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FDA Briefing Document

BLA# 125869/0

Influenza Vaccine, mRNA

(Proposed Trade Name: mFlusiva)

Applicant: Moderna TX, Inc.

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

June 18, 2026

Division of Clinical and Toxicology Review | Office of Vaccines Research and Review

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the benefit-risk assessment of mFlusiva (mRNA-1010) to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AR	adverse reaction
BLA	Biologics License Application
BMI	body mass index
CABG	coronary artery bypass graft
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	confidence interval
CoP	correlate of protection
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CoR	correlate of risk
DBL	database lock
eDiary	electronic diary
EOS	end-of-study
FDA	U.S. Food and Drug Administration
GBS	Guillain-Barré Syndrome
GMFR	geometric fold rise
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutinin inhibition
HD	high-dose
ILI	influenza-like illness
ISS	Integrated Safety Summary
LGE	late gadolinium enhancement
LL	lower limit
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
NH	Northern Hemisphere
NI	noninferiority
NP	nasopharyngeal
PPIS	per-protocol immunogenicity subset
PT	MedDRA preferred term
QIV	quadrivalent influenza vaccine
RD	risk difference
RIV	recombinant influenza vaccine
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
rVE	relative vaccine efficacy
SAE	serious adverse event
SCR	seroconversion rate
SD	standard dose
SMQ	standard MedDRA query
SOC	system organ class
TIV	trivalent influenza vaccine
U.S.	United States
UTI	urinary tract infection

VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
yoa	years of age

1. Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1. Purpose / Objective of the AC Meeting

FDA is convening this meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss the benefit-risk assessment of mFlusiva (mRNA-1010), an mRNA-based trivalent influenza vaccine (TIV) encoding hemagglutinin (HA) glycoproteins for influenza A/H1N1, A/H3N2, and B/Victoria, submitted under BLA 125869/0 by Moderna TX, Inc. The BLA was received on December 5, 2025, and filed on February 17, 2026. The proposed indication is for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine.

The Agency is seeking VRBPAC input on two specific regulatory issues:

- **Issue 1 (Traditional Approval, adults 50 through 64 years of age):** Whether relative vaccine efficacy (rVE) against RT-PCR–confirmed influenza-like illness (ILI) from a Phase 3, randomized, observer-blinded, active-controlled trial in adults 50 years of age and older (Study P304) provides sufficient basis for Traditional Approval of mFlusiva in adults 50 through 64 years of age.
- **Issue 2 (Accelerated Approval, adults 65 years of age and older):** Whether comparative immunogenicity data relative to high-dose (HD) influenza vaccine — a CDC-preferentially recommended vaccine —from a Phase 3, randomized, stratified, observer-blinded, active-controlled trial in adults 65 years of age and older (Study P303 Part C), combined with a required Phase 4 confirmatory study, provides sufficient basis for Accelerated Approval of mFlusiva in adults 65 years of age and older.

1.2. Context for Issues to Be Discussed at the AC

Seasonal influenza causes 3–5 million cases of severe disease and up to 650,000 deaths annually worldwide. The Centers for Disease Control and Prevention (CDC) estimates that influenza has resulted in 9.4 to 51 million illnesses and 6,300 to 52,000 deaths annually in the United States (U.S.) between 2010 and 2025.[1] In the U.S., adults 65 years of age (yoa) and older account for approximately 70–85% of influenza-related deaths and 50–70% of hospitalizations.[2]

Currently licensed influenza vaccines — the majority of which are manufactured in embryonated chicken eggs — achieve up to 60% effectiveness under optimal conditions. Observed effectiveness is reduced when vaccine strains are antigenically mismatched with circulating influenza strains. Egg-based manufacturing introduces egg-adaptive mutations with the potential to alter antigen conformation and create antigenic mismatch. (See Section 2.1.4 Unmet Need)

For adults 65 yoa and older, CDC preferentially recommends HD, recombinant, or adjuvanted over standard-dose (SD) influenza vaccines to address age-related immunosenescence. Accordingly, when designing clinical trials of influenza vaccines in this population, the control group should reflect the relevant standard of care – consistent with ICH E10 guidance ("Choice of Control Group and Related Issues in Clinical Trials," 2000) – which for this age group are the preferentially recommended influenza vaccines.

mFlusiva represents a novel mRNA-based manufacturing technology that eliminates egg-adaptive mutations. The Applicant positions their technology as enabling rapid strain updates.

[1] About Estimated Flu Burden | Flu Burden | CDC
[2] Flu and People 65 Years and Older | Influenza (Flu) | CDC

Key points for VRBPAC consideration include: (1) whether the efficacy and immunogenicity data demonstrate effectiveness of mFlusiva across the proposed age groups; and (2) whether the benefit-risk assessment is favorable considering the reactogenicity profile, identified evidence gaps in special populations, and limited duration-of-protection data.

1.3. Brief Description of Issues for Discussion at the AC

The following key findings and uncertainties frame the issues to be discussed at this meeting:

- **Key Finding 1 — Clinical Efficacy (primary basis for Traditional Approval in adults 50 through 64 yoa):** Study P304 provided the primary efficacy data for mRNA-1010 (TIV) in adults ≥50 yoa. Over one influenza season, mRNA-1010 (TIV) demonstrated a rVE of 26.6% (95% CI: 16.7, 35.4) against RT-PCR–confirmed ILI compared with the SD comparator vaccine. Point estimates of rVE were consistent across age subgroups (50 through 64 yoa: 26.1% [95% CI: 12.3, 37.7]; 65 through 74 yoa: 28.0% [10.4, 42.2]; ≥75 yoa: 25.3% [−10.4, 49.5]) and viral strains. rVE against higher-level healthcare outcomes (hospitalization, emergency room, or urgent care visits) was 47.9% (95% CI: 12.8, 68.9), supporting clinical meaningfulness.
- **Key Finding 2 — Immunogenicity (primary basis for Accelerated Approval in adults ≥65 yoa):** Study P303 Part C demonstrated that mRNA-1010 (QIV) met pre-specified noninferiority and superiority criteria for hemagglutination inhibition (HAI) geometric mean titers (GMT) and seroconversion rates (SCR) relative to Fluzone HD (QIV) for all four vaccine-matched influenza strains in adults ≥65 yoa at Day 29. Immune responses, including GMT and SCR, remained higher in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group at end-of-study (Day 181) in the evaluated subset.
- **Key Finding 3 — Safety Profile:** Solicited adverse reactions (ARs) within 7 days postvaccination were more frequent in mRNA-1010 recipients than in comparator recipients in both pivotal studies but were predominantly mild to moderate in severity with a median duration of approximately 2 days. Unsolicited adverse events through Day 28, serious adverse events (SAEs), adverse events of special interest (AESIs), and deaths through approximately 6 months of follow-up were balanced between treatment groups. No cases of myocarditis or pericarditis were identified within 42 days postvaccination. Subgroup analyses by age, sex, race, and baseline risk status showed no clinically meaningful differences in safety profiles. The Integrated Safety Summary (ISS) pooled data from four Phase 3 studies comprising 35,965 mRNA-1010 recipients and 35,951 standard-dose or high-dose comparator recipients ≥50 yoa. SAEs, deaths, and AESIs were balanced between treatment groups. No cases of myocarditis or pericarditis were assessed as related to mRNA-1010. The pooled analysis identified no adverse event patterns indicative of a safety signal for mRNA-1010 in individuals ≥50 yoa.
- **Key Uncertainty — Evidence Gaps:** Clinical efficacy data are available for one influenza season only. Efficacy in immunocompromised individuals and very frail older adults has not been established. This gap is significant because these populations face the highest absolute risk of severe influenza-related complications and may respond differently to mRNA-based vaccine platforms. The study exclusion of these groups limits direct applicability of the efficacy data to a substantial portion of the intended patient population. Data on concomitant administration with routinely co-administered vaccines (e.g., COVID-19, RSV, pneumococcal vaccines) are not available. The confidence interval for B/Victoria-specific rVE crosses zero (29.1%; 95% CI: −18.5, 57.5) due to limited case accrual for this strain (25 cases in the mRNA-1010 group vs. 35 cases in the SD comparator group).

- **Key Issue — Approval Approach:** The Applicant proposed a bifurcated regulatory pathway — Traditional Approval for adults 50 through 64 yoa based on clinical efficacy, and Accelerated Approval for adults 65 yoa and older based on immunogenicity as a surrogate endpoint — with a required Phase 4 confirmatory trial to verify clinical benefit in the older age group.

1.4. Draft Points for the AC to Consider

The following points are presented for VRBPAC deliberation and vote:

- Do the primary endpoint, age subgroup, and strain-specific vaccine efficacy results from Study P304 demonstrate clinically meaningful efficacy of mFlusiva against influenza disease in adults 50 through 64 years of age?
- Do the immunogenicity results from Study P303 Part C, comparing mRNA-1010 (QIV) to Fluzone High-Dose Quadrivalent, provide a reasonable basis to predict clinical benefit of mFlusiva in adults 65 years of age and older?
- Do the available data indicate that the safety profile of mFlusiva is adequately characterized, that identified risks are acceptable, and that residual risks can be appropriately monitored and managed through postmarketing pharmacovigilance?
- **Voting questions:**
  - Do the benefits of mFlusiva outweigh its risks for the prevention of influenza disease in adults 50 through 64 years of age?
  - Do the benefits of mFlusiva outweigh its risks for the prevention of influenza disease in adults 65 years of age and older?

2. Introduction and Background

2.1. Background of the Condition/Standard of Clinical Care

2.1.1. Disease Burden

Influenza is responsible for 3–5 million cases of severe disease and up to 650,000 deaths annually worldwide (WHO, 2025). In the United States, adults ≥65 yoa account for approximately three-quarters of influenza-associated deaths. Seasonal influenza disproportionately affects older adults, young children, pregnant women, and individuals with underlying cardiac, immunocompromising, metabolic, or respiratory conditions. The cumulative public health burden is substantial, encompassing direct healthcare costs, lost productivity, and excess mortality, particularly during seasons with high antigenic mismatch.

2.1.2. Clinical Manifestations

Following an incubation period of 1 to 4 days, influenza presents with abrupt onset of fever (38–40°C), rigors, myalgia, headache, malaise, and nonproductive cough. Upper respiratory symptoms (nasal congestion, rhinorrhea, sore throat) are common. In immunocompetent adults, systemic symptoms typically resolve within 3–7 days, though cough and fatigue may persist for weeks. High-risk groups are susceptible to serious complications, including primary viral pneumonia, secondary bacterial pneumonia, exacerbation of chronic obstructive pulmonary disease or asthma, myocarditis, encephalitis, and acute respiratory distress syndrome.

2.1.3. Current Treatment and Prevention Options

Four FDA-approved antiviral agents are available for treatment — oseltamivir, zanamivir, peramivir, and baloxavir marboxil — each capable of reducing disease duration, severity, and complication risk when initiated promptly. Nevertheless, annual influenza vaccination remains the primary recommended preventive strategy. CDC recommends vaccination for all individuals ≥6 months of age, with preferential recommendation of HD (Fluzone HD), adjuvanted (Fluad), or recombinant (FluBlok) formulations for adults 65 yoa and older.

2.1.4. Unmet Need

Currently licensed influenza vaccines are generally considered to achieve up to 60% effectiveness under conditions of optimal antigenic match (Demicheli, et al. 2018; Osterholm, et al. 2012), with lower protection during mismatch seasons (Tricco, et al. 2013). Egg-based manufacturing — used by most licensed vaccines — introduces egg-adaptive mutations that can alter HA antigen conformation and may reduce vaccine immunogenicity (Petrova & Russell 2018). There is a need for vaccines with improved effectiveness, particularly in older adults (Osterholm, et al. 2012). High-volume manufacturing capable of rapid strain reformulation is also needed to address antigenic drift and — more critically — antigenic shift, the latter posing pandemic risk.

2.2. Pertinent Drug Development and Regulatory History

2.2.1. Product Description

mFlusiva (mRNA-1010) is a trivalent mRNA influenza vaccine formulated as a solution for intramuscular injection. The product encodes the full-length, membrane-bound HA glycoproteins of influenza A/H1N1, A/H3N2, and B/Victoria-lineage (12.5 µg of each mRNA, total 37.5 µg), encapsulated in lipid nanoparticles. It is supplied as a single-dose prefilled syringe and administered as a 0.375 mL intramuscular dose. The proposed indication is for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine.

2.2.2. Development History

The clinical development program for mRNA-1010 comprises five studies (see Appendix A). Early-phase dose-selection data were generated in Study P101 (Phase 1/2). These, along with Studies P301 and P302, evaluated an earlier formulation with “pre-optimized” influenza B antigens (mRNA-1010, original QIV) and contribute safety data to the Integrated Safety Summary (ISS) only. Study P303 Parts A and B evaluated an “optimized” quadrivalent formulation (mRNA-1010.6 and 1010.4, respectively) in adults ≥18 yoa and 18 through 64 yoa, respectively, and similarly contribute to the ISS. The pivotal Phase 3 program consists of Study P304, providing primary efficacy and safety data for mRNA-1010 (TIV) in adults ≥50 yoa, and Study P303 Part C, providing immunogenicity and safety data for mRNA-1010 (QIV) compared with Fluzone HD (QIV) in adults ≥65 yoa. BLA 125869/0 was submitted and received on December 5, 2025.

2.2.3. Manufacturing Innovation

The mRNA manufacturing technology avoids egg-based manufacturing, eliminating the risk of egg-adaptive mutations. The formulation intended for licensure (mRNA-1010.4) incorporates two stabilizing point mutations in non-surface-exposed regions of influenza B HA — preserving antigenic epitopes while enhancing structural stability and antigen availability — and modified untranslated regions across all influenza strains to extend mRNA durability. The mRNA technology also supports rapid strain reformulation in response to antigenic drift or shift, a meaningful operational advantage over egg-based production.

3. Summary of Issues for the AC

3.1. Efficacy/Effectiveness Issues

No major deficiencies were identified; however, four issues warrant Advisory Committee consideration regarding the adequacy and interpretive scope of the efficacy data, as described below.

The primary efficacy analysis demonstrated that mRNA-1010 (TIV) met all prespecified sequential success criteria—noninferiority, superiority, and super-superiority—relative to the standard-dose (SD) comparator. The primary immunogenicity (effectiveness) analysis demonstrated that mRNA-1010 (QIV) met all prespecified sequential success criteria—noninferiority and superiority—relative to the high-dose (HD) comparator.

Four issues warrant Advisory Committee consideration:

- **Efficacy Issue 1:** Adequacy and clinical meaningfulness of rVE versus a standard-dose (SD) comparator in adults ≥65 yoa, given the availability of preferentially recommended high-dose, recombinant, or adjuvanted influenza vaccines for this age group.
- **Efficacy Issue 2:** Interpretive uncertainty in rVE against influenza B/Victoria due to low case accrual.
- **Efficacy Issue 3:** Adequacy of single-season efficacy data and study population to support licensure.
- **Effectiveness Issue 4:** Use of immunogenicity as a surrogate endpoint reasonably likely to predict clinical benefit in adults 65 yoa and older.

3.1.1. Sources of Data for Efficacy

3.1.1.1 Primary Efficacy Study (50 yoa and older)

Study mRNA-1010-P304 (P304) (**NCT06602024**)**:** Phase 3, randomized, observer-blind (participant- and assessor-blind), active-controlled, case-driven trial evaluating mRNA-1010 trivalent influenza vaccine (TIV) versus a licensed SD comparator (trivalent [TIV] in North America; quadrivalent [QIV] in Europe and East Asia) for the prevention of RT-PCR–confirmed influenza illness in adults ≥50 yoa.

See Appendix B for details of Study P304.

Key design parameters:

- **Total enrollment:** N = 40,805 participants
- **Study sites:** 301 sites across 11 countries (North America, Europe, East Asia)
- **Randomization:** 1:1 allocation (mRNA-1010 [TIV] vs. SD comparator)
- **Age stratification:** prior seasonal influenza vaccination status; 50 to <65 years; ≥65 years
- **Season:** 2024–2025 Northern Hemisphere (NH) influenza season
- **Active comparator:** Licensed SD TIV (Fluarix) or QIV, with trivalent SD formulation as preferred comparator
- **Regimen:** Single intramuscular dose per participant

- **Primary efficacy analysis:** Pre-specified interim analysis at end of NH 2024–2025 season; data cutoff April 30, 2025; database lock June 3, 2025. The interim analysis used the full one-sided alpha of 2.5%. High influenza transmission during the 2024–2025 season resulted in 968 cases accruing—exceeding the target of 836—and the study did not advance to a second season.
- **Primary endpoint:** First episode of RT-PCR–confirmed protocol-defined influenza-like illness (ILI) with onset ≥14 days postvaccination through end of influenza season, caused by any influenza A or B strain
- **Statistical success criteria:** Hierarchical sequential testing for noninferiority (NI; lower limit [LL] of 95% CI of rVE > −10%), superiority (LL > 0%), and super-superiority (LL > 9.1%)
- **Median efficacy follow-up:** 181 days (~6 months)

The study employed a hierarchical sequential testing strategy across nine pre-specified null hypotheses controlling the Type I error rate, progressing across three tiers: (1) protocol-defined ILI, any strain; (2) modified CDC-defined ILI, any strain; (3) protocol-defined ILI, antigenically matched strains. Within each tier, hypotheses were tested sequentially for NI, superiority, and super-superiority; advancement required rejection of the preceding hypothesis.

