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A phase 3 randomized safety and immunogenicity trial of mRNA-1010 seasonal influenza vaccine in adults

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ABSTRACT

Background: Messenger RNA (mRNA)-based influenza vaccines have the potential to improve upon limitations of current vaccine approaches to seasonal influenza.
Methods: Here we report findings on the primary and secondary objectives of the safety, reactogenicity, and humoral immunogenicity of the quadrivalent mRNA vaccine, mRNA-1010, versus licensed standard-dose and high-dose quadrivalent influenza vaccines from a three-part, phase 3 clinical trial in adults aged ≥18 years (Part A), 18–64 years (Part B), and ≥ 65 years (Part C) (NCT05827978).
Results: A single 50-μg dose of mRNA-1010 elicited hemagglutination inhibition titers against vaccine-matched strains that were statistically noninferior and superior to licensed standard-dose and high-dose egg-based quadrivalent vaccine comparators. Solicited adverse reactions were more frequent with receipt of mRNA-1010; adverse reactions were lower in frequency and severity among adults aged ≥65 years than younger adults. No safety concerns were identified.
Conclusions: These findings support the potential benefit of mRNA-1010 as a seasonal influenza vaccine.

1. Introduction

Seasonal influenza viruses remain a threat to global public health [1]. Vaccination is an integral preventive measure to protect against disease, but available seasonal influenza vaccines that employ egg-, cell-, or recombinant protein-based technology may have suboptimal effectiveness [2,3], particularly when vaccine strains differ antigenically from the circulating strains [4]. Vaccines based on messenger RNA (mRNA) technology have demonstrated success against infectious respiratory pathogens (eg, SARS-CoV-2 [5] and respiratory syncytial virus [6]) and have the potential to improve upon limitations of current vaccine approaches to seasonal influenza [7]. In particular, mRNA-based strategies can avoid egg-acquired mutations, induce robust humoral and T-cell immune responses, and provide the potential for combination respiratory vaccines and expanded antigens [8–10]. Further, use of an mRNA platform may reduce the possibility of antigenic mismatch through shortened lag times between strain identification and vaccine development [7,11].

mRNA-1010, an investigational seasonal influenza vaccine, encodes hemagglutinin surface glycoproteins of the influenza strains recommended by the World Health Organization (WHO) [12]. In the first-in-human phase 1/2 trial in adults (NCT04956575), mRNA-1010 elicited higher immunogenicity than a standard-dose active comparator for influenza A/H1N1 and A/H3N2 strains and comparable immunogenicity for influenza B/Victoria and B/Yamagata strains, with no safety concerns identified [12]. Based on phase 1/2 results [12], the safety,

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immunogenicity, and efficacy of a 50-μg dose level of mRNA-1010 was moved forward into phase 3 studies [13–15].

This phase 3 study evaluated the immunogenicity, reactogenicity, and safety of mRNA-1010 in adults aged ≥18 years, including noninferiority and superiority assessments of immune responses elicited by mRNA-1010 versus licensed standard-dose and high-dose quadrivalent seasonal influenza vaccines (NCT05827978). The study was conducted in three parts in adults aged ≥18 years (Part A), aged 18–64 years (Part B), and aged ≥65 years (Part C). Parts B and C were added to the study after the primary analysis of Part A demonstrated noninferior immunogenicity of mRNA-1010 versus a standard-dose comparator vaccine based on prespecified criteria. Parts B and C were added to further characterize the safety and immunogenicity of mRNA-1010 versus standard-dose comparator vaccine in adults aged 18–64 years and versus high-dose comparator vaccine in adults aged ≥65 years, respectively. Here we present final results through 6 months post-vaccination for Part A and interim results through 28 days post-vaccination for Part B and Part C.

2. Methods

2.1. Trial design and participants

This phase 3, randomized, observer-blind, active-controlled study conducted at US sites evaluated the safety, reactogenicity, and immunogenicity of mRNA-1010 in adults (NCT05827978). Part A enrolled medically stable adults aged ≥18 years. After the primary immunogenicity objective was met in the primary analysis of Part A, the study protocol was amended to add Parts B and C to further evaluate the safety and immunogenicity of mRNA-1010 versus standard-dose comparator vaccine in adults aged 18–64 years and versus high-dose comparator vaccine in ≥65 years, respectively.

Medically stable adults aged ≥18 years (Part A), aged 18–64 years (Part B), and aged ≥65 years (Part C) were enrolled. Full inclusion and exclusion criteria are listed in the **Supplement**. Participants were randomly assigned (1:1) using interactive response technology to receive a single dose of either mRNA-1010 50 μg or a licensed seasonal influenza vaccine as an active comparator (standard-dose inactivated influenza vaccine, quadrivalent [SD-IIV4] in Parts A and B; high-dose inactivated influenza vaccine, quadrivalent [HD-IIV4] in Part C). Random assignment in Part A was stratified by age group (18–49 years, 50–64 years, or ≥ 65 years) and by influenza vaccination status in the prior 12 months (received or not received). In Part A, approximately 50 % of participants enrolled (n = 1200) were planned to be aged ≥50 years, including 20 % (n = 480) planned to be aged ≥65 years. Random assignment in Parts B and C was stratified by influenza vaccination status since September 2022 (received or not received; and if received, yes or no whether it was from participation in the mRNA-1010-P302 study [NCT05566639]). Details on blinding are included in the **Supplement**. Participants received a single dose of mRNA-1010 or active comparator on Day 1 and were followed through 6 months (Day 181). Part A has completed, with data available for the final study visit at Day 181; Parts B and C are ongoing with interim data available up to data cut-off (January 28, 2024).

The study was conducted in accordance with the protocol, applicable laws, and regulatory requirements, as well as International Council for Harmonisation Good Clinical Practice guidelines, and the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines. The protocol was approved by the central institutional review board (Advarra, Inc.; Columbia, MD) prior to study initiation, and written informed consent was obtained from all participants before enrollment.

2.2. Vaccines

mRNA-1010 included mRNAs encoding for the hemagglutinin surface glycoproteins of four influenza virus strains formulated in lipid nanoparticles. Strain selection was based on WHO recommendations for cell- or recombinant-based vaccines for the 2022–2023 Northern Hemisphere season in Part A and for the 2023–2024 Northern Hemisphere season in Parts B and C (see **Supplement**). The active comparator contained seasonal influenza vaccine antigens for strains recommended by the WHO for egg-based vaccines for the 2022–2023 Northern Hemisphere in Part A (Fluarix® Quadrivalent [SD-IIV4]; GlaxoSmithKline Biologicals, Dresden, Germany) and for the 2023–2024 Northern Hemisphere season in Parts B (Fluarix® Quadrivalent [SD-IIV4]; GlaxoSmithKline Biologicals, Dresden, Germany) and C (Fluzone® HD Quadrivalent [HD-IIV4]; Sanofi Pasteur Inc., Swiftwater, PA, USA). Vaccines were administered intramuscularly as a single 0.5-mL injection (mRNA-1010 and SD-IIV4) or as a single 0.7-mL injection (HD-IIV4) into the deltoid muscle, preferably into the nondominant arm.

2.3. Trial objectives

The primary objectives of Part A of this phase 3 trial were to evaluate the safety and reactogenicity of a single dose of mRNA-1010 (50 μg) and the humoral immunogenicity of mRNA-1010 (50 μg) relative to SD-IIV4 based on hemagglutination inhibition (HAI) assay against four vaccine-matched influenza virus A and B strains at Day 29. Exploratory objectives of Part A were to further evaluate the humoral immunogenicity of mRNA-1010 based on HAI at Day 181 and alternative assays such as microneutralization (MN) at Day 29.

The primary objectives of Part B were to evaluate the safety and reactogenicity of mRNA-1010 and to assess for noninferiority of humoral immunogenicity of mRNA-1010 relative to SD-IIV4 based on HAI assay against four vaccine-matched influenza virus A and B strains at Day 29. A secondary objective of Part B was to evaluate for superiority of humoral immunogenicity of mRNA-1010 relative to SD-IIV4 based on HAI assay at Day 29.

The primary objectives of Part C were to evaluate the safety and reactogenicity of mRNA-1010 and to assess for noninferiority of humoral immunogenicity of mRNA-1010 relative to HD-IIV4 based on HAI assay against four vaccine-matched influenza virus A and B strains at Day 29. A secondary objective of Part C was to evaluate for superiority of humoral immunogenicity of mRNA-1010 relative to HD-IIV4 based on HAI assay at Day 29.

