Correlation of Humoral Immunogenicity Results Elicited by mRNA-1010 Seasonal Influenza Vaccine in Adults Aged ≥18 Years: A Comparative Phase 3 Analysis

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BACKGROUND

- Seasonal influenza viruses cause respiratory illness and contribute to a global public health burden[1]
- The effectiveness of the licensed seasonal influenza vaccines (produced by egg-, cell-, or recombinant-based methods) varies,[1-3] owing to antigenic mismatch with circulating strains such as A/H3N2[4,5]
- mRNA-based vaccines have the potential for improved relative efficacy compared with other currently licensed influenza vaccines and allow for better strain matching, faster production, and stronger T-cell immunity[3]
- mRNA-1010 is a novel mRNA-based seasonal influenza vaccine encoding hemagglutinin (HA) surface glycoproteins of strains recommended by the World Health Organization (WHO) for the 2023-2024 Northern Hemisphere season[6,7]
  - mRNA-1010 has previously demonstrated superior humoral immunogenicity compared with age-appropriate licensed comparators (standard dose [SD] for participants aged 18-64 years, or high dose [HD] for participants aged ≥65 years), as measured by the hemagglutination inhibition (HAI) assay in a phase 3 randomized trial[7]
- Microneutralization (MN) assays are also used to detect circulating antibodies against influenza viruses, in addition to HAI assays[8]
- Here, we present exploratory MN data from a subset of participants in the mRNA-1010 phase 3 trial and correlate these data with HAI

OBJECTIVE

- To evaluate humoral immunogenicity of mRNA-1010 (50 µg) relative to licensed SD comparator in adults aged 18 to 64 years (**Part B**) or HD comparator in adults aged ≥65 years (**Part C**), using a single-cycle MN assay, and correlate with HAI titers

METHODS

Study Design and Population

- This was a 3-part, phase 3, randomized, double-blind, active-controlled study conducted at multiple sites in the United States (NCT05827978) to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 in adults aged ≥18 years
  - Part A: Participants aged ≥18 years were randomly assigned to receive either a single dose of mRNA-1010 or a licensed SD inactivated influenza vaccine, quadrivalent (SD-QIV; Fluarix® Quadrivalent; GlaxoSmithKline Biologicals, Dresden, Germany)
  - Part B: Participants aged 18 to 64 years were randomly assigned to receive either a single dose of mRNA-1010 or a licensed SD-QIV (Fluarix® Quadrivalent; GlaxoSmithKline Biologicals, Dresden, Germany)
  - Part C: Participants aged ≥65 years were randomly assigned to receive either a single dose of mRNA-1010 or a licensed HD inactivated influenza vaccine, quadrivalent (HD-QIV; Fluzone® HD Quadrivalent; Sanofi Pasteur Inc., Swiftwater, PA, USA)
- This analysis presents the exploratory findings on the humoral responses for 4 influenza strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) in **Parts B and C** of the study based on the WHO recommendations for the 2023-2024 Northern Hemisphere season
- MN titers at baseline and Day 29 were measured in 1000 participants (250 per arm in each part; 17% of study participants)

HAI and MN Assays

- HAI and MN assays were validated using WHO matched cell-propagated viruses and study-specific sera from consenting participants
- The HAI assay was based on guinea pig–derived red blood cells, while the MN assay was validated using Madin-Darby Canine Kidney cells and detection of all antibodies with functional and neutralizing antibody potential against influenza virus
- Serum antibody titers from study participants were derived from a 2-fold sample dilution scheme, starting with 1:10. Results were reported as geometric mean titers (GMTs) from duplicate measurements
- The MN subset represented a randomly stratified subset of the population tested by HAI
- The MN subset was descriptive and not powered for statistical significance, in accordance with the prespecified exploratory objective

Study Objectives and Endpoints

- To conduct exploratory evaluation of the humoral immunogenicity of mRNA-1010 relative to licensed SD-QIV or HD-QIV against vaccine-matched influenza A and B strains
  - GMTs and geometric mean fold rises (GMFRs) of neutralizing antibodies against vaccine-matched strains on Day 29 compared with Day 1 (baseline) based on a validated MN assay
- Pearson correlations were calculated based on log-transformed MN and HAI titers

RESULTS

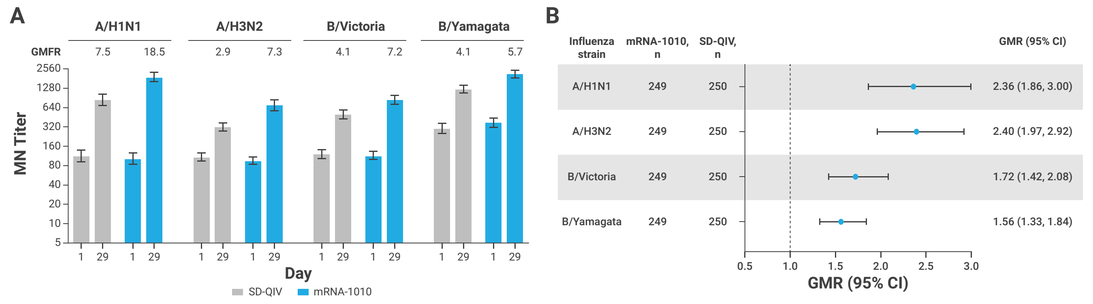
Baseline Demographics and Characteristics