3.1.1.2 Primary Immunogenicity Study (65 yoa and older)

Study P303 Part C (NCT05827978): Phase 3, multicenter, randomized, stratified, observer-blind, active-controlled study evaluating the immunogenicity, reactogenicity, and safety of mRNA-1010 (QIV) relative to Fluzone High-Dose (QIV) (**N.B.** HD influenza vaccine is one of three influenza vaccines preferentially recommended by CDC for adults 65 yoa and older).

See Appendix C for details of Study P303 Part C.

Key design parameters:

- **Total enrollment:** N = 3,003 participants ≥65 yoa
- **Study sites:** 96 U.S. centers
- **Randomization:** 1:1 allocation (mRNA-1010 [QIV] vs. Fluzone HD [QIV])
- **Season:** 2023–2024 Northern Hemisphere (NH) influenza season
- **Active comparator:** Licensed Fluzone HD (QIV)
- **Regimen:** Single intramuscular dose per participant
- **Primary immunogenicity analysis:** Day 29 postvaccination
- **Primary endpoints:**
  - Hemagglutination inhibition (HAI) geometric mean titer (GMT) at Day 29 for all four vaccine-matched influenza strains
  - Seroconversion rate (SCR) at Day 29 for all four vaccine-matched influenza strains
- **Statistical success criteria:**
  - Noninferiority (NI): For GMT ratio, lower limit (LL) of 95% confidence interval (CI) >0.667 for each strain; for SCR difference, LL of 95% CI >−10% for each strain

- Superiority: For GMT ratio, LL of 97.5% CI >1.0 for each strain; for SCR difference, LL of 97.5% CI >0% for each strain

- **Immunogenicity follow-up:** HAI GMT and SCR against vaccine-matched influenza A and B strains at Day 181/EOS in a participant subset

The study employed a hierarchical sequential testing strategy—upon successful demonstration of noninferiority for all eight coprimary immunogenicity endpoints, superiority was evaluated.

3.1.1.3 Supporting Safety Studies

Studies P301, P302, and P303 Parts A/B contribute safety data to the Integrated Safety Summary only and do not provide primary efficacy or immunogenicity data for the purposes of this BLA review.

3.1.2. Effectiveness Summary

3.1.2.1 Primary Efficacy Study (50 yoa and older)

The primary efficacy objective of Study P304 was to demonstrate that mRNA-1010 (TIV) was noninferior to the standard-dose comparator in preventing the first occurrence of protocol-defined influenza-like illness (ILI) (see Appendix B Table 1) starting 14 days after vaccination through the end of the influenza season. ILI cases occurred in 411 participants (2.0%) in the mRNA-1010 (TIV) group and 557 participants (2.8%) in the standard-dose comparator group. As shown in Table 1, the study met this objective, demonstrating a rVE of 26.6% (95% CI: 16.7, 35.4) in participants 50 yoa and older. This result satisfied the prespecified noninferiority criterion (lower limit of the 95% CI >−10%). The study also demonstrated superiority and super-superiority of mRNA-1010 (TIV) over the comparator, with the lower limit of the 95% CI exceeding both 0% and 9.1%.

Additional analyses evaluated the secondary efficacy endpoint of the modified CDC-defined ILI, a more stringent case definition which requires a temperature above 37.2°C, cough and/or sore throat, and RT-PCR confirmation of influenza virus (see Appendix B Table 1 for case definitions). Among adults 50 yoa and older, modified CDC-defined ILI occurred in 1.1% of participants receiving mRNA-1010 (TIV) compared with 1.4% receiving the standard-dose comparator, yielding an rVE of 23.5% (95% CI: 9.0, 35.8). Table 1 demonstrates that noninferiority and superiority criteria, but not super-superiority, were met.

Medically attended influenza-like illness (ILI) cases confirmed by RT-PCR and meeting protocol-defined criteria were assessed as an exploratory endpoint. As shown in Table 1, the observed rVE of mRNA-1010 (TIV) against protocol-defined ILI requiring higher levels of care—including hospitalization, emergency room (ER) visit, or urgent care clinic visit—was 47.9% (95% CI: 12.8, 68.9). These exploratory data provide supportive evidence for the clinical benefit of mRNA-1010 (TIV).

Table 1. Analysis of Relative Vaccine Efficacy (rVE) for mRNA-1010 (TIV) Versus SD Comparator Against Various ILI Case Definitions and Health Care Outcomes Regardless of Vaccine Match in Participants 50 Years of Age and Older, (PP Set), Study P304

Relative Efficacy Endpoint	mRNA-1010 (TIV) N=20,179 Cases, n (%)[a]	SD Comparator N=20,124 Cases, n (%)[a]	rVE (%) (95% CI)[b]	Result
Primary: RT-PCR–confirmed protocol-defined ILI	411 (2.0)	557 (2.8)	26.6 (16.7, 35.4)	✓ NI / Superiority / Super-Superiority
Secondary: Modified CDC-defined ILI (more stringent))	223 (1.1)	290 (1.4)	23.5 (9.0, 35.8)	✓NI/ Superiority X Super-Superiority
Exploratory: Higher Level of Care[c] (hospital/ER/urgent care)	22 (0.1)	42 (0.2)	47.9 (12.8, 68.9)	✓ Supports Clinical Benefit

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1, 14.2.1.2.1.1, 14.2.1.4.1.1, and 14.2.1.6.1.1. Data cutoff: April 30, 2025.

Abbreviations: CDC, U.S. Centers for Disease Control and Prevention; CI, confidence interval; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of ILI cases based on the given case definition; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose

[a] Percentages are based on the number of participants in the analysis set.

[b] rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties.

[c] n represents the number of participants with a case, which is a healthcare encounter seeking a higher level of care associated with the first occurrence of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match. If an event is associated with multiple healthcare encounter types or multiple healthcare encounter of the same type, the participant will be counted only once.

Table 2 presents descriptive analyses of primary efficacy endpoint of rVE by age subgroup. Point estimates were consistent across all age subgroups and the overall population (see Table 1). In participants 65 yoa and older, rVE was 27.4% (95% CI: 12.1%, 40.0%) against the standard-dose comparator vaccine, which was not the preferred comparator for this age group; this limitation should be considered when interpreting results in this subgroup. In the 75 yoa and older subgroup, the 95% CI was wide with the lower limit crossing zero, reflecting the smaller sample size and lower event count in this stratum.

Table 2. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for mRNA-1010 (TIV) Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strains by Age Group (PP Set), Study P304

Age Group	mRNA-1010 (TIV) N=20,179 Cases, n/N (%)[a]	SD Comparator N=20,124 Cases, n/N (%)	rVE (%) (95% CI)[b]	Interpretation
50 through 64 yoa	229/10,542 (2.2)	307/10,501 (2.9)	26.1 (12.3, 37.7)	CI excludes zero; suggest superiority
65 through 74 yoa	138/7307 (1.9)	191/7289 (2.6)	28.0 (10.4, 42.2)	CI excludes zero; suggest superiority
75 yoa and older	44/2230 (1.9)	59/2334 (2.5)	25.3 (−10.4, 49.5)	CI crosses zero; wide CI due to small N; directionally consistent

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1, Table 14.2.1.1.4.1. Data cutoff: April 30, 2025.

Abbreviations: CI, confidence interval; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of cases of protocol-defined ILI in the given age subgroup; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose; yoa, years of age

The case is the first RT-PCR–confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match.

[a] Percentages are based on the number of participants in the analysis set in each subgroup.

[b] rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties.

Table 3 presents rVE against RT-PCR–confirmed, protocol-defined ILI stratified by influenza strain. Point estimates of rVE were consistent across all strains. For influenza B/Victoria, the rVE point estimate aligned with the overall estimate; however, the 95% CI was wide with a lower limit below zero (−18.5%), reflecting the limited number of influenza B cases. Influenza A strains predominated, accounting for 94.0% of all influenza cases and driving the overall estimate. Antigenic match between circulating and vaccine strains varied: A/H1N1 (~98%), B/Victoria (~94%), and A/H3N2 (~52–56%). For A/H3N2, rVE trended higher against antigenically matched strains [30.5% (95% CI: 4.6, 49.4)] compared with rVE against all strains [22.2% (95% CI: 4.3, 36.9)], suggesting higher efficacy in seasons with greater antigenic concordance.

Table 3. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for mRNA-1010 (TIV) Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Influenza Strain Type in Participants 50 Years of Age and Older (PP Set), Study P304

Influenza Strain Type	mRNA-1010 (TIV) N=20,179 Cases, n (%)[a]	SD Comparator N=20,124 Cases, n (%)[a]	rVE (%) (95% CI)[b]	Interpretation
Any influenza A strain	386 (1.9)	522 (2.6)	26.5 (16.1, 35.5)	CI excludes zero; robust
Influenza A/H1N1	223 (1.1)	315 (1.6)	29.6 (16.4, 40.7)	CI excludes zero; robust
Influenza A/H3N2	158 (0.8)	202 (1.0)	22.2 (4.3, 36.9)	CI excludes zero; 44-48% antigenically mismatched
Influenza B/Victoria strain	25 (0.1)	35 (0.2)	29.1 (-18.5, 57.5)	CI crosses zero; limited accrual; point estimate consistent

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1 and 14.2.1.1.3.1. Data cutoff: April 30, 2025.
Abbreviations: CI, confidence interval; ILI, influenza-like illness; N, number of participants in the PP analysis set; n, number of cases of RT-PCR confirmed ILI; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose
[a] Percentages are based on the number of participants in the analysis set. The case is the first RT-PCR–confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match. Participants can have more than one influenza strain infection simultaneously.
[b] rVE was defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties. If there were <20 events total in the two vaccination groups combined, rVE was not provided.

3.1.2.2 Primary Immunogenicity Study (65 yoa and older)

A formal correlate of protection (CoP) has not been established for mFlusiva to support traditional approval. Therefore, the application relies on HAI as a surrogate endpoint reasonably likely to predict clinical benefit, under the Accelerated Approval pathway. Immunogenicity data from Study P303 Part C provide the primary evidence to support effectiveness of mRNA-1010 (TIV) in adults aged 65 years and older, based on HAI GMT and SCR as surrogate endpoints reasonably likely to predict clinical benefit. Primary immunogenicity endpoints (HAI assay) for vaccine-matched influenza strains at Day 29 are presented in Table 4 and Table 5. Baseline geometric mean titers (GMTs) were comparable between mRNA-1010 (QIV) and Fluzone HD (QIV). At Day 29, mRNA-1010 (QIV) demonstrated higher GMTs and seroconversion rates (SCRs) than Fluzone HD (QIV) across all four strains.

Noninferiority was met for all four strains based on GMT ratio (95% CI LL >0.667) and SCR difference (95% CI LL >−10%). Superiority was demonstrated for all four strains based on GMT ratio (97.5% CI LL >1) and SCR difference (97.5% CI LL >0%). This finding constitutes the principal basis for the effectiveness determination in this age group.

Table 4. Analyses of Primary Immunogenicity Endpoint of GMTs as Measured by Hemagglutination Inhibition (HAI) for Vaccine-Matched Influenza Strains at Day 29 Postvaccination, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Endpoint	mRNA-1010 (QIV) N=1425 GMT (95% CI)	Fluzone HD (QIV) N=1409 GMT (95% CI)	GMT Ratio (mRNA-1010 [QIV] / Fluzone HD [QIV]) (95% CI) (97.5% CI)
Influenza A/H1N1	168.3 (160.4, 176.7)	125.7 (119.7, 131.9)	1.3 (1.3, 1.4) (1.2, 1.4)
Influenza A/H3N2	137.9 (130.9, 145.4)	113.8 (107.9, 120)	1.2 (1.1, 1.3) (1.1, 1.3)
Influenza B/Victoria	242.1 (232.9, 251.6)	193.7 (186.3, 201.3)	1.3 (1.2, 1.3) (1.2, 1.3)
Influenza B/Yamagata	102.7 (99.2, 106.2)	89.8 (86.8, 92.9)	1.1 (1.1, 1.2) (1.1, 1.2)

Source: Adapted from STN 125869/0, mRNA-1010 P303 Clinical Study Report, Table 14.2.1.1.c. Data cutoff: June 24, 2024.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GMT, geometric mean titer; HAI, hemagglutination inhibition; HD, high dose; LLOQ, lower limit of quantification; N, number of participants with nonmissing HAI data at corresponding visit; PPIS, per protocol immunogenicity set; QIV, quadrivalent; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
The log-transformed antibody levels are 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: Influenza Vaccine Status Since September 2022 to 6 Months Ago (not received seasonal flu vaccine, received seasonal flu vaccine from non mRNA-1010-P302, and received seasonal flu vaccine from mRNA-1010-P302).
The model based GMT and GMT ratio, and its corresponding 95% CI and/or 97.5% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Table 5. Analyses of Primary Immunogenicity Endpoint of SCRs as Measured by Hemagglutination Inhibition (HAI)cr for Vaccine-Matched Influenza Strains at Day 29 Postvaccination, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Endpoint	mRNA-1010 (QIV) N=1425 SCR%[a] (95% CI)	Fluzone HD (QIV) N=1409 SCR%[a] (95% CI)	Difference in SCR (mRNA-1010 [QIV]−Fluzone HD [QIV]) (95% CI)[b] (97.5%CI)[c]
Influenza A/H1N1	49.7 (47.1, 52.3)	36.3 (33.8, 38.8)	13.4 (9.8, 17) (9.3, 17.5)
Influenza A/H3N2	56.4 (53.8, 59)	47.8 (45.2, 50.5)	8.6 (4.9, 12.2) (4.4, 12.8)
Influenza B/Victoria	29.8 (27.5, 32.3)	20.2 (18.1, 22.4)	9.7 (6.5, 12.8) (6.0, 13.3)
Influenza B/Yamagata	26.0 (23.8, 28.4)	20.2 (18.1, 22.4)	5.9 (2.8, 8.9) (2.3, 9.4)

Source: Adapted from STN 125869/0, mRNA-1010 P303 Clinical Study Report, Table 14.2.1.1.c. Data cutoff: June 24, 2024
Abbreviations: CI, confidence interval; HAI, hemagglutination inhibition; HD, high dose; LLOQ, lower limit of quantification; N, number of participants with nonmissing HAI data at baseline (Day 1) and the corresponding visit; PPIS, per protocol immunogenicity set; QIV, quadrivalent influenza vaccine; SCR, seroconversion rate; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
[a] Rate of seroconversion is defined as the proportion of participants with either a baseline HAI titer <1:10 and a postbaseline titer ≥1:40 or a baseline HAI titer ≥1:10 and a minimum 4-fold rise in postbaseline HAI antibody titer.
[b] 95% CI is calculated using the Clopper-Pearson method.
[c] 95% CI, 97.5% CI are calculated using the Miettinen-Nurminen (score) method.

As described in detail in Appendix C, additional immunogenicity outcomes and subgroup analyses support a conclusion that mRNA-1010 (TIV) is effective in adults 65 yoa and older, subject to the caveats regarding surrogate endpoint use and the limitations of the QIV-to-TIV bridging analysis described in Section 3.1.3 below.

Additional Immunogenicity Outcomes

Descriptive secondary endpoints demonstrated superior immune responses in the mRNA-1010 (QIV) group compared with Fluzone HD (QIV) across all four influenza strains. Specifically, the percentage of participants achieving HAI titers ≥1:40 and geometric mean fold rise (GMFR) from baseline to Day 29 were both higher in the mRNA-1010 group.

At Day 181, GMTs remained numerically higher in the mRNA-1010 group for all four strains, though confidence intervals overlapped for three strains; only A/H3N2 demonstrated non-overlapping confidence intervals (see Appendix C Table 8). The percentage of participants with seroconversion at Day 181 was also higher in the mRNA-1010 group across all four strains, with overlapping confidence intervals for all strains except A/H1N1 (see Appendix C Table 9).

Microneutralization (MN) titers were evaluated at Day 29 in a subset of 500 participants (250 per group) (see Appendix C). MN titers were higher in the mRNA-1010 group for all four strains and demonstrated positive correlation with HAI titers for each strain.

Subgroup Analyses

The Applicant conducted descriptive subgroup analyses for the primary immunogenicity endpoints. The noninferiority criteria based on GMT ratio and SCR difference would have been met across all four strains in every subgroup with a sufficient sample size for meaningful interpretation.

Post Hoc Analysis of mRNA-1010 (QIV) and mRNA-1010 (TIV)

To support licensure of mRNA-1010 (TIV) in adults 65 yoa and older, the Applicant conducted a post hoc analysis comparing Day 29 HAI GMTs between the Per-Protocol Immunogenicity Sets of Study P303 Part C (mRNA-1010 [QIV]) and Study P304 (mRNA-1010 [TIV]), restricted to participants 65 yoa and older. Noninferiority of the Day 29 HAI GMT ratio (mRNA-1010 [QIV] / mRNA-1010 [TIV]) was demonstrated for all three shared strains, with the LL of the 95% CI >0.667 (see Appendix C Table 7).

