ORIGINAL ARTICLE

Efficacy and Safety of an mRNA Seasonal Influenza Vaccine in Adults

Isabel Leroux-Roels, M.D.,[1] Grace Huang, M.D.,[2] Murdo Ferguson, M.D.,[3] Anita Kohli, M.D.,[4] Rebecca Clark, M.D.,[5] Markus Bickel, M.D.,[6] Mieke Soens, M.D.,[2] Evelyn Du, Ph.D.,[2] Alicia Pucci, R.N.,[2] Bryony Hicks, B.Sc.,[7] Colbie Eschen, B.Sc.,[2] Rituparna Das, M.D., Ph.D.,[2] and Eleanor Wilson, M.D.,[2] for the Fluent Trial Investigators*

ABSTRACT

BACKGROUND

Seasonal influenza causes substantial illness and death in adults 50 years of age or older, even with current vaccines. An investigational messenger RNA (mRNA)–based vaccine called mRNA-1010 encodes hemagglutinin glycoproteins from World Health Organization–recommended influenza strains.

METHODS

In this phase 3, double-blind, active-controlled trial, we randomly assigned adults 50 years of age or older to receive trivalent mRNA-1010 (37.5 μg, which includes 12.5 μg of each strain) or a licensed standard-dose comparator. The primary efficacy end point was relative vaccine efficacy against reverse-transcriptase–polymerase-chain-reaction (RT-PCR)–confirmed, protocol-defined influenza-like illness caused by influenza A or B, from at least 14 days after vaccination through the end of the influenza season. Hypothesis testing was conducted hierarchically to assess noninferiority (lower boundary of the 95% confidence interval [CI], >−10%), superiority (lower boundary of the 95% CI, >0%), and a higher level of superiority (lower boundary of the 95% CI, >9.1%).

RESULTS

A total of 40,703 participants received mRNA-1010 (20,350 participants) or the standard-dose comparator (20,353 participants); the median follow-up was 181 days (range, 1 to 227). RT-PCR–confirmed, protocol-defined influenza-like illness was observed in 411 of 20,179 recipients of mRNA-1010 (2.0%) and 557 of 20,124 recipients of the standard-dose comparator (2.8%), which corresponds to a relative vaccine efficacy of 26.6% (95% CI, 16.7 to 35.4), thereby meeting the criteria for noninferiority, superiority, and higher-level superiority. Solicited adverse reactions were more frequent with mRNA-1010 than with the standard-dose comparator (injection-site pain in 65.8% vs. 29.8%, fatigue in 45.1% vs. 20.3%, headache in 37.8% vs. 18.0%, and myalgia in 35.4% vs. 11.6%); most reactions were mild to moderate and transient. Serious adverse events were reported in 2.2% of the recipients of mRNA-1010 (with three events considered by the investigator to be vaccine-related) and in 1.9% of the recipients of the standard-dose comparator (with two events considered by the investigator to be vaccine-related).

CONCLUSIONS

In this trial, mRNA-1010 was superior to standard-dose licensed vaccines for prevention of RT-PCR–confirmed, protocol-defined influenza-like illness in adults 50 years of age or older. Solicited adverse reactions were more frequent with mRNA-1010. (Funded by Blackstone Life Sciences and Moderna; Fluent ClinicalTrials.gov number, NCT06602024.)

Author affiliations are listed at the end of the article. Grace Huang can be contacted at grace.huang@modernatx.com or at Moderna, 325 Binney St., Cambridge, MA 02142

*A list of the investigators in the Fluent trial is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Seasonal influenza viruses are estimated by the World Health Organization (WHO) to cause 3 to 5 million cases of severe illness and up to 650,000 deaths annually, posing a persistent global public health challenge.[1] Improved vaccine efficacy in adults 50 years of age or older is needed, given the increased morbidity and mortality in this population.[2,3]

Enhanced (high-dose, adjuvanted, or recombinant-based) influenza vaccines provide greater protection in older adults than standard-dose formulations, although effectiveness varies according to season and match to circulating strains.[4,5] Most licensed vaccines rely on egg-based platforms.[6] Egg-based production is time-consuming and can introduce egg-adaptive mutations, which reduce antigenic match with circulating strains.[6] A need remains for influenza vaccines that can be rapidly updated to evolving strains and elicit robust protection.

The investigational seasonal influenza vaccine mRNA-1010 encodes surface hemagglutinin (HA) antigens from the three WHO-recommended 2024–2025 strains for cell- or recombinant-based vaccines: A/H1N1, A/H3N2, and B/Victoria.[7] By avoiding egg-based production and enabling rapid strain updates, the messenger RNA (mRNA) platform addresses key limitations of current influenza vaccines and may improve protection in older adults.[8]

The Fluent trial was conducted during the 2024–2025 Northern Hemisphere influenza season to evaluate the relative vaccine efficacy of mRNA-1010 as compared with licensed standard-dose influenza vaccines in preventing laboratory-confirmed influenza-like illness in adults 50 years of age or older. Here, we report the findings from the primary analyses of this pivotal phase 3 trial.