2.4. Safety assessments

Safety endpoints in each part included solicited local and systemic adverse reactions (ARs) through 7 days after study vaccination; unsolicited adverse events (AEs) through 28 days after study vaccination; and medically attended AEs, AEs of special interest (AESIs), serious adverse events (SAEs), and AEs leading to study discontinuation through to the end of the study (Day 181). Participants used an electronic diary to record local (injection site pain, erythema, swelling/induration, and axillary swelling/tenderness) and systemic (headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever) ARs.

2.5. Immunogenicity assessments

Blood samples for immunogenicity assessments were collected on Day 1 (baseline), Day 29, and Day 181. Primary immunogenicity endpoints included geometric mean titers (GMTs) and seroconversion rates (SCRs) at Day 29 as measured by HAI assay as described in the **Supplement**. Secondary immunogenicity endpoints included the proportion of participants with an HAI titer of ≥40 at Day 29 and geometric mean fold rise (GMFR; Day 29 over Day 1) in HAI titers. HAI GMTs and SCRs at Day 181 were exploratory immunogenicity endpoints. Another

exploratory endpoint in Part A was to provide Day 29 GMTs and GMFRs by measuring neutralizing activity using cell-derived viruses with a validated MN assay (fully described in the **Supplement**) in a stratified random subset of 499 participants.

2.6. Statistical analyses

Sample sizes were considered sufficient for immunogenicity hypothesis testing in each study part (see **Supplement**). Evaluable populations are defined in the **Supplement**. HAI GMTs and GMFRs with corresponding 95 % CIs were calculated for each vaccination group; and the number and percentage of participants with seroconversion or titer ≥40 were determined, with two-sided 95 % CIs calculated using the Clopper-Pearson method. SCR was defined as the proportion of participants with either a baseline HAI titer <10 and a post-baseline titer ≥40 or a baseline HAI titer ≥10 and ≥ 4-fold rise in post-baseline HAI antibody titer. MN data from Part A were evaluated in a random subset of participants using similar analysis methods as described for the HAI data.

Hypothesis testing was performed to assess the primary immunogenicity objective in Parts A-C. The null hypothesis was that immunogenic response to mRNA-1010, as measured by HAI GMTs and SCRs at Day 29, is inferior compared with the response in participants who received SD-IIV4 (Parts A and B) or HD-IIV4 (Part C) for each of the four vaccine-matched influenza strains. Each of the eight coprimary immunogenicity endpoints were evaluated for noninferiority of mRNA-1010 versus SD-IIV4 in Part A at a two-sided alpha level of 0.05 and versus SD-IIV4 in Part B or HD-IIV4 in Part C at a one-sided alpha level of 0.025. The study part was to be considered a success if all eight coprimary immunogenicity endpoints met noninferiority criteria. The prespecified criteria for noninferiority in GMTs was the lower bounds of the 95 % CIs of the GMT ratios (GMRs; ratios of HAI GMTs in mRNA-1010 vs SD-IIV4 or HD-IIV4) ruling out 0.667 (ie, 95 % CI lower bounds >0.667). The GMRs and 95 % CIs for each strain were calculated using an analysis of covariance model with log-transformed HAI titers at Day 29 as the dependent variable, vaccine group as the fixed variable, and log-transformed HAI titers at baseline as a fixed covariate, adjusting for stratification factors (see **Supplement**). The prespecified criteria for noninferiority in SCRs was the lower bounds of the 95 % CIs for the SCR differences (mRNA-1010 vs SD-IIV4 or HD-IIV4) ruling out −10 % (ie, 95 % CI lower bounds > − 10 %). The Miettinen-Nurminen's method was used to compare the SCR between the vaccine groups by calculating the SCR difference and corresponding 95 % CI. In Parts B and C, upon successful demonstration of noninferiority for all eight coprimary immunogenicity endpoints, superiority hypothesis testing was performed to assess the secondary immunogenicity objective (see **Supplement**). The prespecified criteria for superiority in GMTs at Day 29 was the GMR (mRNA-1010 vs SD-IIV4 or HD-IIV4) 97.5 % or 98.8 % CI lower bounds >1 and for SCR at Day 29 was the SCR difference (mRNA-1010 vs SD-IIV4 or HD-IIV4) 97.5 % or 98.8 % CI lower bounds >0 %. Statistical analyses were performed using SAS version 9.4.

3. Results

3.1. Trial population

Part A of the trial randomly assigned 2414 participants aged ≥18 years to receive mRNA-1010 50 µg or SD-IIV4, initiating on April 17, 2023, and completing on May 5, 2023 (Fig. 1). Most participants vaccinated with mRNA-1010 (91.2 % [1113/1220]) and SD-IIV4 (93.7 % [1106/1180]) completed the study (completed the Day 181 final study visit). The most common reasons for study discontinuation in the mRNA-1010 and SD-IIV4 groups were loss to follow-up ($n = 88$ and $n = 57$, respectively) and participant withdrawal ($n = 16$ and $n = 17$, respectively). Part B randomly assigned 2994 participants aged 18–64 years to receive mRNA-1010 50 µg ($n = 1500$) or SD-IIV4 ($n = 1494$) between November 13, 2023, and December 2, 2023; as of the interim data cut-off (January 28, 2024), 1498 (99.9 %) and 1490 (99.7 %) participants had received study vaccines (Fig. 1). Part C enrollment of participants aged ≥65 years occurred between November 13, 2023, and December 13, 2023. A total of 3003 participants were randomly assigned to receive mRNA-1010 50 µg ($n = 1507$) or HD-IIV4 ($n = 1496$); 1504 (99.8 %) and 1492 (99.7 %) participants received study vaccine as of the interim data cut-off (January 28, 2024) (Fig. 1).

For all three trial parts, baseline participant demographics and characteristics were comparable between vaccine groups (Table 1). Most participants were female, White and non-Hispanic/Latino. Median age was 50 years, 49 years, and 70 years in Part A (aged ≥18 years), Part B (aged 18–64 years) and Part C (aged ≥65 years), respectively. Respective proportions of participants who had received the previous season's influenza vaccine were 39 %, 34 %, and 53 %.

3.2. Reactogenicity

In all three trial parts, rates of solicited ARs within 7 days after study vaccination were higher with mRNA-1010 than with SD-IIV4 (Part A [aged ≥18 years] and Part B [aged 18–64 years]) or HD-IIV4 (Part C [aged ≥65 years]) (Fig. 2). In the mRNA-1010 and comparator vaccine groups, frequencies and severities of solicited ARs tended to be lower among older adults (aged ≥65 years; Part C) than in younger adults

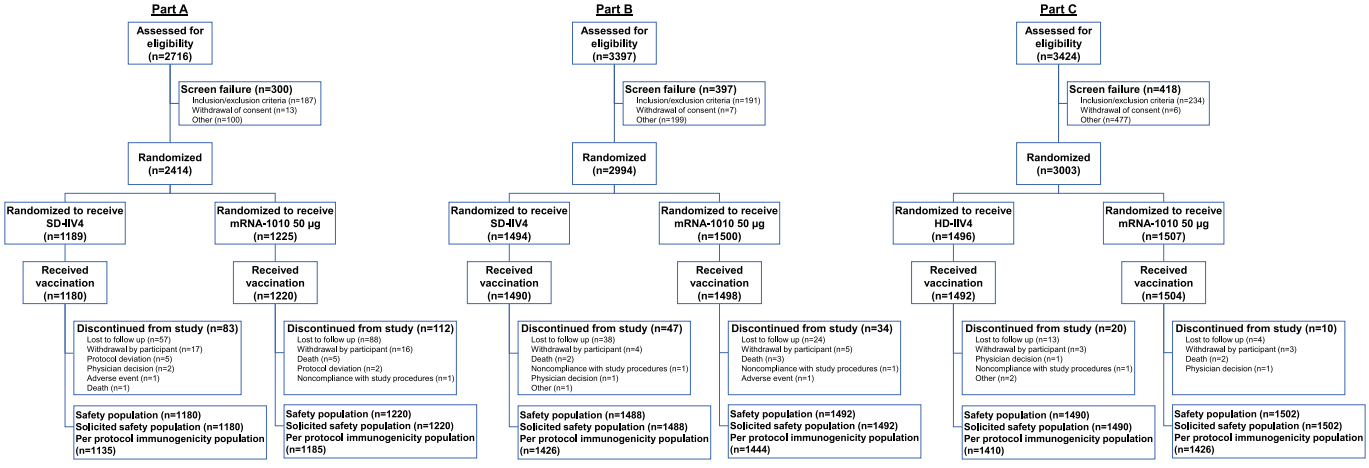


Fig. 1. Participant disposition. Median follow-up: Part A, 172 days (IQR 168–180); Part B, 65 days (IQR 61–70); Part C, 54 days (IQR 49–59).
IQR interquartile range.

