Overview of mRNA-1647: Investigational CMV Vaccine

ACIP

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Outline of Presentation

- Unmet medical need for a CMV vaccine
- Description of Moderna's investigational CMV vaccine
- Overview of clinical program
- Phase 2 safety and immunogenicity study results
- Design of ongoing Phase 3 efficacy trial
- Summary

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Impact and Global Burden of Congenital CMV

Congenital CMV: A Major Public Health Burden

- Most common congenital viral infection and non-genetic cause of sensorineural hearing loss[1]
- Major under-recognized cause of miscarriage, stillbirth, preterm birth, and infant death[2-5]

Annual Birth Prevalence

Global

1 in 70 to 1 in 208 births[6]

US

~1 in 200 births[7]

Economic & Clinical Impact

- $6-7 billion annual healthcare costs in US (as of 2018)[8]
- Management of congenital CMV challenging due to limited prevention, inconsistent screening, and lack of treatment options[1]

World Health Organization

NATIONAL ACADEMY of MEDICINE

Significant Unmet Medical Need
High Priority for Vaccine Development by WHO & NAM

1. Boppana SB, et al. Vaccine. 2023;41:S53-S75. 2. Song X, et al. Front Pediatr. 2022;10:803568. 3. Iwasenko JM, et al. J Infect Dis. 2011;203(11):1526-1533. 4. Bryne J, et al. Am J Obstet Gynecol. 2015;213(6):905-906. 5. Kimberlin DW, et al. 2021. Red Book: 2021–2024 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; doi:10.1542/9781610025782-S3_037. 6. Ssentongo P, et al. JAMA Netw Open; 2021;4(8):e2120736. 7. CDC | CMV in Newborns. Updated January 7, 2025. https://www.cdc.gov/cytomegalovirus/congenital-infection/index.html. 8. Grosse SD, et al. Perinatol. 2021;45(3):151393.

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Clinical Manifestations of Congenital CMV (cCMV)

May be present at birth & may develop or progress throughout childhood

Infants with Congenital CMV (cCMV)

10%-15% Symptomatic at Birth

- CMV-associated **death** occurs during in **~5%** of these infants
- **40%-58%** develop long-term disability
  - Symptoms include hearing loss, cognitive impairment, developmental delay, and seizures

85%-90% Asymptomatic at Birth

- **10%-15%** develop long-term disability, most commonly sensorineural hearing loss

~1 in 5 infants with cCMV (symptomatic or asymptomatic at birth) develop long-term disability

Source: Dollard SC, et al. Rev Med Virol. 2007;17(5):355-363. doi:10.1002/rmv.544

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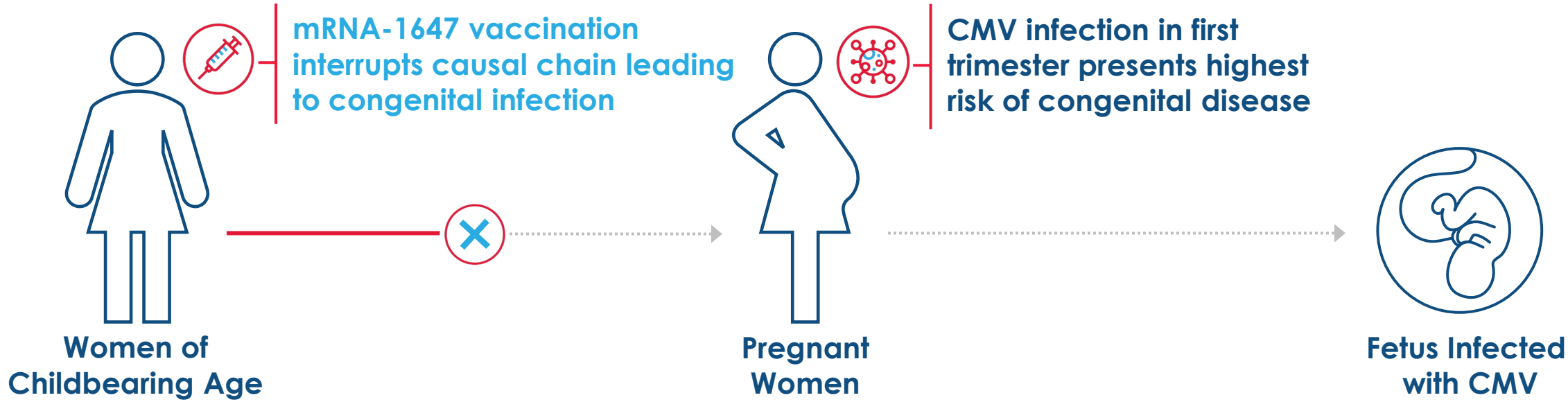
CMV Vaccine Development Objective: Prevent CMV Infection in CMV-seronegative Women

Current Focus

- Prevent CMV infection during pregnancy to reduce congenital CMV
- Vaccinate women of child-bearing potential prior to pregnancy



Indication

- Prevention of CMV infection in females, 16-40 years of age, regardless of CMV serostatus