Methods

Trial Design and Oversight

This phase 3, double-blind, randomized, active-controlled trial enrolled participants at 301 sites in 11 countries in the Northern Hemisphere. The trial was approved by appropriate institutional review boards and was conducted according to the applicable principles of the International Council for Harmonisation Good Clinical Practice guidelines, the E6(R2) Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and all local laws or regulations. All the participants provided written informed consent before enrollment. Oversight was provided by an independent data and safety monitoring board.

A sponsor, Moderna, was responsible for overall trial design, site selection, monitoring, and data analysis, which were facilitated by Parexel International. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan. The manuscript was prepared by employees of Moderna with assistance from medical writers funded by Moderna. Additional information is provided in the Supplementary Appendix, protocol, and statistical analysis plan, all available with the full text of this article at NEJM.org.

Trial Participants

Eligible participants were adults 50 years of age or older who were in medically stable condition. A complete list of eligibility criteria is provided in the Supplementary Appendix.

Trial Procedures

The mRNA-1010 vaccine contained mRNAs encoding HA antigens of the WHO-recommended 2024–2025 cell- or recombinant-based influenza strains for the 2024–2025 Northern Hemisphere season. Participants were randomly assigned (in a 1:1 ratio) to receive a single intramuscular injection of mRNA-1010 (37.5-μg trivalent formulation, which includes 12.5 μg of each strain) or a licensed standard-dose inactivated seasonal influenza vaccine (Fluarix, Fluarix Tetra, Influsplit Tetra, or Alpharix Tetra) with the use of a centralized interactive response technology system that implemented the prespecified randomization schedule and concealed treatment allocation until assignment. A licensed trivalent standard-dose comparator was preferred; a licensed quadrivalent comparator was used where a trivalent vaccine was not available. In countries recommending higher-dose or adjuvanted influenza vaccines in older adults, potential participants were informed of this recommendation. Vaccines were shipped frozen and stored at clinical sites before preparation and injection (see the Supplementary Appendix).

Efficacy Assessments

The primary efficacy objective was to evaluate the relative vaccine efficacy of mRNA-1010 as compared with a standard-dose comparator against the first episode of protocol-defined influenza-

like illness caused by any influenza A or B strain confirmed by a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, beginning at least 14 days after injection through the end of the influenza season. Efficacy end-point events were identified through active surveillance, including twice-weekly e-diary prompts to report respiratory symptoms from day 1 through the end of the influenza season.

If a participant met criteria for protocol-defined respiratory illness, a nasopharyngeal swab was collected within 72 hours after symptom onset and tested for influenza with an RT-PCR assay (see the Supplementary Appendix). Protocol-defined influenza-like illness was an influenza infection confirmed by RT-PCR assay and the presence of at least one systemic symptom (temperature >37.2°C, chills, feverish, tiredness, headaches, or myalgia) and at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) within 7 days before or after the positive test. Key secondary objectives were to evaluate the relative vaccine efficacy of mRNA-1010 as compared with the standard-dose comparator against RT-PCR–confirmed, modified Centers for Disease Control and Prevention (CDC)–defined influenza-like illness (temperature >37.2°C and cough or sore throat[9]) and against protocol-defined influenza-like illness with strains with antigenic match to the vaccine strains.

SAFETY ASSESSMENTS

The primary safety objective was to evaluate the safety and reactogenicity of mRNA-1010. Unsolicited adverse events were assessed though 28 days after injection with the use of active and passive surveillance. Data on adverse events leading to discontinuation of trial participation, medically attended adverse events, serious adverse events, and adverse events of special interest were collected through day 181 or the data cut-off date (April 30, 2025). Unsolicited adverse events were graded as mild, moderate, or severe. Data on solicited local and systemic adverse reactions were collected from approximately 6000 participants who used an e-diary for the first 7 days after injection (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The planned sample size was approximately 56,000 participants undergoing randomization over two influenza seasons, with approximately 70% enrolled during the first year. Accrual of 836 cases in the per-protocol efficacy analysis population was estimated to provide approximately 80% power to show noninferiority with a noninferiority margin of 10%, under the assumption of a true relative vaccine efficacy of 10% at an overall one-sided type I error rate of 2.5% (additional details are provided in the Supplementary Appendix). Efficacy analyses were prespecified at the end of both seasons, with the Pocock spending function used to control the overall type I error rate. A stratified Cox proportional-hazards model was used to estimate the hazard ratio. Relative vaccine efficacy was calculated as (1−hazard ratio [mRNA-1010 vs. standard-dose comparator]) × 100%, with stratification according to age (50 to 64 or ≥65 years) and status with respect to influenza vaccination during the previous influenza season. Missing efficacy data were not imputed.

The primary objective was assessed sequentially for noninferiority (lower boundary of the 95% confidence interval [CI] of the relative vaccine efficacy, >−10%), superiority (lower boundary of the 95% CI, >0%), and higher-level superiority (lower boundary of the 95% CI, >9.1%), on the basis of correspondence with the Food and Drug Administration; these values corresponded to hazard ratios of less than 1.1, less than 1.0, and less than 0.909, respectively. Noninferiority was concluded if the one-sided P value for rejecting the null hypothesis (hazard ratio, ≥1.10) was below the Pocock-adjusted significance level. If noninferiority was met, superiority and higher-level superiority were tested sequentially with the use of the same alpha-spending framework (null hypothesis: hazard ratio, ≥1.00 and ≥0.909, respectively).