Table 1
Baseline participant demographics/characteristics.

	Part A[a]		Part B[b]		Part C[b]	
	SD-IIV4 (*N* = 1180)	mRNA-1010 50 µg (*N* = 1220)	SD-IIV4 (*N* = 1488)	mRNA-1010 50 µg (*N* = 1492)	HD-IIV4 (*N* = 1490)	mRNA-1010 50 µg (*N* = 1502)
Age, years						
Mean ± std. dev	49.7 ± 17.15	49.8 ± 16.50	46.4 ± 12.83	46.0 ± 12.95	71.0 ± 4.95	71.1 ± 4.92
Median (range)	50 (18, 91)	50 (18, 86)	50 (18, 64)	49 (18, 64)	70 (64, 93)	70 (65, 93)
Age group, years, *n* (%)						
18–49	577 (48.9)	593 (48.6)	736 (49.5)	755 (50.6)	0	0
50–64	335 (28.4)	353 (28.9)	752 (50.5)	737 (49.4)	1 (<0.1)	0
65–74	159 (13.5)	183 (15.0)	0	0	1154 (77.4)	1176 (78.3)
≥75	109 (9.2)	91 (7.5)	0	0	335 (22.5)	326 (21.7)
Sex, *n* (%)						
Female	623 (52.8)	660 (54.1)	904 (60.8)	877 (58.8)	852 (57.2)	878 (58.5)
Male	557 (47.2)	560 (45.9)	584 (39.2)	615 (41.2)	638 (42.8)	624 (41.5)
Race, *n* (%)						
White	851 (72.1)	919 (75.3)	966 (64.9)	1012 (67.8)	1220 (81.9)	1255 (83.6)
Black/ African American	270 (22.9)	248 (20.3)	444 (29.8)	420 (28.2)	235 (15.8)	224 (14.9)
Asian	34 (2.9)	27 (2.2)	28 (1.9)	24 (1.6)	10 (0.7)	10 (0.7)
American Indian or Alaska Native	5 (0.4)	7 (0.6)	12 (0.8)	12 (0.8)	9 (0.6)	4 (0.3)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	3 (0.2)	4 (0.3)	4 (0.3)	0	2 (0.1)
Multiple	11 (0.9)	11 (0.9)	18 (1.2)	6 (0.4)	6 (0.4)	2 (0.1)
Other	3 (0.3)	3 (0.2)	7 (0.5)	11 (0.7)	4 (0.3)	1 (<0.1)
Not reported	3 (0.3)	0	6 (0.4)	2 (0.1)	2 (0.1)	3 (0.2)
Unknown	2 (0.2)	2 (0.2)	3 (0.2)	1 (<0.1)	4 (0.3)	1 (<0.1)
Ethnicity, *n* (%)						
Hispanic or Latino	225 (19.1)	261 (21.4)	390 (26.2)	401 (26.9)	454 (30.5)	450 (30.0)
Not Hispanic or Latino	940 (79.7)	937 (76.8)	1079 (72.5)	1073 (71.9)	1021 (68.5)	1037 (69.0)
Not reported	15 (1.3)	19 (1.6)	15 (1.0)	15 (1.0)	14 (0.9)	14 (0.9)
Unknown	0	3 (0.2)	4 (0.3)	3 (0.2)	1 (<0.1)	1 (<0.1)
Receipt of seasonal influenza vaccine, *n* (%)[c]						
No	723 (61.3)	736 (60.3)	992 (66.7)	980 (65.7)	703 (47.2)	715 (47.6)
Yes	457 (38.7)	484 (39.7)	496 (33.3)	512 (34.3)	787 (52.8)	787 (52.4)

HD-IIV4, high-dose inactivated influenza vaccine, quadrivalent; SD-IIV4, standard-dose inactivated influenza vaccine, quadrivalent;
std dev, standard deviation.

[a] The full analysis population consisted of all participants who were randomized and received any study vaccination.
[b] The safety population consisted of all participants in the full analysis population (all participants who were randomized and received study vaccination).
[c] In the last 5 to 12 months in Part A; since September 2022 to 6 months prior to study in Parts B and C.

(aged 18–64 years; Part B). Most solicited ARs in the mRNA-1010 and comparator vaccine groups were grade 1 or 2 and had a median duration of 2 or 3 days. In the mRNA-1010 group, grade 4 events of fever were reported in two (0.2 %) participants in Part A, two (0.1 %) participants in Part B, and four (0.3 %) participants in Part C. In the SD-IIV4 group, two (0.1 %) participants reported three grade 4 events of fever, chills, or nausea/vomiting in Part B. The most common ARs across the mRNA-1010 and comparator vaccine groups in all three trial parts were injection site pain, fatigue, myalgia, and headache (Fig. 2).

3.3. Safety

Overall, the three trial parts enabled the evaluation of mRNA-1010 safety in >4200 participants. In Part A (aged ≥18 years), within 28 days after vaccination, unsolicited AEs were reported by 144 (11.8 %) mRNA-1010 recipients and 134 (11.4 %) SD-IIV4 recipients (Table 2); most were not considered vaccination-related by the investigator (vaccination-related: mRNA-1010: 1.5 %; comparator: 1.1 %). Throughout the study (median follow-up: 172 [IQR 168–180] days), unsolicited AEs were reported by 280 (23.0 %) mRNA-1010 recipients and 254 (21.5 %) SD-IIV4 recipients. AESIs occurred in one (<0.1 %) mRNA-1010 recipient (seizure) and two (0.2 %) SD-IIV4 recipients (thrombocytopenia [*n* = 1], seizure [n = 1]) and were not considered related to vaccination. Medically attended AEs assessed as vaccination-related by the investigator occurred in seven (0.6 %) mRNA-1010 recipients and four (0.3 %) SD-IIV4 recipients (**Supplementary Table S1**). Twenty-one SD-IIV4 recipients (1.8 %) had SAEs during the study, including one death; none were considered vaccination-related. Twenty-seven mRNA-1010 recipients (2.2 %) had SAEs, including five deaths. Two (0.2 %) participants had SAEs classified as vaccination-related by the investigator. One mRNA-1010 recipient with bilateral Baker's cyst and severe varicose veins had SAEs of deep vein thrombosis (onset Day 128) after injury to the affected leg and pulmonary embolism (onset Day 132). Another was an unwitnessed death of unknown cause on Day 2 after study vaccination in a 76-year-old participant who had significant cardiovascular disease and concomitant use of sotalol, with recent electrocardiograms showing sinus bradycardia with sinus arrhythmia and prolonged QTc.

In Part B (aged 18–64 years), 148 (9.9 %) mRNA-1010 recipients and 134 (9.0 %) SD-IIV4 recipients reported unsolicited AEs within 28 days after vaccination (Table 2). Few participants had AEs that were considered related to mRNA-1010 (0.7 %) or SD-IIV4 vaccination (0.1 %). One AESI of Bell's palsy was assessed as vaccination-related by the investigator in the mRNA-1010 group. Medically attended AEs assessed as vaccination-related by the investigator occurred in two (0.1 %) mRNA-1010 recipients, and included the aforementioned Bell's palsy event, as well as an immunization stress-related response (**Supplementary Table S1**). No fatal AEs occurred and no SAEs or AEs leading to study discontinuation were considered vaccination-related by the investigator.

In Part C (aged ≥65 years), unsolicited AEs within 28 days after vaccination were reported by 153 (10.2 %) mRNA-1010 and 141 (9.5 %) HD-IIV4 recipients (Table 2). A total of eight (0.5 %) and three (0.2 %) participants had AEs that were considered related to the mRNA-1010 and HD-IIV4 vaccinations, respectively. One AESI assessed as vaccination-related by the investigator occurred in an mRNA-1010 recipient (facial swelling). Medically attended AEs assessed as vaccination-related by the investigator occurred in four (0.3 %) mRNA-1010 recipients (cough, pruritus, chest discomfort, and facial swelling;