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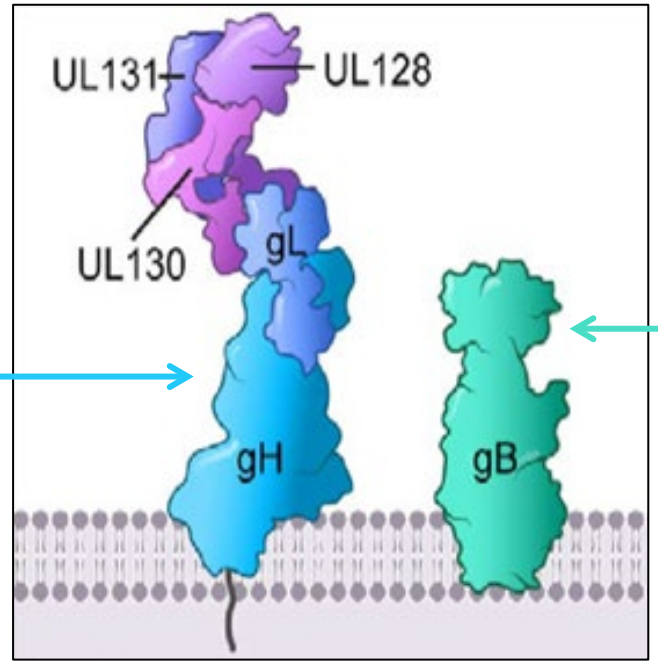
Moderna's Investigational CMV Vaccine (mRNA-1647) Composed of 6 mRNAs Designed to Elicit Humoral and Cellular immunity to CMV Infection

Pentamer

- 5 mRNAs encode the pentamer subunits
- Required for CMV entry into most cell types, including epithelial and endothelial cells



gB

- 1 mRNA encodes glycoprotein B
- Mediates fusion of virus and host membranes during cell entry
- Necessary for viral infectivity in all cell types

- **Antigen selection chosen to:**
  - Prevent CMV infection and subsequent fetal transmission
  - Induce both humoral and cellular immune responses[2-5]
- **43-50% efficacy for CMV infection in 2 previous trials of recombinant gB candidate vaccine[1]**

mRNA-1647 is an investigational vaccine, and the above diagram is for illustrative purposes only

CMV, cytomegalovirus; gB, glycoprotein B.

1. Diamond DJ, et al. Expert Rev Vaccines. 2018;17:889-911. 2. John S, et al. Vaccine. 2018;36:1689-1699. 3. Plotkin SA and Boppana SB. Vaccine. 2019;37:7437-7442.
4. Kabanova A, et al. PNAS. 2014;111:17965-17970. 5. Scarpani S, et al. Vaccines. 2021;9:1-26. 6. Pass et al. N Engl J Med 2009;360: 1191-9. 7. Bernstein, et al. Vaccine 2016; 34:313-319.

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CMV Vaccine (mRNA-1647) Clinical Trials in Adults

Completed and ongoing trials

Population	Study	Phase	Age (Years)	mRNA-1647 Dose Levels (µg)	Objectives	Study Start	Status
Healthy Adults	101	1	18-49	30-300	Safety and immunogenicity	Nov 2017	Completed
	202	2	18-40	50-150	Safety, immunogenicity, and dose selection	Jan 2020	Completed
	202-Extension	2	18-40	50-150	Safety and immune persistence	May 2021	Ongoing
	301	3	16-40	100	Efficacy, safety, and immunogenicity in females	Oct 2021	Ongoing

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Summary: mRNA-1647 Phase 1 Trial in Adults (18-40 Years)

Design	• Randomized, observer blind, placebo-controlled trial • 154 healthy participants, 18-49 years of age (13-19 per treatment group) • 80 CMV-seronegative and 74 CMV-seropositive • Followed for 12 months after last dose
Safety	• Generally well tolerated; no new safety concerns identified
Immunogenicity	• Neutralizing antibody responses • Exploratory analysis of cell mediated immunity

- Data from Phase 1 allowed evaluation of an optimized dose range in Phase 2

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CMV mRNA-1647 Phase 2 Dose Selection Trial in 18-40 Year Olds

Design	• Randomized (3:1), observer blind, placebo-controlled trial • 315 adult participants 18-40 years of age (63-109 per treatment group) • 218 CMV-seronegative and 97 CMV-seropositive participants • Followed for 12 months after last dose

Dosing
3-Dose Series
(Month 0, 2 & 6)

Part 1: Dose Selection			Part 2: Safety Expansion		
mRNA-1647 50 µg	or	Placebo	mRNA-1647 100 µg	or	Placebo
mRNA-1647 100 µg	or	Placebo			
mRNA-1647 150 µg	or	Placebo			

Objectives	• **Primary:** Safety and neutralizing antibody responses • **Secondary:** Binding antibody responses