Hypothesis testing was prespecified for the two key secondary end points with the use of a hierarchical testing procedure after successful demonstration of all primary objectives to sequentially evaluate noninferiority, superiority, and higher-level superiority, first for RT-PCR–confirmed, modified CDC-defined influenza-like illness and then for RT-PCR–confirmed, protocol-defined influenza-like illness with antigenic match to the vaccine strains. If testing failed at any step, no further hypothesis testing was conducted.

Per-strain and subgroup analyses, including subgroups defined according to age, influenza vaccination during the previous influenza season, race, sex, body-mass index (BMI), frailty,

geographic region, comparator vaccine (trivalent or quadrivalent), and risk status, were performed in an exploratory analysis of the end point of RT-PCR–confirmed, protocol-defined influenza-like illness (see the Supplementary Appendix). Data on RT-PCR–confirmed, protocol-defined influenza-like illness–associated health care encounters were also analyzed. No hypothesis testing was conducted for the exploratory analyses; the 95% confidence interval was provided as a descriptive measure. Safety analyses are described in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

Randomization began on September 16, 2024, with a total enrollment of 40,805 participants; 20,402 were randomly assigned to receive mRNA-1010 and 20,403 to receive the standard-dose comparator. The safety analysis population included 20,350 recipients of mRNA-1010 and 20,353 recipients of the standard-dose comparator, with 20,179 and 20,124 in the per-protocol efficacy analysis population, respectively (Fig. S1 in the Supplementary Appendix).

Baseline demographic and clinical characteristics were balanced between the two groups (Table 1). The majority of the participants were female (56.9%) and White (82.6%); the mean age was 64.2 years, with 47.8% of the participants being 65 years of age or older. Among participants 65 years of age or older, more than 25% were considered to be vulnerable or frail (Edmonton Frail Scale score, ≥4; scores range from 0 to 17, with higher scores indicating greater frailty). Almost half the participants (47.0%) had received a seasonal influenza vaccine in the previous influenza season. The trial population was representative of persons at increased risk for severe influenza (Table S1).

The data-cutoff date (April 30, 2025) was prespecified to coincide with the end of the 2024–2025 Northern Hemisphere influenza season. The median follow-up was 181 days (range, 1 to 227).

RELATIVE VACCINE EFFICACY

In total, 968 cases of RT-PCR–confirmed, protocol-defined influenza-like illness had accrued by the end of the 2024–2025 Northern Hemisphere influenza season (April 30, 2025) in the per-protocol efficacy analysis population, from 411 of 20,179 recipients of mRNA-1010 (2.0%) and in 557 of 20,124 recipients of the standard-dose comparator (2.8%). Because the case accrual exceeded the total target of 836 cases planned for the trial, the hypothesis testing was conducted with the one-sided 2.5% alpha level.

The relative vaccine efficacy for the primary end point was 26.6% (95% CI, 16.7 to 35.4), which met all prespecified noninferiority and superiority efficacy thresholds, including the higher superiority threshold (one-sided $P<0.001$ for comparisons) (Table 2). Under the prespecified hierarchical testing sequence, the relative vaccine efficacy for RT-PCR–confirmed influenza-like illness

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Safety Analysis Population).*

Characteristic	mRNA-1010 (N = 20,350)	Standard-Dose Comparator (N = 20,353)	Total (N = 40,703)
Age at enrollment — yr	64.2±8.3	64.2±8.4	64.2±8.3
Age group — no. (%)			
≥50 to <65 yr	10,624 (52.2)	10,615 (52.2)	21,239 (52.2)
≥65 yr	9,726 (47.8)	9,738 (47.8)	19,464 (47.8)
65 to <75 yr	7,372 (36.2)	7,375 (36.2)	14,747 (36.2)
≥75 yr	2,354 (11.6)	2,363 (11.6)	4,717 (11.6)
Sex — no. (%)			
Male	8,834 (43.4)	8,720 (42.8)	17,554 (43.1)
Female	11,516 (56.6)	11,633 (57.2)	23,149 (56.9)

Table 1. (Continued.)

Characteristic	mRNA-1010 (N=20,350)	Standard-Dose Comparator (N=20,353)	Total (N=40,703)
Race or ethnic group — no. (%)†			
White	16,814 (82.6)	16,811 (82.6)	33,625 (82.6)
Black	2,687 (13.2)	2,698 (13.3)	5,385 (13.2)
Asian	496 (2.4)	483 (2.4)	979 (2.4)
Other	252 (1.2)	264 (1.3)	516 (1.3)
Unknown or not reported	101 (0.5)	97 (0.5)	198 (0.5)
Hispanic or Latino ethnic group — no. (%)†			
Yes	2,147 (10.6)	2,067 (10.2)	4,214 (10.4)
No	17,908 (88.0)	17,985 (88.4)	35,893 (88.2)
Unknown or not reported	295 (1.4)	301 (1.5)	596 (1.5)
Geographic region — no. (%)			
North America	14,333 (70.4)	14,340 (70.5)	28,673 (70.4)
Rest of the world‡	6,017 (29.6)	6,013 (29.5)	12,030 (29.6)
Body-mass index§	29.4±6.3	29.5±6.4	29.4±6.4
Influenza vaccination in the previous influenza season — no. (%)			
Received	9,569 (47.0)	9,547 (46.9)	19,116 (47.0)
Not received	10,781 (53.0)	10,806 (53.1)	21,587 (53.0)
Frailty status of participants ≥65 yr of age — no./total no. (%)¶			
Fit	7136/9726 (73.4)	7135/9738 (73.3)	14,271/19,464 (73.3)
Vulnerable	1755/9726 (18.0)	1740/9738 (17.9)	3,495/19,464 (18.0)
Frail	820/9726 (8.4)	843/9738 (8.7)	1,663/19,464 (8.5)
Missing data	15/9726 (0.2)	20/9738 (0.2)	35/19,464 (0.2)
High-risk status — no. (%)‖			
Yes	11,591 (57.0)	11,614 (57.1)	23,205 (57.0)
No	8,759 (43.0)	8,739 (42.9)	17,498 (43.0)

