

Immunostimulatory/Immunodynamic Model of an mRNA-Based Vaccine Against Cytomegalovirus Infection to Guide Vaccine Dose Selection

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BACKGROUND

- Congenital cytomegalovirus (cCMV) is the most common congenital viral infection and a leading cause of childhood sensorineural hearing loss and neurodevelopmental delay¹
 - In the United States, 1 out of every 200 infants is born with a cCMV infection; of these, approximately 1 out of 5 will be affected by long-term health conditions²
- There are currently no approved vaccines to prevent cytomegalovirus (CMV) infection, and the availability of a safe and effective vaccine remains a significant unmet healthcare need^{3,4}
- An investigational mRNA-based CMV vaccine, mRNA-1647, is in development
 - mRNA-1647 is comprised of 6 distinct mRNA sequences in a lipid nanoparticle formulation: 1 mRNA sequence encodes the full-length CMV glycoprotein B (gB) and 5 mRNA sequences encode the subunits of the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex (pentamer), which are endogenously translated, assembled, and expressed
 - mRNA-1647 was recently evaluated in a phase 1 study (NCT03382405) and clinical development is ongoing
- Modeling and simulation studies can be used as a practical tool to help guide dose selection for clinical vaccine studies and accelerate vaccine development⁵
 - Analogous to pharmacokinetic (PK)/pharmacodynamic (PD) modeling, immunostimulatory/immunodynamic (IS/ID) models are semi-mechanistic mathematical models that describe the immune response stimulated by vaccines (IS) and the resulting immune response dynamics (ID)⁵

OBJECTIVES

- To develop an in silico IS/ID model to adequately describe and predict neutralizing antibody (nAb) titers against epithelial cell infection and against fibroblast infection following mRNA-1647 injection
- To evaluate the utility of this IS/ID model as a data-driven tool to guide vaccine dose selection of mRNA-1647 for future clinical studies