This analysis has several limitations. Studies P303 Part C and P304 were conducted in different influenza seasons using different WHO-recommended strains. Although the analysis adjusted for baseline demographics, the non-randomized design introduces potential residual confounding. For Influenza A/H1N1, the GMT ratio of 1.0 indicates no meaningful difference between formulations. For Influenza A/H3N2 and B/Victoria, mRNA-1010 (QIV) elicited lower antibody responses than mRNA-1010 (TIV), with GMT ratio point estimates and upper 95% CI bounds both <1.0, although noninferiority was met for both strains. The inclusion of B/Yamagata in the quadrivalent formulation may have reduced immune responses to A/H3N2 and B/Victoria; however, this bias would favor mRNA-1010 (TIV), not mRNA-1010 (QIV).

Despite these limitations, FDA's preliminary assessment is that mRNA-1010 (QIV) immunogenicity data may support the effectiveness of mRNA-1010 (TIV) in adults 65 yoa and older.

3.1.3. Efficacy Issues in Detail

3.1.3.1 Efficacy Issue 1: Adequacy and Clinical Meaningfulness of rVE vs. SD Comparator in Adults 65 Years of Age and older

The active comparator in Study P304 was a licensed SD inactivated influenza vaccine (Fluarix [TIV] in North America; Fluarix [QIV] in Europe and East Asia). For adults 65 yoa and older, high-dose (HD-IIV4), recombinant (RIV), and adjuvanted (aIIV4) influenza vaccines are preferentially recommended by the Advisory Committee on Immunization Practices (ACIP) over SD formulations. Accordingly, the SD comparator used in P304 is not the preferred standard of care in this age stratum.

Although mRNA-1010 (TIV) demonstrated superiority over the SD comparator in participants 65 yoa and older (rVE 27.4%; 95% CI: 12.1, 40.0), the clinical meaningfulness of an rVE advantage over a non-preferentially recommended comparator in this age group requires consideration. Specifically, the rVE does not directly establish the magnitude of benefit relative to HD, RIV or adjuvanted vaccines—the vaccines most adults 65 yoa and older would otherwise receive.[3] This limitation affects interpretation of the net clinical benefit in the 65 yoa and older population and is a key issue for Advisory Committee deliberation.

3.1.3.2 Efficacy Issue 2: Influenza B/Victoria Low Case Accrual

The rVE point estimate against influenza B/Victoria (29.1%; 95% CI: −18.5, 57.5) was consistent with the overall efficacy estimate; however, the 95% CI is wide and crosses zero, reflecting limited statistical precision due to low case counts (25 cases in the mRNA-1010 [TIV] group vs. 35 in the

[3] If none of the three preferentially recommended vaccines are available at a vaccination site, the CDC recommends that individuals 65 yoa and older should get any other age-appropriate standard influenza vaccine rather than going unvaccinated.

SD comparator group). The limited influenza B/Victoria case accrual reflects the overall dominance of influenza A strains in the 2024-2025 season (94.0% of confirmed cases). While the point estimate is directionally consistent with overall efficacy, uncertainty regarding the magnitude of protection against influenza B/Victoria cannot be resolved from single-season data alone, particularly in a season with limited influenza B circulation.

In addition, the following limitations warrant consideration:

- **Immunogenicity as supporting evidence:** Immunogenicity data may provide mechanistic support for the observed efficacy for all three vaccine strains (A/H1N1, A/H3N2, B/Victoria). However, a CoP has not been established for mFlusiva. Formal correlate of risk (CoR)/CoP analyses (see Appendix B **Secondary Immunogenicity Objectives**) are ongoing and outside the scope of this briefing document.
- **Cell-derived, mRNA-1010-matched virus as a potential source of assay-dependent immunogenicity assessment bias:** The exclusive use of Madin-Darby Canine Kidney (MDCK) cell-derived influenza virus matched to mRNA-1010 vaccine strains in HAI assays may introduce systematic bias in immunogenicity comparisons with egg-based comparator vaccines. Specifically, the use of MDCK-derived mRNA-1010-matched viruses may underestimate the comparative immunogenicity of egg-based vaccines relative to mRNA-1010, particularly for influenza A(H3N2), where egg-adaptive mutations are most frequent. Although cell-derived viruses generally better represent circulating wild-type viruses, the assay design choice to use exclusively cell-derived, mRNA-1010-matched viruses could systematically favor mFlusiva in comparative immunogenicity assessments. Review of how assay virus selection affects the relative immunogenicity of mFlusiva versus the egg-based comparator are ongoing and outside the scope of this briefing document.

3.1.3.3 Efficacy Issue 3: Adequacy of Single-Season Data and Study Population

Study P304 was originally designed to enroll participants across up to two NH influenza seasons, with an interim analysis planned at the end of the first season when approximately 70% of target cases were expected. Due to high influenza transmission during the 2024–2025 NH season, the prespecified case target of 836 was exceeded (968 cases accrued), and the study concluded after a single season. The interim analysis was therefore designated the primary efficacy analysis, using the full one-sided alpha of 2.5%.

While robust efficacy was demonstrated within a single season, the following limitations warrant consideration:

- **Generalizability across seasons:** Efficacy was evaluated under a single set of circulating strains and season-specific epidemiologic conditions. Performance in seasons with different dominant strains (e.g., influenza B-predominant seasons, or seasons with greater antigenic mismatch) is not directly assessed.
- **Antigenic mismatch:** A/H3N2 antigenic match was approximately 52–56%, and rVE improved when restricted to matched cases (30.5% vs. 22.2%), suggesting season-specific factors influenced efficacy estimates.

The following limitation on the P304 study population warrants consideration:

- **Study population generalizability:** The P304 study population was healthier and less frail than the general U.S. target population, as the study excluded immunocompromised individuals and enrolled participants with a lower prevalence of high-risk conditions (see Appendix G for definitions). In contrast, the general U.S. target population has a substantially higher prevalence of high-risk conditions (78–93%) compared with the P304 study population (57%) [Watson et al., 2025], although this difference may be partially attributable to differences in how high-risk conditions are defined.

  Relative vaccine effectiveness (rVE) was lower in high-risk P304 participants [22.3%; 95% CI: 8.0–34.3%] compared with non-high-risk participants [32.1%; 95% CI: 17.5–44.2%] (see Appendix B Table 10). The 95% confidence intervals overlap, and the study was not powered to detect a statistically significant difference in rVE between risk strata; therefore, this finding should be interpreted cautiously. Nevertheless, the direction of the difference suggests that rVE in the healthier study population may overestimate effectiveness in the general U.S. target population.

3.1.3.4 Effectiveness Issue 4: Surrogate Endpoint Reasonably Likely to Predict Benefit in Adults 65 yoa and older

Given the uncertainty of the adequacy and clinical meaningfulness of rVE of mRNA-1010 (TIV) versus SD comparator in adults 65 yoa and older (see Section 3.1.3.1), effectiveness in this population was assessed using HAI GMT and SCR as surrogate endpoints reasonably likely to predict clinical benefit. Because direct demonstration of rVE in adults 65 yoa and older versus preferred standard of care in this population is absent, if mFlusiva is approved for use in this age group, FDA will require the Applicant to conduct a Phase 4 confirmatory study to verify and describe the clinical benefit of mFlusiva in this population as a postmarketing requirement under the proposed Accelerated Approval pathway.

In Study P303 Part C, mRNA-1010 (QIV) demonstrated noninferiority and superiority to Fluzone HD (QIV)—an established high-dose comparator with demonstrated efficacy superiority over Fluzone (a SD influenza vaccine) in adults 65 yoa and older—for all eight coprimary HAI-based endpoints (GMT ratio and seroconversion rate [SCR] difference for all four vaccine-matched strains) at Day 29 postvaccination. Because licensure is sought for mRNA-1010 as a trivalent formulation (TIV) rather than the quadrivalent formulation (QIV) evaluated in P303 Part C, the Applicant conducted a post hoc QIV-to-TIV bridging analysis comparing Day 29 HAI GMTs between the per-protocol immunogenicity sets of both studies, restricted to participants 65 yoa and older. Noninferiority of the GMT ratio was demonstrated for all three shared influenza strains (lower limit of 95% CI >0.667 for each); point estimates and upper bounds of the 95% CI for A/H3N2 and B/Victoria were <1.0, indicating slightly lower antibody responses for these strains in the QIV group, consistent with potential immune competition from the B/Yamagata component. Although the studies were conducted in different influenza seasons and participants were not randomized between studies, the directionality of any immunogenic attenuation favors mRNA-1010 (TIV). FDA's assessment is that the P303 Part C immunogenicity data may be used to support effectiveness of mRNA-1010 (TIV) in this age group, subject to verification through the required Phase 4 confirmatory study.

In addition, the following limitations apply to the use of immunogenicity data as surrogate endpoints reasonably likely to predict clinical benefit in adults 65 yoa and older:

- **Status of CoR/CoP analyses:** Immunogenicity endpoints (HAI GMT and SCR) are used as primary evidence to infer effectiveness of mFlusiva in adults 65 yoa and older. As noted in Section 3.1.3.2, formal CoR/CoP analyses (see Appendix B **Secondary Immunogenicity Objectives**)are ongoing.

- **Potential source of assay-dependent immunogenicity assessment bias:** HAI assays used exclusively MDCK cell-derived, mRNA-1010-matched virus. This assay design choice may introduce systematic bias favoring mFlusiva in the surrogate endpoint comparisons used to infer effectiveness in adults 65 yoa and older. As noted in Section 3.1.3.2, analyses of the effect of assay virus selection on relative immunogenicity are ongoing.

3.2. Safety Issues

The integrated safety data for mRNA-1010 do not reveal major safety issues or deficiencies. This assessment is based on approximately 6 months of follow-up in a population that excluded immunocompromised individuals and the very frail; generalizability to these groups is limited. Rare adverse events may not be detectable in the current dataset and will require ongoing postmarket surveillance.

Three issues warrant Advisory Committee consideration:

- **Potential Safety Issue 1:** Higher solicited adverse reaction rates relative to the standard-dose comparator
- **Potential Safety Issue 2:** Numerical imbalances in SAEs between mRNA-1010 and comparator recipients: unspecified deaths (23 vs. 9), anemia SAEs (14 vs. 8), and UTI SAEs (38 vs. 22)
- **Potential Safety Issue 3:** Rare adverse events (myocarditis, GBS, neurologic events)

FDA's assessment of each issue is provided in Section 3.2.3.

3.2.1. Sources of Data for Safety

3.2.1.1 Primary Studies

The two primary sources for the safety evaluation are Study P304 (see Appendix B) and Study P303 Part C (see Appendix C), each with approximately 6 months of follow-up. These studies provide the most direct characterization of the safety profile of the mRNA-1010 formulation intended for licensure and the proposed indication.

3.2.1.2 Integrated Safety Summary (ISS)

To support a broader characterization of safety, the Applicant conducted an ISS, pooling data from all four Phase 3 studies: P301, P302, P303, and P304 (see Appendix D). The ISS includes all randomized participants 50 yoa and older who received at least one study injection. The ISS population comprised 71,916 participants: 35,965 mRNA-1010 recipients and 35,951 SD/HD comparator recipients. Median follow-up was 198 days in both groups (range: 1–449 days, mRNA-1010; 1–445 days, SD/HD comparator). Study completion rates were high and comparable (95.1% vs. 95.2%). The pooled mRNA-1010 group includes participants from trivalent (TIV) and quadrivalent (QIV) formulations across studies; the pooled comparator group includes standard-dose and high-dose licensed influenza vaccines (Fluarix TIV/QIV; Fluzone HD QIV). Adverse events were coded using MedDRA version 25.0.

3.2.2. Safety Summary

The pooled ISS analysis across all four Phase 3 studies did not identify adverse event patterns definitively indicative of a safety concern for mFlusiva. Table 6 summarizes key findings that

characterize the overall safety profile. SAEs, deaths, and AESIs are summarized in the text below.

Table 6. Safety Profile of mRNA-1010 versus Comparator: Summary of Key Findings from Study P304[a,b,c] and Pooled Phase 3 Studies[d,e,f,g,h]

Safety Domain	mRNA-1010	Comparator	FDA Assessment
Solicited Local Reactions (7 days)[a]	67.5%	32.1%	More frequent; Grade 3: 1.7%; median 2 days
Solicited Systemic Reactions (7 days)[b]	58.0%	32.4%	More frequent; Grade 3: 5.5%; median 2 days
Unsolicited AEs (28 days)[c]	5.9%	5.7%	Balanced
Serious Adverse Events (median follow-up 198 days)[d]	3.1%	2.9%	Balanced; <0.1% assessed as related
Deaths (median follow-up 198 days)[d]	0.3%	0.3%	Balanced; none assessed as related
AESIs (median follow-up 198 days)[d]	0.1%	0.1%	Balanced
Myocarditis/Pericarditis[d]	10 cases	7 cases	No signal; no cases in 42-day risk window
Guillain-Barré Syndrome[d]	1 case (Day 134)	0 cases	Outside 42-day risk window; not related
Bell's Palsy[d]	1 case	4 cases	No signal; 1 case in each group in 42-day risk window

[a]Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.3.1.2.1.f. Data cutoff: April 30, 2025.
[b]Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.3.1.2.1.8.f. Data cutoff: April 30, 2025.
[c]Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.3.1.2.1.f and Appendix D (Integrated Safety Summary, pooled Phase 3 studies). Data cutoff: August 21, 2025 (P304); June 24, 2024 (ISS).
[d]Source: Adapted from STN 125869/0, Integrated Safety Summary (see Appendix below), pooled data from Studies P301, P302, P303, and P304. Data cutoff: June 24, 2024. Median follow-up was 198 days in both groups (range: 1–449 days in the mRNA-1010 group; 1–445 days in the SD/HD comparator group). Study completion rates were high and comparable: 95.1% in the mRNA-1010 group and 95.2% in the SD/HD comparator group.

3.2.2.1 Serious Adverse Events (SAEs)

Within 28 days postvaccination, SAEs occurred in 0.5% of mRNA-1010 recipients and 0.5% of SD/HD comparator recipients. Over the full study period (median follow-up of 198 days), SAEs were reported in 3.1% vs. 2.9% of participants, respectively. The most frequently reported SAEs were in the infections and infestations SOC (0.7% vs. 0.6%). The most frequently reported SAEs by PT included pneumonia (36 vs. 32), COPD (35 vs. 24), and cerebrovascular accident (32 vs. 29), all occurring in <0.1% of participants in either group. Six PTs with SAEs occurring in at least four participants per group had risk differences with 95% confidence intervals (CIs) excluding zero. Three PTs were numerically higher in the mRNA-1010 group: death (unspecified) (23 vs. 9), UTI (25 vs. 12), and anemia (9 vs. 2), all reported in <0.1% of participants in either group, discussed below in Section 3.2.3.2.

Nine mRNA-1010 recipients (<0.1%) and 3 SD/HD comparator recipients (<0.1%) had at least one SAE assessed as vaccine-related by the Investigator. See Appendix D Investigator-Assessed Vaccine-Related SAEs.

3.2.2.2 Deaths

Over the full study period, deaths were reported in 102 mRNA-1010 recipients (0.3%) and 97 SD/HD comparator recipients (0.3%). Within 28 days of vaccination, deaths were few and comparable across groups (13 vs. 14). By System Organ Class (SOC), deaths were most commonly attributed to cardiac disorders (24 vs. 30). A numerical imbalance was identified in preferred term (PT) death (unspecified cause): 23 mRNA-1010 recipients versus 9 comparator recipients. When pooling related death categories (sudden death, sudden cardiac death, and unspecified fatal events), the imbalance widened to 29 mRNA-1010 recipients versus 12 comparator recipients. Detailed case-level analyses are presented in Section 3.2.3.2.1 and **Appendix D.1. Deaths**

The interpretation of this imbalance is constrained by the absence of autopsy data in the mRNA-1010 group, which limits definitive cause-of-death ascertainment. FDA's assessment, based on temporal distribution of events, overall mortality balance across the trial, and documented pre-existing comorbidities, suggests that this imbalance is unlikely to represent a causal relationship with vaccination.

3.2.2.3 Adverse Events of Special Interest (AESIs)

Through the full study period, AESIs were reported in 36 (0.1%) vs. 37 (0.1%) participants, respectively. Through 28 days postvaccination, AESIs were reported in 7 mRNA-1010 recipients (<0.1%) and 4 SD/HD comparator recipients (<0.1%). There were no cardiac AESIs (myocarditis, pericarditis, myopericarditis) reported in the 42-day risk window. Beyond the 42-day risk window and throughout the studies, cardiac AESIs (myocarditis, pericarditis, myopericarditis) were reported in 10 mRNA-1010 recipients and 7 SD/HD comparator recipients; Cardiac Event Adjudication Committee (CEAC)-confirmed cases were balanced (4 vs. 3). No cases of GBS were reported in the SD/HD comparator group; one GBS event (PT: demyelinating polyneuropathy) occurred in the mRNA-1010 group at Day 134, outside the established 42-day risk window. Bell's palsy within the 42-day risk window was reported in one participant per group. See Appendix D.3.

3.2.3. Safety Issues in Detail

See Appendix D for details.

