Interim Results From a Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Trial of an mRNA-Based Cytomegalovirus Vaccine in Healthy Adults

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BACKGROUND

- Cytomegalovirus (CMV) is a common virus that can infect individuals at any age[1]
- Infection in healthy individuals is typically mild or asymptomatic; however, serious complications can result if infection occurs in immunocompromised populations (ie, transplant recipients, persons living with HIV) or a developing fetus[1,2]
- CMV infection during pregnancy, or congenital CMV (cCMV), is the most common infectious cause of birth defects and can cause severe long-term health consequences, including hearing loss and neurodevelopmental delay[3]
- No vaccines are approved for the prevention of CMV infection[2]
  - A safe and effective prophylactic vaccine for CMV infection is an unmet need and a public health priority[4]
- An mRNA-based vaccine against CMV, mRNA-1647, is in development
  - mRNA-1647 consists of 6 mRNA sequences encoding for glycoprotein B (1 mRNA sequence) and the glycoprotein subunits of the pentameric complex (5 mRNA sequences) in a lipid nanoparticle formulation
  - These mRNA sequences are endogenously translated into conformationally intact antigens that are recognized by the immune system in the same manner as natural CMV infection and are intended to elicit humoral and cell-mediated immunity

OBJECTIVE

- To present the safety and immunogenicity from an interim analysis of a phase 2 clinical trial of different dose levels of mRNA-1647 in healthy adults

METHODS

Study Design and Participants

- This phase 2, randomized, placebo-controlled, observer-blind, dose-finding study of the safety and immunogenicity of mRNA-1647 was conducted in the United States and began in January 2020 (protocol number mRNA-1647-P202; ClinicalTrials.gov NCT04232280)
- Eligible participants included healthy CMV-seronegative and CMV-seropositive adults 18 to 40 years of age
- The study was conducted in 2 parts:
  - In Part 1, men and women were randomized 3:1 to receive 3 intramuscular injections of mRNA-1647 (50 µg, 100 µg, or 150 µg) or placebo at Months 0, 2, and 6
  - In Part 2, women were randomized 3:1 to receive 3 intramuscular injections of 100 µg of mRNA-1647 or placebo at Months 0, 2, and 6
- Although the study is ongoing, this interim analysis includes safety and immunogenicity data through Month 18 (12 months after dose 3 [end of study]) from Part 1 and through Month 7 (1 month after dose 3) from Part 2; the data cut-off date for this interim analysis was February 18, 2022

Study Endpoints

- Safety endpoints included solicited local and systemic adverse reactions (ARs) and unsolicited adverse events (AEs) through 7 and 28 days after each dose, respectively; medically attended AEs (MAAEs) through 6 months after the last dose; and serious AEs (SAEs) from time of informed consent through the end of the study
- Antibody-mediated immunogenicity endpoints included geometric mean titers (GMTs) of serum neutralizing antibodies (nAbs) against epithelial cell infection and against fibroblast infection as measured by cell-based neutralizing assays at Months 0, 1, 2, 3, 6, 7, 12, and 18, as applicable
  - nAb GMTs at baseline in the CMV-seropositive cohort represented naturally acquired immunity and served as benchmarks for vaccine-induced nAb GMTs in the CMV-seronegative group

RESULTS

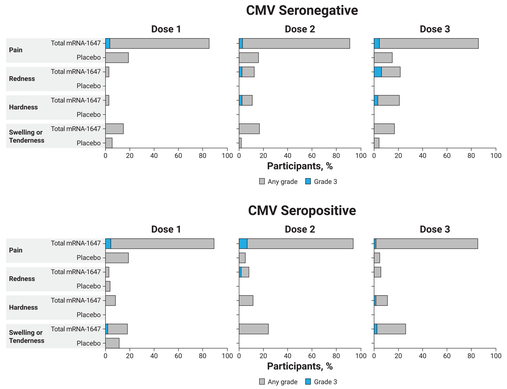
Participants

- A total of 315 participants (Part 1, 252; Part 2, 63) were randomly allocated to receive mRNA-1647 or placebo
  - In the mRNA-1647 group, 235 participants received dose 1, 205 (87%) received dose 2, and 179 (76%) received dose 3
  - In the placebo group, 80 participants received dose 1, 71 (89%) received dose 2, and 66 (83%) received dose 3
- Most participants were female (n = 206; 65%) and White (n = 265; 84%); mean age was 29 ± 7 years

Safety

- Among mRNA-1647 recipients, injection site pain was the most commonly reported solicited local AR (**Figure 1**); headache, fatigue, myalgia, arthralgia, and chills were the most commonly reported solicited systemic ARs (**Figure 2**)
- Unsolicited AEs were reported by 86 (37%) mRNA-1647 recipients (176 unsolicited AEs) and 29 (36%) placebo recipients (52 unsolicited AEs)
  - Treatment-related unsolicited AEs were reported by 30 (19%) CMV-seronegative and 10 (14%) CMV-seropositive mRNA-1647 recipients, and in 6 (11%) CMV-seronegative and 3 (11%) CMV-seropositive placebo recipients
- Unsolicited MAAEs were reported by 31 (19%) CMV-seronegative and 11 (15%) CMV-seropositive mRNA-1647 recipients, and in 10 (19%) CMV-seronegative and 6 (22%) CMV-seropositive placebo recipients
- A total of 4 SAEs were reported by 3 participants in the mRNA-1647 100-µg treatment group, none of which were considered treatment related
- No deaths were reported
- Six (3%) mRNA-1647 recipients reported an unsolicited treatment-emergent AE leading to discontinuation of the study vaccine; of these, 4 participants had treatment-emergent AEs that were considered treatment related