METHODS

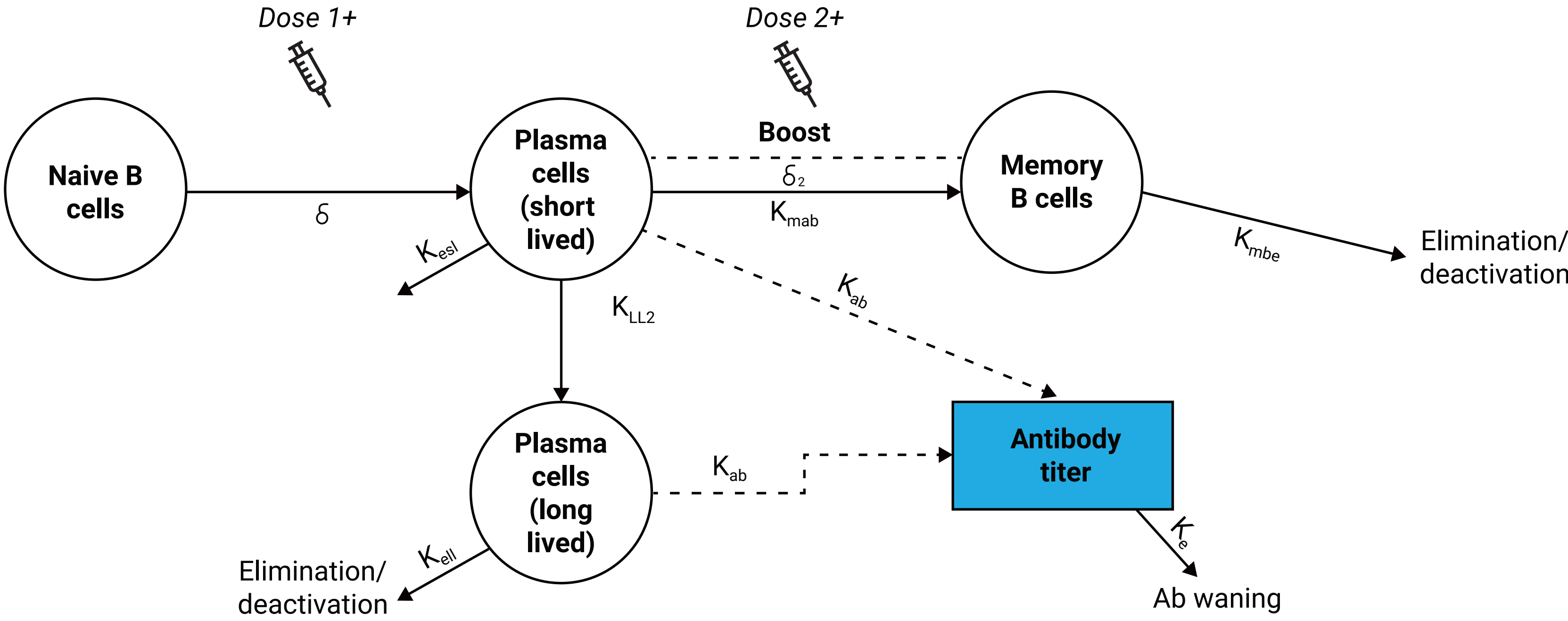
Clinical Data

- Data from a phase 1, randomized, observer-blind, placebo-controlled, dose-ranging study of mRNA-1647 (NCT03382405) was used to develop the IS/ID model
 - Healthy CMV-seronegative and CMV-seropositive adults aged 18 to 49 years (n = 80 and 74, respectively) received 1 to 3 injections of mRNA-1647 (30, 90, 180, or 300 µg; n = 29-30 per group) or placebo (n = 30) on Day (D) 1, Month (M) 2, and M6
 - nAbs against epithelial cell infection and against fibroblast infection were analyzed on D1, M1, M3, M6, M7, M12, and M18

Model Development

- A traditional PK/PD model was utilized to develop a semi-mechanistic IS/ID model (adapted from Rhodes et al⁵) to describe the nAb immune response following vaccination with mRNA-1647 and the resulting immune response dynamics (**Figure 1**)
 - Nonlinear mixed-effects modeling in Pumas v1.0.4 software (Pumas-AI, Inc., Baltimore, MD) was utilized to develop the model
 - The IS/ID model was based on 10 differential equations and 17 parameters and followed a typical time course of immune response after vaccination
 - Model performance was evaluated using goodness-of-fit plots and visual predictive checks

Figure 1. Simplified Schematic of Vaccine-Mediated Biological Mechanisms (Including B-cell Activation and Differentiation), Secretion of nAbs, and In Vivo Disposition of nAbs Following mRNA-1647 Administration



Ab, antibody; K_{ab}, secretion rate of antibody by plasma cells; K_{elim}, elimination rate for antibody; K_{LL2}, transition rate to long-lived plasma cells; K_{mab}, transition rate to memory B cells; K_{mbe}, memory B-cell antibody elimination rate; nAb, neutralizing antibody.

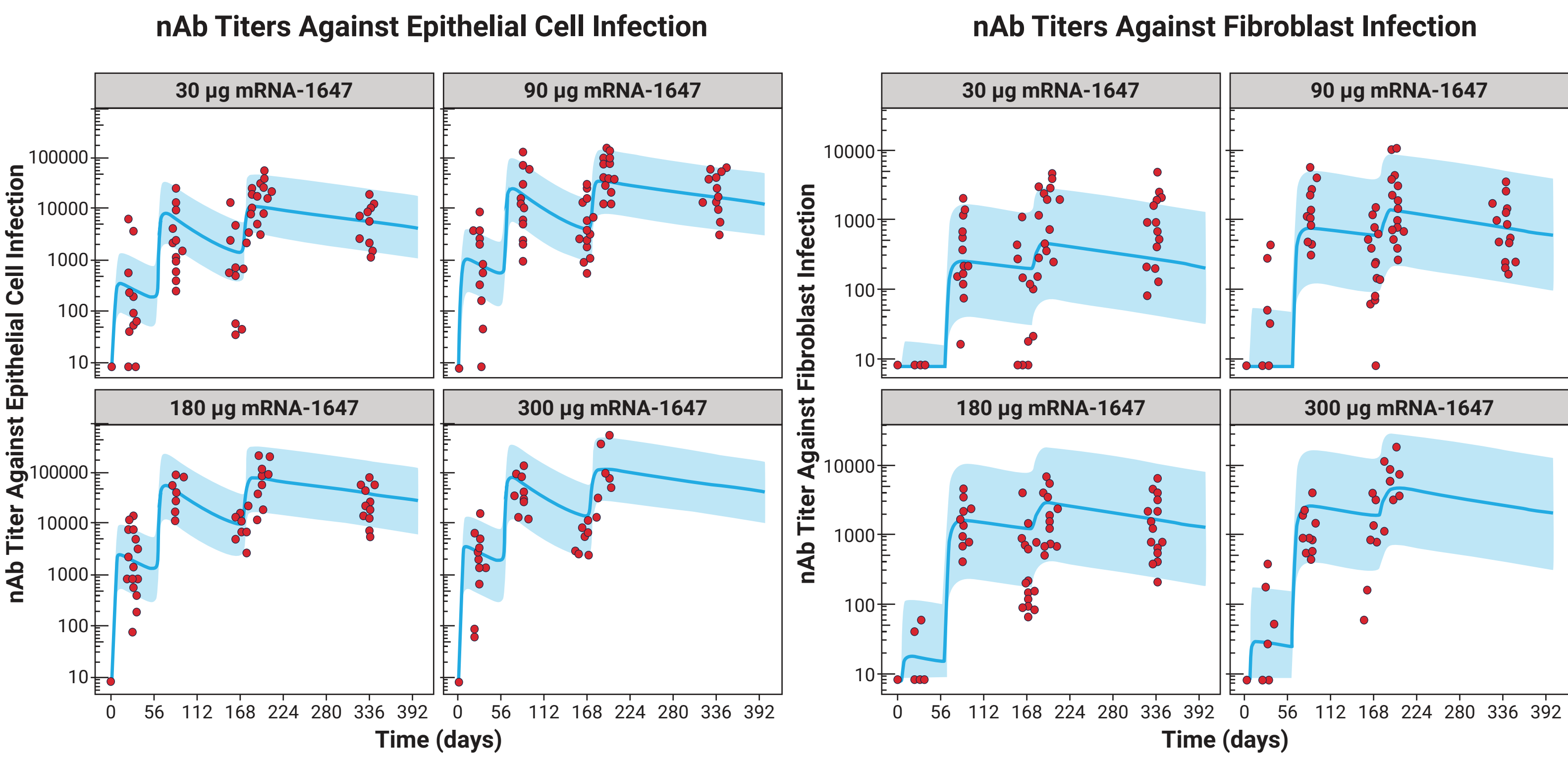
- A logistic regression model was also developed to evaluate the relationship between vaccine dose and the risk of adverse reactions using R programming language