3.2.3.1 Higher Solicited Adverse Reaction Rates vs. Standard-Dose Comparator

Solicited local and systemic adverse reaction rates were higher in mRNA-1010 recipients compared with standard-dose comparator recipients, consistent with the reactogenicity profile expected of an mRNA-based vaccine. Solicited adverse reactions in mRNA-1010 recipients were predominantly mild to moderate in severity (Grade 1–2), with a median duration of approximately 2 days. Grade 3 solicited systemic adverse reactions were reported in 5.5% of mRNA-1010 recipients compared with 0.9% of SD comparator recipients; no Grade 4 solicited systemic adverse reactions were reported. These reactions are transient and expected to resolve without medical intervention for the majority of recipients. Detailed solicited adverse reaction data and FDA assessments are presented in the primary study review for Study P304. Solicited adverse reaction rates were also higher in mRNA-1010 (QIV) recipients compared with high-dose comparator recipients (see Study P303 Part C). FDA considers the reactogenicity profile acceptable for the intended population and consistent with the benefit-risk assessment for mRNA-1010.

3.2.3.2 Numerical Imbalances in Unspecified Deaths, Anemia SAEs, and UTI SAEs

3.2.3.2.1 **Deaths of Unspecified Cause**

A numerical imbalance was identified in the PT death (unspecified): 23 mRNA-1010 recipients vs. 9 SD/HD comparator recipients. An expanded analysis pooling the PTs of death, sudden death, and sudden cardiac death identified 29 mRNA-1010 recipients and 12 SD/HD comparator recipients with unspecified fatal events. Median time to onset was approximately 131 days (range: 2–319 days) in the mRNA-1010 group and 87 days (range: 9–343 days) in the SD/HD comparator group; deaths within 28 days of vaccination under these PTs were few and similar across groups (3 vs. 2). Approximately 60% of participants with unspecified fatal events were ≥65 yoa. Nearly all had multiple pre-existing comorbidities, including hypertension, diabetes mellitus, chronic kidney disease, hyperlipidemia, coronary artery disease, atrial fibrillation, prior myocardial infarction, congestive heart failure, and COPD. Causes of death were predominantly recorded as unknown or natural causes. No autopsies were conducted in the mRNA-1010 group deaths.

One death occurring on Day 2 in Study P303 Part A — in a 76-year-old female with significant cardiac history [prior coronary artery bypass graft (CABG), atrial fibrillation, type 2 diabetes mellitus] — was assessed as vaccine-related by the Investigator based on temporality. FDA considers the participant's underlying cardiac disease a more plausible alternative etiology, though a contribution from a vaccine-related inflammatory response cannot be fully excluded.

FDA Assessment: The temporal distribution of deaths from unspecified causes does not suggest a causal relationship to vaccination. Deaths of unspecified cause within 28 days of vaccination were few and comparable across groups (3 in the mRNA-1010 group vs. 2 in the SD/HD comparator group), and the remaining deaths were distributed across later time intervals without apparent pattern or clustering. The overall balance in all-cause mortality and in cause-specific deaths by PT further supports this interpretation. Also supporting this assessment are the presence of extensive pre-existing comorbidities among study participants, lack of imbalance observed in cardiac SAEs, including in cardiac arrhythmias, and the lack of investigator assessment of relatedness for these events, with one exception. Considering the totality of available evidence, the numerical imbalance in unspecified deaths is unlikely to represent a vaccine safety signal for mRNA-1010.

3.2.3.2.2 **Anemia SAEs**

An expanded analysis across related anemia PTs (anemia of chronic disease, blood loss anemia, hypochromic anemia, iron deficiency anemia, normocytic anemia) identified 14 mRNA-1010 recipients and 8 SD/HD comparator recipients with anemia SAEs. No events were assessed as vaccine-related by the Investigator. Most events occurred more than 90 days post-injection, with no temporal clustering. All mRNA-1010 recipients with anemia SAEs had identifiable alternative etiologies, including iron deficiency, gastrointestinal bleeding, renal or hepatic disease, serious infection, and concomitant medication use. A review of medically attended adverse events (MAAEs) of anemia in Study P304 identified comparable rates between groups (31 mRNA-1010 [TIV] vs. 30 SD comparator recipients).

FDA Assessment: The late onset, absence of temporal clustering, presence of plausible alternative etiologies, and balanced MAAE rates in Study P304 collectively indicate that the numerical imbalance in anemia SAEs is unlikely to reflect a causal association with mRNA-1010.

3.2.3.2.3 **Urinary Tract Infection (UTI) SAEs**

An expanded analysis across related UTI PTs (urinary tract infection bacterial, *Escherichia* urinary tract infection, cystitis, kidney infection, pyelonephritis, acute pyelonephritis, urosepsis) identified 38 mRNA-1010 recipients and 22 SD/HD comparator recipients with UTI SAEs. No events were assessed as vaccine-related by the Investigator. Median time to onset was 135 days (mRNA-1010) and 112.5 days (SD/HD comparator); no temporal clustering was observed. The majority of participants in both groups had established UTI risk factors, including advanced age, female sex, postmenopausal status, diabetes mellitus, obstructive uropathies, chronic kidney disease, and use of concomitant medications associated with increased UTI risk. MAAEs of UTI in Study P304 were comparable between groups (153 mRNA-1010 [TIV] vs. 158 SD comparator recipients).

FDA Assessment: The late and non-clustered onset, the presence of recognized risk factors in the majority of affected participants, and the balanced MAAE rates in Study P304 indicate that the numerical imbalance in UTI SAEs is unlikely to reflect a causal association with mRNA-1010.

3.2.3.3 Rare Adverse Events

The primary safety database for mRNA-1010 is based on Studies P303 Part C and P304. While this sample size is adequate to characterize relatively frequent acute and subacute safety profile, it is insufficient to detect rare adverse events, including myocarditis, Guillain-Barré syndrome (GBS), and other neurological events of interest. Current AESI analyses for myocarditis/pericarditis and new-onset or worsening neurological disease identified no meaningful differences between the mRNA-1010 and SD/HD comparator groups, though the power to detect any rare adverse events is limited by sample size.

FDA Assessment: Post-licensure monitoring will be required to fully characterize the risk of rare adverse events. Routine postmarket pharmacovigilance activities will be the primary mechanism for ongoing safety monitoring following licensure.

3.3. Risk Mitigation

3.3.1 Postmarketing Confirmatory Phase 4 Study

Under the Accelerated Approval regulations, a Phase 4 confirmatory study is required to verify and describe the clinical benefit of mFlusiva in individuals 65 yoa and older. The Applicant has proposed to conduct a Phase 4, cluster-randomized, active-controlled, pragmatic study to evaluate the relative vaccine effectiveness of mFlusiva compared with agreed upon CDC-preferentially recommended vaccine in U.S. adults 65 yoa and older (see Appendix H). The study protocol and proposed timeline are currently under review and are the subject of ongoing discussions between FDA and the Applicant.

3.3.2 Pharmacovigilance Activities

Moderna submitted a Pharmacovigilance Plan (Version 1.0, dated January 28, 2026) to monitor safety concerns that could be associated with mFlusiva. The Applicant identified no important identified or potential risks and no missing information requiring additional pharmacovigilance beyond routine surveillance at this time.

The Applicant will conduct routine postmarketing pharmacovigilance surveillance activities per 21 CFR 600.80, including submissions of periodic safety reports (Periodic Adverse Experience Reports) to monitor for and assess any emerging risks associated with the vaccine.

Although no safety concerns were identified in the pre-licensure clinical program for the protocol-defined AESIs, the Applicant plans to provide aggregate safety assessments (based on interval and cumulative data) of the following AESIs in their periodic safety reports for the first 3 years postapproval:

- Thrombocytopenia
- Guillain-Barré syndrome
- Acute disseminated encephalomyelitis
- Idiopathic peripheral facial nerve palsy (Bell's palsy)
- Seizures, including but not limited to febrile seizures and/or generalized seizures/ convulsions
- Anaphylaxis
- Myocarditis
- Pericarditis
- Myopericarditis

The Applicant identified these AESIs as medical concepts that are generally of interest in vaccine safety surveillance as well as events inconsistently associated with previously licensed influenza vaccines. Aggregate safety assessments for AESIs will include review of available safety data from spontaneous AE reporting, postmarketing studies, and literature reports.

Because no important identified or potential risks and no missing information were identified in the pre-licensure safety database, the applicant has not proposed any additional pharmacovigilance studies at this time. The details of the pharmacovigilance plan remain subject to discussion between FDA and the Applicant.

Under the National Childhood Vaccine Injury Act (NCVIA) and implementing regulations, health care providers are required to report events listed in the VAERS Reportable Events Table occurring within designated time intervals following vaccination, as well as manufacturer-listed contraindications to further vaccination (https://vaers.hhs.gov/resources/infoproviders.html).

The NCVIA also requires dissemination of CDC-issued Vaccine Information Statements (VISs) to vaccine recipients prior to administration of covered vaccines.

4. Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	Influenza is a high-burden, vaccine-preventable infectious disease with significant morbidity and mortality, disproportionately affecting adults ≥65 years of age, who account for ~75% of influenza-related deaths in the U.S. The condition is associated with serious complications including pneumonia, myocarditis, and multi-organ failure.	Serious, high-burden disease with substantial unmet need, particularly in older adults. The magnitude of influenza-related morbidity and mortality in the target population provides important context for evaluating the benefit-risk profile of mFlusiva.
	The ever-present threat of pandemic Influenza A as a result of a substantial	There is a need for manufacturing technologies capable of rapid strain

	antigenic shift creates urgent, unmet medical need for expedited vaccine development and deployment to prevent widespread morbidity and mortality in at-risk populations.	reformulation, particularly to respond to antigenic shifts.
Current Treatment Options	Annual influenza vaccination is the primary preventive strategy. CDC preferentially recommends HD (Fluzone HD), adjuvanted (Fluad), or recombinant (FluBlok) vaccines for adults ≥65 yoa. Standard-dose vaccines achieve up to 60% effectiveness; efficacy declines further with antigenic mismatch. Antivirals are available for treatment, but vaccination remains preferred prevention.	Existing vaccines have variable effectiveness, particularly for older adults. There is a need for vaccines with improved effectiveness, particularly when antigenically mismatched to circulating strains.
Benefits	Study P304: rVE 26.6% [95% CI: 16.7, 35.4] vs. SD comparator in adults ≥50 yoa. Consistent rVE across age subgroups (25.3%–28.0%) and influenza strains (22.2%–29.6%). Healthcare outcome rVE 47.9% [95% CI: 12.8, 68.9]. Study P303 Part C: Superior HAI GMT and SCR vs. Fluzone HD for all four vaccine-matched strains in adults ≥65 yoa; immune persistence at Day 181.	**Points to Consider:** (1) Do the primary endpoint, age subgroup, and strain-specific rVE results from Study P304 demonstrate clinically meaningful efficacy of mFlusiva in adults 50 through 64 yoa? (2) Do the immunogenicity results from Study P303 Part C provide a reasonable basis to predict clinical benefit of mFlusiva in adults ≥65 yoa?
Risks and Risk Management	Solicited ARs more frequent than comparators (local: 67.5% vs. 32.1%; systemic: 58.0% vs. 32.4%) but predominantly mild-moderate, median duration ~2 days. SAEs balanced (3.1% vs. 2.9%). No myocarditis/pericarditis within 42 days. Numerical imbalances in unspecified deaths, anemia SAEs, and UTI SAEs in ISS; assessed as unlikely to be vaccine-related. Single-season follow-up; sparse data in immunocompromised or very frail older adults; no concomitant vaccine data. Risk mitigation: Phase 4 confirmatory trial; routine pharmacovigilance per 21 CFR 600.80; aggregate AESI monitoring; VAERS reporting; VIS distribution.	**Point to Consider:** Do the available data indicate that the safety profile of mFlusiva is adequately characterized, that identified risks are acceptable, and that residual risks can be appropriately monitored and managed through postmarketing pharmacovigilance?
Summary of Benefit-Risk	mFlusiva demonstrated superior rVE vs. SD comparator in adults ≥50 yoa and superior immunogenicity vs. a CDC-preferred HD comparator in adults ≥65 yoa. The reactogenicity profile, while elevated relative to comparators, appears acceptable.	**Voting questions:** Do the benefits of mFlusiva outweigh its risks for the prevention of influenza disease in adults 50 through 64 years of age?

	SAEs, deaths, and AESIs are balanced. Evidence gaps in frail and high-risk older adults, special populations and duration of protection are acknowledged. A Phase 4 confirmatory study and postmarketing pharmacovigilance plan are under review.	Do the benefits of mFlusiva outweigh its risks for the prevention of influenza disease in adults 65 years of age and older?

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Appendix A – Clinical Studies Submitted in Support of mRNA-1010 Efficacy and Safety Determinations

Study Number (Country); Study Dates	Study Design	Total mRNA-1010 Recipients Total Comparator Recipients	Formulation and Dose Levels of mRNA-1010 Evaluated
mRNA-1010-P304 (Belgium, Bulgaria, Canada, Estonia, Finland, Georgia, Germany, South Korea, Taiwan, UK, U.S.) September 16, 2024 to August 21, 2025	Phase 3, randomized, stratified, observer blinded (participant and assessor-blind), active-controlled, safety, efficacy, and immunogenicity study in adults ≥50 years of age.	mRNA-1010 (TIV): N=20,350 SD comparator (TIV or QIV): N=20,353	mRNA-1010.4 (TIV) 37.5 µg
mRNA-1010-P303 (U.S.) Part A*: April 17, 2023 to November 28, 2023 Part B*: November 13, 2023 to June 20, 2024 Part C: November 13, 2023 to June 24, 2024	Phase 3, randomized, stratified, observer blind, active-controlled, immunogenicity, reactogenicity, and safety study. Part A*: adults ≥18 years Part B*: adults 18 to <65 years Part C: adults ≥65 years	Part A*: mRNA-1010 (QIV): N=1220 SD comparator (QIV): N=1180 Part B*: mRNA-1010 (QIV): N=1492 SD comparator (QIV): N=1488 Part C: mRNA-1010 (QIV): N=1502 Fluzone HD (QIV): N=1490	Part A*: mRNA-1010.6[#] (QIV) 50 µg Part B*: mRNA-1010.4 (QIV) 50 µg Part C: mRNA-1010.4 (QIV) 50 µg
mRNA-1010-P101* (U.S.) June 28, 2021 to September 27, 2022	Phase 1/2, randomized, stratified, observer blind, dose-ranging safety, reactogenicity, and immunogenicity study in healthy adults ≥18 years of age.	mRNA-1010 (original, QIV): N=736 Afluria (QIV): N=104 Placebo: N=45	mRNA-1010 (original, QIV) 6.25 µg 12.5 µg 25 µg 50 µg 100 µg 200 µg
mRNA-1010-P301* (Argentina, Australia, Colombia, Panama, and Philippines) June 6, 2022 to September 4, 2023	Phase 3, randomized, stratified, observer blind, active-controlled, immunogenicity, reactogenicity, and safety study in adults ≥18 years of age.	mRNA-1010 (original, QIV): N=3035 SD comparator (QIV): N=3048	mRNA-1010 (original, QIV) 50 µg
mRNA-1010-P302* (Bulgaria, Canada, Denmark, Estonia, Germany, Poland, Spain, Taiwan, UK, U.S.) September 14, 2022 to January 5, 2024	Phase 3, randomized, observer-blind, active-controlled, safety, reactogenicity, and efficacy, study in adults ≥50 years of age.	mRNA-1010 (original, QIV): N=11,210 SD comparator (QIV): N=11,200	mRNA-1010 (original, QIV) 50 µg

Source: Adapted from STN 125869/0, Clinical Overview.
Abbreviations: HD, high dose; QIV, quadrivalent influenza vaccine; SD, standard dose; TIV, trivalent influenza vaccine; UK, United Kingdom; U.S., United States
* P301, P302, and P303 Parts A and B contribute to the Integrated Summary of Safety only and will not be discussed individually in this memo. P101 did not contribute substantially to the overall safety and effectiveness conclusions and also will not be discussed individually in this memo
[#] mRNA-1010.4 and mRNA1010.6 are identical, with the only difference being the scale of manufacturing. They both include optimized influenza B antigen(s) encoding 2 stabilizing point mutations in non-surface exposed regions that do not impact antigenic epitopes.

Appendix B – Study P304 Efficacy and Safety

Study mRNA-1010-P304

NCT06602024

Title: "A Phase 3, randomized, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 candidate seasonal influenza vaccine compared with a licensed inactivated seasonal influenza vaccine in adults ≥50 years of age"

Study Overview

Study mRNA-1010-P304 (P304) was a Phase 3, randomized, observer-blind (participant- and assessor-blind), active-controlled study evaluating the safety, efficacy, and immunogenicity of trivalent mRNA-1010.4 seasonal influenza vaccine (mRNA-1010 [TIV]) compared with a licensed standard-dose trivalent or quadrivalent inactivated seasonal influenza vaccine (SD comparator [TIV] or SD comparator [QIV], respectively) for the prevention of influenza disease caused by any influenza A or B strain in adults ≥50 yoa.

The study was initiated on September 16, 2024, and completed on August 21, 2025. The primary efficacy and immunogenicity analyses used a data cutoff of April 30, 2025 (end of influenza season), with a database lock (DBL) of June 3, 2025. Supportive end-of-study (EOS) analyses used a data cutoff of August 21, 2025, with a DBL of September 16, 2025.