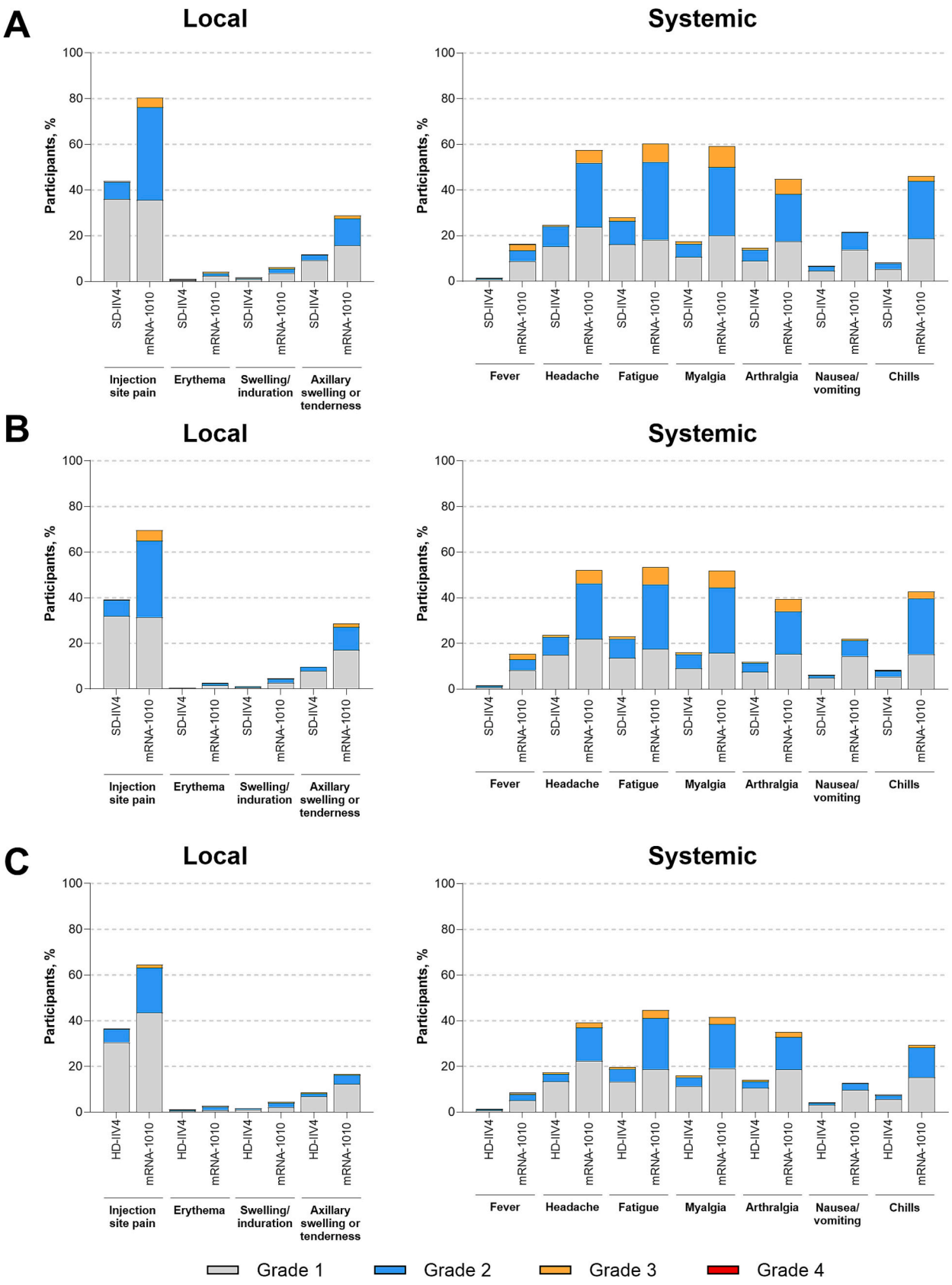


Fig. 2. Summary of local and systemic solicited adverse reactions within 7 days after vaccination in Parts A, B, or C (solicited safety population). Percentages of participants in the solicited safety population reporting solicited local or systemic adverse reactions (A) in Part A, (B) in Part B, or (C) in Part C. Part A (≥18 years): SD-IIV4, $n = 1180$; mRNA-1010, $n = 1220$. Part B (18–64 years): SD-IIV4, $n = 1488$; mRNA-1010, $n = 1492$. Part C (≥65 years): HD-IIV4, $n = 1490$; mRNA-1010, $n = 1502$.

AR adverse reaction, *SD-IIV4* standard-dose inactivated influenza vaccine, quadrivalent.

Table 2
Unsolicited AEs within 28 days after study vaccination and throughout the study duration (safety population).

Participants, no. (%)[a]	Part A		Part B		Part C	
	SD-IIV4 (*N* = 1180)	mRNA-1010 50 µg (*N* = 1220)	SD-IIV4 (*N* = 1488)	mRNA-1010 50 µg (*N* = 1492)	HD-IIV4 (*N* = 1490)	mRNA-1010 50 µg (*N* = 1502)
Unsolicited AEs within 28 days						
Regardless of relationship to vaccination[b]						
Any AE	134 (11.4)	144 (11.8)	134 (9.0)	148 (9.9)	141 (9.5)	153 (10.2)
Severe	2 (0.2)	6 (0.5)	1 (<0.1)	8 (0.5)	4 (0.3)	9 (0.6)
Serious	1 (<0.1)	6 (0.5)	2 (0.1)	10 (0.7)	6 (0.4)	9 (0.6)
Fatal	0	2 (0.2)	0	0	0	1 (<0.1)
Medically attended	70 (5.9)	83 (6.8)	69 (4.6)	74 (5.0)	87 (5.8)	90 (6.0)
Leading to study discontinuation	0	2 (0.2)	0	1 (<0.1)	0	0
AESI	0	0	0	1 (<0.1)	0	1 (<0.1)
Related to study vaccination[b]						
Any vaccination-related AE	13 (1.1)	18 (1.5)	2 (0.1)	10 (0.7)	3 (0.2)	8 (0.5)
Severe	0	1 (<0.1)	0	0	0	0
Serious	0	1 (<0.1)	0	0	0	0
Fatal	0	1 (<0.1)	0	0	0	0
Medically attended[c]	4 (0.3)	5 (0.4)	0	2 (0.1)	0	4 (0.3)
Leading to study discontinuation	0	1 (<0.1)	0	0	0	0
AESI	0	0	0	1 (<0.1)	0	1 (<0.1)
Unsolicited AEs throughout study duration[d]						
Regardless of relationship to vaccination[b]						
Any AE	254 (21.5)	280 (23.0)	NA	NA	NA	NA
Serious	21 (1.8)	27 (2.2)	NA	NA	NA	NA
Fatal	1 (<0.1)	5 (0.4)	NA	NA	NA	NA
Medically attended	195 (16.5)	226 (18.5)	NA	NA	NA	NA
Leading to study discontinuation	2 (0.2)	5 (0.4)	NA	NA	NA	NA
AESI	2 (0.2)	1 (<0.1)	NA	NA	NA	NA
Related to study vaccination[b]						
Any vaccination-related AE	13 (1.1)	19 (1.6)	NA	NA	NA	NA
Serious	0	2 (0.2)	NA	NA	NA	NA
Fatal	0	1 (<0.1)	NA	NA	NA	NA
Medically attended[c]	4 (0.3)	7 (0.6)	NA	NA	NA	NA
Leading to study discontinuation	0	1 (<0.1)	NA	NA	NA	NA
AESI	0	0	NA	NA	NA	NA

AE adverse event, *AESI* adverse event of special interest, *HD-IIV4* high-dose inactivated influenza vaccine, quadrivalent, *IQR* interquartile range, *NA* not assessed in this analysis, *SD-IIV4* standard-dose inactivated influenza vaccine, quadrivalent.

[a] The safety population consisted of all participants in the full analysis population (all participants who were randomized and received study vaccination).

[b] Per the study protocol, the investigator assessed each occurrence of an AE and reported it as related (a reasonable possibility) or not related (not a reasonable possibility) to study vaccination.

[c] Vaccination-related medically attended AEs are listed in Supplementary Table S1.

[d] Median follow-up: Part A, 172 (IQR 168–180) days. For Parts B and C, safety data were only available through 28 days after vaccination.

Supplementary Table S1). No AEs led to study discontinuation and no SAEs were assessed as related to study vaccination by the investigator. One death occurred in the mRNA-1010 group (acute myocardial infarction) within 28 days after vaccination and was assessed as unrelated to study vaccination.