RESULTS

Data and Modeling Analyses

- In the phase 1 trial, we observed an increase in CMV-specific nAb titers against gB and pentamer across all mRNA-1647 dose groups in baseline CMV-seronegative and CMV-seropositive participants (**Figure 2**)
- The final IS/ID model adequately described the time course and relationship between dose and nAbs for mRNA-1647, and was qualified using diagnostics and predictive checks (**Figure 2**)

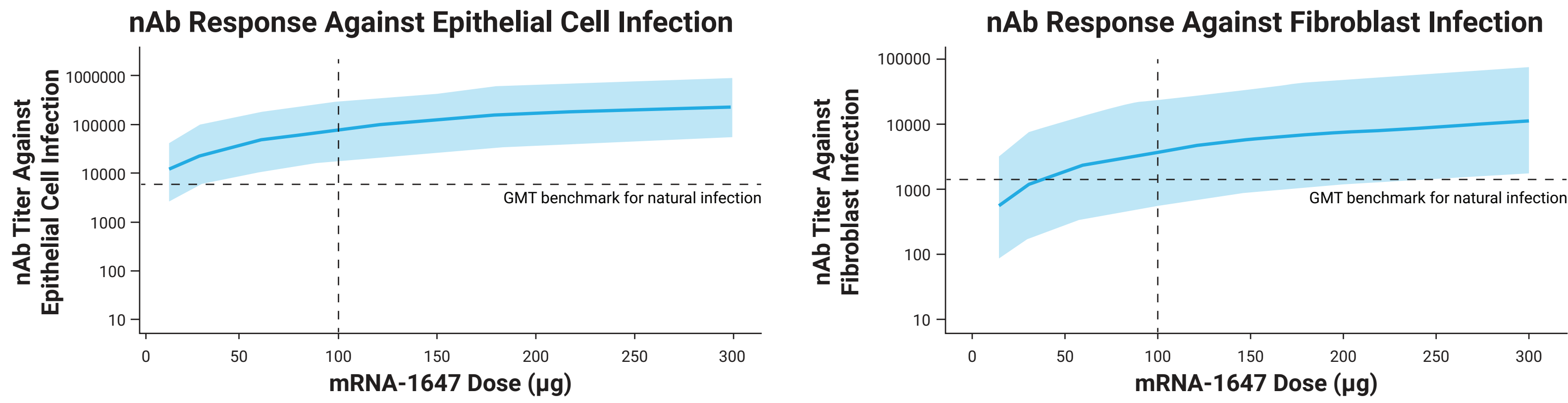
Figure 2. nAb Titers Against Epithelial Cell Infection and Against Fibroblast Infection Observed in the mRNA-1647 Phase 1 Clinical Trial and Predicted Using the IS/ID Model



nAb, neutralizing antibody; IS/ID, immunostimulatory/immunodynamic.
Red dots, observed clinical data; blue line, IS/ID model predictions (median); blue shaded area, 5th to 95th percentile of IS/ID model predictions.