Objectives

Primary Objectives

Primary Efficacy Objective

To evaluate the relative vaccine efficacy (rVE) of mRNA-1010 (TIV) versus the SD comparator against RT-PCR–confirmed protocol-defined influenza-like illness (ILI) (see Appendix B Table 1 for case definitions) caused by any influenza A or B strain.

> **Endpoint:** First episode of RT-PCR–confirmed protocol-defined ILI with onset at least 14 days after study intervention through the end of the influenza season, caused by any influenza A or B strain.
>
> **Statistical Criterion for Success:** Noninferiority (NI) was demonstrated if the lower limit (LL) of the two-sided 95% confidence interval (CI) of rVE of mRNA-1010 relative to the SD comparator was greater than −10%. Once NI was demonstrated, the same endpoint was tested sequentially for superiority (LL of two-sided 95% CI of rVE >0%) and then super-superiority (LL of two-sided 95% CI of rVE >9.1%).

Primary Safety Objective

To evaluate the safety and reactogenicity of mRNA-1010 (TIV).

> **Endpoints:** Solicited local and systemic adverse reactions (ARs) through Day 7; unsolicited adverse events (AEs) through Day 28; and serious adverse events (SAEs), medically attended adverse events (MAAEs), AEs leading to study discontinuation, and adverse events of special interest (AESIs) through Month 6/Day 181.

Secondary Objectives

Secondary Efficacy Objectives

To evaluate rVE of mRNA-1010 (TIV) versus the SD comparator against RT-PCR–confirmed modified Centers for Disease Control and Prevention (CDC)-defined ILI (see Appendix B Table 1 for case definitions) caused by any influenza A or B strain.

> **Endpoint:** First episode of RT-PCR–confirmed modified CDC-defined ILI with onset at least 14 days after study intervention through the end of the influenza season, caused by any influenza A or B strain.
>
> **Statistical Criteria for Success:** Same sequential testing for NI, superiority, and super-superiority, and same success margins, as the primary efficacy endpoint.

To evaluate rVE of mRNA-1010 (TIV) versus the SD comparator against RT-PCR–confirmed protocol-defined ILI or modified CDC-defined ILI caused by influenza A or B strains with antigenic match to the vaccine strains.

> **Endpoint:** First episode of RT-PCR–confirmed protocol-defined ILI or modified CDC-defined ILI with onset at least 14 days after study intervention through the end of the influenza season, caused by influenza A or B strains with antigenic match to the vaccine strains.
>
> **Statistical Criteria for Success:** Same sequential testing and success margins as the primary efficacy endpoint.

Secondary Immunogenicity Objectives (Descriptive Analyses; No Hypothesis Testing)

To evaluate the humoral immunogenicity of mRNA-1010 (TIV) relative to the SD comparator against vaccine-matched influenza A and B strains in a prespecified subset of approximately 2,400 participants.

> **Endpoints, as measured by hemagglutinin inhibition (HAI) assay:**
>
> - Geometric mean titers (GMTs) at Day 29
> - Proportion of participants achieving seroconversion at Day 29
> - Proportion of participants with an HAI titer ≥1:40 at Day 29
> - Geometric mean fold rise (GMFR) from Day 1 (Baseline) to Day 29

To evaluate HAI titers as a correlate of risk (CoR) and correlate of protection (CoP) against RT-PCR–confirmed protocol-defined ILI for mRNA-1010 (TIV) and the SD comparator.

> **Endpoints:**
>
> - HAI titers at Day 29
> - First episode of RT-PCR–confirmed protocol-defined ILI with onset at least 14 days after study intervention through the end of the influenza season, caused by any influenza A or B strain

Select Exploratory Objectives (Descriptive Analyses; No Hypothesis Testing)

To evaluate rVE of mRNA-1010 (TIV) versus the SD comparator against RT-PCR–confirmed CDC-defined ILI, World Health Organization (WHO)-defined ILI, and ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302) (see Appendix B Table 1 for case definitions) caused by any influenza A or B strain.

Endpoints: First episode of each respective RT-PCR–confirmed ILI definition with onset at least 14 days after study intervention through the end of the influenza season, caused by any influenza A or B strain.

To evaluate the humoral immunogenicity of mRNA-1010 (TIV) relative to the SD comparator against vaccine-matched influenza A and B strains as measured by microneutralization (MN) assay in a subset of participants.

Endpoints, as measured by MN assay:

- GMT at Day 29
- GMFR from Day 1 (Baseline) to Day 29

To evaluate rVE of mRNA-1010 (TIV) versus the SD comparator in preventing health outcomes associated with protocol-defined ILI.

Endpoints: Healthcare encounters (e.g., hospitalization, emergency room [ER] visit, outpatient visit) beginning within 30 days after respiratory symptom onset.

Design

Study P304 was conducted at 301 sites in 11 countries across North America, Europe, and East Asia. A total of 40,805 participants were randomized 1:1 to receive a single intramuscular injection of either mRNA-1010 (TIV) or the SD comparator.

The trivalent SD comparator was the preferred comparator and was used in North America; the quadrivalent SD comparator was used in countries where the trivalent formulation was not available (Europe and East Asia). All participants in the mRNA-1010 group received the trivalent formulation. The influenza strains encoded in mRNA-1010 (TIV) were aligned with FDA recommendations for the 2024–2025 Northern Hemisphere influenza vaccine for cell- or recombinant-based vaccines.

Randomization was stratified by age category at screening (50 to <65 yoa or ≥65 yoa) and by influenza vaccination status in the previous influenza season (received or not received). Participants were followed through the end of the influenza season, approximately 6 to 8 months after vaccination.

The study enrolled healthy adults and those with certain stable chronic diseases. Participants with immunocompromising conditions, congenital or acquired immunodeficiency, recent malignancy, history of Guillain-Barré syndrome (GBS) after influenza vaccination, history of myocarditis or pericarditis within the past 180 days, or a positive test or treatment for influenza within the past 180 days were excluded.

Following the screening visit, participants completed up to two scheduled clinic visits (Baseline and Day 29) and four scheduled telephone visits (Days 8, 91, 181, and the End of Influenza Season Visit). The End of Study (EOS) occurred at either the Day 181 Visit or the End of Influenza Season Visit, whichever was later.

Evaluation of Efficacy

All participants completed a symptom electronic diary (eDiary) twice weekly from Day 1 through the end of the influenza season (April 30, 2025) and were prompted to report respiratory symptoms as they occurred. Participants with respiratory symptoms were instructed to contact study staff immediately; staff followed up within 24 hours to review symptoms and confirm protocol-defined respiratory illness.

Participants meeting criteria for protocol-defined respiratory illness (Table 2) underwent an unscheduled illness visit that included assessment of symptom history and onset dates, vital signs, healthcare provider visits related to the illness, and new or modified concomitant medications (e.g., antivirals). Nasopharyngeal (NP) swabs were collected at the visit, prior to antiviral initiation and preferably within 72 hours of symptom onset (up to 5 days was acceptable). Swabs could be performed at home by qualified personnel.

If an NP swab could not be obtained, any available influenza test results from outside the study were captured in the electronic Case Report Form (eCRF). Results from specimens obtained using a local diagnostic test at an external healthcare visit were accepted if the results were obtained using FDA-cleared or FDA-approved kits or were performed in Clinical Laboratory Improvement Amendments (CLIA)-certified (or equivalent) laboratories.

NP swabs were tested using an RT-PCR–based assay for influenza A and B and other respiratory viruses. Influenza-positive samples underwent additional characterization by genetic sequencing and/or viral culture with antigenicity testing. Repeat swabs were not required within 14 days of a prior collection for participants with ongoing symptoms. Study staff contacted participants twice weekly throughout the illness to collect information on symptom duration, healthcare utilization, and concomitant medications.

The study protocol was designed to enroll participants across up to two Northern Hemisphere (NH) influenza seasons (NH 2024/2025 and NH 2025/2026), with an interim analysis planned at the end of the first influenza season when approximately 70% of target cases were expected to have accrued. High influenza transmission during the 2024/2025 NH season resulted in 968 cases accruing by the end of that season—exceeding the study target of 836 cases—and therefore the study did not continue into a second influenza season.

The interim analysis at the end of the 2024/2025 NH influenza season used the full one-sided alpha of 2.5% to evaluate the primary efficacy endpoint and constitutes the primary efficacy analysis for this study. Additional descriptive analyses were conducted after all participants completed the study.

The study employed a hierarchical sequential testing strategy across nine pre-specified null hypotheses to control the Type I error rate. Testing progressed through three sequential tiers: (1) rVE against protocol-defined ILI caused by any strain; (2) rVE against modified CDC-defined ILI caused by any strain; and (3) rVE against protocol-defined ILI with antigenic match. Within each tier, hypotheses were tested sequentially for NI, superiority, and super-superiority. Advancement to the next hypothesis required rejection of the preceding one.

Case Definitions

The case definitions for the efficacy endpoints in Study P304 are shown in Appendix B Table 1.

Appendix B Table 1. Case Definitions for Respiratory Illness, ILI, and Confirmed Influenza Illness

Term	Case Definition
Protocol-defined respiratory illness	New onset or worsening (>24 hours) of at least 1 of the following symptoms: sneezing, nasal congestion, rhinorrhea, sore throat, cough, sputum production, wheezing, or difficulty breathing.
Protocol-defined ILI	At least 1 systemic symptom (temperature >37.2°C (>99.0°F), chills, feverish, tiredness, headaches, or myalgia). AND at least 1 respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing).
Modified CDC-defined ILI	Body temperature >37.2°C (>99.0°F) accompanied by cough and/or sore throat
CDC-defined ILI	Body temperature ≥37.8°C (≥100°F) accompanied by cough and/or sore throat (CDC 2017).
WHO-defined ILI	An acute respiratory infection with measured fever of ≥38.0°C (100.4°F) and cough, with onset within the last 10 days (WHO 2014).
ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302)	Body temperature ≥37.5°C (≥99.5°F) accompanied by at least 1 respiratory illness symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing).
RT-PCR–confirmed influenza illness	Positive influenza result by RT-PCR.
Culture-confirmed influenza illness[a]	Positive influenza result by viral culture.

Source: Adapted from STN 125869/0, Study P304 Protocol Table 4.
Abbreviations: CDC, U.S. Centers for Disease Control and Prevention; ILI, influenza-like illness; RT-PCR, reverse transcription polymerase chain reaction; WHO, World Health Organization
[a] Viral cultures were performed on samples with a positive influenza result by RT-PCR assay performed by the central laboratory.

Evaluation of Immunogenicity

All participants provided blood samples on Day 1 (Baseline, prior to study intervention) and Day 29. Samples from a prespecified subset of approximately 2,400 participants from North America (where the SD comparator [TIV] was used) were analyzed for HAI titers at Baseline and Day 29 for humoral immunogenicity endpoints. All immunogenicity analyses were descriptive; no hypothesis testing was performed.

For each strain, HAI titers were summarized as GMTs with 95% CIs at Baseline and Day 29. CIs were calculated based on the t-distribution of log-transformed values, then back-transformed to the original scale. The GMFR with 95% CI was reported at Day 29 relative to Baseline.

An analysis of covariance (ANCOVA) model—adjusting for randomization stratification factors, log-transformed Baseline HAI titers (covariate), and intervention group (fixed variable)—was used to estimate model-based GMTs, GMT ratios, and corresponding two-sided 95% CIs at Day 29 for mRNA-1010 (TIV) versus the SD comparator.

Seroconversion rates (SCRs) and the proportion of participants with HAI titers ≥1:40 at Day 29 were reported with 95% CIs calculated using the Clopper-Pearson method. Between-group SCR differences were reported with 95% CIs calculated using the Miettinen-Nurminen method.

As an exploratory analysis, the same ANCOVA model and descriptive statistics were applied to Day 29 GMTs measured by MN assay, and the correlation between HAI and MN antibody levels was assessed.

The analysis of HAI as a CoR/CoP used a case-cohort study design conducted on the per-protocol correlate analysis set (PPCAS). This analysis is still under review and is outside the scope of this briefing document.

Evaluation of Safety

Study oversight included Institutional Review Board (IRB) or Independent Ethics Committee (IEC) review. An independent Data Safety Monitoring Board (DSMB) reviewed blinded and unblinded safety data on a routine basis, made recommendations based on prespecified rules in the DSMB charter, and reviewed the results of the interim analysis. An independent Cardiac Event Adjudication Committee (CEAC) reviewed investigator-reported suspected cases of myocarditis, pericarditis, or myopericarditis to determine whether they met CDC criteria (see Appendix B) for a 'probable' or 'confirmed' event, and to assess severity.

A subset of approximately 6,000 participants reported solicited local and systemic ARs in a Reactogenicity eDiary from Day 1 through Day 7 (the day of vaccination and the 6 subsequent days). Solicited local ARs monitored were injection site pain, erythema, swelling/induration, and axillary swelling or tenderness ipsilateral to the injection site. Solicited systemic ARs monitored were headache, fatigue, myalgia, arthralgia, nausea/vomiting, fever, and chills.

Unsolicited AEs occurring within 28 days after vaccination (the day of vaccination and 27 subsequent days) were recorded. All AEs, SAEs, AESIs, and MAAEs were followed at least monthly until resolution, stabilization, the event was otherwise explained, or the participant was lost to follow-up.

Analysis Populations

The analysis populations used in Study P304 are defined in Appendix B Table 2.

Appendix B Table 2. Analysis Sets

Analysis Set	Description
Randomization Set	All participants who were randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received any study intervention. Participants were analyzed according to the study intervention group to which they were randomized.
Per Protocol (PP) Set	All participants in the FAS, excluding those with important protocol deviations that could adversely impact efficacy (e.g., disease or therapeutic intervention that might cause suboptimal response to study intervention). The PP Set was used as the primary analysis set for efficacy endpoints. Participants were analyzed according to the study intervention group to which they were randomized.
Immunogenicity Subset	A prespecified subset of participants from North America in the FAS who received TIV and have baseline and Day 29 antibody assessments by HAI assay. Participants were analyzed according to the study intervention group to which they were randomized.

Analysis Set	Description
Per Protocol Immunogenicity Set (PPIS)	All participants in the Immunogenicity Subset who received the planned dose of study intervention and had no important protocol deviations that impact the immunogenicity assessment. Participants with RT-PCR–confirmed influenza infection between Day 1 (Baseline) and Day 29 were removed from the PPIS. The PPIS was used for all analyses of immunogenicity unless specified otherwise. Participants were analyzed according to the study intervention group to which they were randomized.
PPIS Microneutralization (MN) Subset	A stratified random subset of approximately 500 participants selected from the PPIS for exploratory MN immunogenicity analyses.
Safety Set	All randomized participants who received any study intervention. The Safety Set was used for all analyses of safety except for solicited ARs. Participants were analyzed according to the study intervention they actually received.
Solicited Safety Subset	All randomized participants who received any study intervention and contributed any solicited AR data in the Reactogenicity eDiary. The Solicited Safety Set was used for all analyses of solicited ARs. Participants were analyzed according to the study intervention they actually received.

Source: Adapted from STN 125869/0, Study P304 Protocol Table 7; Study P304 CSR Table 5.
Abbreviations: AR, adverse reaction; eDiary, electronic diary; HAI, hemagglutination inhibition; NI, noninferiority; RT-PCR, reverse transcription polymerase chain reaction; TIV, trivalent influenza vaccine

Sensitivity and Subgroup Analyses

Efficacy, immunogenicity, and safety subgroup analyses were conducted by age group (50 to <65 years, ≥65 years, and ≥75 years), race, sex, and baseline high-risk status (see Appendix G). Efficacy and immunogenicity subgroup analyses were also conducted by influenza vaccine status in the previous season, body mass index (BMI), baseline frailty score (for participants ≥65 years), geographic region, and active comparator type.

Participant Disposition and Inclusion in Analysis Populations

Participant disposition by analysis population is presented in Appendix B Table 3 (efficacy and immunogenicity populations) and Appendix B Table 4 (safety population).

The proportion of participants excluded from the Per-Protocol (PP) Set was comparable across the mRNA-1010 (TIV) and SD comparator groups (0.8% and 1.1%, respectively). The higher proportion of SD comparator recipients excluded due to important protocol deviations (0.8% versus 0.2%) was driven by 68 SD comparator recipients from three sites who were excluded due to a temperature excursion of the comparator vaccine. There were no notable differences in PP Set exclusions when comparing SD comparator (TIV) and SD comparator (QIV) recipients.

The proportion of participants in the Immunogenicity Subset excluded from the Per-Protocol Immunogenicity Subset (PPIS) was also comparable across groups (2.6% in the mRNA-1010 [TIV] group and 1.8% in the SD comparator group). Most exclusions were due to non-compliance with the timing of immunogenicity blood sampling (1.2% in the mRNA-1010 [TIV] group and 1.0% in the SD comparator group).

