMQs will be implemented in this study:

- Anaphylactic Reaction (Algorithmic). For this study, when a combination of terms are searched based on the algorithm, the identified terms need to occur within 24 hours of each other based on AE onset date and time (when available) to qualify as a case for this algorithmic SMQ.
- Cardiomyopathy (Narrow).
- Hypersensitivity (Narrow).
- Cardiac Arrhythmias (Narrow).
- Embolic and Thrombotic Events (Narrow).
- Cardiac Failure (Narrow).
- Ischaemic Heart Disease (Narrow).
- Immune-Mediated/Autoimmune Disorders (Narrow).
- Angioedema (Narrow).
- Central Nervous System Haemorrhages and Cerebrovascular Conditions (Narrow; Level 2 Subordinate SMQ under the Level 1 SMQ of Central Nervous System Vascular Disorders).

6.3.2. Solicited Adverse Reactions

The term "Solicited Adverse Reactions" refers to selected signs and symptoms occurring after vaccination administration during a specified post-vaccination follow-up period (day of vaccination and 6 subsequent days). The solicited ARs are recorded by the subject in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-vaccination follow-up period (day of vaccination and 6 subsequent days), using a pre-defined checklist in the eDiary (ie, solicited ARs).

The following local ARs will be solicited: pain at injection site, erythema (redness) at injection site, swelling (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 solicited ARs will be graded based on the grading scales presented in Table 3 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent

Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). Investigator will assess the Grading for rash and Grade 4 events (with exception of fever). 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

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.

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

All solicited ARs analyses will be based on Solicited Safety Set. All solicited ARs analyses will be provided by CMV serostatus (CMV-seropositive, CMV-seronegative and overall) and vaccination group as defined in Section 6.1 for each vaccination (first, second, or third), unless otherwise specified.

The number and percentage of subjects who reported any solicited AR, any solicited local AR, and any systemic solicited AR during the 7-day follow-up period after each vaccination will be tabulated by CMV serostatus, vaccination group, and vaccination, with a two-sided 95% exact CI using the Clopper-Pearson method.

The number and percentage of subjects who reported each individual solicited local AR (has a severity grade of Grade 1 or greater) and solicited systemic AR (has a severity grade of Grade 1 or greater) during the 7-day follow-up period after each vaccination will be tabulated by CMV serostatus, vaccination group, severity grade and vaccination.

The number and percentage of subjects who reported each individual solicited AR will also be summarized by CMV serostatus, vaccination group, severity grade, day of reporting and vaccination. The number and percentage of subjects experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral, axillary, or tympanic route) by severity grade and the number and percentage of subjects experiencing a fever of Grade 3 or higher temperature (a temperature greater than or equal to 39.0°C/102.1°F by the oral, axillary, or tympanic route) in cumulative half-degree (°F) increments will be provided.

The onset of individual solicited AR is defined as the time point after each vaccination at which the respective solicited AR first occurred. The number and percentage of subjects with onset of individual solicited AR will be summarized by CMV serostatus, vaccination group, study day relative to corresponding vaccination (Day 1 through Day 7) and vaccination.

The duration (days) of each solicited AR will be summarized by CMV serostatus, vaccination group and vaccination. Duration will be calculated as the end day/date of the solicited AR event – the start day/date of the solicited AR event + 1, regardless of whether it is intermittent or continued. If the solicited AR continues beyond 7 days, the consecutive days a solicited AR is reported after 7 days will be included (eg, an event that lasted 5 days in the first 7 days post vaccination and 3 consecutive days beyond 7 days post vaccination, the duration will be reported as 8 (5+3) days.).

All solicited ARs (including rash) that continue beyond 7 days post vaccination will be presented in separate data listings.

6.3.3. Clinical Laboratory Evaluations

Safety laboratory testing will include hematology (hemoglobin, platelet count, and total and differential white blood cell count), serum chemistry (liver function tests including alanine aminotransferase [ALT], alkaline phosphatase [AST], total bilirubin, and creatinine) and coagulation (partial thromboplastin time [PTT] and prothrombin time [PT]).

A pregnancy test will be performed on all female subjects of childbearing potential at Screening (serum test), before each study vaccination on Visits Day 1, Month 2, and Month 6 (urine test), and as needed at unscheduled visits (urine or serum pregnancy test based on the Investigator’s discretion).

Screening only laboratory test will include CMV IgG with reflex to IgM, screening serology (hepatitis B virus surface antigen [HBsAg], hepatitis C virus antibody, human immunodeficiency virus [HIV] type 1 and 2 antibodies), and follicle-stimulating hormone (FSH) level (may be measured to confirm menopausal status at the discretion of the Investigator).