- **Focus of today's presentation on 100 ug dose selected for further study**

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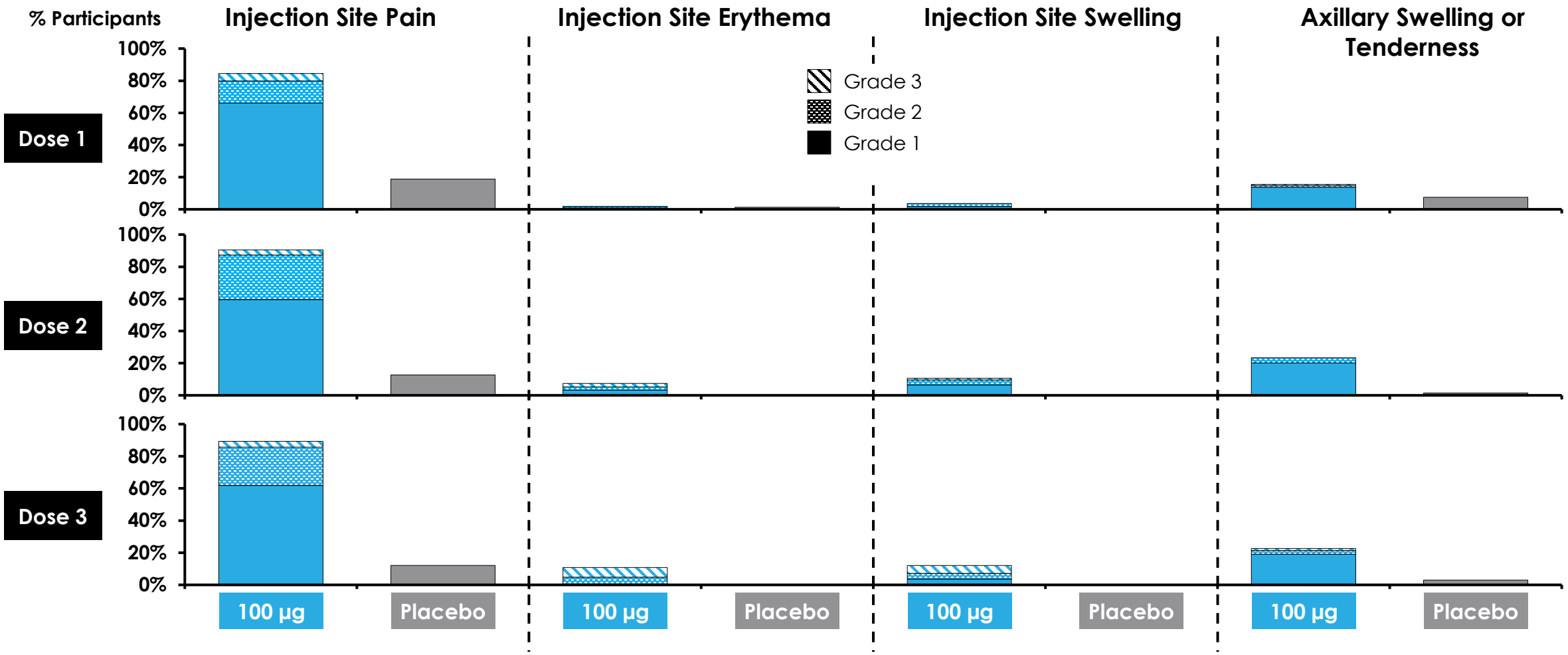
Solicited Local Reactions within 7 Days of injection

CMV mRNA-1647 Phase 2 Trial in Adults



- Pain most frequent local reaction
- Local reactions mostly grade 1 or 2 and generally 1-3 days duration

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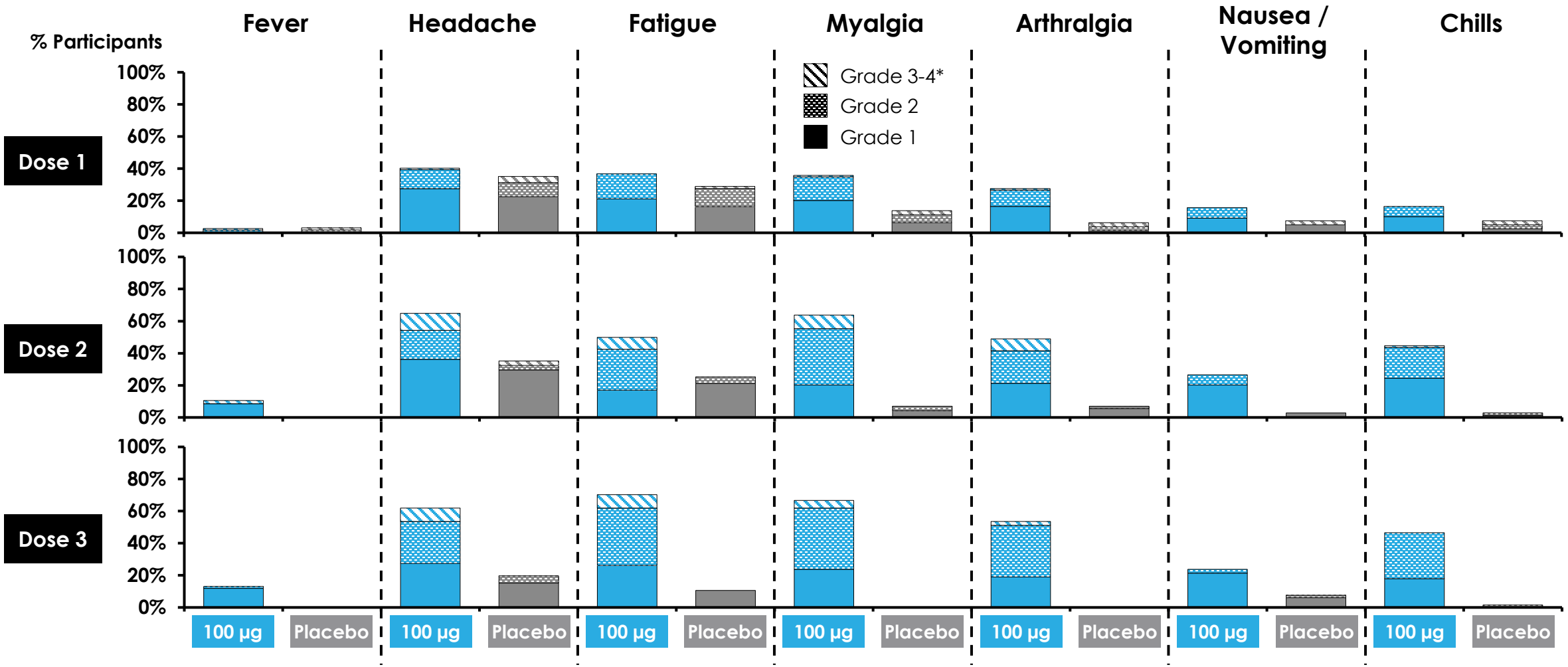
Solicited Systemic Reactions within 7 Days of Injection