3.4. Immunogenicity

In Part A (aged ≥18 years), all coprimary immunogenicity endpoints were achieved for all four vaccine-matched strains based on the prespecified criteria for noninferiority (mRNA-1010 vs SD-IIV4). The lower bounds of the 95 % CIs for the HAI GMRs (mRNA-1010 over SD-IIV4) at Day 29 exceeded 0.667, and the lower bounds of the 95 % CIs for the SCR differences (mRNA-1010 vs SD-IIV4) > −10 % (Fig. 3). Although not prespecified, superiority criteria (mRNA-1010 vs SD-IIV4) were met for all four strains based on HAI GMRs (95 % CI lower bounds >1) and SCR differences (95 % CI lower bounds >0 %). HAI GMRs (95 % CI) were 1.48 (1.38, 1.60) for A/H1N1, 1.42 (1.33, 1.52) for A/H3N2, 1.27 (1.19, 1.35) for B/Victoria, and 1.26 (1.19, 1.34) for B/Yamagata (Fig. 3A). mRNA-1010 elicited higher HAI GMTs than SD-IIV4 for all four influenza strains at Day 29 regardless of participant age (**Supplementary Table S2**). GMRs were numerically higher in participants aged ≥65 years compared with the younger age groups (Fig. 3A). GMRs were > 1 regardless of whether participants had received the previous season's influenza vaccine and were higher in participants who had versus had not received the previous season's vaccine (**Supplementary Fig. S1A**). Similarly, Day 29 HAI SCR differences between mRNA-1010 and SD-IIV4 were generally consistent across age groups but were numerically higher in participants aged ≥65 years for all strains except B/Yamagata (Fig. 3B). SCR differences were higher among participants who had received the previous season's influenza vaccine than among those who had not (**Supplementary Fig. S1B**). HAI GMTs for all four influenza strains peaked at Day 29 and subsequently decreased over time but remained above baseline through Day 181; at Day 181 they were higher for both influenza A strains and similar for the influenza B strains in the mRNA-1010 group relative to the SD-IIV4 group, both overall and across age groups (**Supplementary Fig. S2, Supplementary Table S2**). Day 181 SCRs were similar between vaccine groups and consistent across age groups (**Supplementary Table S2**).

In Part A, MN titers were positively correlated with HAI titers for each influenza strain (Pearson correlation coefficients of 0.664–0.808; **Supplementary Fig. S3**). mRNA-1010 induced strong MN responses at Day 29 post vaccination (Fig. 4). Compared with the SD-IIV4 group, Day 29 MN GMTs and GMFRs from baseline in the mRNA-1010 group were numerically higher for all four influenza strains, particularly for the influenza A strains (non-overlapping 95 % CIs).

In Part B (aged 18–64 years), the primary and secondary immunogenicity objectives were achieved for all four vaccine-matched strains based on prespecified criteria and showed that mRNA-1010 elicited robust HAI GMTs at Day 29 that met the thresholds for noninferiority

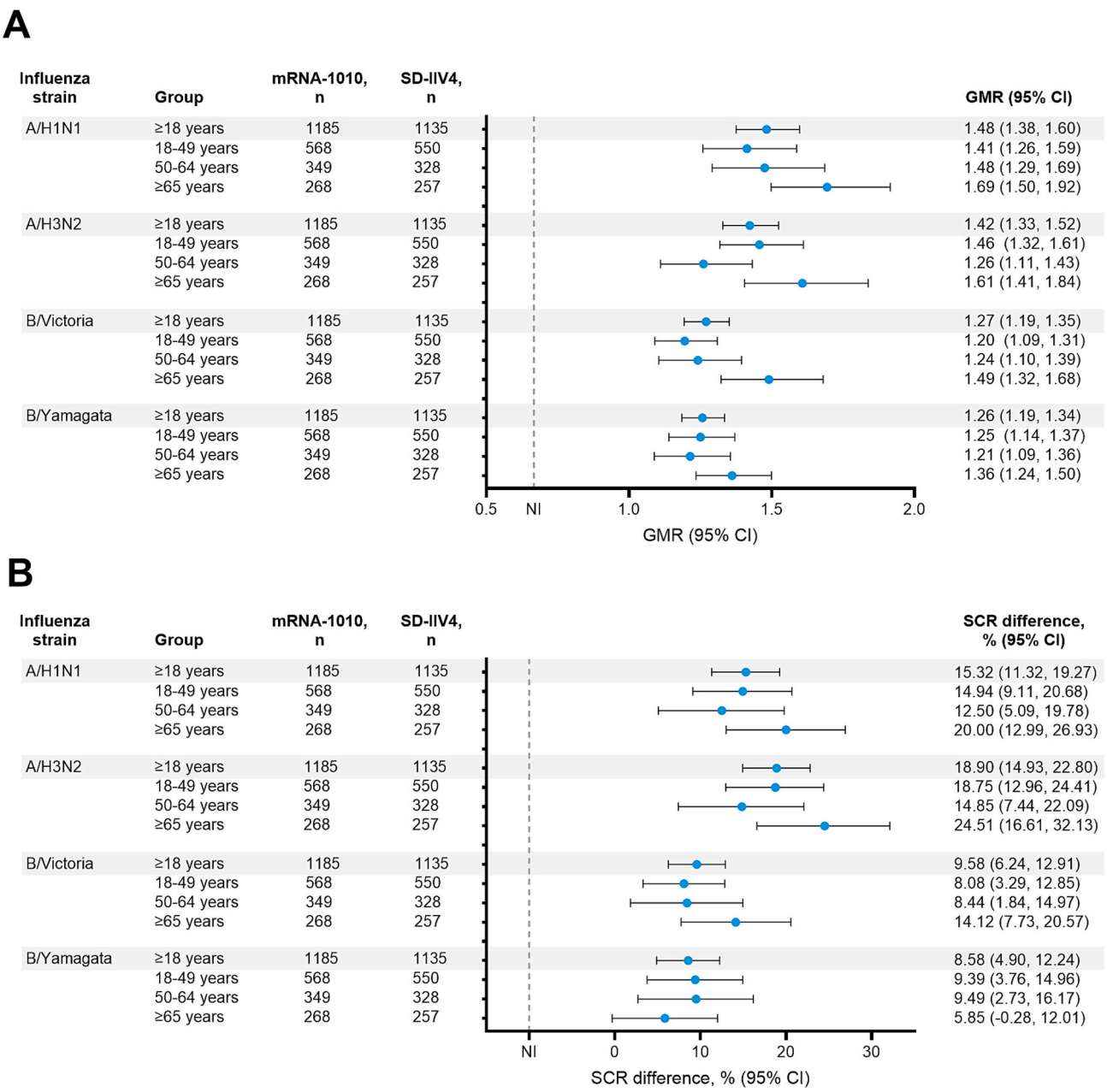


Fig. 3. (A) GMR and (B) SCR difference of anti-hemagglutinin antibodies for mRNA-1010 versus SD-IIV4 by age group at Day 29 in Part A (per-protocol immunogenicity population). HAI GMRs and SCR differences with associated 95 % CIs (error bars) for mRNA-1010 over SD-IIV4 at Day 29 are shown for participants by age group in the per-protocol immunogenicity population. For GMRs, log-transformed antibody levels were analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the randomization stratification factors: age group (18–49 years, 50–64 years, and ≥ 65 years) and seasonal influenza vaccine status in the last 5 to 12 months (received, or not received). The model-based GMR and its corresponding 95 % CI were obtained by transforming the least squares mean estimate and its CI back to the original scale for presentation. For GMR, the dashed line indicates the prespecified NI threshold (95 % CI lower bound >0.667). SCR was defined as the proportion of participants with either a baseline HAI titer <10 and a post-baseline titer ≥40 or a baseline HAI titer ≥10 and ≥ 4-fold rise in post-baseline HAI antibody titer. 95 % CI of SCR difference was calculated using the Miettinen-Nurminen (score) method. For SCR difference, the dashed line indicates the prespecified NI threshold (95 % CI lower bound > −10 %). LLOQ were 10 for A/H1N1, A/H3N2, B/Victoria, and B/Yamagata. ULOQ were 4305 for A/H1N1 and A/H3N2, 4561 for B/Victoria, and 5120 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.
ANCOVA analysis of covariance, *CI* confidence interval, *GMR* geometric mean titer ratio, *HAI* hemagglutination inhibition, *LLOQ* lower limit of quantification, *NI* noninferiority, *SCR* seroconversion rate, *SD-IIV4* standard-dose inactivated influenza vaccine, quadrivalent, *ULOQ* upper limit of quantification.