* Plus–minus values are means ±SD. Participants are included in the vaccine group in which they actually received vaccination. Standard-dose comparator indicates licensed standard-dose influenza vaccines. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the participant. Other included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, or multiple.

‡ The rest of the world included Europe and East Asia.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 20,320 recipients of the mRNA-1010 vaccine and 20,327 recipients of the standard-dose comparator. Height and weight data were missing for 53 participants; either height or weight data were missing for 3 additional participants.

¶ Frailty status was measured with the use of the Edmonton Frail Scale across nine domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. Scores range from 0 to 17 points, with a score of 0 to 3 indicating fit, a score of 4 or 5 indicating vulnerable, and a score of 6 to 17 indicating frail. The scale is applicable only to participants 65 years of age or older, and the percentages are based on the number of participants 65 years of age or older in the safety analysis population.

‖ High-risk status was defined as having a baseline body-mass index of 30 or more or having a medical history of any of the following: autoimmune or immune-mediated disease, blood disorders, cardiac disorders, diabetes mellitus, hepatic disorders, mental impairment disorders, nervous system disorders, pulmonary disorders, or renal disorders.

according to the modified CDC definition was 23.5% (95% CI, 9.0 to 35.8), which met noninferiority and superiority criteria but not the higher superiority threshold (Table 2). Subsequently, no further hypothesis was tested. The relative vaccine efficacy for RT-PCR–confirmed influenza-like illness against protocol-defined influenza-like illness with strains with antigenic match to the vaccine strains are not reported because data for antigenic testing for vaccine match and genetic testing were not available for the end-of-season analysis.

Similar results were observed in the supplementary analysis including all randomly assigned participants who received any trial vaccine (full analysis population) (Table S2). In supportive analyses, the relative vaccine efficacy of mRNA-1010 appeared to be generally consistent across the three influenza strains. The relative vaccine efficacy against A/H1N1, A/H3N2, and B/Victoria was 29.6% (95% CI, 16.4 to 40.7), 22.2% (95% CI, 4.3 to 36.9), and 29.1% (95% CI, –18.5 to 57.5), respectively (Table 2).

The favorable relative vaccine efficacy of mRNA-1010 over the standard-dose comparator also appeared evident across subgroups defined according to age, sex, race, BMI, comparator vac-

Table 2. Relative Vaccine Efficacy (Per-Protocol Efficacy Population).*

End Point	mRNA-1010 (N = 20,179)	Standard-Dose Comparator (N = 20,124)	Relative Vaccine Efficacy (95% CI)
	no. of participants (%)		*percent*
Primary end point: first occurrence of RT-PCR–confirmed, protocol-defined influenza-like illness caused by any influenza A or B strain	411 (2.0)	557 (2.8)	26.6 (16.7 to 35.4)†‡
Caused by any influenza A	386 (1.9)	522 (2.6)	26.5 (16.1 to 35.5)§
Caused by influenza A/H1N1	223 (1.1)	315 (1.6)	29.6 (16.4 to 40.7)§
Caused by influenza A/H3N2	158 (0.8)	202 (1.0)	22.2 (4.3 to 36.9)§
Caused by influenza B	25 (0.1)	35 (0.2)	29.1 (–18.5 to 57.5)§
First occurrence of RT-PCR–confirmed, modified CDC-defined influenza-like illness caused by any influenza A or B strain	223 (1.1)	290 (1.4)	23.5 (9.0 to 35.8)†¶
Caused by any influenza A	211 (1.0)	276 (1.4)	24.0 (9.1 to 36.5)§
Caused by influenza A/H1N1	125 (0.6)	172 (0.9)	27.7 (9.0 to 42.6)§
Caused by influenza A/H3N2	83 (0.4)	102 (0.5)	19.1 (–8.1 to 39.5)§
Caused by influenza B	12 (<0.1)	14 (<0.1)	14.8 (–84.3 to 60.6)§