CMV mRNA-1647 Phase 2 Trial in Adults



- Headache, fatigue, myalgia, and chills most common
- Some increase in systemic reactions with 2nd & 3rd dose
- Systemic reactions generally grade 1 or 2 of 1-2 days duration

*Only grade 4 reactions were fevers - 1 vaccine recipient & 1 placebo recipient after dose 1; 2 vaccine recipients after dose 2

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Incidence of Unsolicited Treatment Emergent Adverse Events Within 28 Days After Vaccine/Placebo

CMV mRNA-1647 Phase 2 Trial in Adults (All Dose Levels)

	mRNA-1647 N=235		Placebo N=80	
	All	Related	All	Related
Participants reporting any adverse event (AE)	87 **(37.0%)**	42 **(17.9%)**	29 **(36.3%)**	9 **(11.3%)**
Serious AEs	1 **(0.4%)**	0	0	0
Non-serious AEs	86 **(36.6%)**	42 **(17.9%)**	29 **(36.3%)**	9 **(11.3%)**
Participants reporting clinically relevant events				
Fatal	0	0	0	0
Medically-attended AEs	43 **(18.3%)**	17 **(7.2%)**	17 **(21.3%)**	2 **(2.5%)**
Grade 3 or higher (all non-serious AEs)	26 **(11.1%)**	6 **(2.6%)**	7 **(8.8%)**	0
AEs leading to discontinuation from study vaccine	7 **(3.0%)**	5 **(2.1%)**	1 **(1.3%)**	0
AEs leading to discontinuation from study	0	0	0	0

- Related MAAEs higher in vaccine recipients; majority due to local reactions
- No significant safety concerns identified during study

Percentages based on number of events / total number of participants in either the mRNA-1647 group (n=235) or in the placebo group (n=80), as applicable.

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Neutralizing Antibody Response to mRNA-1647 Based on Both Epithelial and Fibroblast Cell Assays

Neutralizing Antibody	Vaccine Antigen	Biological Relevance
Epithelial cell	Pentamer	• CMV infection of epithelial, endothelial, myeloid cells requires pentameric complex
Fibroblast cell	gB	• Essential for viral entry and cell fusion • Used to assess antibody responses to gB and other viral antigens • Pentamer-specific antibodies not effectively measured by this assay

- Today we will present neutralizing antibody data
- Analysis of T-cell data is ongoing

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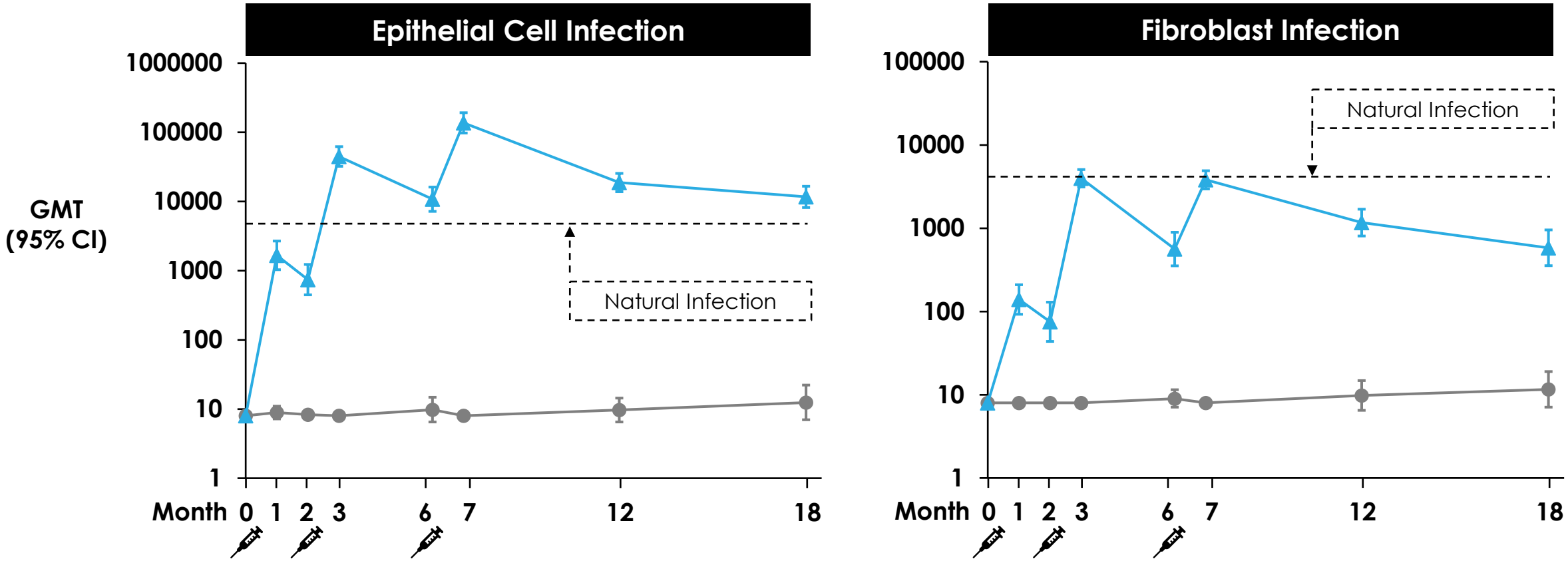
Neutralizing Antibody Response Demonstrated in CMV Seronegative Adults