Appendix B Table 3. Participant Disposition, Participants 50 Years of Age and Older, Immunogenicity and Efficacy Populations, Study P304

Population	mRNA-1010 (TIV) N=20,402 n (%)	SD Comparator (TIV + QIV)* N=20,403 n (%)
Full Analysis Set (FAS)[a]	20,349 (99.7)	20,354 (99.8)
Per-Protocol Set (PP Set)[a, d]	20,178 (98.9)	20,122 (98.6)
Excluded from PP Set[a]	171 (0.8)	232 (1.1)
Reason for exclusion from PP Set	--	--
Major dosing error	4 (<0.1)	7 (<0.1)
Had prohibited medication/vaccination	67 (0.3)	52 (0.3)
Had important protocol deviations that impact key or critical data	51 (0.2)	171 (0.8)
Other[b]	49 (0.2)	2 (<0.1)
Immunogenicity Subset	1198	1196
Per-Protocol Immunogenicity Subset (PPIS)[c]	1167 (97.4)	1175 (98.2)
Excluded from PPIS[c]	31 (2.6)	21 (1.8)
Reason for exclusion from PPIS	--	--
Major dosing error	0	1 (<0.1)
Had prohibited medication/vaccination by Day 29	5 (0.4)	2 (0.2)
RT-PCR–confirmed influenza infection between baseline and Day 29	2 (0.2)	0
Did not comply with timing of immunogenicity blood sampling	14 (1.2)	12 (1.0)
Had important protocol deviations that impact key or critical data	3 (0.3)	6 (0.5)
Other[b]	7 (0.6)	0

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Tables 14.1.2.2.1.f and 14.1.2.2.3.f. Data cutoff: August 21, 2025.

Abbreviations: FAS, full analysis set; IRT, interactive response technology; N, number of participants in the randomization set; n, number of participants in a given subpopulation or category; PP, per protocol; PPIS, per protocol immunogenicity subset; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine

* Numbers in the immunogenicity subset and the PPIS reflect only the SD comparator (TIV).

A participant who has multiple reasons that caused exclusion from analysis population is counted only once based on the primary exclusion reason.

[a] Numbers are based on planned vaccination group and percentages are based on the number of participants in the Randomization Set.

[b] Other exclusion reasons include 1) participants that were enrolled into site US147 (48 mRNA-1010 and 55 SD comparator recipients) were excluded due to errors in the unblinded pharmacist preparation of the comparator vaccine; mRNA-1010 recipients were excluded to minimize risk of biases in the per-protocol analyses; 2) participants enrolled into the study multiple times are excluded from per-protocol analysis.

[c] Numbers are based on planned vaccination group and percentages are based on the number of participants in the Immunogenicity Subset.

[d] The PP Set in this End of Study Analysis (data cutoff August 21, 2025) had 3 fewer participants overall compared to the end of season analysis (data cutoff April 30, 2025) because 4 additional participants were excluded due to delayed reporting of a prohibited medication/ vaccine or important protocol deviation (1 in the mRNA-1010 [TIV] and 3 in the SD comparator group). One participant previously excluded at the end of season analysis was reincluded due to a prohibited vaccine being incorrectly reported. The number of participants in the other analyses sets were the same when performed at the end of influenza season.

Of the 40,703 participants in the Safety Set, 3.8% of mRNA-1010 (TIV) recipients and 3.6% of SD comparator recipients discontinued from the study. The most common reasons for discontinuation were lost to follow-up (2.1% across both groups) and withdrawal of consent (1.2% in the mRNA-1010 [TIV] group and 1.1% in the SD comparator group). The median duration of safety follow-up was 184 days in both groups. Study completion (defined as completing either the Month 6 [Day 181] visit or the end of influenza season visit, whichever occurred later) was similar across groups (96.2% in the mRNA-1010 [TIV] group and 96.4% in the SD comparator group).

Study discontinuation was higher in the SD comparator (TIV) group compared with the SD comparator (QIV) group (4.7% versus 0.9%, respectively), primarily due to a higher rate of loss to follow-up (2.8% versus 0.4%). The median follow-up time was slightly longer for SD comparator (TIV) recipients compared with SD comparator (QIV) recipients (188 versus 178 days).

Appendix B Table 4. Participant Disposition, Participants 50 Years of Age and Older, Safety Populations, Study P304

Population	mRNA-1010 N=20,350 n (%)	SD Comparator (TIV + QIV) N=20,353 n (%)
Safety Set	20,350 (100)	20,353 (100)
Solicited Safety Subset[a]	3015 (14.8)	2997 (14.7)
Excluded from Solicited Safety Subset[a]	17,335 (85.2)	17,356 (85.3)
Reason for exclusion from Solicited Safety Subset	--	--
Was not assigned to Solicited Safety Subset via IRT at randomization	17,325 (85.1)	17,339 (85.2)
Did not contribute any solicited adverse reaction data in Reactogenicity eDiary	10 (<0.1)	17 (<0.1)
Completed the study [a,b]	19,569 (96.2)	19,621 (96.4)
Discontinued the study [a]	781 (3.8)	732 (3.6)
Reason for discontinuation	--	--
Adverse event	3 (<0.1)	1 (<0.1)
Death	40 (0.2)	34 (0.2)
Lost to follow-up	434 (2.1)	418 (2.1)
Physician decision	39 (0.2)	24 (0.1)
Protocol deviation	2 (<0.1)	1 (<0.1)
Withdrawal of consent by participant	238 (1.2)	232 (1.1)
Other	25 (0.1)	22 (0.1)
Median follow-up (days) (min, max)	184 (1, 254)	184 (1, 252)

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Tables 14.1.1.1.2.f, 14.1.1.1.6.f, 14.1.2.2.1f, 14.1.3.4.1.f, and 14.1.3.4.3.f. Data cutoff: August 21, 2025.
Abbreviations: IRT, interactive response technology; N, number of participants in the safety set; n, number of participants in a given subpopulation or category; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine
There is one more participant in the active comparator group and one fewer participant in the mRNA-1010 group in the FAS compared with the Safety Set due to medication errors: Three participants randomized to mRNA-1010 but received active comparator, and four participants randomized to active comparator, but received mRNA-1010. A participant who has multiple reasons that caused exclusion from analysis population is counted only once based on the primary exclusion reason.
[a] Numbers are based on actual vaccination group and percentages are based on the number of participants in the Safety Set.
[b] Participants are considered to have completed the study if they completed either the Month 6 (Day 181) visit or the end of the influenza season visit, whichever occurred later.

Demographics and Other Baseline Characteristics

The demographics and baseline characteristics of participants in the Safety Set are shown in Appendix B Table 5 and were similar in the PP Set. Overall, baseline characteristics were balanced between the mRNA-1010 (TIV) and SD comparator groups.

The median age was 64 years (range 50–97 years). Across both groups, 52.2% of participants were 50 to <65 yoa, 47.8% were ≥65 yoa, and 11.6% were ≥75 yoa. More than half of participants were female (56.9%). The majority were White (82.6%), not Hispanic or Latino (88.2%), and enrolled at sites in North America (70.4%). Overall, 47.0% had received a seasonal influenza vaccine in the previous influenza season.

At least one high-risk condition (see Appendix G) was reported by 57.0% of participants, with baseline BMI ≥30 kg/m² being the most common. The proportion of participants with a high-risk condition in Study P304 was lower than reported for the general U.S. population (78% among adults 35 to 64 yoa and 93% among adults ≥65 yoa [Watson et al., 2025]). This likely reflects differences in how high-risk conditions were defined, as well as the exclusion of certain high-risk participants (e.g., those who were immunocompromised or taking immunosuppressive medications).

Among participants ≥65 yoa, the majority were considered fit and not vulnerable or frail (73.3%) based on the Edmonton Frail Scale (EFS); fewer than 1% were considered moderately or severely frail (EFS score ≥10). The study did not collect data on nursing home or assisted living residence. Therefore, the generalizability of these findings to all high-risk groups—particularly immunocompromised or frail individuals—may be limited.

The proportion of participants with prior seasonal influenza vaccination was lower than national rates (44.9% among adults 50 to 64 yoa and 67.1% among adults ≥65 yoa [NCHS 2024]).

The demographics and baseline characteristics were generally similar across the SD comparator (TIV) and SD comparator (QIV) groups, with the following notable exceptions: the TIV group was more racially and ethnically diverse, with higher proportions of participants identifying as African American/Black (18.7% versus 0.3%) and Hispanic or Latino (14.1% versus 0.7%). A lower proportion of QIV recipients had a baseline BMI ≥30 kg/m² (24.7% versus 45.4%) or at least one high-risk condition (42.7% versus 63.1%). These differences are likely attributable to geographic differences in the study populations (TIV used in North America; QIV used in Europe and East Asia).

Appendix B Table 5. Demographic and Baseline Characteristics, Participants 50 Years of Age and Older, Safety Set, Study mRNA P304

Characteristic	mRNA-1010 (TIV) N=20,350	SD Comparator (TIV + QIV) N=20,353
Sex, n (%)	--	--
Male	8834 (43.4)	8720 (42.8)
Female	11,516 (56.6)	11,633 (57.2)
Age, years	--	--
Median age (min, max)	64.0 (50, 97)	64.0 (50, 96)
50 to <65 years of age	10,624 (52.2)	10,615 (52.2)
≥65 years of age	9726 (47.8)	9738 (47.8)
65 to <75 years of age	7372 (36.2)	7375 (36.2)
≥75 years of age	2354 (11.6)	2363 (11.6)
Race, n (%)	--	--
African American/Black	2687 (13.2)	2698 (13.3)
American Indian or Alaska Native	72 (0.4)	86 (0.4)
Asian	496 (2.4)	483 (2.4)
Native Hawaiian or other Pacific Islander	20 (<0.1)	19 (<0.1)
White	16,814 (82.6)	16,811 (82.6)
Multiracial	109 (0.5)	104 (0.5)
Unknown	15 (<0.1)	16 (<0.1)
Not reported	86 (0.4)	81 (0.4)
Other	51 (0.3)	55 (0.3)

Characteristic	mRNA-1010 (TIV) N=20,350	SD Comparator (TIV + QIV) N=20,353
Ethnicity, n (%)	--	--
Hispanic/Latino	2147 (10.6)	2067 (10.2)
Not Hispanic/Latino	17,908 (88.0)	17,985 (88.4)
Not reported	279 (1.4)	271 (1.3)
Unknown	16 (<0.1)	30 (0.1)
Region, n (%)	--	--
North America	14,333 (70.4)	14,340 (70.5)
Canada	647 (3.2)	610 (3.0)
U.S.	13,686 (67.3)	13,730 (67.5)
Europe	5843 (28.7)	5833 (28.7)
Belgium	512 (2.5)	461 (2.3)
Bulgaria	1836 (9.0)	1895 (9.3)
Estonia	606 (3.0)	645 (3.2)
Finland	206 (1.0)	198 (1.0)
Georgia	176 (0.9)	178 (0.9)
Germany	1356 (6.7)	1324 (6.5)
United Kingdom	1151 (5.7)	1132 (5.6)
East Asia[a]	174 (0.9)	180 (0.9)
South Korea	117 (0.6)	114 (0.6)
Taiwan	57 (0.3)	66 (0.3)
Body mass index (kg/m^2)	--	--
Median (min, max)	28.3 (12.4, 95.8)	28.4 (12.9, 75.7)
<30 kg/m^2	12290 (60.4)	12325 (60.6)
≥30 kg/m^2	8030 (39.5)	8002 (39.3)
≥40 kg/m^2	1296 (6.4)	1312 (6.4)
Missing	30 (0.1)	26 (0.1)
Influenza vaccine status, n (%)	--	--
Received seasonal flu vaccine	9569 (47.0)	9546 (46.9)
Not received previous seasonal flu vaccine	10,781 (53.0)	10,807 (53.1)
EFS Total score[b]	--	--
n	9711	9718
Median (min, max)	2.0 (0, 16)	2.0 (0, 17)
0-3: Fit, n (%)	7136 (73.4)	7135 (73.3)
4-5: Vulnerable, n (%)	1755 (18.0)	1740 (17.9)
≥6: Frail, n (%)	820 (8.4)	843 (8.7)

Characteristic	mRNA-1010 (TIV) N=20,350	SD Comparator (TIV + QIV) N=20,353
Baseline high-risk factors, n (%)	--	--
High-risk[c]	11595 (57.0)	11620 (57.1)
Autoimmune/immune-mediated disease	798 (3.9)	830 (4.1)
Baseline BMI ≥30 kg/m^2 [d]	8030 (39.5)	8002 (39.3)
Blood disorders	50 (0.3)	56 (0.3)
Cardiac disorders	1836 (9.0)	1839 (9.0)
Diabetes mellitus	3607 (17.7)	3557 (17.5)
Hepatic disorders	205 (1.0)	249 (1.2)
Mental impairment disorders	16 (<0.1)	22 (0.1)
Nervous system disorders	84 (0.4)	62 (0.3)
Pulmonary disorders	2114 (10.4)	2225 (10.9)
Renal disorders	277 (1.4)	263 (1.3)
Non high-risk	8755 (43.0)	8733 (42.9)

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Table 14.1.3.1.3.f and 14.1.3.1.8.f., Amendment 48.
Abbreviations: BMI, body mass index (body weight in kilograms)/(height in meters)^2; CSR, clinical study report; EFS, Edmonton Frail Scale; IR, information request; max, maximum; min, minimum; N, number of participants in the Safety Set; n, number of participants in the vaccination group in the given subpopulation; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine
Numbers are based on actual vaccination group and percentages are based on the number of participants in the Safety Set.
[a] The Safety Subset included all randomized participants who received any study vaccination. Participants are analyzed according to the study vaccination they actually received.
[b] EFS total score is only applicable to participants of ≥65 years old and the percentages are based on the number of participants of ≥65 years old in the Safety Set.
[c] High risk is defined as having at least one of the following: baseline BMI ≥30 kg/m^2, autoimmune/immune-mediated disease, blood disorders, cardiac disorders, diabetes mellitus, hepatic disorders, mental impairment disorders, nervous system disorders, pulmonary disorders, or renal disorders.
[d] The original demographic data submitted in support of this BLA reported a participant with a BMI of 139.0. After an information request, the Applicant clarified on that this value was confirmed by the site to be an error due to an incorrectly recorded height value. In response to a follow-up IR, the Applicant provided the corrected BMI value and corrected CSR tables.

Appendix B Table 6 shows the demographic and baseline characteristics of the PPIS. All PPIS participants were enrolled in North America and received the SD comparator (TIV). There were no notable differences between the mRNA-1010 (TIV) and SD comparator (TIV) groups within the PPIS. Compared with the overall Safety Set and PP Set, the PPIS had higher proportions of participants who were African American/Black, Hispanic or Latino, had a BMI ≥30 kg/m², or had at least one high-risk condition.

Appendix B Table 6. Demographic and Baseline Characteristics, Participants 50 Years of Age and Older, Per Protocol Immunogenicity Subset (PPIS), Study P304

Characteristic	mRNA-1010 (TIV) N=1167	SD Comparator (TIV) N=1175
Sex, n (%)	--	--
Male	485 (41.6)	490 (41.7)
Female	682 (58.4)	685 (58.3)
Age, years	--	--
Median age (min, max)	65.0 (50, 97)	64.0 (50, 92)
50 to <65 years of age	581 (49.8)	592 (50.4)
≥65 years of age	586 (50.2)	583 (49.6)
65 to <75 years of age	437 (37.4)	434 (36.9)
≥75 years of age	149 (12.8)	149 (12.7)

Characteristic	mRNA-1010 (TIV) N=1167	SD Comparator (TIV) N=1175
Race, n (%)	--	--
African American/Black	193 (16.5)	200 (17.0)
American Indian or Alaska Native	8 (0.7)	3 (0.3)
Asian	27 (2.3)	33 (2.8)
Native Hawaiian or other Pacific Islander	1 (<0.1)	3 (0.3)
White	914 (78.3)	910 (77.4)
Multiracial	9 (0.8)	13 (1.1)
Unknown	2 (0.2)	2 (0.2)
Not reported	11 (0.9)	9 (0.8)
Other	2 (0.2)	2 (0.2)
Ethnicity, n (%)	--	--
Hispanic/Latino	163 (14.0)	165 (14.0)
Not Hispanic/Latino	982 (84.1)	991 (84.3)
Not reported	19 (1.6)	18 (1.5)
Unknown	3 (0.3)	1 (<0.1)
Country, n (%)	--	--
Canada	56 (4.8)	50 (4.3)
U.S.	1111 (95.2)	1125 (95.7)
Body Mass Index (kg/m^2)	--	--
Median (min, max)	29.5 (15.0, 75.3)	29.4 (16.3, 65.7)
<30 kg/m^2	623 (53.4)	637 (54.2)
≥30 kg/m^2	542 (46.4)	538 (45.8)
≥40 kg/m^2	104 (8.9)	98 (8.3)
Missing	2 (0.2)	0
Influenza vaccine status in the previous influenza season, n (%)	--	--
Received seasonal flu vaccine	594 (50.9)	596 (50.7)
Not received previous seasonal flu vaccine	573 (49.1)	579 (49.3)
EFS total score[b]	--	--
n	585	581
Median (min, max)	2.0 (0, 10)	2.0 (0, 14)
0-3: Fit, n (%)	437 (74.6)	440 (75.5)
4-5: Vulnerable, n (%)	106 (18.1)	93 (16.0)
≥6: Frail, n (%)	42 (7.2)	48 (8.2)

Characteristic	mRNA-1010 (TIV) N=1167	SD Comparator (TIV) N=1175
Baseline high-risk factors, n (%)	--	--
High-risk[c]	740 (63.4)	753 (64.1)
Autoimmune/immune-mediated disease	47 (4.0)	44 (3.7)
Baseline BMI ≥30 kg/m^2	542 (46.4)	538 (45.8)
Blood disorders	3 (0.3)	5 (0.4)
Cardiac disorders	103 (8.8)	96 (8.2)
Diabetes mellitus	221 (18.9)	228 (19.4)
Hepatic disorders	12 (1.0)	26 (2.2)
Mental impairment disorders	2 (0.2)	2 (0.2)
Nervous system disorders	4 (0.3)	6 (0.5)
Pulmonary disorders	130 (11.1)	155 (13.2)
Renal disorders	19 (1.6)	13 (1.1)
Non high-risk	427 (36.6)	422 (35.9)

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Tables 14.1.3.1.5.f and 14.1.3.1.10.f.
Abbreviations: BMI, body mass index (body weight in kilograms)/(height in meters)^2; EFS, Edmonton Frail Scale; max, maximum; min, minimum; N, number of participants in the PPIS; n, number of the participants in a given subpopulation/category; PPIS, per protocol immunogenicity subset; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine
Numbers are based on planned vaccination group and percentages are based on the number of participants in the PPIS.
The PPIS included participants in the Immunogenicity Subset and without any important protocol deviations that could adversely impact immunogenicity assessment.
[a] East Asia includes Republic of Korea (i.e., South Korea) and Taiwan.
[b] EFS total score is only applicable to participants of ≥65 years old and the percentages are based on the number of participants of ≥65 years old in the Per Protocol Immunogenicity Subset.
[c] High risk is defined as having at least one of the following: baseline BMI ≥30 kg/m^2,autoimmune/immune-mediated disease, blood disorders, cardiac disorders, diabetes mellitus, hepatic disorders mental impairment disorders, nervous system disorders, pulmonary disorders, or renal disorders.

