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Long-Term Safety and Immunogenicity of Cytomegalovirus mRNA-1647 Vaccine in Healthy Adults: 36-Month Results from a Phase 2 Extension Trial

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BACKGROUND

- Cytomegalovirus (CMV) is a widespread herpesvirus that is the primary infectious cause of birth defects in the United States and a substantial cause of illness in immunocompromised individuals[1-3]
- Despite this burden, there are no approved CMV vaccines available[3]; a safe and effective vaccine for the prevention of CMV infection is a public health priority[4]
- mRNA-1647 is an investigational mRNA-based vaccine consisting of 6 distinct mRNA sequences encoding both the glycoprotein B (gB) and pentamer CMV antigens
- In a phase 1 trial, mRNA-1647, administered in a 3-dose series at dose levels ranging between 30 and 300 µg, demonstrated an acceptable safety profile and elicited both humoral and cell-mediated immunogenicity[5]
- A phase 2 trial demonstrated that mRNA-1647 administered as a 3-dose series at the 50-, 100-, or 150-µg dose levels had an acceptable safety profile, was generally well-tolerated, and induced vaccine-specific immunogenicity after the first dose that was sustained through 18 months in adults[6]

OBJECTIVES

- To evaluate the long-term safety and immunogenicity of mRNA-1647 from the final visit in the phase 2 trial up to 36 months

METHODS

Trial Design and Participants

- This is a nonrandomised, long-term extension trial (NCT04975893) being conducted in a subset of participants who completed the phase 2 trial (NCT04232280); the follow-up time for the two studies combined is 54 months
- Eligible participants are
  - Healthy adults aged 18-40 years
  - CMV-seronegative at baseline and were randomly assigned to receive mRNA-1647 (50, 100, or 150 µg) or placebo in the primary phase 2 trial, and had not seroconverted before enrolling in the extension trial
  - CMV-seropositive at baseline and were randomly assigned to receive mRNA-1647 (50, 100, or 150 µg) in the primary phase 2 trial
- No vaccines were administered in the long-term extension trial reported herein

Trial Objectives and Endpoints

- The primary objective of this ongoing trial is to evaluate long-term immunogenicity of mRNA-1647
  - Endpoints include neutralising antibody (nAb) geometric mean titres (GMTs) against epithelial cell and fibroblast infection, as well as pentamer-specific and gB-specific binding antibody (bAb) GMTs, assessed every 6 months for 3 years from the final visit in the phase 2 trial (Month 18) through the end of the extension trial (Month 54)
- The secondary objective is to evaluate the long-term safety of mRNA-1647
  - Endpoints include deaths, adverse events (AEs) leading to trial discontinuation, and serious AEs (SAEs) from the final visit in the phase 2 trial (Month 18) through the end of the extension trial (Month 54)
- Interim findings through Month 36 of the long-term extension trial are presented herein

RESULTS

Participants

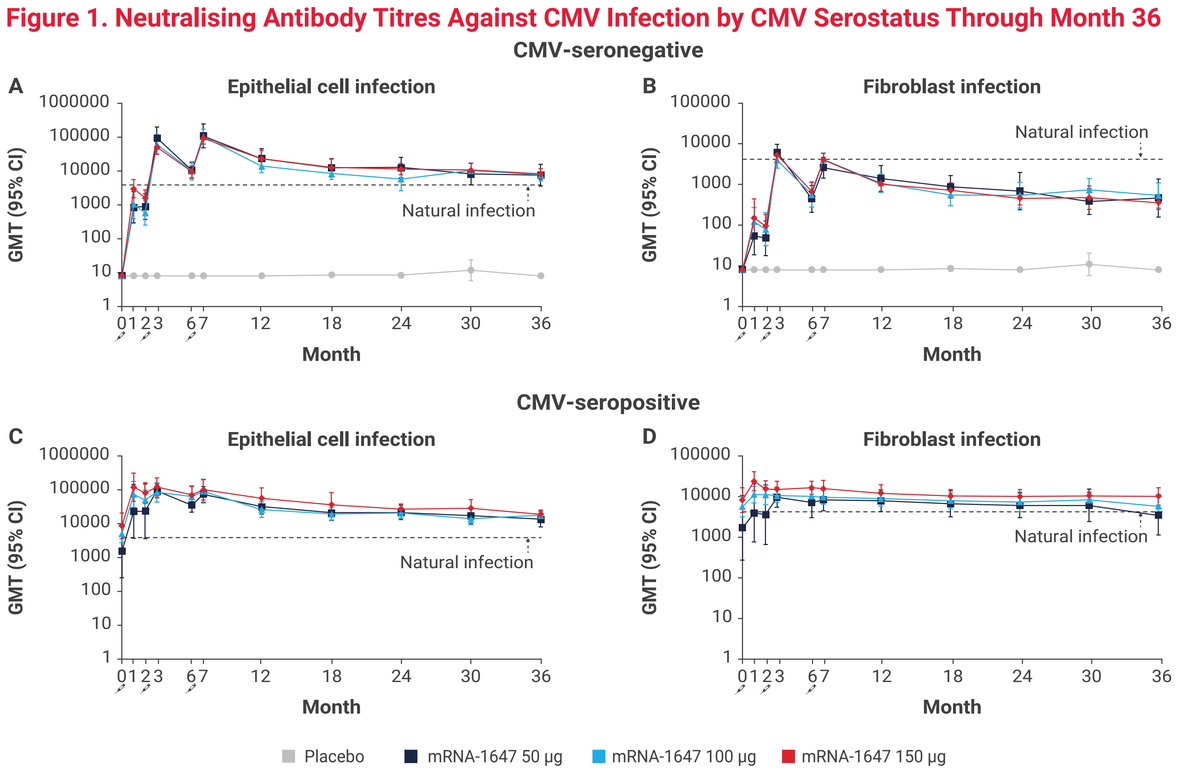
- A total of 135 participants were enrolled in the phase 2 extension trial (mRNA-1647, n = 109; placebo, n = 26)
  - Of 109 mRNA-1647 recipients, 73 were CMV-seronegative and 36 were CMV-seropositive
- Participants were between 19 and 42 years of age (median: 32.0 years), and the majority were female (n = 89; 65.9%) and White (n = 117; 86.7%)
- Demographics and baseline characteristics were generally well-matched across the treatment and CMV serostatus groups