mRNA-1647 Phase 2 Trial

mRNA-1647 100 µg Placebo



- Epithelial cell infection: GMTs Increased after each dose and remained above natural infection GMT through 18 months
- Fibroblast infection: GMTs reached natural infection GMT at months 3 & 7, then declined at months 12 & 18

GMT – geometric mean titer; Natural infection defined as GMT at baseline in CMV seropositives

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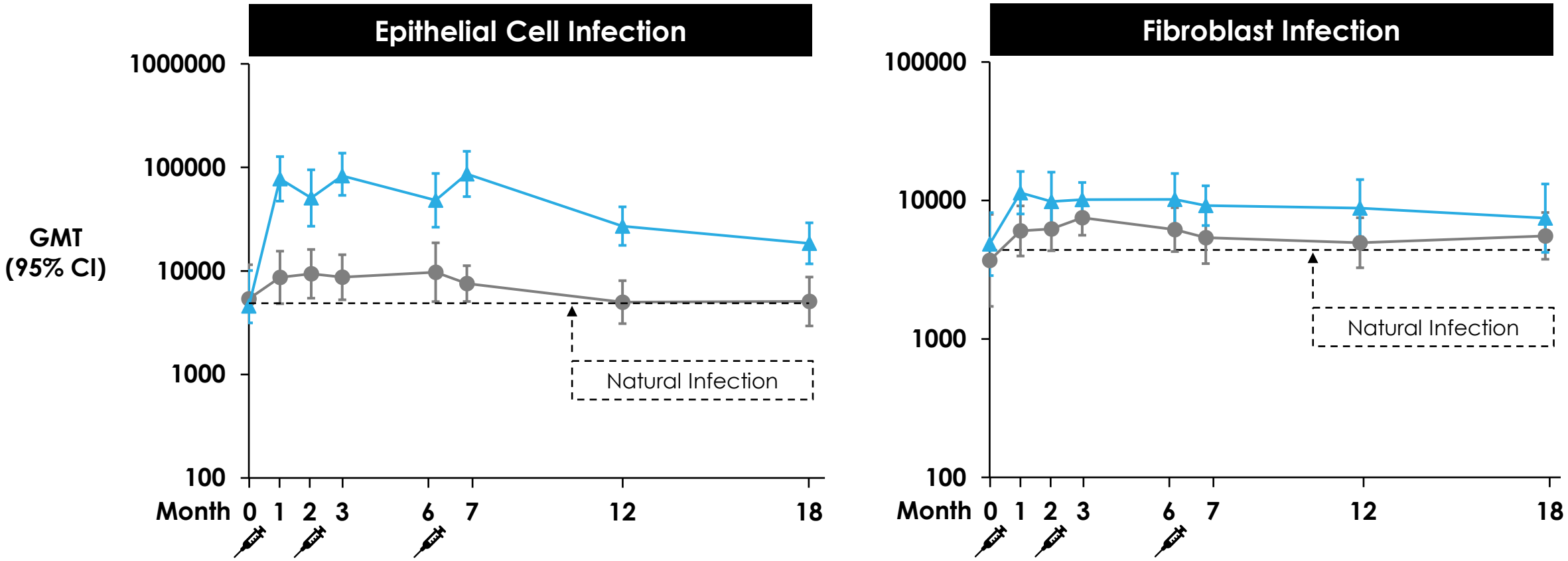
Neutralizing Antibody Response Demonstrated in CMV Seropositive Adults

mRNA-1647 Phase 2 Trial

mRNA-1647 100 µg Placebo



- GMTs for both assays remained above natural infection GMT through Month 18

GMT – geometric mean titer; Natural infection defined as GMT at baseline in CMV seropositives