(GMR 95 % CI lower bounds >0.667 and SCR difference 95 % CI lower bounds > − 10 %; Fig. 5) and superiority (GMR 97.5 %/98.8 % CI lower bounds >1 and SCR difference 97.5 %/98.8 % CI lower bounds >0 %; **Supplementary Table S3**). Additionally, noninferiority and superiority criteria for all four influenza strains were met in subgroups aged 18–49 years and 50–64 years (Fig. 5**; Supplementary Table S3**). GMRs were > 1 and SCR differences were > 0 % regardless of the previous season's influenza vaccination status and were generally numerically higher in participants who had versus had not received the previous season's influenza vaccine, except for SCR difference for B/Yamagata (**Supplementary Fig. S4**). Compared with the SD-IIV4 group, Day 29 HAI GMFRs from baseline in the mRNA-1010 group were numerically higher

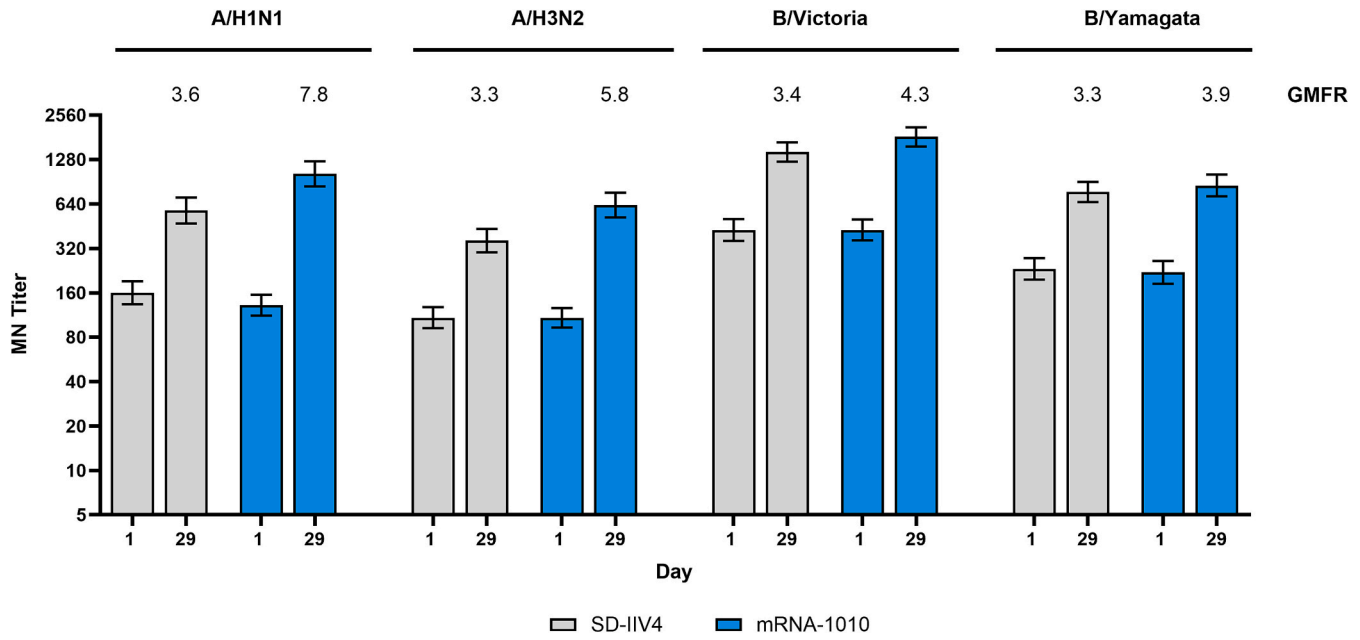


Fig. 4. Microneutralization GMTs for mRNA-1010 or active comparator through Day 29 in Part A (per-protocol immunogenicity population – microneutralization subset). Microneutralization GMTs with associated 95 % CIs (error bars) against vaccine-matched seasonal influenza strains (WHO-recommended strains for the 2023–24 NH season) are shown at Day 1 (baseline) and Day 29 among participants in the per-protocol immunogenicity population – microneutralization subset: mRNA-1010, $n = 250$; active comparator, $n = 249$. GMFRs at Day 29 from Day 1 are shown above each Day 29 bar plot. LLOQ were 12 for A/H1N1, 17 for A/H3N2, 14 for B/Victoria, and 18 for B/Yamagata. ULOQ were 10,240 for A/H1N1, A/H3N2, and B/Victoria, and 9373 for B/Yamagata.
CI confidence interval, *GMFR* geometric mean fold rise, *GMT* geometric mean titer, *LLOQ* lower limit of quantification, *MN* microneutralization, *NH* Northern Hemisphere, *SD-IIV4* standard-dose inactivated influenza vaccine, quadrivalent, *ULOQ* upper limit of quantification.

for all four influenza strains (**Supplementary Table S4**).

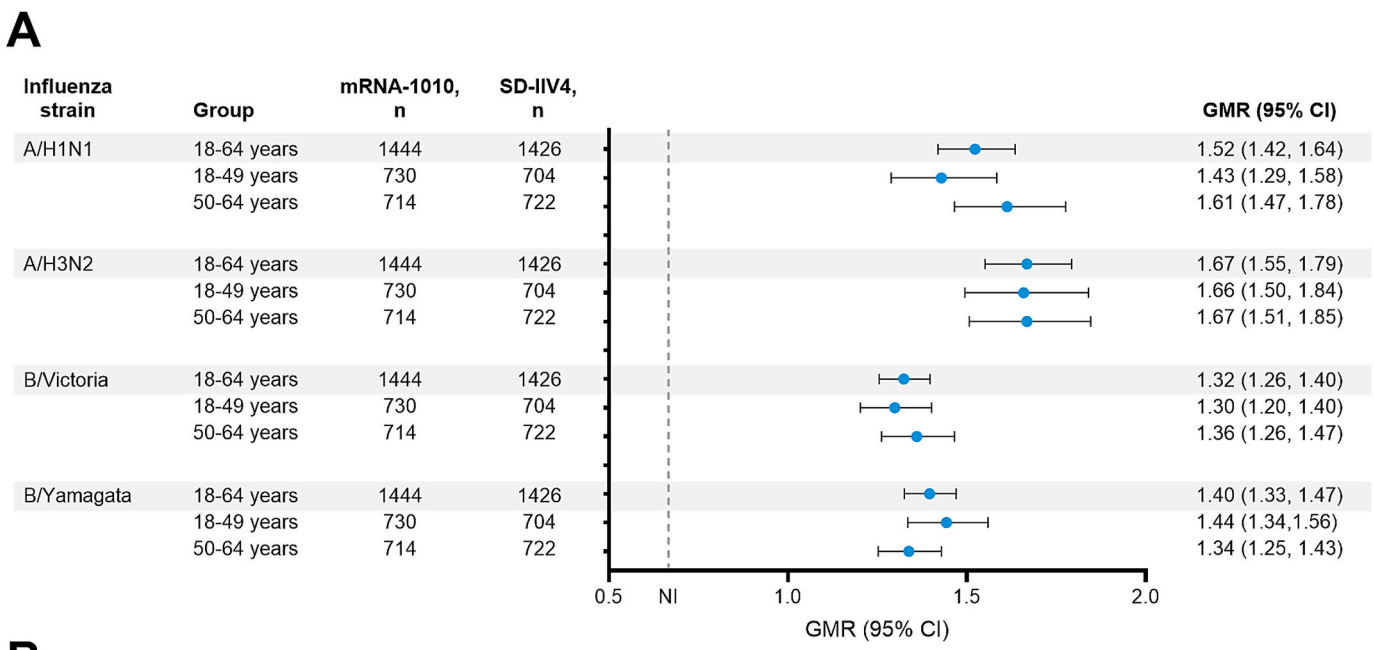
In Part C (aged ≥65 years), the primary immunogenicity objective was achieved for all four vaccine-matched strains based on prespecified criteria for noninferiority of mRNA-1010 versus HD-IIV4 per Day 29 HAI GMRs (95 % CI lower bounds >0.667) and SCR differences (95 % CI lower bounds > − 10 %) (Fig. 6). Prespecified superiority criteria for all four influenza strains were met based on Day 29 HAI GMRs (97.5 %/98.8 % CI lower bounds >1) and SCR differences (97.5 %/98.8 % CI lower bounds >0 %) (**Supplementary Table S5**). mRNA-1010 met noninferiority criteria for all four influenza strains among subgroups aged 65–74 years and ≥ 75 years (**Supplementary Table S5**). GMRs were > 1 and SCR differences were > 0 % regardless of the previous season's influenza vaccination status and were higher in participants who had versus had not received the previous season's influenza vaccine (**Supplementary Fig. S5**). For all four influenza strains, Day 29 HAI GMFRs from baseline and proportions of participants with an HAI titer of ≥40 at Day 29 were numerically higher in the mRNA-1010 group versus the HD-IIV4 group (**Supplementary Table S4**).