Immunogenicity

Neutralising Antibodies

- CMV-seronegative
  - In mRNA-1647 recipients, nAb GMTs against epithelial cell infection (**Figure 1A**) and fibroblast infection (**Figure 1B**) remained stable from Month 18 through Month 36; as a qualitative comparison, nAb GMTs against epithelial cell infection remained higher than the GMTs observed in CMV-seropositive participants with natural infection
  - There was no clear dose-related trend in nAb GMTs observed through Month 36 in the mRNA-1647 arms
- CMV-seropositive
  - Among participants who received mRNA-1647, nAb GMTs against epithelial cell infection (**Figure 1C**) and fibroblast infection (**Figure 1D**) remained generally stable from Month 18 through Month 36
  - There was no clear dose-related trend in nAb GMTs against epithelial cell infection observed through Month 36 in the mRNA-1647 arms

Figure 1. Neutralising Antibody Titres Against CMV Infection by CMV Serostatus Through Month 36

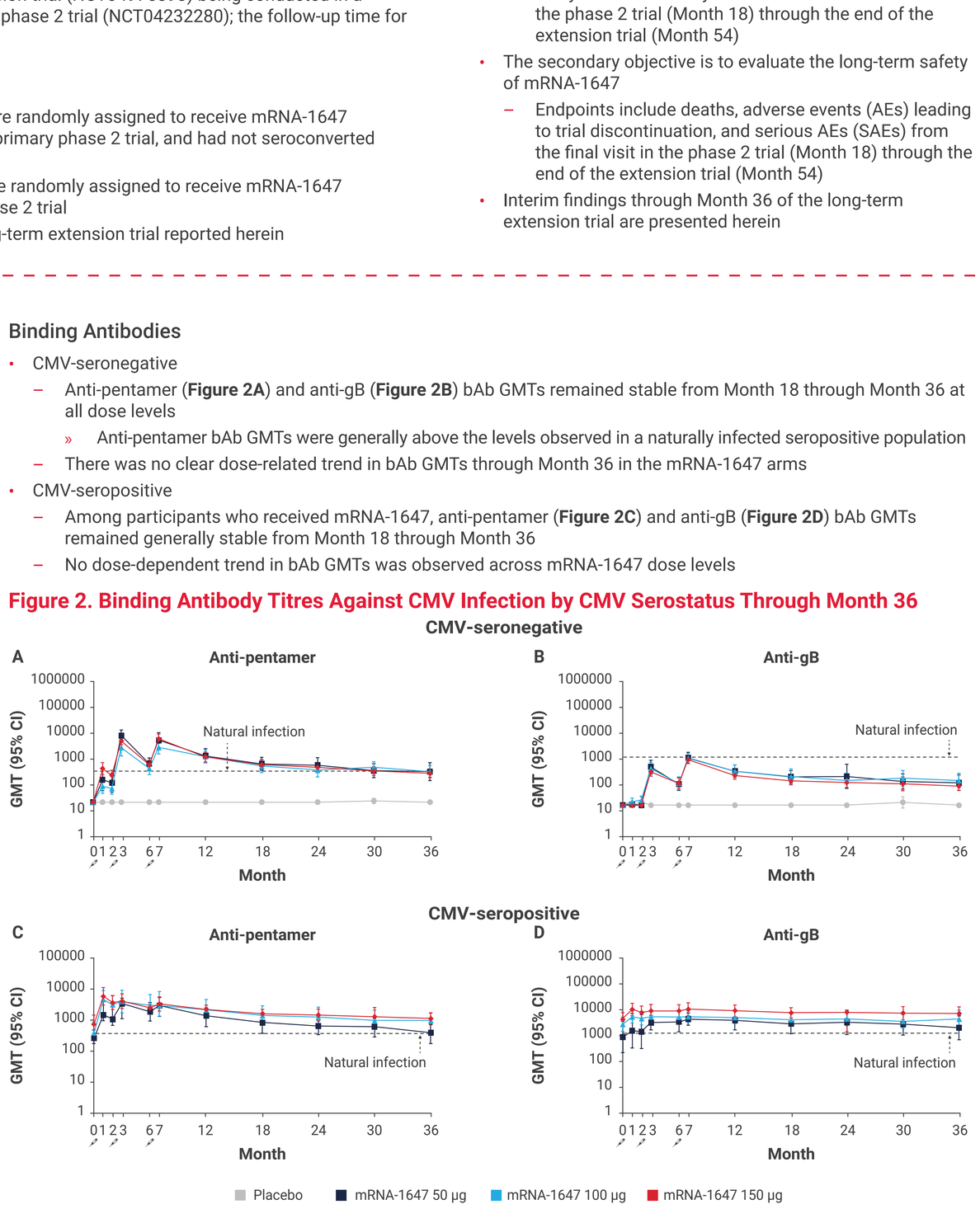


CI, confidence interval; CMV, cytomegalovirus; GMT, geometric mean titre. The horizontal dashed line indicates the GMT of the CMV-seropositive cohort at baseline.

Binding Antibodies

- CMV-seronegative
  - Anti-pentamer (**Figure 2A**) and anti-gB (**Figure 2B**) bAb GMTs remained stable from Month 18 through Month 36 at all dose levels
    - Anti-pentamer bAb GMTs were generally above the levels observed in a naturally infected seropositive population
  - There was no clear dose-related trend in bAb GMTs through Month 36 in the mRNA-1647 arms
- CMV-seropositive
  - Among participants who received mRNA-1647, anti-pentamer (**Figure 2C**) and anti-gB (**Figure 2D**) bAb GMTs remained generally stable from Month 18 through Month 36
  - No dose-dependent trend in bAb GMTs was observed across mRNA-1647 dose levels

Figure 2. Binding Antibody Titres Against CMV Infection by CMV Serostatus Through Month 36



CI, confidence interval; CMV, cytomegalovirus; gB, glycoprotein B; GMT, geometric mean titre. The horizontal dashed line indicates the baseline GMT of the CMV-seropositive cohort.

Safety

- A total of 7 SAEs occurred in 6 of 135 participants (4.4%) through Month 36 (CMV-seronegative, 5 of 99 participants; CMV-seropositive, 1 of 36 participants); none led to trial discontinuation or were considered related to trial injection