All laboratory test results will be presented in the data listings. The results that are outside the reference ranges will be flagged in the data listings. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any safety laboratory (hematology, serum chemistry and coagulation) will be listed separately. If a subject has a laboratory test with

Grade 2 or higher abnormality at any post vaccination visit, then all results for that subject and laboratory test will be presented in the listing.

For continuous hematology, serum chemistry, and coagulation measurements, the observed values and changes from baseline will be summarized at each scheduled visit by CMV serostatus (CMV-seropositive, CMV-seronegative and overall) and vaccination group as defined in Section 6.1. Shift from baseline in the toxicity grades to the worst post-baseline result will also be summarized by CMV serostatus (CMV-seropositive, CMV-seronegative and overall) and vaccination group.

6.3.4. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values meeting the toxicity grading criteria will be flagged in the data listing. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a subject has a vital sign result with Grade 2 or higher abnormality at any post vaccination visit, then all results of vital sign measurement for that subject will be presented in the listing.

Observed values and changes from baseline for all vital sign measurements will be summarized at each scheduled visit by CMV serostatus (CMV-seropositive, CMV-seronegative, and overall) and vaccination group as defined in Section 6.1. Shift from baseline in the toxicity grades will also be summarized at each scheduled visit by CMV serostatus and vaccination group.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Set and will be by serostatus group (ie, CMV-seropositive and CMV-seronegative groups) and vaccination group as defined in Section 6.1. 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% (for each serostatus group), supportive analyses of antibody-mediated immunogenicity may be conducted using the FAS. The supportive analysis is required if the condition is met at end of study; it is optional for the interim analyses.

The GMT will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers.

The geometric mean ratio (GMR) measures the changes in immunogenicity titers within subjects. The GMR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers for subject i at time points j and k, $j \neq k$

6.4.1. Immunogenicity Assessments

There will be two types of immunogenicity assessments:

- Antibody-mediated immunogenicity assessments include serum neutralizing anti-CMV antibodies, anti-gB IgG, and anti-Pentamer IgG.
- CMI assessments include gB-specific and Pentamer-specific CD4 and CD8 cytokine secreting T-cells as measured by ICS. Blood for CMI will be collected for a subset of up to 16 participants (approximately 8 CMV-seropositive and 8 CMV-seronegative) for each dose level. Other exploratory CMI assessments may be performed.

6.4.2. Analysis of Antibody-Mediated Immunogenicity Endpoints

For each group, the following evaluations will be performed at each time point at which blood samples are collected for antibody-mediated immunogenicity (unless otherwise specified):

- GMT of the serum anti-CMV neutralizing antibody titers against epithelial cell infection and anti-CMV neutralizing antibody titers against fibroblast infection will be provided at each time point with corresponding 95% CI. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. GMT and corresponding 95% CI

will be plotted over time. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

- GMRs of anti-CMV neutralizing antibody titers against epithelial cell infection and anti-CMV neutralizing antibody titers against fibroblast infection at each individual post-vaccination time point over pre-vaccination (eg, Visit Day 1 [baseline]) will be tabulated with 95% CI. The 95% CIs will be calculated based on the t distribution of the difference in the log-transformed values then back transformed to the original scale for presentation. GMR and corresponding 95% CI will be plotted over time.
- In the CMV-seronegative groups, proportion of subjects with titers above baseline GMT of all CMV-seropositive subjects at each timepoint after baseline (Day 1) will be tabulated.
- Proportion of subjects with a ≥2-fold, 3-fold, and 4-fold increase in serum anti-CMV neutralizing antibody titers against epithelial cell infection and anti-CMV neutralizing antibody titers against fibroblast infection from Visit Day 1 (baseline) to post-vaccination time points will be tabulated with 2-sided 95% Clopper-Pearson CIs.
- Proportion of subjects with overall seroresponse in serum anti-CMV neutralizing antibody titers against epithelial cell infection and anti-CMV neutralizing antibody titers against fibroblast infection at each individual post vaccination time point will be tabulated with 2-sided 95% Clopper-Pearson CIs. Overall seroresponse is defined as subjects who either had an undetectable titer (LLOQ) at baseline and a ≥ 2 x LLOQ titer after vaccination, or a detectable titer (≥ LLOQ) at baseline and at least a 4-fold increase of baseline titer after vaccination.
- In the CMV-seropositive groups, proportion of subjects who achieve serum anti-CMV neutralizing antibody titers against epithelial cell infection and anti-CMV antibody titers against fibroblast infection greater than the third quartile of the serum anti-CMV antibody titers overall distribution at baseline (Day 1) will be tabulated.
- Anti-CMV neutralizing antibody titers against epithelial cell infection and anti-CMV neutralizing antibody titers against fibroblast infection will be displayed using reverse cumulative curves.
- For serum anti-CMV neutralizing antibody titers against epithelial cell infection and anti-CMV neutralizing antibody titers against fibroblast infection respectively, the GMT at Month 3, Month 7, Month 12, and Month 18 for each vaccination group, and