* Data are from the per-protocol efficacy analysis population, which included participants who had undergone randomization, received a trial vaccine, and had no major protocol deviations affecting the efficacy outcomes as determined before database lock and unblinding. The event is the first reverse-transcriptase–polymerase-chain-reaction (RT-PCR)–confirmed, protocol-defined influenza-like illness or first RT-PCR–confirmed, modified Centers for Disease Control and Prevention (CDC)–defined influenza-like illness that begins at least 14 days after trial vaccination through the end of influenza season caused by any influenza A or B strain, regardless of vaccine match. Data for participants without the event are censored at early discontinuation of trial participation or death unrelated to influenza; the date of early RT-PCR–confirmed, protocol-defined influenza-like illness starting fewer than 14 days after trial vaccination; the end of the trial; the end of influenza season; or the data-cutoff date, whichever occurs the earliest. Relative vaccine efficacy is defined as (1 – hazard ratio [mRNA-1010 vs. standard-dose comparator]) × 100. The relative vaccine efficacy and the confidence interval are based on a stratified Cox proportional-hazards model with vaccine group as a fixed effect, with adjustment for the randomization stratification factors: age group (50 to <65 years or ≥65 years) and the status with respect to influenza vaccination during the previous influenza season (received or not received). Efron's method was used to handle ties.

† Hypothesis testing was conducted for noninferiority, superiority, and higher-level superiority in a hierarchical fashion at a one-sided significance level of 2.5%. The success criteria were equivalent to a lower boundary of the 95% confidence interval of the relative vaccine efficacy of more than –10% for noninferiority, more than 0% for superiority, and more than 9.1% for higher-level superiority.

‡ One-sided P<0.001 for noninferiority, superiority, and higher-level superiority.

§ No hypothesis testing was conducted; the 95% confidence interval was provided as a descriptive measure. The width of the confidence interval was not adjusted for multiplicity and should not be used for hypothesis testing.

¶ One-sided P<0.001 for noninferiority; one-sided P=0.001 for superiority; and one-sided P=0.03 for higher-level superiority.

cine (trivalent or quadrivalent), geographic region, baseline risk status, frailty, and status with respect to influenza vaccination during the previous influenza seasons (Table S3). The estimates of relative vaccine efficacy were generally consistent for trivalent and quadrivalent comparator vaccines, with overlapping confidence intervals. Among the 19,260 participants 65 years of age or older, the relative vaccine efficacy was 27.4% (95% CI, 12.1 to 40.0). The estimates of relative vaccine efficacy were also consistent in high-risk persons (Fig. 1). An analysis of the cumulative number of cases over time suggested that the efficacy advantage for mRNA-1010 was observed early and maintained throughout the full influenza season (Fig. 2).

In exploratory analyses, medically attended influenza-associated outcomes across all health care settings occurred in 80 recipients of mRNA-1010 and 120 recipients of the standard-dose comparator, which corresponded to a relative vaccine efficacy of 33.7% (95% CI, 12.0 to 50.0) (Fig. S2). Among 64 participants who sought higher-level care (hospitalization, emergency department, or urgent care), health care encounters occurred in 22 recipients of mRNA-1010 and 42 recipients of the standard-dose comparator, which corresponded to a relative vaccine efficacy of 47.9% (95% CI, 12.8 to 68.9). The number of participants who were hospitalized was lower with mRNA-1010 than with the standard-dose comparator (4 vs. 8), as was the number of participants who visited the emergency department (6 vs. 12), findings consistent with the overall relative vaccine efficacy for higher-level care.

SAFETY

Solicited local and systemic adverse reactions were reported more frequently with mRNA-1010 than with the standard-dose comparator; most reactions were mild to moderate and transient (median duration, 1 to 2 days) (Fig. 3). Injection-site pain was the most common solicited local adverse reaction both with mRNA-1010 and with the standard-dose comparator (65.8% vs. 29.8%); the most frequent solicited systemic adverse re-

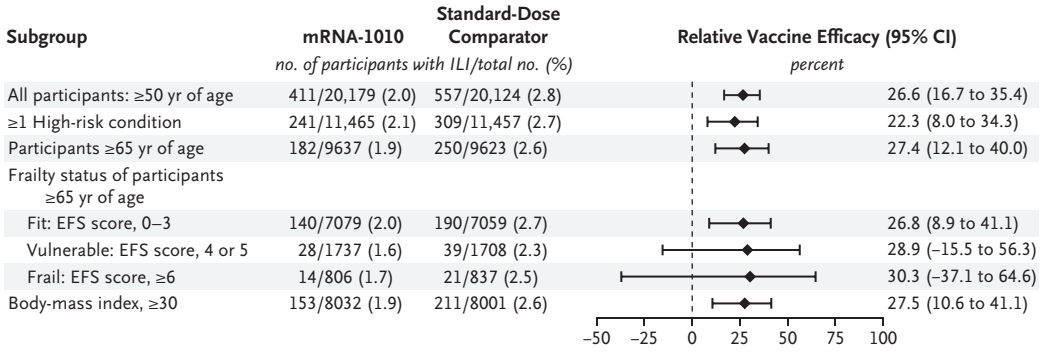
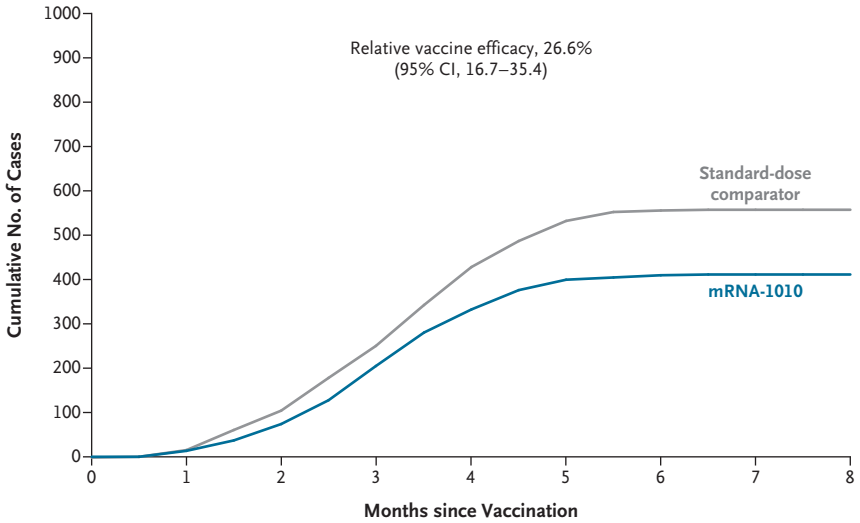