- Clinical trial simulations using the model suggested that a 100-µg dose of mRNA-1647 in baseline CMV-seronegative participants would yield nAb titers that would exceed the CMV-seropositive benchmark of natural infection 1 month following dose 3 (**Figure 3**)

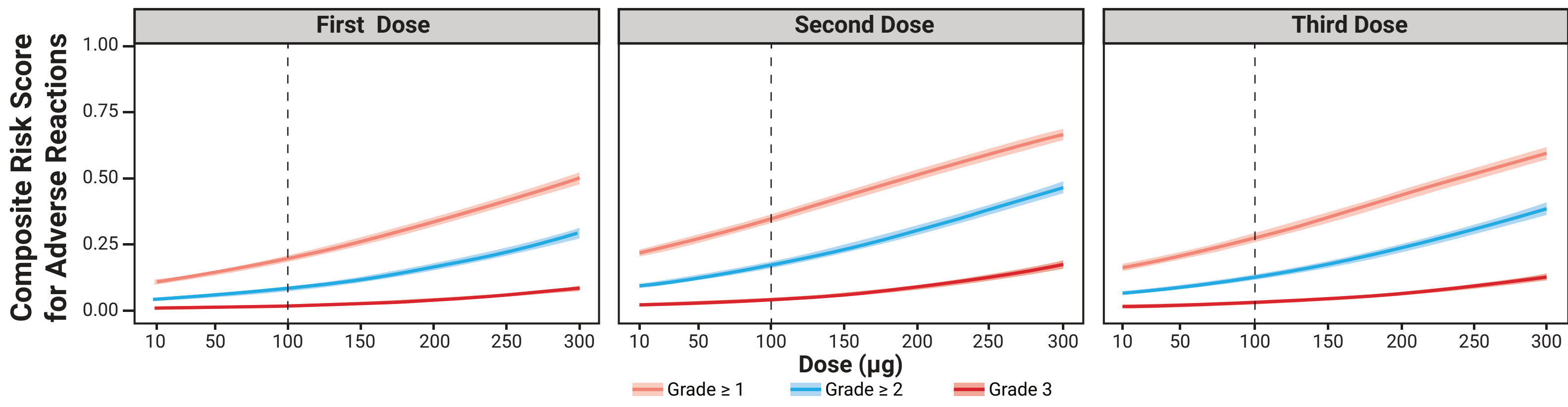
Figure 3. Predicted mRNA-1647 Dose Level Required to Yield nAb Titers Against Epithelial Cell Infection and Against Fibroblast Infection



GMT, geometric mean titer; nAb, neutralizing antibody.
Model predictions: blue line, geometric mean; blue shaded area, 5th to 95th percentile prediction interval; dotted black line, GMT benchmark for natural infection.

- Reactogenicity modeling supported selection of a 100-µg dose level for the phase 3 clinical study (**Figure 4**)
 - The risk of adverse reactions (especially grade 3) was predicted to remain low at a ≤100-µg dose

Figure 4. Reactogenicity Modeling of mRNA-1647^a



^aComposite risk of adverse reactions was derived using probabilities of individual adverse reactions (0 = no risk; 1 = maximum risk).

- The 100-µg dose was predicted to yield nAb titers against epithelial cell infection and against fibroblast infection above the CMV-seropositive benchmark for natural infection in most CMV-seronegative individuals and was predicted to have minimal risk of adverse reactions (**Figure 3** and **Figure 4**)

CONCLUSIONS

- The IS/ID model adequately described the observed nAb responses against epithelial cell infection and against fibroblast infection following mRNA-1647 injection
- Modeling and simulation using an IS/ID model can help drive data-driven decision making for clinical dose selection of vaccines
 - Simulations from this IS/ID model and reactogenicity models are being used to guide the ongoing clinical development of mRNA-1647, which is currently being investigated in a phase 3 clinical trial in healthy participants 16 to 40 years of age (NCT05085366)



ABSTRACT PLAIN LANGUAGE SUMMARY

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Disclosures

SG, JFK, LP, and AN are employees of Moderna, Inc., and hold stock/stock options in the company. HA was an employee of Moderna, Inc., at the time of writing the poster and held stock/stock options in the company. VI and BG-L were paid by Moderna, Inc., to perform the analysis.