- The exploratory MN analysis was conducted in a subset of participants in the per-protocol immunogenicity set from Parts B and C of the study and included participants who had MN values at Day 1 and Day 29
  - Overall, 499 participants in Part B (mRNA-1010 group, n = 249; SD-QIV group, n = 250), and 500 participants in Part C (mRNA-1010 group, n = 250; SD-QIV group, n = 250) were included in the analysis
- There were no notable differences in the demographic characteristics among participants with MN data in the mRNA-1010 group and the respective licensed QIV comparator groups in each part (SD-QIV, Part B; HD-QIV, Part C)
- In both parts, the majority of participants were female (Part B: 293/499 [58.7%]; Part C: 276/500 [55.2%]), White (Part B: 319/499 [63.9%]; Part C: 415/500 [83.0%]), and non-Hispanic/Latino (Part B: 376/499 [75.4%]; Part C: 322/500 [64.4%]); the median age of participants was 48.0 years (range, 18-64 years) in Part B and 70.0 years (range, 65-88 years) in Part C

Immunogenicity

- In Part B, mRNA-1010 showed superior MN immune responses compared with SD-QIV across all 4 strains (**Figure 1**)
  - Day 29 GMTs and GMFRs from baseline were higher in mRNA-1010 compared with SD-QIV (**Figure 1A**)
  - Overall, geometric mean ratios (GMRs) of mRNA-1010 compared with SD-QIV were 2.36, 2.40, 1.72, and 1.56 for A/H1N1, AH3N2, B/Victoria, and B/Yamagata, respectively (**Figure 1B**)

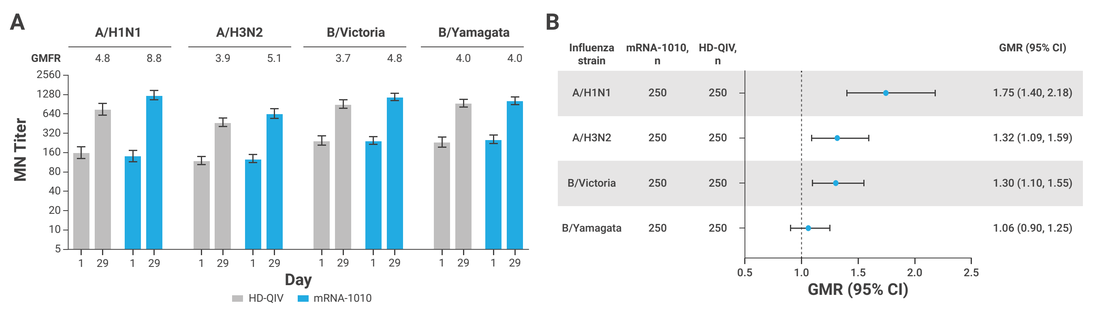
Figure 1. (A) MN GMTs and GMFRs for mRNA-1010 and SD-QIV and (B) Overall GMRs of Antibody Levels for mRNA-1010 Compared With SD-QIV Through Day 29



CI, confidence interval; GMFR, geometric mean fold rise; GMR, geometric mean ratio; GMT, geometric mean titer; LLOQ, lower limit of quantification; MN, microneutralization; QIV, quadrivalent influenza vaccine; SD, standard dose; ULOQ, upper limit of quantitation.
Per-protocol immunogenicity population (participants with MN immunogenicity values) included participants without major protocol deviations impacting immunogenicity assessment.
Dashed line indicates a GMR = 1.0.
LLOQ was 17 for A/H1N1 and A/H3N2, 14 for B/Victoria, and 18 for B/Yamagata. ULOQ was 9738 for A/H1N1, 10,240 for A/H3N2 and B/Victoria, and 9373 for B/Yamagata. Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values greater than the ULOQ were converted to the ULOQ.

- In Part C, mRNA-1010 elicited superior or comparable MN immune responses for all 4 strains compared with HD-QIV (**Figure 2**)
  - Day 29 GMTs and GMFR from baseline were higher in mRNA-1010 compared with HD-QIV (**Figure 2A**)
  - Overall, GMRs of mRNA-1010 compared with HD-QIV were 1.75, 1.32, 1.30, and 1.06 for A/H1N1, AH3N2, B/Victoria, and B/Yamagata, respectively (**Figure 2B**)