the ratio of GMT of mRNA-1647 CCI mRNA-1647 CCI, and mRNA-1647 CCI vs. Placebo respectively, will be estimated based on an analysis of covariance (ANCOVA) model that will be carried out for CMV-seropositive groups and CMV-seronegative groups separately using the PP Set. For Month 3, the dependent variable will be the nAb at Month 3 with the vaccination group as a factor and the baseline values as covariate (if applicable, ie, for CMV-seropositive groups only). The GMT and corresponding 95% CI for each vaccination group, and the ratio of GMT of mRNA-1647 CCI mRNA-1647 CCI, and mRNA-1647 CCI vs. Placebo respectively, together with corresponding 95% CI will be provided. A similar model at Month 7, Month 12, and Month 18 will be carried out for those who were CMV-seronegative groups, and CMV-seropositive groups separately using the PP set.

Similar analyses will be performed for gB-binding antibodies and Pentamer-binding antibodies as measured by ELISA.

6.4.3. Analysis of CMI Endpoints

Descriptive summary statistics for the observed and change from baseline will be provided at each scheduled visit by serostatus group (ie, CMV-seropositive and CMV-seronegative groups) and vaccination group for CMI parameters, based on the PP Set for CMI. Descriptive statistics for the observed and change from baseline values will be plotted over time.

6.4.4. Sensitivity/Supportive Analysis

In the final analysis of antibody-mediated immunogenicity endpoints, the following sensitivity analyses may be performed to assess the impact of widened visit window and missing data due to COVID-19 pandemic.

1. In Part 1, protocol amendment 2 widened the visit window in response to the COVID-19 pandemic. A sensitivity analysis may be carried out to assess the impact on the widened visit windows on immunogenicity endpoints. In this sensitivity analysis, immunogenicity data which complied with the vaccination and/or immunogenicity assessment schedules under protocol amendment 2, but which did not comply with the schedules under protocol amendment 1, the last version of protocol before the protocol amendment 2, will be excluded from this sensitivity analysis.
2. A restricted maximum likelihood (REML)-based mixed-effect model for repeated measures (MMRM), a model-based missing data approach, will be used for the log-

transformed titer based on the PP set. MMRM is based on the assumption of missing at random.

The analysis will be carried out using SAS PROC MIXED and conducted for CMV-seropositive groups and CMV-seronegative groups separately. The model will include all available log-transformed anti-body titers at each post-baseline visit as the dependent variable, vaccination groups, visit (as a class variable), baseline values (if applicable, ie, for CMV-seropositive groups only), and interaction of vaccination group and visit as fixed effects, and subject as a random effect. An unstructured covariance structure will be used to model the within-subject errors. If the model fails to converge, a compound symmetry covariance structure will be considered. The degrees of freedom of the denominator will be approximated by the Kenward-Roger method. The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for the anti-body titers for each vaccination group will be provided by visit. In addition, the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference between each of mRNA-1647 group CCI [redacted] vs. the Placebo group at each visit. The GLSM, difference in GLSM, and corresponding 95% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale.

6.5. Planned Analyses

The following analyses have been or 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 had completed 3 months of safety and immunogenicity assessments as of 26 May 2020. This analysis served as the basis for selection of the mRNA-1647 dose level for implementation in Part 2 and in subsequent trials. Pre-identified Sponsor team members were unblinded to treatment group-level results. Participants, Investigators, and study sites remained blinded. Additional analyses of safety and immunogenicity data collected from Visit Day 1 through Day 84 (Month 3) could have been performed for all participants in Part 1 and for all participants in Part 2 after all participants in Part 2 had completed 3 months of assessments, and available safety or immunogenicity data up to Day 196 (Month 7) could

also have been summarized as part of these interim analyses. However, these additional 3-month interim analyses were deemed unnecessary by the Sponsor and hence were not performed.