Analyses of Vaccine Effectiveness

Analyses of Primary Efficacy Endpoint

The primary efficacy analysis was based on the pre-specified interim analysis conducted at the end of the NH 2024/2025 influenza season. This analysis includes cases of the first RT-PCR–confirmed protocol-defined ILI with onset at least 14 days after study vaccination through the data cutoff of April 30, 2025. The median duration of follow-up for efficacy was 181 days (approximately 6 months).

The primary efficacy objective was to demonstrate that mRNA-1010 (TIV) is noninferior to the SD comparator in preventing the first episode of protocol-defined ILI. As shown in Appendix B Table 7, mRNA-1010 (TIV) demonstrated an rVE of 26.6% (95% CI: 16.7, 35.4) in all participants ≥50 yoa, meeting the prespecified NI criterion (LL of 95% CI of rVE >−10%). The case split was 411 cases (2.0%) in the mRNA-1010 (TIV) group and 557 cases (2.8%) in the SD comparator group. Sequential testing for superiority (LL of 95% CI >0%) and super-superiority (LL of 95% CI >9.1%) were then conducted and both were also demonstrated.

Appendix B Table 7. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for mRNA-1010 (TIV) Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strains in Participants 50 Years of Age and Older (PP Set), Study P304

mRNA-1010 (TIV) N=20,179 Cases n (%)[a]	SD Comparator N=20,124 Cases n (%)[a]	rVE (%) (95% CI)[b]
411 (2.0)	557 (2.8)	26.6 (16.7, 35.4)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1, Table 14.2.1.1.4.1. Data cutoff: April 30, 2025.

Abbreviations: CI, confidence interval; ILI, influenza-like illness; N, number of participants in the PP analysis set; n: number of protocol-defined ILI cases; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose

The case is the first RT-PCR–confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match.

[a] Percentages are based on the number of participants in the analysis set.

[b] rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not).

The time from vaccination to the first RT-PCR–confirmed protocol-defined ILI was similar across treatment groups (median of 91.0 days in the mRNA-1010 [TIV] group and 96.0 days in the SD comparator group). More cases accrued in the SD comparator group compared with the mRNA-1010 (TIV) group at all time periods through the study, with the exception of the period beyond 6 months postvaccination to the end of the influenza season, during which only two cases were observed in each group.

Supportive Analyses of the Primary Efficacy Endpoint

Analysis by Influenza Strain

Appendix B Table 8 presents a supportive analysis of rVE against RT-PCR–confirmed protocol-defined ILI by influenza strain. Point estimates for rVE were consistent across all strains. For B/Victoria, the rVE point estimate was consistent with the overall estimate, but the 95% CI was wide with a LL below zero (LL of 95% CI: −18.5), likely due to the small number of influenza B cases. The rVE analysis was primarily driven by results against influenza A strains, which accounted for 94.0% of influenza cases across both groups.

Appendix B Table 8. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for mRNA-1010 (TIV) Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Influenza Strain Type in Participants 50 Years of Age and Older (PP Set), Study P304

Relative Efficacy Endpoint	mRNA-1010 (TIV) N=20,179 Cases, n (%)[a]	SD Comparator N=20,124 Cases, n (%)[a]	rVE (%) (95% CI)[b]
Any influenza A strain	386 (1.9)	522 (2.6)	26.5 (16.1, 35.5)
Influenza A/H1N1 strain only	223 (1.1)	315 (1.6)	29.6 (16.4, 40.7)
Influenza A/H3N2 strain only	158 (0.8)	202 (1.0)	22.2 (4.3, 36.9)
Influenza B strain only	25 (0.1)	35 (0.2)	29.1 (-18.5, 57.5)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1 and 14.2.1.1.3.1. Data cutoff: April 30, 2025.
Abbreviations: CI, confidence interval; ILI, influenza-like illness; N, number of participants in the PP analysis set; n, number of cases of RT-PCR confirmed ILI; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose
[a] Percentages are based on the number of participants in the analysis set. The case is the first RT-PCR–confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match. Participants can have more than one influenza strain infection simultaneously.
[b] rVE was defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties. If there were <20 events total in the two vaccination groups combined, rVE was not provided.

Analyses of Cases Starting from Day 1

Descriptive analysis of rVE against RT-PCR–confirmed protocol-defined ILI caused by any influenza A or B strain, beginning from Day 1, was 27.2% (95% CI: 17.3, 35.9). Strain-specific rVE from Day 1: A/H1N1, 30.8% (95% CI: 18.0, 41.7); A/H3N2, 21.8% (95% CI: 3.7, 36.4); B/Victoria, 29.1% (95% CI: −18.5, 57.5). Inclusion of cases occurring in the first 14 days did not meaningfully change the rVE estimates for any strain, suggesting that the case-counting window definition did not materially affect the efficacy estimates.

Analyses of Coinfection

Coinfection with any respiratory virus accounted for 4.6% of all protocol-defined ILI cases and was similar across the mRNA-1010 (TIV) and SD comparator groups. Coinfection with SARS-CoV-2 or respiratory syncytial virus (RSV) accounted for 0.2% of all cases in the mRNA-1010 (TIV) group and 1.1% in the SD comparator group. Removing coinfection cases from the efficacy analyses did not meaningfully change rVE estimates or associated CIs.

End-of-Study Analyses

Supportive EOS analyses of the primary efficacy endpoint (RT-PCR–confirmed protocol-defined ILI caused by any influenza A or B strain) were consistent with the primary efficacy results from the 2024/2025 influenza season.

Subpopulation Analyses

Subgroup Analyses by Age

Descriptive analyses of rVE by age subgroup are shown in Appendix B Table 9. The rVE point estimate for each age subgroup was consistent with the overall study population. Although the use of a non-preferentially recommended SD comparator for participants ≥65 yoa limits the interpretation of

rVE in this subgroup, the rVE was 27.4% (95% CI: 12.1%, 40.0%), indicating superiority to the SD comparator. In the ≥75 years age subgroup, a wide CI was observed around the rVE point estimate, with the LL crossing zero, likely due to the smaller number of participants and cases in this subgroup. Strain-specific rVE was also similar between participants 50 to 64 yoa and those ≥65 yoa (data not shown).

Appendix B Table 9. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for mRNA-1010 (TIV) Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strains by Age Group (PP Set), Study P304

Age Group	mRNA-1010 (TIV) N=20,179 Cases, n/N (%)	SD Comparator N=20,124 Cases, n/N (%)	rVE (%) (95% CI)[b]
≥50 years of age[a]	411/20,179 (2.0)	557/20,124 (2.8)	26.6 (16.7, 35.4)
50 to <65 years of age[c]	229/10,542 (2.2)	307/10,501 (2.9)	26.1 (12.3, 37.7)
≥65 years of age[c, d]	182/9637 (1.9)	250/9623 (2.6)	27.4 (12.1, 40.0)
65 to <75 years of age[c]	138/7307 (1.9)	191/7289 (2.6)	28.0 (10.4, 42.2)
≥75 years of age[c]	44/2230 (1.9)	59/2334 (2.5)	25.3 (−10.4, 49.5)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1, Table 14.2.1.1.4.1. Data cutoff: April 30, 2025.
Abbreviations: CI, confidence interval; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of cases of protocol-defined ILI in the given age subgroup; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose
The case is the first RT-PCR–confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match.
[a] Percentages are based on the number of participants in the analysis set.
[b] rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties.
[c] Percentages are based on the number of participants in the analysis set in each subgroup.
[d] Age group ≥65 years includes the age group ≥75 years.

Additional Subgroup Analyses

The Applicant also conducted subgroup analyses of rVE (shown in Appendix B Table 10) in the PP Set by influenza vaccine status in the previous season, sex, race, BMI, SD comparator type (TIV versus QIV), region, baseline EFS frailty score, and high-risk status. Although Study P304 was not powered to assess rVE in individual subgroups, rVE point estimates generally remained supportive of mRNA-1010 (TIV) efficacy, with wider CIs observed in smaller subgroups.

rVE was similar when comparing participants who had or had not received an influenza vaccine in the previous season, and when comparing participants with a baseline BMI below or at or above 30 kg/m². rVE was higher in female participants (30.7%; 95% CI: 17.9, 41.4) than in male participants (20.9%; 95% CI: 3.9, 34.9), which may reflect sex-based differences in humoral immune responses previously described in the literature (Fischinger et al., 2019). A lower rVE was observed in participants with high-risk factors (22.3%) compared with those without (32.1%), though CIs overlapped. In participants considered vulnerable or frail, rVE point estimates remained robust;

however, small sample sizes and wide 95% CIs crossing zero limit the interpretability and generalizability of these findings to elderly frail individuals.

Appendix B Table 10. Subgroup Analyses of rVE for mRNA-1010 (TIV) Versus SD Comparator Against RT PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza Strain Type by Subgroup, Adults 50 Years of Age and Older (PP Set), Study P304

Subgroup	mRNA-1010 (TIV) % (Case/N)	SD Comparator % (Case/N)	rVE (%) (95% CI[a])
Sex	--	--	--
Male	2.1 (183/8775)	2.6 (226/8619)	20.9 (3.9,34.9)
Female	2.0 (228/11404)	2.9 (331/11505)	30.7 (17.9,41.4)
Race	--	--	--
African American/Black	0.8 (21/2650)	1.4 (38/2657)	43.9 (4.5,67.1)
American Indian or Alaska Native	2.8 (2/71)	1.2 (1/85)	--
Asian	1.8 (9/494)	1.7 (8/481)	--
Native Hawaiian or other Pacific Islander	0.0 (0/20)	0.0 (0/19)	--
White	2.2 (375/16686)	3.0 (504/16628)	26.2 (15.6,35.4)
Other (including multiple, not reported, and unknown)	1.6 (4/258)	2.4 (6/254)	--
Region	--	--	--
North America	1.8 (253/14176)	2.5 (353/14162)	28.5 (16.0,39.2)
Europe	2.7 (158/5829)	3.5 (204/5783)	23.7 (6.1,38.0)
East Asia[c]	0.0 (0/174)	0.0 (0/179)	--
Body mass index (kg/m^2)	--	--	--
<30 kg/m^2	2.1 (257/12193)	2.9 (348/12206)	26.2 (13.2,37.1)
≥30 kg/m^2	1.9 (153/7957)	2.6 (208/7892)	27.5 (10.6,41.1)
Active comparator type			
Countries using TIV active comparator (North America)	1.8 (253/14176)	2.5 (353/14162)	28.5 (16.0,39.2)
Countries using QIV active comparator (not North America)	2.6 (158/6003)	3.4 (204/5962)	23.6 (6.0,37.9)
Influenza vaccine status	--	--	--
Received seasonal flu vaccine	2.5 (238/9456)	3.4 (316/9421)	25.2 (11.5,36.8)
Not received previous seasonal flu vaccine	1.6 (173/10723)	2.3 (241/10703)	28.6 (13.2,41.3)
EFS Total score[d]	--	--	--
0-3: Fit	2.0 (140/7079)	2.7 (190/7059)	26.8 (8.9,41.1)
4-5: Vulnerable	1.6 (28/1737)	2.3 (39/1708)	28.9 (−15.5,56.3)
≥6: Frail	1.7 (14/806)	2.5 (21/837)	30.3 (−37.1,64.6)

Subgroup	mRNA-1010 (TIV) % (Case/N)	SD Comparator % (Case/N)	rVE (%) (95% CI[a])
Baseline high-risk factors	--	--	--
High-risk[e]	2.1 (241/11465)	2.7 (309/11457)	22.3 (8.0,34.3)
Not high-risk	2.0 (170/8714)	2.9 (248/8667)	32.1 (17.5,44.2)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.2.1.1.4.1.r. Data cutoff: April 30, 2025.
Abbreviations: BMI, body mass index; CI, confidence interval; eCRF, electronic case report; EFS, Edmonton Frail Scale; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of cases of protocol-defined ILI; PP, per protocol; QIV, quadrivalent influenza vaccine; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose; TIV, trivalent influenza vaccine
rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]).
The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect adjusting by the randomized stratification factor: age group (≥50 to <65 years or ≥65 years) and/or the status of influenza vaccine in the previous influenza season (received or not received), as applicable. Efron´s method is used to handle ties.
[a] If there are <20 events total in the two vaccination groups combined, rVE is not provided.
[b] Age group ≥65 years includes the age group of ≥75 years.
[c] East Asia includes Republic of Korea and Taiwan. There were no observed cases in East Asia, which contributed 353 participants to the study. Participants in East Asia were enrolled relatively late compared to other regions (November 25, 2024 to March 7, 2025). The relatively small sample size along with the later timing of enrollment likely contributed to the absence of protocol-defined IILI cases in this region.
[d] EFS total score is only applicable to participants of ≥65 years old.
[e] High-risk factors include baseline BMI ≥30 kg/m^2, or having a medical history of autoimmune/immune-mediated disease, blood disorders, cardiac disorders, diabetes mellitus, hepatic disorders, mental impairment disorders, nervous system disorders, pulmonary disorders, or renal disorders.

Analyses of Secondary Efficacy Endpoints

rVE Based on RT-PCR–Confirmed Modified CDC-Defined ILI Caused by Any Influenza Strain

The secondary efficacy endpoint of modified CDC-defined ILI requires a temperature above 37.2°C, cough and/or sore throat, and RT-PCR confirmation of influenza virus (see Table 2 for case definitions). rVE based on this endpoint was evaluated sequentially for NI, superiority, and super-superiority using the same prespecified rules as for the primary endpoint.

As shown in Appendix B Table 11, RT-PCR–confirmed modified CDC-defined ILI was reported in 223 (1.1%) mRNA-1010 (TIV) recipients and 290 (1.4%) SD comparator recipients in adults ≥50 yoa, with an rVE of 23.5% (95% CI: 9.0, 35.8). This met prespecified success criteria for NI and superiority, but not super-superiority. The more stringent fever requirement and the lower likelihood of fever during influenza illness in adults ≥65 yoa (Smith et al., 2020) likely contributed to the smaller number of modified CDC-defined ILI cases compared with protocol-defined ILI cases in both groups. Nonetheless, mRNA-1010 (TIV) demonstrated superiority to the SD comparator with a robust rVE point estimate across all participants ≥50 yoa.

Appendix B Table 11. Analysis of rVE for mRNA-1010 (TIV) Versus SD Comparator Against RT-PCR Confirmed Modified CDC-Defined ILI Regardless of Vaccine Match, Overall and by Age Subgroup (PP Set), Study P304

Variable	mRNA-1010 (TIV) N=20,179 Cases, n (%)[a]	SD Comparator N=20,124 Cases, n (%)[a]	rVE (%) (95% CI)[b]
≥50 years of age	223 (1.1)	290 (1.4)	23.5 (9.0, 35.8)
50 through 64 years of age	129 (1.2)	162 (1.5)	21.1 (0.5, 37.4)
≥65 years of age	94 (1.0)	128 (1.3)	26.7 (4.4, 43.9)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1, 14.2.1.2.1.1, and 14.2.1.4.1.1. Data cutoff: April 30, 2025.

Abbreviations: CDC, U.S. Centers for Disease Control and Prevention; CI, confidence interval; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of cases of protocol-defined ILI in the age subgroup; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose

[a] Percentages are based on the number of participants in the analysis set.