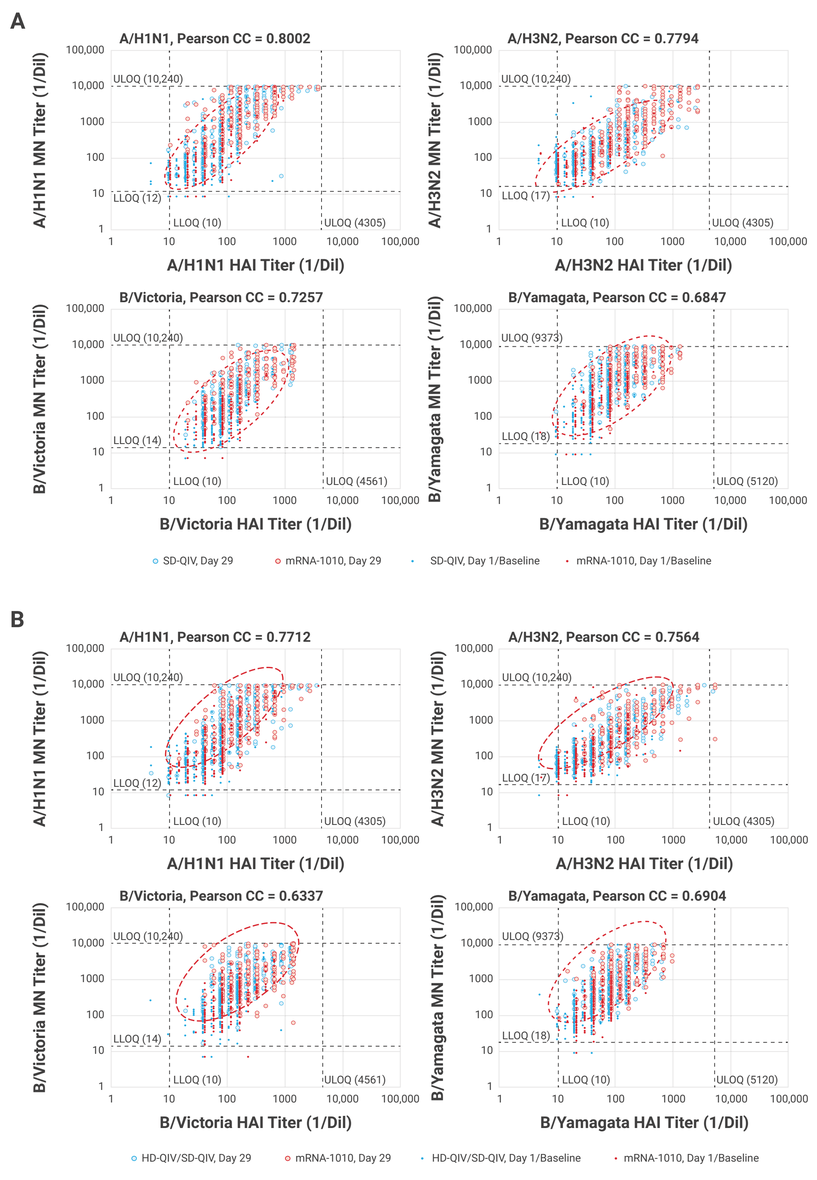
Figure 2. (A) MN GMTs and GMFRs for mRNA-1010 and HD-QIV and (B) Overall GMRs of Antibody Levels for mRNA-1010 Compared With HD-QIV Through Day 29



CI, confidence interval; GMFR, geometric mean fold rise; GMR, geometric mean ratio; GMT, geometric mean titer; HD, high dose; LLOQ, lower limit of quantification; MN, microneutralization; QIV, quadrivalent influenza vaccine; ULOQ, upper limit of quantitation.
Per-protocol immunogenicity population (participants with MN immunogenicity values) included participants without major protocol deviations impacting immunogenicity assessment; 500 selected participants were included.
Dashed line indicates GMR = 1.0.
LLOQ was 17 for A/H1N1 and A/H3N2, 14 for B/Victoria, and 18 for B/Yamagata. ULOQ was 9738 for A/H1N1, 10,240 for A/H3N2 and B/Victoria, and 9373 for B/Yamagata. Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values greater than the ULOQ were converted to the ULOQ.

- Pearson correlations demonstrated MN and HAI titers following vaccination were positively correlated in all strains (**Figure 3**)
  - High correlation coefficients of ≥0.7 were observed for both A strains in Parts B and C, as well as B/Victoria in Part B

Figure 3. Correlation Between MN and HAI Titers at Days 1 and 29 in (A) Part B and (B) Part C



HAI, hemagglutination inhibition; HD, high dose; LLOQ, lower limit of quantification; MN, microneutralization; QIV, quadrivalent influenza vaccine; SD, standard dose; ULOQ, upper limit of quantification.

CONCLUSIONS

- MN immune responses to mRNA-1010 are higher than or comparable to licensed QIV comparators, either SD or HD administered as per standard of care; MN immune responses are strongly correlated with HAI titers across all strains
- The strong correlation between single-cycle MN and HAI provides further support for HAI as a predictor of disease prevention with mRNA-based influenza vaccination

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Disclosures

GH, MS, ED, RC, AA, LZ, BD, EW, and RD are employees of Moderna, Inc., and may hold stock or stock options.

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