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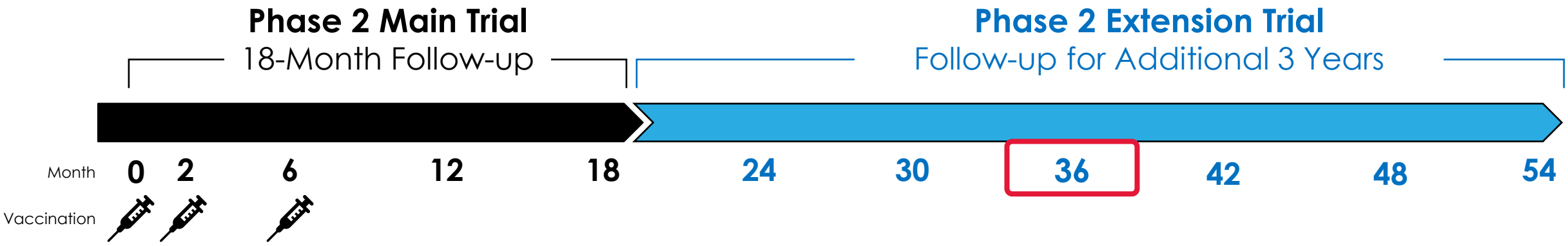
Phase 2 Extension Trial in Adults to Assess Persistence of Antibody

Design	• 3-year long-term follow-up of immunogenicity and safety in participants who completed the phase 2 original study • Provides ~4 years total follow-up after last vaccine dose
Objectives	• **Primary:** Safety and neutralizing antibody-mediated immunogenicity • **Secondary:** Binding antibody-mediated immunogenicity



ESCMID, 2025

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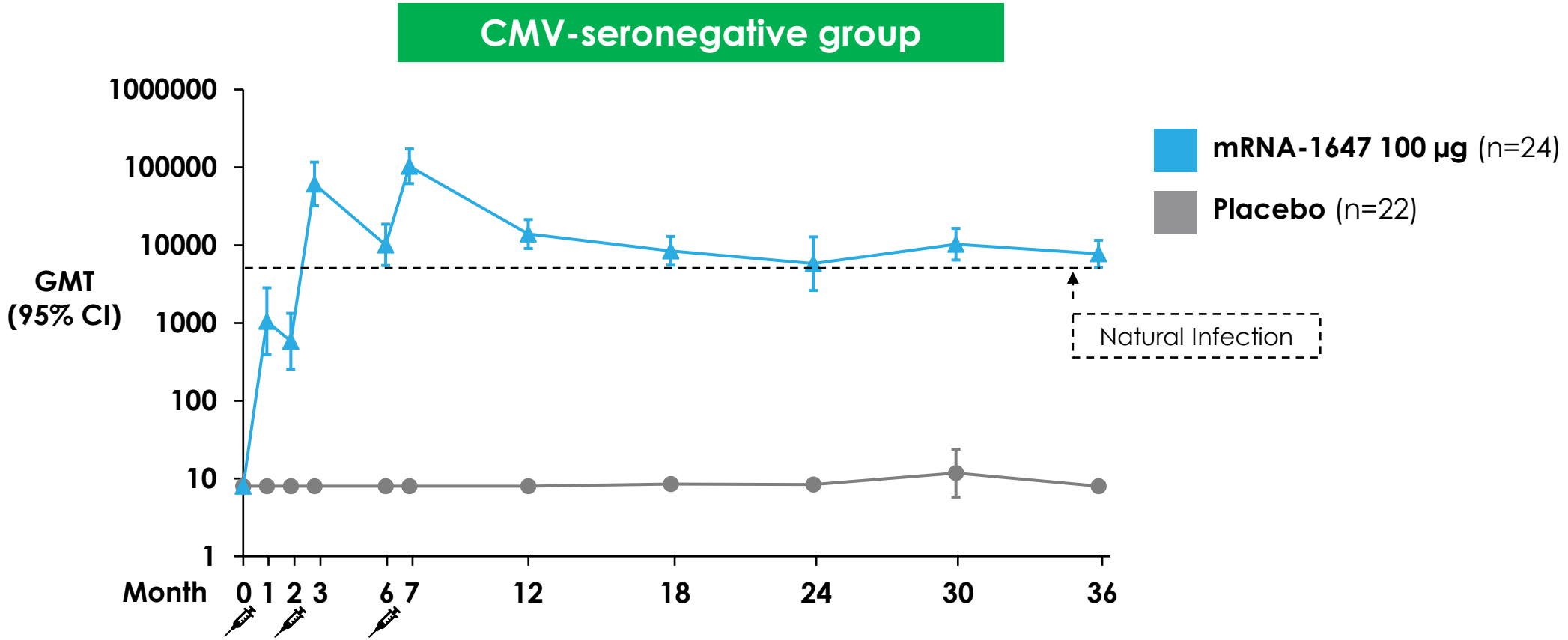
Persistence of Neutralizing Antibodies Against Epithelial Cell Infection Demonstrated Through 3 Years After Vaccination

Interim analysis of participants followed for 36 months



- Antibody GMTs remained stable
- nAb GMTs in CMV-seronegatives continued to exceed natural infection GMT through 3 years