4. Discussion

This three-part, phase 3 clinical trial demonstrated a single 50-μg dose of mRNA-1010 had an acceptable safety profile and induced strong immune responses against influenza A and B strains, meeting prespecified noninferiority success criteria for all four influenza strains versus standard-dose licensed vaccine in adults aged ≥18 years (Part A) and 18–64 years (Part B), and versus high-dose licensed vaccine in adults aged ≥65 years (Part C). Prespecified analyses in Parts B and C demonstrated superiority of mRNA-1010 versus standard-dose and high-dose licensed vaccines for all four strains. These data support the application of the mRNA vaccine platform to seasonal influenza and mRNA-1010 as a vaccine with an enhanced influenza vaccine profile for adults aged ≥65 years. The US Advisory Committee on Immunization Practices preferentially recommends licensed enhanced influenza vaccines, including high-dose and adjuvanted vaccines, for adults aged ≥65 years because of the relative benefit compared with the standard-dose vaccine in protecting against laboratory-confirmed influenza outcomes [16].

The immunogenicity profile of mRNA-1010 relative to SD-IIV4 and HD-IIV4 licensed comparators was consistent across age groups, with superior immunogenicity observed in Part C participants aged ≥65 years. Further, immune responses in the subgroup of participants aged ≥75 years (Part C) were similar between mRNA-1010 and HD-IIV4. This suggests that mRNA-1010 could be a particularly promising vaccine candidate among older adults, who are most likely to experience severe influenza outcomes [2], and could offer an alternative enhanced vaccine to the current standard of care. Importantly, in this study, mRNA-1010 elicited robust immunogenicity regardless of whether participants had received the previous season's influenza vaccine but performed better than the licensed comparator vaccine among those who had. As vaccine effectiveness can be attenuated in certain seasons upon successive revaccination using currently available influenza vaccines, particularly against A/H3N2 [17,18], mRNA-1010 could be particularly beneficial in populations who receive annual influenza vaccinations. Notably, antibody responses at Day 29 were higher for mRNA-1010 than SD-IIV4 and HD-IIV4 when measured by either HAI (Parts A-C) or MN (SD-IIV4; Part A), correlation was observed between HAI and MN titers at Day 29 (Part A), and HAI immunogenicity against influenza A strains continued to be higher than SD-IIV4 to the end of season (6 months; Part A).

In general, mRNA-1010 and the comparators SD-IIV4 and HD-IIV4 had lower frequencies and severities of solicited ARs among older adults (aged ≥65 years) than in younger adults (aged 18–64 years). In all study parts (≥18 years, 18–64 years, and ≥ 65 years), AEs and SAEs were balanced between the vaccine groups. Among mRNA-1010 recipients aged ≥18 years (Part A), two participants had three SAEs classified as vaccination-related throughout the study duration (6 months). There were no SAEs considered related to vaccination among mRNA-1010 recipients aged 18–64 years (Part B) nor recipients aged ≥65 years (Part C) within 28 days after vaccination. A review of SAEs grouped by system organ class and preferred term did not reveal any



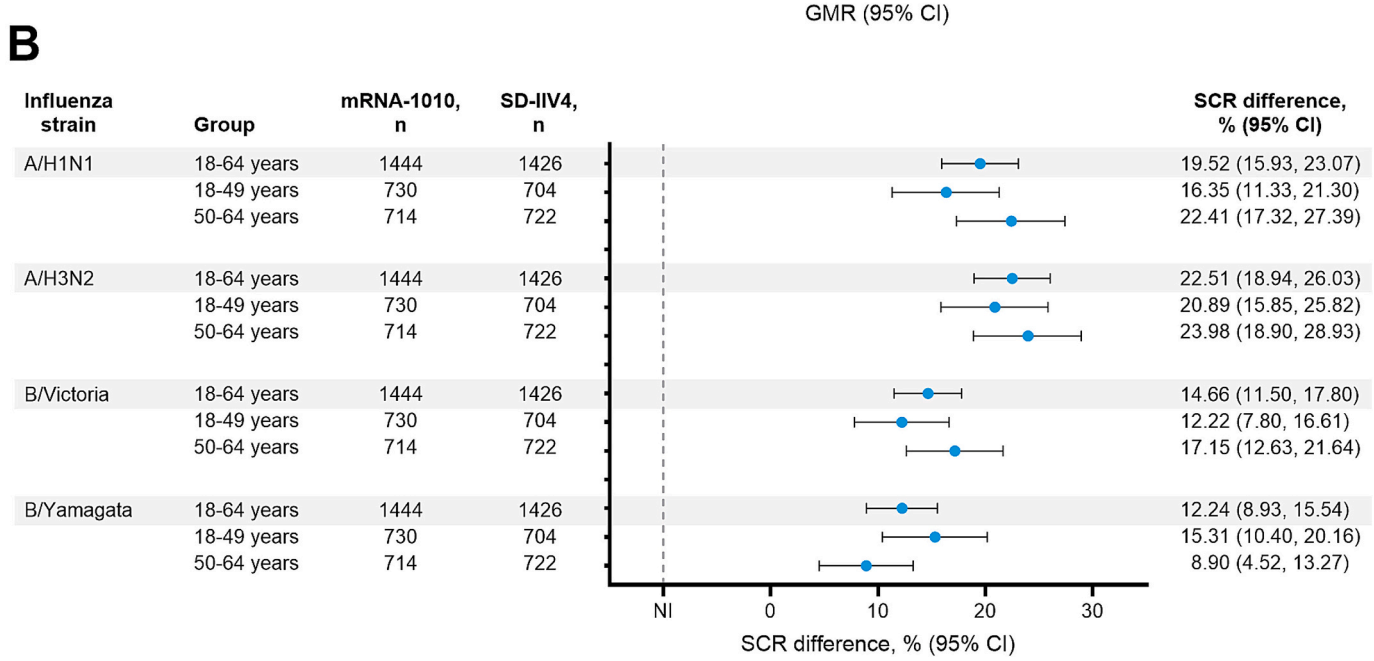


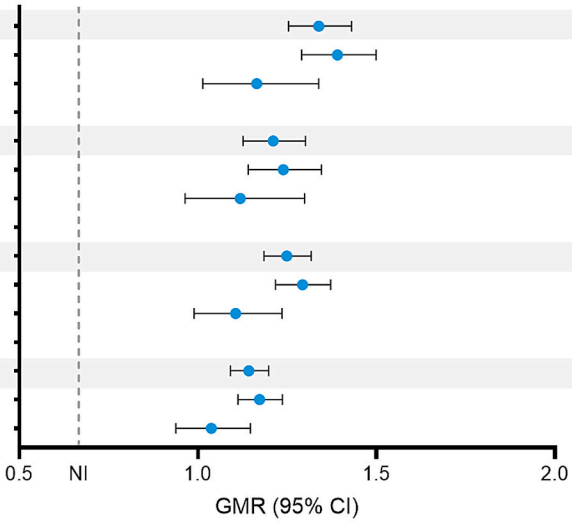
Fig. 5. (A) GMR and (B) SCR difference of anti-hemagglutinin antibodies for mRNA-1010 versus SD-IIV4 at Day 29 in Part B (per-protocol immunogenicity population). HAI GMRs and SCR differences with associated 95 % CIs (error bars) for mRNA-1010 over SD-IIV4 at Day 29 are shown for Part B participants (aged 18–64 years) by age group in the per-protocol immunogenicity population. For GMRs, log-transformed antibody levels were analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the randomization stratification factor: seasonal influenza vaccine status since September 2022 to 6 months prior to study (not received, received from P302 study, received but not from P302 study). The model-based GMR and its corresponding 95 % CI were obtained by transforming the least squares mean estimate and its CI back to the original scale for presentation. For GMR, the dashed line indicates the prespecified NI threshold (95 % CI lower bound >0.667). SCR was defined as the proportion of participants with either a baseline HAI titer <10 and a post-baseline titer ≥40 or a baseline HAI titer ≥10 and ≥ 4-fold rise in post-baseline HAI antibody titer. 95 % CI of SCR difference was calculated using the Miettinen-Nurminen (score) method. For SCR difference, the dashed line indicates the prespecified NI threshold (95 % CI lower bound > −10 %). LLOQ were 10 for A/H1N1, A/H3N2, B/Victoria, and B/Yamagata. ULOQ were 3620 for A/H1N1, 5120 for A/H3N2, 1356 for B/Victoria, and 1280 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.
ANCOVA analysis of covariance, *CI* confidence interval, *GMR* geometric mean titer ratio, *HAI* hemagglutination inhibition, *LLOQ* lower limit of quantification, *NI* noninferiority, *SCR* seroconversion rate, *SD-IIV4* standard-dose inactivated influenza vaccine, quadrivalent, *ULOQ* upper limit of quantification.

pattern or trend indicating a potential relationship between the events and mRNA-1010 in any study part. Additionally, the majority of participants who experienced SAEs in each study part had pre-existing medical conditions that could explain the occurrence of the SAEs. However, we note that careful surveillance of vaccines post-licensure is important to identify any potential safety signals that are not detected in phase 3 trials.