Figure 1. Relative Vaccine Efficacy of mRNA-1010 as Compared with Licensed Influenza Vaccines According to High-Risk Subgroup (Per-Protocol Efficacy Population).

The figure shows estimates of relative vaccine efficacy with 95% confidence intervals for mRNA-1010 as compared with licensed standard-dose influenza vaccines (standard-dose comparator) across prespecified subgroups: participants 50 years of age or older with at least one high-risk medical condition, frailty status among participants 65 years of age or older (categorized as fit, vulnerable, or frail according to the Edmonton Frail Scale [EFS] score), and participants 50 years of age or older with obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥30). Cases were based on reverse-transcriptase–polymerase-chain-reaction (RT-PCR)–confirmed, protocol-defined influenza-like illness (ILI), regardless of influenza strain. Relative vaccine efficacy was calculated as (1 – hazard ratio [mRNA-1010 vs. standard-dose comparator) × 100, with the hazard ratio estimated with the use of a stratified Cox proportional-hazards model (stratified according to age group and status with respect to influenza vaccination during the previous influenza season), with vaccine group as a fixed effect. High-risk medical conditions included obesity, diabetes, pulmonary disorders, cardiac disorders, nervous system disorders, and other Centers for Disease Control and Prevention–defined risk factors. No hypothesis testing was conducted for the high-risk subgroups; the 95% confidence intervals were provided as a descriptive measure. The widths of the confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing.



No. at Risk									
Standard-dose comparator	20,124	19,871	19,663	19,383	19,027	18,774	10,098	1932	0
mRNA-1010	20,179	19,930	19,765	19,506	19,151	18,925	10,180	1962	0
Cumulative No. of Events									
Standard-dose comparator	0	16	104	250	428	532	555	557	557
mRNA-1010	0	14	74	205	333	400	409	411	411

Figure 2. First Occurrence of Protocol-Defined Influenza-like Illness Caused by Any Influenza A or B Strain.

Shown are the cumulative case numbers for the first occurrence of RT-PCR–confirmed, protocol-defined influenza-like illness that began at least 14 days after trial vaccination and continued through the end of the influenza season, caused by any influenza A or B strain, regardless of vaccine match. The median follow-up was 6 months. Relative vaccine efficacy was calculated as (1 – hazard ratio [mRNA-1010 vs. standard-dose comparator]) × 100. The relative vaccine efficacy and the 95% confidence interval were based on a stratified Cox proportional-hazards model with the vaccine group as a fixed effect, with adjustment for the randomization stratification factors: age group (50 to <65 years or ≥65 years) and status with respect to influenza vaccination during the previous influenza season (received or not received). Efron's method was used to handle ties.

actions were fatigue (45.1% vs. 20.3%), headache (37.8% vs. 18.0%), and myalgia (35.4% vs. 11.6%). Grade 3 solicited adverse reactions were reported by 6.4% of recipients of mRNA-1010 and 1.0% of recipients of the standard-dose comparator (Table S4). No grade 4 solicited adverse reactions were reported. The frequency of solicited adverse reactions was lower among older participants than among younger participants (Table S5).

The frequency of unsolicited adverse events, including serious adverse events, adverse events leading to discontinuation of trial participation, adverse events of special interest, and medically attended adverse events, was similar in the two groups through day 28 and through the data-cutoff date (Tables S6 and S7, respectively). Vaccine-related unsolicited adverse events through the data-cutoff date occurred more frequently with mRNA-1010 than with the standard-dose comparator (0.5% [104 of 20,350 participants] vs. 0.3% [51 of 20,353 participants]) and were primarily driven by nonserious reactogenicity-type events reported within the first 7 days after vaccination.

Serious adverse events were reported in 2.2% of recipients of mRNA-1010 and 1.9% of recipients of the standard-dose comparator through the data-cutoff date (Table S7) and were most frequently classified under the *Medical Dictionary for Regulatory Activities* system organ class of infections and infestations (0.4% in each group) (Table S8). Three recipients of mRNA-1010 (<0.1%) and two recipients of the standard-dose comparator (<0.1%) had serious adverse events considered by the investigator to be vaccine-related (Tables S7 and S9). Fatal events occurred in 0.2% of the participants in each group; none were considered by the investigator to be vaccine-related.