ESCMID, 2025; GMT – geometric mean titer

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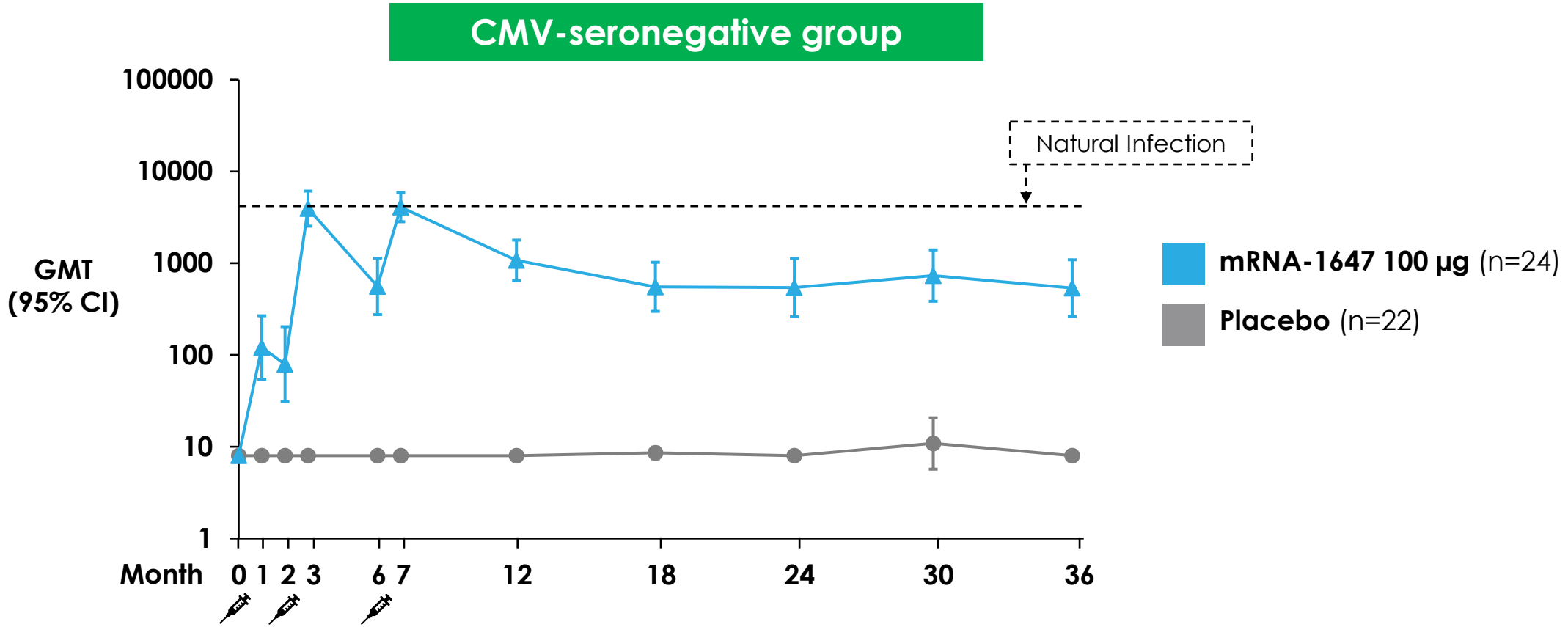
Persistence of Neutralizing Antibodies Against Fibroblast Infection Demonstrated Through 3 Years After Vaccination

Interim analysis of participants followed for 36 months



- Antibody GMTs remained stable through 3 years

ESCMID, 2025; GMT – geometric mean titer

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Summary: mRNA-1647 Phase 2 Trial in Adults (18-40 Years)

Safety	• Generally well tolerated; no safety concerns identified • 3-dose 100 µg regimen regardless of serostatus
Immunogenicity	• Highly immunogenic at 100 µg dose level • Neutralizing antibody GMTs against epithelial cell infection remained above natural infection GMT through 12 months after the last vaccination in CMV-seronegative participants • Boosting effect observed in CMV-seropositive participants
Persistence of Antibody	• Persistence of neutralizing antibodies against epithelial cell infection demonstrated through 3 years after vaccination in CMV-seronegative & seropositive participants

NCT05085366

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Design of mRNA-1647 Phase 3 Pivotal Efficacy Trial

Design	• Randomized, observer-blind, placebo-controlled study
Study Population	• CMV-seronegative (80%) and CMV-seropositive females (20%), 16 - 40 years of age • Participants ≥ 20 years of age expected to have direct exposure in the home, socially, or occupationally to at least one child ≤ 5 years of age • Pregnancy was exclusionary
Treatment Groups	• Randomized 1:1 to receive 100 µg mRNA-1647 or placebo • Doses at 0, 2, 6 months
Duration of Follow-up	• 30 months

NCT05085366

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mRNA-1647 Phase 3 Trial: Key Objectives and Endpoints

Objective		CMV Seronegatives	CMV Seropositives
Primary	• **Efficacy:** Seroconversion from negative to positive serum CMV IgG starting 28 days after 3rd injection	✓	
	• **Safety:** Reactogenicity, adverse events	✓	✓
Secondary	• **Immunogenicity:** Neutralizing and binding antibody	✓	✓
Additional	• **CMV Viral Shedding:** Kinetics of CMV shedding in seronegatives who seroconverted	✓	
	• **CMV Viral Shedding:** Longitudinal shedding in urine of CMV seropositives		✓