2. A Part 1 7-month interim analysis of safety and immunogenicity data collected from Visit Day 1 through Day 196 (Month 7) was performed after all Part 1 participants had completed 7 months of safety and immunogenicity assessments (data cutoff date 16 Sep 2020). Pre-identified Sponsor team members were unblinded to both treatment group-level results and individual listings. Study participants, Investigators, and study sites remained blinded.
3. A Part 2 7-month interim analysis of safety and immunogenicity data collected from Visit Day 1 through Day 196 (Month 7) was performed after all Part 2 participants had completed 7 months of safety and immunogenicity assessments (data cutoff date 18 Feb 2022). Available safety and immunogenicity data from Visit Day 1 through the end of the trial for all Part 1 participants were also summarized as part of this interim analysis. Pre-identified Sponsor team members were unblinded to both treatment group-level results and individual listings. Study participants, Investigators, and study sites remained blinded until the completion of each individual participant's final study procedures, including final assessment and recording of MAAEs and SAEs, at which point the individual participant's treatment assignment may be unblinded using the IRT system to the Investigator, participant, Sponsor, and Sponsor representatives/delegates, as outlined in protocol Section 8.11 "Unblinding".
4. The final unblinded analysis of safety and immunogenicity data collected from Visit Day 1 through the end of the trial for all participants 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.

At an interim analysis when data from both Part 1 and Part 2 were available and in scope for the analysis, or at the final analysis when all participants in Part 1 and Part 2 have completed or discontinued from the study, data were/will be summarized and analyzed with Part 1 and Part 2 combined, unless otherwise specified.

7. Changes from Planned Analyses in Protocol

For the planned 7-month IAs, protocol Section 9.7 states "Available safety or immunogenicity data up to Day 336 (Month 12) may also be summarized as part of these interim analyses." However, at the time of planning the Part 2 7-month IA with the latest

data cutoff date of 18 Feb 2022 for Part 2 participants, all Part 1 participants either discontinued or completed the study up to the final visit at Month 18 for participants completing all 3 vaccinations. Therefore, the Part 2 7-month IA instead included all available safety and immunogenicity data from Visit Day 1 through the end of the trial for all Part 1 participants to make this analysis more comprehensive. This change did not impact the primary and/or key secondary objectives/hypotheses or the related statistical methods.

For the final analysis, the ELISpot assay planned in protocol Section 3.2.3 for the exploratory CMI endpoints was updated to an intracellular cytokine staining (ICS) assay internally qualified at Moderna Clinical Biomarker Lab (CBL) to measure a larger set of T-cell responses including the planned IFN-γ. The ICS assay was chosen since it can provide information about multiple T-cell responses utilizing the same number of PBMCs with higher sensitivity. The clinical protocol was not amended for this change in the CMI assay which was deemed to have no impact on the primary and/or key secondary objectives/hypotheses or the related statistical methods.

8. References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 2017 Jul 27] [10 screens]. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

9. List of Appendices

9.1. Appendix A Standards for Safety and Immunogenicity Variable Display in TFLs

Continuous Variables

The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results. The GMT and corresponding 95% CI will be presented to one decimal place more than the original results. The GMR and corresponding 95% CI will be presented to two decimal places more than the original results. A maximum of three decimal places will be displayed.

Categorical Variables: Percentages and corresponding 95% CI will be presented to 1 decimal place.

9.2. Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window:

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, ie, nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 1 below.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 1 Visit Window Mapping Rules

Labs (Hematology, Chemistry, and Coagulation) and Vital Signs		
Visit	**Target Study Day**	**Visit Window in Study Day**
Day 1	1 (Date of First Vaccination)	≤ 1 Pre-dose
Day 1, 1-hour post dose (if Vital Signs)	1	1-hour Post-dose
Day 8	8	[1 Post-dose, 18], if Labs; [After 1 Hour Post-dose, 18], if Vital Signs
Month 1	29	[19, 42]
Month 2	56 (Date of Second Vaccination)	[43, 59]
Day 63	63	[60, 73]
Month 3	84	[74, 125]
Month 6	168 (Date of Third Vaccination)	[126, 171]
Day 175	175	[172, 185]
Month 7	196	[186, 265]
Month 12 (Vital Signs Only)	336	[266, 419]
Antibody-Mediated Immunogenicity		
Visit	**Target Study Day**	**Visit Window**
Subjects completing all vaccinations and subjects completing first and third vaccinations only		
Day 1	1 (Date of First Vaccination)	≤1 Pre-dose
Month 1	29	[1 Post-dose, 42]
Month 2	56 (Date of Second Vaccination)	[43, 70] Pre-second-dose
Month 3	84	[70 Post-second-dose, 125]
Month 6	168 (Date of Third Vaccination)	[126, 182] Pre-third-dose
Month 7	196	[182 Post-third-dose, 265]
Month 12	336	[266, 419]