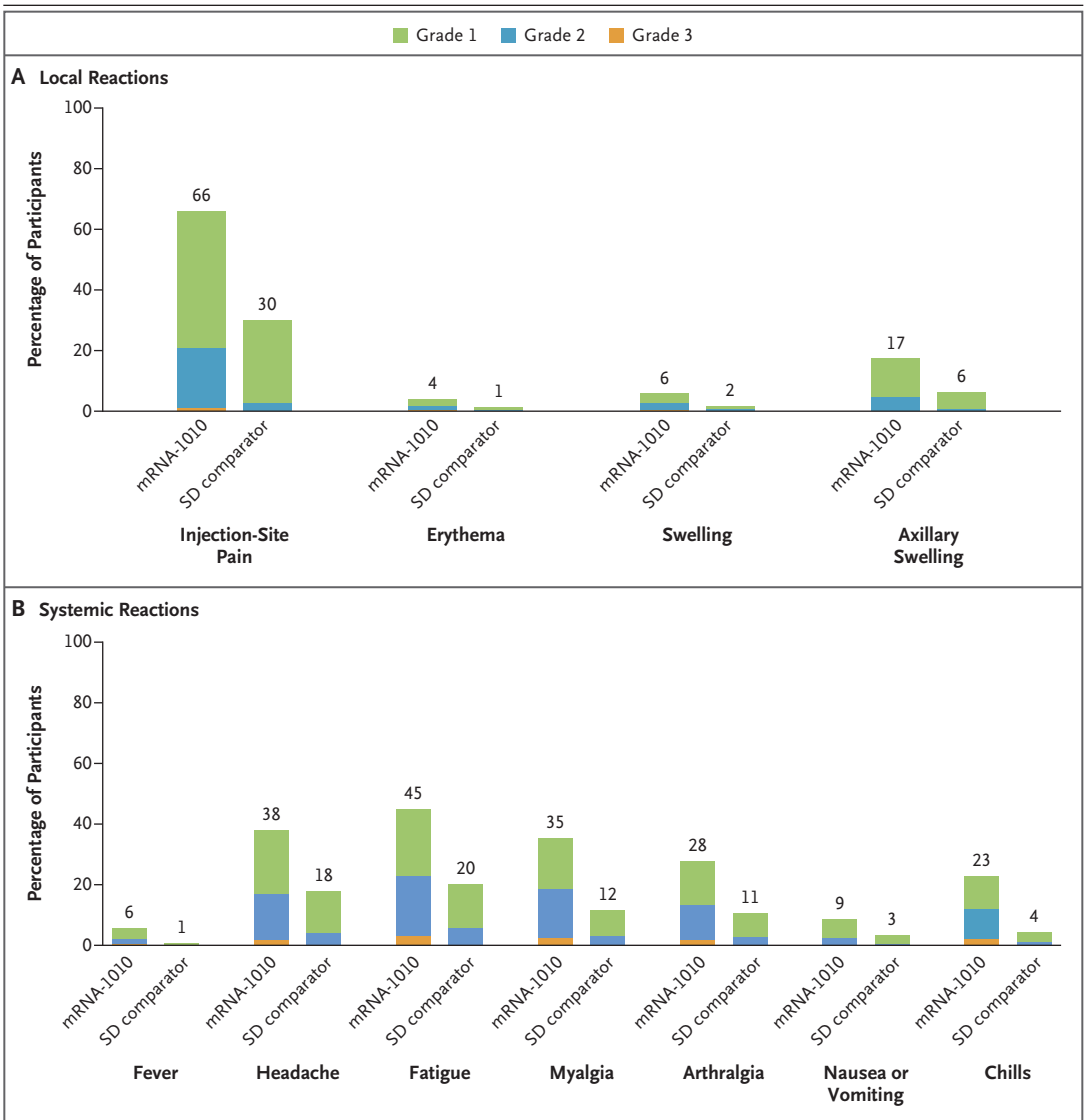


Figure 3. Solicited Local and Systemic Reactions.

Shown are solicited adverse reactions within 7 days after receipt of mRNA-1010 or the standard-dose (SD) comparator. Panel A shows local adverse reactions, and Panel B shows systemic adverse reactions. Percentages are based on the number of exposed participants who submitted data for the event. The toxicity grade is the maximum toxicity grade reported on any day from day 1.

Protocol-defined adverse events of special interest were reported in 15 participants (<0.1%) in each group through the data-cutoff date. A total of 4 participants (2 per group) had adverse events of special interest that were considered by the investigator to be vaccine-related, one of which occurred within 28 days after vaccination (Bell's palsy in a recipient of the standard-dose comparator). Adverse events of special interest in recipients of mRNA-1010 included thrombocytopenia 84 days after vaccination and cardiomyopathy 95 days after vaccination, which was not considered by the independent Cardiac Event Adjudication Committee (CEAC) to be an event of myopericarditis. One recipient of the standard-dose comparator had pericarditis 60 days after vaccination. As assessed by the CEAC, there were no cases of acute myocarditis, myopericarditis, or pericarditis among recipients of mRNA-1010 within the conservative risk window of 42 days after vaccination.