NCT05085366

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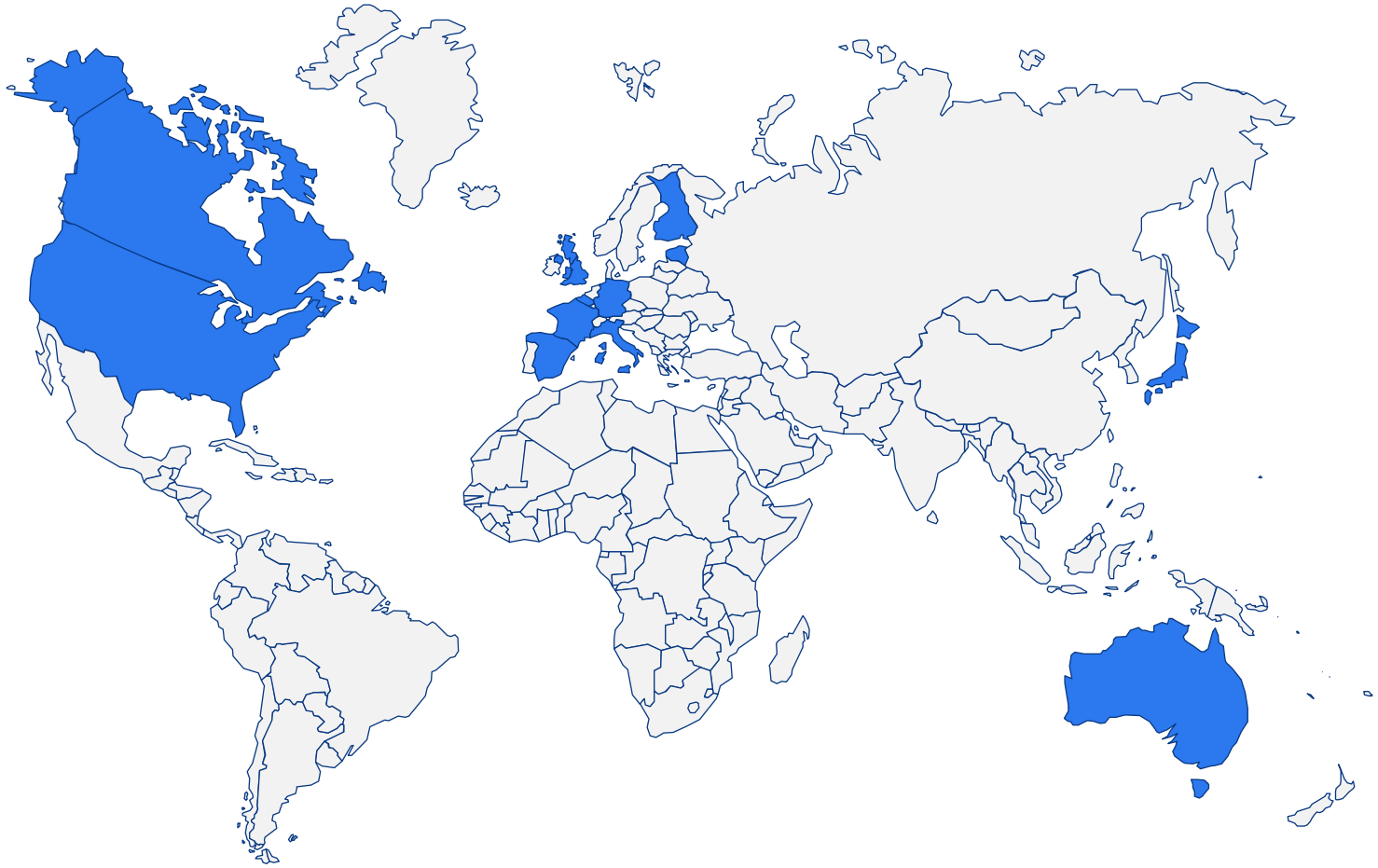
Phase 3 Pivotal Efficacy Trial in 16–40-Year-Old Females is Ongoing

- 290 sites, 13 countries
- Enrollment completed Oct 2023
- 7,484 participants enrolled
  - 5,987 (80%) CMV-seronegative
  - 1,497 (20%) CMV-seropositive



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mRNA-1647 Phase 3 Efficacy Trial: Two Planned Analyses

Interim Efficacy Analysis

- Independent Data Safety Monitoring Board (DSMB) conducted comprehensive safety and efficacy evaluation, Dec 2024
- Notified Moderna that:
  - No safety concerns identified
  - Study should continue as planned in blinded manner

Final Efficacy Analysis

- Data anticipated late 2025

DSMB – Data Safety Monitoring Board

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Summary: Investigational CMV Vaccine mRNA-1647 in Adults

Safety

- Vaccine generally well tolerated in adults, 18-40 years, regardless of CMV serostatus, in Phase 1 & 2 trials
- No safety concerns identified from DSMB review of unblinded data in Phase 3 efficacy trial.

Immunogenicity

CMV Seronegatives:

- Vaccination elicited antibody-mediated immunogenicity that exceeded levels observed in natural infection
- Immune persistence observed through 3 years after vaccination

CMV Seropositives:

- Vaccination boosted immune responses above baseline after first dose

Efficacy

- Trial ongoing in seronegative and seropositive females, 16-40 years of age

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THANK YOU

- Investigators
- Study site personnel
- Laboratory personnel
- **Most importantly, the individuals who participated in these trials**

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