Month 18	504	≥ 420
Subjects completing the first 2 vaccination only		
Day 1	1 (Date of First Vaccination)	≤1 Pre-dose
Month 1	29	[1 Post-dose, 42]
Month 2	56 (Date of Second Vaccination)	[43, 70] Pre-second-dose
Month 3	84	[70 Post-second-dose, 167]
Month 8	252	[168, 335]
Month 14	420	≥ 336
Subjects completing the first vaccination only		
Day 1	1 (Date of First Vaccination)	≤1 Pre-dose
Month 1	29	[1 Post-dose, 98]
Month 6	168	[99, 251]
Month 12	336	≥ 252
CMI		
Visit	**Target Study Day**	**Visit Window**
Subjects completing all vaccinations and subjects completing first and third vaccinations only		
Day 1	1 (Date of First Vaccination)	≤1 Pre-dose
Day 8	8	[1 Post-dose, 31]
Month 2	56 (Date of Second Vaccination)	[32, 59] Pre-second-dose
Day 63	63	[59 Post-second-dose, 115]
Month 6	168 (Date of Third Vaccination)	[116, 171] Pre-third-dose
Day 175	175	[171 Post-third-dose, 255]
Month 12	336	[256, 419]

Month 18	504	≥ 420
Subjects completing the first 2 vaccination only		
Day 1	1 (Date of First Vaccination)	≤1 Pre-dose
Day 8	8	[1 Post-dose, 31]
Month 2	56 (Date of Second Vaccination)	[32, 59] Pre-second-dose
Day 63	63	[59 Post-second-dose, 157]
Month 8	252	[158, 335]
Month 14	420	≥ 336
Subjects completing the first vaccination only		
Day 1	1 (Date of First Vaccination)	≤1 Pre-dose
Day 8	8	[1 Post-dose, 87]
Month 6	168	[88, 251]
Month 12	336	≥ 252

9.3. Appendix C Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first vaccination for purposes of determining if status is prior or concomitant.
2. Missing or partial medication stop date:

a. If only DAY is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).

b. If DAY and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).

c. If DAY, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in Table 2 below.

Table 2 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Vaccination**	**≥ First Dose Date and ≤ 28 Days After Last Vaccination [3]**	**> 28 Days After Last Vaccination [2]**
< First dose date of study vaccination [1]	P	PC	PCA
≥ First dose date and ≤ 28 days after last vaccination	-	C	CA
> 28 days after last vaccination	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date
[3] calculated as Date of Last Study Vaccination + 27 days

9.4. Appendix D Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:
   - If only DAY is missing, use the first day of the month, unless:
     - The AE end date is after the date of first vaccination or is missing AND the start month and year of the AE coincide with the start month and year of the first vaccination. In this case, use the date of first vaccination
   - If DAY and Month are both missing, use the first day of the year, unless:
     - The AE end date is after the date of first vaccination or is missing AND the start year of the AE coincides with the start year of the first vaccination. In this case, use the date of first vaccination
   - If DAY, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first vaccination, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.
2. Missing or partial AE end dates will not be imputed.

9.5. Appendix E Schedule of Events

Please refer to Table 1 in Section 1.3 Schedule of Events, Table 6 and Table 7 in Appendix 2 Additional Schedule of Assessments in the protocol.

9.6. Appendix F Immunogenicity Assessments

The following laboratory assays are planned to measure the immune response to mRNA-1647 (Table 3):

- Functional (neutralizing) antibody titers against epithelial cell infection and against fibroblast infection will be measured by a neutralization assay.
- gB and Pentamer-binding antibody titers will be measured by ELISA.
- gB-specific IFN-γ secreting CD4 and CD8 T-cells will be determined by ICS.

- Pentamer-specific IFN-γ secreting CD4 and CD8 T-cells will be determined by ICS.

Table 3 Antibody-Mediated and Cell-Mediated Immunity Against Cytomegalovirus

Material	Component	Method	Unit
Serum	Neutralizing antibodies against epithelial cell infection and against fibroblast infection	Neutralization assay	Fold dilution (titer)
Serum	Anti-gB and anti-Pentamer antibodies	ELISA	Fold dilution (titer)
PBMC	gB and pentamer-specific CD4 and CD8 cytokine secreting T-cells	ICS	% cytokine secreting CD4 and CD8 T-cells

Abbreviations: ELISA, enzyme-linked immunosorbent assay; gB, glycoprotein B; ICS, intracellular cytokine staining; PBMC, peripheral blood mononuclear cell; Pentamer, gH/gL/UL128/UL130/UL131A glycoprotein complex.