DISCUSSION

The investigational vaccine mRNA-1010 is based on a proprietary mRNA platform designed to prevent influenza disease caused by influenza A or B strains. Other mRNA vaccines on this platform have shown clinical success against respiratory tract infections.[10,11] The effectiveness of influenza vaccines varies according to season and circulating strains. For the 2024–2025 season, efficacy estimates of licensed, predominately egg-based influenza vaccines ranged from 36 to 54% in the United States and Europe.[12,13] The mRNA platform enables high-fidelity antigen encoding, avoids egg-based production, and can be rapidly updated to minimize antigen mismatch and manufacturing time,[14,15] which may contribute to improved vaccine efficacy.

In this international, phase 3 trial involving adults 50 years of age or older, a single dose of mRNA-1010 met the prespecified criterion of higher-level superiority relative to a licensed standard-dose comparator, with an estimated relative vaccine efficacy of 26.6% (95% CI, 16.7 to 35.4). The superior relative vaccine efficacy of mRNA-1010 was observed early and maintained throughout the full influenza season. In the high-transmission 2024–2025 Northern Hemisphere influenza season, the efficacy advantage for mRNA-1010 was observed across influenza strains. Similar estimates of relative vaccine efficacy were observed across all vaccine-included strains: A/H1N1 (29.6%), A/H3N2 (22.2%), and B/Victoria (29.1%). The mRNA platform enables precise HA sequence matching to circulating strains, reflected in consistent efficacy across subtypes.

Among more than 19,000 adults 65 years of age or older, a population particularly susceptible to severe influenza, the relative vaccine efficacy of mRNA-1010 was 27.4% (95% CI, 12.1 to 40.0), which suggests benefits similar to those of enhanced (high-dose, adjuvanted, or recombinant-based) influenza vaccines in older adults.[16] Similar efficacy was observed in other prespecified high-risk subgroups, including participants with obesity or underlying high-risk medical conditions.

In exploratory analyses, recipients of mRNA-1010 had fewer cases of medically attended influenza illness across all levels of health care use than recipients of the standard-dose comparator. These results align with those of previous studies showing reduced influenza-like illness–associated hospitalizations with high-dose influenza vaccines as compared with standard-dose formulations in adults 65 years of age or older.[17-22] Although the trial was not powered for these outcomes, the consistency of case distribution between vaccine groups and relative vaccine efficacy support the potential for reductions in severe, influenza-associated illness with mRNA vaccination. The consistency of relative vaccine efficacy across these many outcomes suggests that mRNA-1010 efficacy is broadly applicable across diverse populations and the spectrum of influenza disease.

The overall safety profile of mRNA-1010 was consistent with findings from previous phase 3 trials.[23] Solicited adverse reactions occurred more frequently with mRNA-1010 than with the standard-dose comparator; most reactions were mild to moderate and transient. Serious adverse events were balanced between the two groups (2.2% with mRNA-1010 and 1.9% with the standard-dose comparator).

This trial had several strengths and limitations. Its global design and inclusion of demographically and clinically diverse participants support the generalizability of the findings. Although case numbers were limited in some subgroups (including participants ≥75 years of age and vulnerable or frail adults), which resulted in wide confidence intervals, the magnitude of the point estimate of relative vaccine efficacy was similar to that for the primary end point. Although the analysis covered only one influenza season, it included 968 confirmed cases across all three circulating strains. The number of influenza B cases was small (60 cases); however, the point estimate of relative vaccine efficacy was consistent with overall relative vaccine efficacy and aligned with previous data showing superior immune responses against B lineages with mRNA-1010.[23] Because persons 65 years of age or older are at increased risk for severe influenza, some countries recommend enhanced influenza vaccines. However, this multinational Northern Hemisphere trial was conducted across regions with differing standards of care; therefore, a standard-dose comparator was selected, and this information was included in the informed consent. The magnitude of the relative vaccine efficacy observed with mRNA-1010 relative to the standard-dose comparator appears to

be consistent with that of other enhanced vaccines[16] and consistent with previous results in which mRNA-1010 showed superior immunogenicity as compared with a licensed standard-dose and high-dose comparator in older adults.[23]

In this trial, vaccination with mRNA-1010 was superior to a licensed standard-dose comparator in preventing influenza. Solicited adverse reactions were more common in the mRNA-1010 group, which suggests a need for balancing assessment of temporary vaccine-induced reactogenicity events with the magnitude of protection against influenza. Serious adverse events were infrequent and similar in the two groups. These findings support the role of mRNA-1010 in improving influenza prevention.

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AUTHOR INFORMATION

[1] Center for Vaccinology, Ghent University and Ghent University Hospital, Ghent, Belgium; [2] Moderna, Cambridge, MA; [3] Colchester Research Group, Truro, NS, Canada; [4] Institute for Liver Health Arizona, Tucson; [5] Layton Medical Centre–General Practice, Blackpool, United Kingdom; [6] Infektiologikum Frankfurt, Frankfurt, Germany; [7] Moderna Biopharma Canada, Toronto.

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