Study strengths include the randomized, active comparator-controlled design that allowed for noninferiority testing compared with licensed quadrivalent seasonal influenza vaccines. Study limitations include enrollment of US participants only, potentially limiting the generalizability of the study results. However, the trial population was

A

Influenza strain	Group	mRNA-1010, n	HD-IIV4, n	GMR (95% CI)
A/H1N1	≥65 years	1426	1410	1.34 (1.25, 1.43)
	65-74 years	1115	1092	1.39 (1.29, 1.50)
	≥75 years	311	317	1.17 (1.01, 1.34)
A/H3N2	≥65 years	1426	1410	1.21 (1.13, 1.30)
	65-74 years	1115	1092	1.24 (1.14, 1.35)
	≥75 years	311	317	1.12 (0.96, 1.30)
B/Victoria	≥65 years	1426	1410	1.25 (1.19, 1.32)
	65-74 years	1115	1092	1.29 (1.22, 1.37)
	≥75 years	311	317	1.11 (0.99, 1.24)
B/Yamagata	≥65 years	1426	1410	1.14 (1.09, 1.20)
	65-74 years	1115	1092	1.17 (1.11, 1.24)
	≥75 years	311	317	1.04 (0.94, 1.15)



B

Influenza strain	Group	mRNA-1010, n	HD-IIV4, n	SCR difference, % (95% CI)
A/H1N1	≥65 years	1426	1410	13.41 (9.78, 17.00)
	65-74 years	1115	1092	15.11 (10.99, 19.18)
	≥75 years	311	317	7.41 (-0.18, 14.92)
A/H3N2	≥65 years	1426	1410	8.58 (4.91, 12.23)
	65-74 years	1115	1092	9.69 (5.53, 13.81)
	≥75 years	311	317	4.78 (-3.04, 12.55)
B/Victoria	≥65 years	1426	1410	9.66 (6.49, 12.82)
	65-74 years	1115	1092	11.41 (7.76, 15.05)
	≥75 years	311	317	3.25 (-3.02, 9.53)
B/Yamagata	≥65 years	1426	1410	5.87 (2.78, 8.97)
	65-74 years	1115	1092	7.75 (4.20, 11.29)
	≥75 years	311	317	-0.88 (-7.20, 5.45)

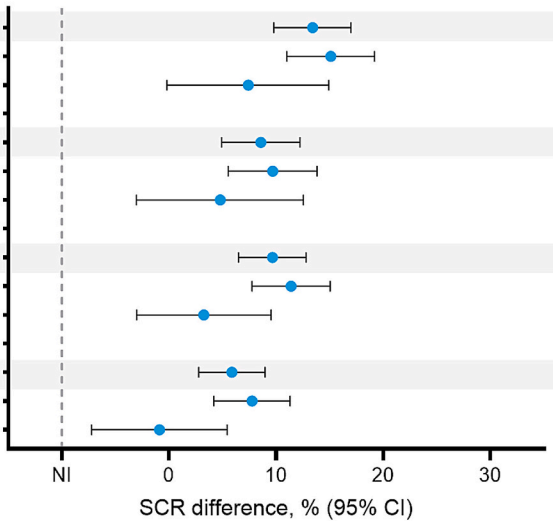


Fig. 6. (A) GMR and (B) SCR difference of anti-hemagglutinin antibodies for mRNA-1010 versus HD-IIV4 at Day 29 in Part C (per-protocol immunogenicity population). HAI GMRs and SCR differences with associated 95 % CIs (error bars) for mRNA-1010 over HD-IIV4 at Day 29 are shown for Part C participants (aged ≥65 years) by age group in the per-protocol immunogenicity population. For GMRs, log-transformed antibody levels were analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the randomization stratification factor: seasonal influenza vaccine status since September 2022 to 6 months prior to study (not received, received from P302 study, received but not from P302 study). The model-based GMR and its corresponding 95 % CI were obtained by transforming the least squares mean estimate and its CI back to the original scale for presentation. For GMR, the dashed line indicates the prespecified NI threshold (95 % CI lower bound >0.667). SCR was defined as the proportion of participants with either a baseline HAI titer <10 and a post-baseline titer ≥40 or a baseline HAI titer ≥10 and ≥ 4-fold rise in post-baseline HAI antibody titer. 95 % CI of SCR difference was calculated using the Miettinen-Nurminen (score) method. For SCR difference, the dashed line indicates the prespecified NI threshold (95 % CI lower bound > −10 %). LLOQ were 10 for A/H1N1, A/H3N2, B/Victoria, and B/Yamagata. ULOQ were 3620 for A/H1N1, 5120 for A/H3N2, 1356 for B/Victoria, and 1280 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.
ANCOVA analysis of covariance, *CI* confidence interval, *GMR* geometric mean titer ratio, *HAI* hemagglutination inhibition, *HD-IIV4* high-dose inactivated influenza vaccine, quadrivalent, *LLOQ* lower limit of quantification, *NI* noninferiority, *SCR* seroconversion rate, *ULOQ* upper limit of quantification.

racially and ethnically diverse, and generally reflective of the US population. This study was designed to only examine safety and immunogenicity (and not efficacy) of mRNA-1010 relative to licensed vaccines; however, HAI titers are recognized as a surrogate marker for vaccine-mediated protection against influenza infection and reasonably predict clinical benefit. An additional phase 3 study will examine the relative vaccine efficacy of mRNA-1010 versus licensed vaccines against influenza-like illness in adults aged ≥50 years (NCT06602024). The study was initiated before the 2024/2025 Northern Hemisphere influenza season, will span at least 1 influenza season, and for the first season will include approximately 34,000 adults randomly assigned in a 1:1 ratio to receive mRNA-1010 or licensed vaccine. Trials are also assessing

future iterations of mRNA-based seasonal influenza vaccines, including evaluation of candidates with additional hemagglutinin antigens for broader coverage against A/H3N2 in a phase 1/2 study (NCT05827068) [19,20] and assessment of combination respiratory vaccines (influenza and COVID-19) in a phase 3 study (NCT06097273) [21].

In conclusion, findings from this phase 3 study demonstrate that mRNA-1010 elicited superior immune responses relative to licensed standard- or high-dose seasonal influenza vaccines in adults of all ages and raised no new safety concerns. The robust immunogenicity observed in adults aged ≥65 years could represent a meaningful benefit for this vulnerable population and a phase 3 efficacy trial is in progress. Overall, these findings support the potential of mRNA-1010 as an enhanced seasonal influenza vaccine candidate with the benefits of the mRNA platform.

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CRediT authorship contribution statement

Mieke Soens: Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Jintanat Ananworanich:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Bryony Hicks:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Kathryn Jean Lucas:** Writing – review & editing, Visualization, Investigation. **Jose Cardona:** Writing – review & editing, Visualization, Investigation. **Lawrence Sher:** Writing – review & editing, Visualization, Investigation. **Greg Livermore:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Kristi Schaefers:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Carole Henry:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Angela Choi:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Andrei Avanesov:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Ren Chen:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Evelyn Du:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Alicia Pucci:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Rituparna Das:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Jacqueline Miller:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Raffael Nachbagauer:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mieke Soens reports financial support was provided by Moderna Inc. Jintanat Ananworanich, Bryony Hicks, Kathryn Jean Lucas, Jose Cardona, Lawrence Sher, Greg Livermore, Kristi Schaefers, Carole Henry, Angela Choi, Andrei Avanesov, Ren Chen, Evelyn Du, Alicia Pucci, Rituparna Das, Jacqueline Miller, Raffael Nachbagauer reports financial support was provided by Moderna Inc. Mieke Soens, Bryony Hicks, Greg Livermore, Kristi Schaefers, Carole Henry, Angela Choi, Andrei Avanesov, Ren Chen, Evelyn Du, Alicia Pucci, Rituparna Das, Jacqueline Miller, Raffael Nachbagauer reports a relationship with Moderna Inc that includes: employment and equity or stocks. Kathryn Jean Lucas reports a relationship with Moderna Inc that includes: consulting or advisory. Lawrence Sher reports a relationship with Moderna Inc that includes: non-financial support. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.126847.

Data availability

Access to participant-level data presented in this article and supporting clinical documents with external researchers who provide methodologically sound scientific proposals will be available upon reasonable request for products or indications that have been approved by regulators in the relevant markets and subject to review from 24 months after study completion. Such requests can be made to Moderna Inc., 325 Binney St, Cambridge, MA 02142 < <data_sharing@modernatx.com>>. A materials transfer and/or data access agreement with the sponsor will be required for accessing shared data. All other relevant data are presented in the paper. The protocol is available online at ClinicalTrials.gov: NCT05827978.

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