  - Among the 5 CMV-seronegative participants, SAEs included seizure (2 events reported by 1 participant in the mRNA-1647 150 µg group), trigeminal neuralgia (1 event reported by 1 participant in the mRNA-1647 100 µg group), spontaneous abortion (1 event reported by 1 participant in the placebo group; 1 event reported by 1 participant in the mRNA-1647 100 µg group), and upper limb fracture (1 event reported by 1 participant in the mRNA-1647 100 µg group)
  - In the mRNA-1647 100 µg group, 1 CMV-seropositive participant reported an SAE of urinary tract infection
- Overall, 7 pregnancies were reported in 5 participants, with pregnancy outcomes of term birth without complications (n = 2, placebo), normal delivery (n = 1, mRNA-1647 100 µg), preterm birth (n = 1, placebo), and spontaneous abortion (n = 3 [2, placebo; 1, mRNA-1647 100 µg]; note: 1 spontaneous abortion in the placebo arm was reported after the participant's Month 36 data cutoff date and was therefore not included as an SAE)
- There were no deaths and no AEs reported that led to trial discontinuation

CONCLUSIONS

- In this phase 2 extension trial, antibody-mediated immune responses to mRNA-1647, as measured by GMTs of nAbs against epithelial cell infection, nAbs against fibroblast infection, pentamer-specific bAbs, and gB-specific bAbs, remained stable from Month 18 through Month 36 and exceeded the primary phase 2 trial baseline levels in both CMV-seronegative and CMV-seropositive participants
- In CMV-seronegative participants, nAb GMTs against epithelial cell infection and anti-pentamer bAb GMTs were above or approached the GMTs of a naturally infected population (also known as the seropositive benchmark); while nAb GMTs against fibroblast infection and anti-gB bAb GMTs were below the seropositive benchmark, they remained stable and above baseline
- These data support that mRNA vaccination can create durable immune responses
- mRNA-1647 maintained an acceptable safety profile at all dose levels assessed, with no new safety concerns identified
- The durable antibody responses and favourable safety profile observed support continued development of mRNA-1647

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Disclosures

RCC, BL, AI, SM, JL, SK, JH, and LP are employees of Moderna, Inc., and may hold stock/stock options in the company.

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