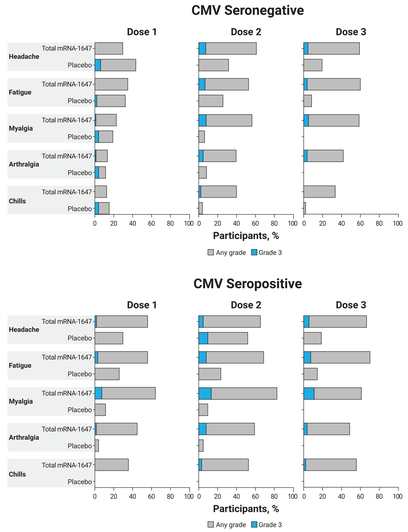
Figure 1. Summary of Solicited Local ARs by CMV Serostatus[a]



AR, adverse reaction; CMV, cytomegalovirus.

[a]Solicited local ARs included injection site pain, erythema (redness), and swelling (hardness), and localized axillary swelling or tenderness ipsilateral to the injection arm. No grade 4 local ARs were reported.

Figure 2. Most Common Solicited Systemic ARs by CMV Serostatus[a]



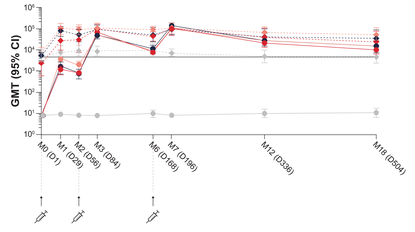
AR, adverse reaction; CMV, cytomegalovirus.

[a]No grade 4 ARs were reported for the systemic ARs shown; grade 4 ARs were reported for fever only (data not shown).

Immunogenicity

- CMV-seronegative participants
  - mRNA-1647 treatment groups
    - nAb GMTs against epithelial cell infection increased above baseline after dose 1 and continued to increase after doses 2 and 3 (**Figure 3**)
      - nAb GMTs exceeded the CMV-seropositive baseline GMT benchmark in all treatment groups after doses 2 and 3, and remained above the benchmark at Months 12 and 18
    - nAb GMTs against fibroblast infection increased above baseline after dose 1; nAb GMTs increased after dose 2 and were comparable after doses 2 and 3 (**Figure 4**)
      - nAb GMTs increased after dose 2 and approached or exceeded the CMV-seropositive baseline GMT benchmark in all treatment groups
  - Placebo group
    - nAb GMTs against epithelial cell infection and against fibroblast infection remained constant across all time points assessed
- CMV-seropositive participants
  - mRNA-1647 treatment groups
    - nAb GMTs against epithelial cell infection increased over baseline in a dose-related manner after dose 1, and GMTs after doses 2 and 3 were comparable to or exceeded the GMTs observed after dose 1 (**Figure 3**)
    - nAb GMTs against fibroblast infection increased over baseline in all treatment groups after dose 1, and GMTs after doses 2 and 3 were generally comparable to or exceeded the GMTs observed after dose 1 (**Figure 4**)
  - Placebo group
    - nAb GMTs against epithelial cell infection and against fibroblast infection were higher postbaseline compared to the respective baseline GMTs

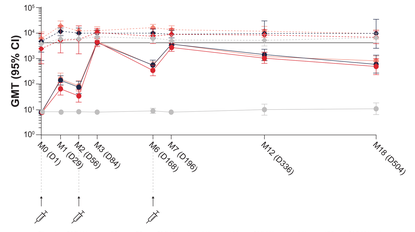
Figure 3. nAb GMTs Against Epithelial Cell Infection by CMV Serostatus and Dose Level[a]



CI, confidence interval; CMV, cytomegalovirus; D, day; GMT, geometric mean titer; M, month; nAb, neutralizing antibody; Neg, negative; Pos, positive.

[a]The solid black line indicates the baseline nAb GMT against epithelial cell infection of all CMV-seropositive participants at baseline (GMT = 4575.7). Doses 1, 2, and 3 were administered at Months 0, 2, and 6, respectively, as represented by an arrow and syringe. *n* is the number of participants with non-missing data at baseline and the corresponding time point.

Figure 4. nAb GMTs Against Fibroblast Infection by CMV Serostatus and Dose Level[a]



CI, confidence interval; CMV, cytomegalovirus; D, day; GMT, geometric mean titer; M, month; nAb, neutralizing antibody; Neg, negative; Pos, positive.

[a]The solid black line indicates the baseline nAb GMT against fibroblast infection of all CMV-seropositive participants at baseline (GMT = 4215.5). Doses 1, 2, and 3 were administered at Months 0, 2, and 6, respectively, as represented by an arrow and syringe. *n* is the number of participants with non-missing data at baseline and the corresponding time point.

CONCLUSIONS

- This interim analysis of safety and immunogenicity from a phase 2 dose-finding study indicates that mRNA-1647 was well-tolerated and immunogenic at all dose levels assessed
- Clinical development of mRNA-1647 for the prevention of CMV infection is ongoing

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LP, JL, KW, HL, RH, AN, and JM are employees of Moderna, Inc., and hold stock/stock options in the company. RL is a contract employee of Crossroads Clinical Research. JP received payment as a study investigator. CF, DB, and PP have nothing to disclose.