[b] rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties.

rVE Based on Antigenically Matched Cases (Descriptive)

The majority of RT-PCR–confirmed protocol-defined ILI cases in both groups were antigenically matched to the vaccine strains. Among cases with an antigenic typing result, antigenic match was high for influenza A/H1N1 (97.8% in the mRNA-1010 [TIV] group and 98.1% in the SD comparator group) and influenza B/Victoria (93.8% in the mRNA-1010 [TIV] group and 95.0% in the SD comparator group). Antigenic match was lower for influenza A/H3N2, though more than half of cases remained antigenically matched (51.6% in the mRNA-1010 [TIV] group and 56.4% in the SD comparator group).

rVE against antigenically matched RT-PCR–confirmed protocol-defined ILI and modified CDC-defined ILI cases are shown in Appendix B Table 12. Overall, rVE remained consistent when limited to antigenically matched cases for both case definitions. For influenza A/H3N2, which had the highest proportion of antigenic mismatch, rVE against protocol-defined ILI increased from 22.2% (95% CI: 4.3, 36.9) across all cases to 30.5% (95% CI: 4.6, 49.4) when limited to antigenically matched cases, suggesting that rVE against A/H3N2 may be higher in seasons with greater antigenic match between vaccine and circulating strains.

Appendix B Table 12. Analyses of rVE for mRNA-1010 (TIV) vs SD Comparator Against Protocol-Defined ILI and Modified CDC-Defined ILI With Antigenic Match, Participants 50 Years of Age and Older, (PP Set), Study P304

Relative Efficacy Endpoint	mRNA-1010 (TIV) N=20,178 Cases, n (%)[a]	SD Comparator N=20,122 Cases, n (%)[a]	rVE (%) (95% CI)[b]
Protocol-defined ILI	--	--	--
Any influenza A or B strains	261 (1.3)	364 (1.8)	28.7 (16.4, 39.2)
Any influenza A strain	246 (1.2)	345 (1.7)	29.1 (16.5, 39.8)
Influenza A/H1N1 strain only	181 (0.9)	252 (1.3)	28.5 (13.5, 41.0)
Influenza A/H3N2 strain only	65 (0.3)	93 (0.5)	30.5 (4.6, 49.4)
Influenza B strain only	15 (<0.1)	19 (<0.1)	21.6 (−54.3, 60.2)
Modified CDC-defined ILI	--	--	--
Any influenza A or B strains	143 (0.7)	198 (1.0)	28.2 (10.9, 42.1)
Any influenza A strain	137 (0.7)	189 (0.9)	27.9 (10.2, 42.1)
Influenza A/H1N1 strain only	107 (0.5)	143 (0.7)	25.6 (4.4, 42.1)
Influenza A/H3N2 strain only	30 (0.1)	46 (0.2)	35.2 (−2.6, 59.1)
Influenza B strain only	6 (<0.1)	9 (<0.1)	NC

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.2.1.3.1.1.f, Table 14.2.1.3.3.1.f, and Table 14.2.1.3.3.6.f. Data cutoff: August 21, 2025.

Abbreviations: CDC, U.S. Centers for Disease Control; CI, confidence interval; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of cases of protocol-defined or modified CDC-defined ILI with antigenic match; NC, not calculated; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose

[a] Percentages are based on the number of participants in the analysis set. The event is the first RT-PCR–confirmed protocol-defined ILI or modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains with antigenic match to the vaccine strains. b rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron's method is used to handle ties. If there are <20 events total in the two vaccination groups combined, rVE is not provided.

Analysis of Exploratory Efficacy Endpoints

rVE for mRNA-1010 (TIV) Compared with SD Comparator Across Case Definitions

Appendix B Table 13 shows rVE of mRNA-1010 (TIV) compared with the SD comparator across additional ILI case definitions (see Appendix B Table 1). rVE was consistent across all case definitions with no notable differences.

Appendix B Table 13. Analysis of Relative Vaccine Efficacy (rVE) for mRNA-1010 (TIV) Versus SD Comparator Against Various ILI Case Definitions Regardless of Vaccine Match, Participants 50 Years of Age and Older, (PP Set), Study P304

Relative Efficacy Endpoint	mRNA-1010 (TIV) N=20,179 Cases, n (%)[a]	SD Comparator N=20,124 Cases, n (%)[a]	rVE (%) (95% CI)[b]
RT-PCR–confirmed protocol-defined ILI	411 (2.0)	557 (2.8)	26.6 (16.7, 35.4)
RT-PCR–confirmed modified CDC-defined ILI	223 (1.1)	290 (1.4)	23.5 (9.0, 35.8)
RT-PCR–confirmed CDC-defined ILI	149 (0.7)	203 (1.0)	27.0 (9.8, 40.9)
RT-PCR–confirmed WHO-defined ILI	118 (0.6)	167 (0.8)	29.7 (11.1, 44.5)
RT-PCR–confirmed previous study protocol (mRNA-1010-P302) Defined ILI	194 (1.0)	261 (1.3)	26.1 (11.0, 38.6)
RT-PCR–confirmed influenza infection	557 (2.8)	730 (3.6)	24.2 (15.4, 32.1)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1, 14.2.1.2.1.1, and 14.2.1.4.1.1. Data cutoff: April 30, 2025.

Abbreviations: CDC, U.S. Centers for Disease Control and Prevention; CI, confidence interval; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of ILI cases based on the given case definition; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose; WHO, World Health Organization

[a] Percentages are based on the number of participants in the analysis set.

[b] rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties.

Medically Attended Outcomes Associated with the Primary Efficacy Endpoint

Appendix B Table 14 shows medically attended outcomes associated with the first RT-PCR–confirmed protocol-defined ILI, assessed as an exploratory endpoint. The rVE of mRNA-1010 (TIV) versus the SD comparator for protocol-defined ILI cases seeking a higher level of care (hospitalization, ER visit, or urgent care visit) was 47.9% (95% CI: 12.8, 68.9). Although rVE could not be calculated for hospitalizations and ER visits individually due to limited case counts, the consistently lower case counts in the mRNA-1010 (TIV) group suggest a clinical benefit.

While the study was not powered to evaluate healthcare outcomes associated with protocol-defined ILI, these exploratory results suggest that mRNA-1010 (TIV) may offer greater efficacy than the SD comparator in preventing more severe influenza-associated illness. The effect appeared most pronounced in participants ≥65 yoa (7 cases seeking higher-level care in the mRNA-1010 [TIV] group versus 20 in the SD comparator group; rVE 65.1%, 95% CI: 17.4, 85.2; data not shown). The majority of higher-level-of-care cases in both groups occurred in adults 50 to 64 yoa (68.2% in the mRNA-1010 [TIV] group and 52.4% in the SD comparator group) and in participants with a baseline high-risk factor (90.9% in the mRNA-1010 [TIV] group and 76.2% in the SD comparator group; data not shown).

Appendix B Table 14. Analysis of Health Care Outcomes Associated With the First RT-PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strains, Regardless of Vaccine Match in Participants 50 Years of Age and Older (PP Set), Study P304

Variable	mRNA-1010 (TIV) N=20,179 Cases, n (%)	SD Comparator N=20,124 Cases, n (%)	rVE (%) (95% CI)[a]
Health care encounter[b]	80 (0.4)	120 (0.6)	33.7 (12.0, 50.0)
Seeking higher level of care[b]	22 (0.1)	42 (0.2)	47.9 (12.8, 68.9)
Hospitalization[c]	4 (<0.1)	8 (<0.1)	--
ER Visit[c]	6 (<0.1)	12 (<0.1)	--
Urgent care clinic visit[c]	13 (<0.1)	24 (0.1)	46.1 (−5.8, 72.6)
Outpatient clinic visit[c]	59 (0.3)	81 (0.4)	27.6 (−1.3, 48.2)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.2.1.6.1.1. Data cutoff: April 30, 2025.
Abbreviations: CI, confidence interval; ER, emergency room; ILI, influenza-like illness; N, number of participants in the analysis set; n, number of participants with a case, which is a healthcare encounter associated with the first occurrence of RT-PCR–confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match; PP, per protocol; RT-PCR, real-time reverse transcription polymerase chain reaction; rVE, relative vaccine efficacy; SD, standard dose
[a] rVE is defined as 100×(1−hazard ratio [mRNA-1010 versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron's method is used to handle ties. If there are <20 events total in the two vaccination groups combined, rVE is not provided.
[b] If an event is associated with multiple healthcare encounter types or multiple healthcare encounter of the same type, the participant will be counted only once.
[c] If an event is associated with multiple healthcare encounter of the same type, the participant will be counted only once.

Analyses of Secondary Immunogenicity Endpoints

The secondary immunogenicity objective was to describe HAI antibody titers at Baseline and Day 29 (GMT and SCR) in the PPIS. Baseline GMTs were similar across groups for all three vaccine-matched strains.

Appendix B Table 15 shows Day 29 HAI GMTs in the mRNA-1010 (TIV) and SD comparator groups for each vaccine-matched influenza strain. Day 29 GMTs were higher in the mRNA-1010 (TIV) group compared with the SD comparator group for all three strains.

Appendix B Table 15. Analyses of Secondary Immunogenicity Endpoints of GMTs as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29 Postvaccination in Participants 50 Years of Age and Older, PPIS, Study P304

Endpoint	mRNA-1010 (TIV) N=1167 GMT (95% CI)	SD Comparator N=1175 GMT (95% CI)	GMT Ratio (mRNA-1010 / SD Comparator) (95% CI)
Influenza A/H1N1	146.3 (138.7, 154.4)	80.2 (76.1, 84.6)	1.8 (1.7, 1.9)
Influenza A/H3N2	148.5 (140.9, 156.5)	93.4 (88.7, 98.5)	1.6 (1.5, 1.7)
Influenza B/Victoria	250.9 (240.3, 261.9)	149.9 (143.7, 156.6)	1.7 (1.6, 1.8)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.2.2.1.1. Data cutoff: April 30, 2025.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GLSM, geometric least squares mean; GMT, geometric mean titer, estimated by GLSM; HAI, hemagglutination inhibition; LLOQ, lower limit of quantification; N, number of participants with nonmissing HAI data at baseline (Day 1) and the corresponding visit; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
The log-transformed antibody levels are 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(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine).
The model based GMT and GMT ratio, and its corresponding 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Appendix B Table 16 shows Day 29 HAI SCRs in the mRNA-1010 (TIV) and SD comparator groups for each strain. SCRs were higher in the mRNA-1010 (TIV) group for all three strains, with the lower bound of the 95% CI for the SCR difference exceeding 10% for each strain. Immunogenicity results for GMT and SCR analyses conducted at EOS were consistent with end-of-season results.

Appendix B Table 16. Analysis of Secondary Immunogenicity Endpoints of SCR as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29 Postvaccination, Participants ≥50 Years of Age, PPIS, Study P304

Endpoint	mRNA-1010 (TIV) N=1167 SCR[a] (95% CI)[b]	SD Comparator N=1175 SCR[a] (95% CI)[b]	Difference in SCR (mRNA-1010 / SD Comparator) [95% CI][c]
Influenza A/H1N1	55.0 (52.1, 57.9)	27.1 (24.5, 29.7)	27.9 (24.1, 31.7)
Influenza A/H3N2	60.8 (57.9, 63.6)	40.9 (38.0, 43.7)	19.9 (15.9, 23.9)
Influenza B/Victoria	45.1 (42.1, 47.9)	19.7 (17.5, 22.1)	25.3 (21.7, 28.9)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.2.2.1.1. Data cutoff: April 30, 2025.
Abbreviations: CI, confidence interval; HAI, hemagglutination inhibition; N, number of participants with nonmissing HAI data at baseline (Day 1) and the corresponding visit; PPIS, per-protocol immunogenicity set; SCR, seroconversion rate; SD, standard dose; TIV, trivalent influenza vaccine
[a] Rate of seroconversion is defined as the proportion of participants with either a baseline HAI titer <1:10 and a postbaseline titer ≥1:40 or a baseline HAI titer ≥1:10 and a minimum 4-fold rise in postbaseline HAI antibody titer.
[b] 95% CI is calculated using the Clopper-Pearson method.
[c] 95% CI is calculated using the Miettinen-Nurminen (score) method.

Subpopulation Immunogenicity Analyses

The Applicant assessed the Day 29 GMT ratio and SCR differences for each influenza strain by subgroups of age, sex, race, BMI, prior-year influenza vaccine status, and high-risk status. Although some subgroups had limited participant numbers, participants who received mRNA-1010 (TIV) had consistently higher immune responses compared with SD comparator recipients across all subgroups evaluated.

Exploratory Immunogenicity Endpoints

The Applicant assessed neutralizing antibody responses by MN assay for each influenza strain in the PPIS MN subset. Baseline MN GMTs were similar across both groups for all three strains. As shown in Appendix B Table 17, Day 29 MN antibody responses were higher in the mRNA-1010 (TIV) group compared with the SD comparator group for all three influenza strains. Results were similar in participants 50 to 64 yoa and ≥65 yoa.

Appendix B Table 17. Summary of nAb Levels (GMT by MN Assay) and GMT Ratio at Day 29 for Vaccine-Matched Influenza A and B Strains in Participants 50 Years of Age and Older (PPIS MN Subset), Study P304

Endpoint	mRNA-1010 (TIV) N=247 GMT (95% CI)[a]	Active Comparator N=253 GMT (95% CI)[a]	GMT Ratio [mRNA-1010 (TIV) / SD Comparator] (95% CI)[b]
Influenza A/H1N1	514.4 (419.4, 630.9)	190.9 (153.5, 237.4)	2.8 (2.2, 3.5)
Influenza A/H3N2	429.1 (382.8, 480.9)	320.2 (290.6, 352.8)	1.4 (1.2, 1.6)
Influenza B/Victoria	1233.8 (1063.7, 1431.2)	608.5 (523.8, 706.9)	2.1 (1.8, 2.5)

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Table 14.2.2.4.f. Data cutoff: August 21, 2025.
Abbreviations: ANCOVA, analysis of covariance; CDC, U.S. Centers for Disease Control; CI, confidence interval; GM, geometric mean titer; ILI, influenza-like illness; LLOQ, lower limit of quantification; MN, microneutralization; N, number of participants with nonmissing HAI data at baseline (Day 1) and the corresponding visit; nAb, neutralizing antibody; PPIS, per-protocol immunogenicity set; RT-PCR, real-time reverse transcription polymerase chain reaction; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
[a] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log transformed values for GM titer and GM fold-rise, respectively, then back transformed to the original scale for presentation.
[b] The log-transformed antibody levels are analyzed using an ANCOVA model with vaccination group as the fixed variable, log transformed baseline MN titers as a fixed covariate, adjusting for the randomization stratification factor(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine). The model based GMR and its 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Safety Analyses

The Safety Set included 40,703 participants: 20,350 in the mRNA-1010 (TIV) group and 20,353 in the SD comparator group. As of study completion on August 21, 2025, the median duration of safety follow-up was 184 days in both groups.

Overview of Adverse Events

Appendix B Table 18 provides an overview of solicited ARs and unsolicited AEs in the mRNA-1010 (TIV) group compared with the SD comparator. Rates of solicited ARs through Day 7 were higher in the mRNA-1010 (TIV) group. Rates of unsolicited AEs through Day 28, and SAEs and AESIs through study completion, were similar across groups.

Appendix B Table 18. Overall Number and Percentage of Participants Reporting at Least One Safety Event, Participants 50 Years of Age and Older, Safety Set and Solicited Safety Subset, Study P304

Event Type	mRNA-1010 (TIV) % (n/N1)	SD Comparator (TIV + QIV) % (n/N1)
Solicited adverse reactions within 7 days	--	--
Any solicited adverse reaction	75.7 (2283/3015)	46.7 (1400/2997)
Solicited local adverse reaction[a]	67.5 (2034/3015)	32.1 (961/2997)
Grade 3 or above solicited local adverse reaction	1.7 (51/3015)	0.1 (4/2997)
Solicited systemic adverse reaction[b]	58.0 (1750/3015)	32.4 (970/2997)
Grade 3 or above solicited systemic adverse reaction	5.5 (167/3015)	0.9 (27/2997)
Unsolicited adverse events	--	--
Unsolicited adverse event through 28 days after vaccination	5.9 (1204/20,350)	5.7 (1167/20,353)
Nonserious unsolicited adverse event	5.6 (1145/20,350)	5.4 (1106/20,353)
Severe nonserious unsolicited AE[c]	0.1 (25/20,350)	<0.1 (18/20,353)

Event Type	mRNA-1010 (TIV) % (n/N1)	SD Comparator (TIV + QIV) % (n/N1)
Medically attended adverse events throughout the study	12.3 (2509/20,350)	12.0 (2439/20,353)
Related MAAE[d]	0.1 (23/20,350)	<0.1 (14/20,353)
SAE throughout the study	2.2 (455/20,350)	1.9 (392/20,353)
Related SAE[d]	<0.1 (4/20,350)	<0.1 (2/20,353)
AESI throughout the study	<0.1 (17/20,350)	<0.1 (15/20,353)
Related AESI[d]	<0.1 (3/20,350)	<0.1 (2/20,353)
Deaths throughout the study	0.2 (40/20,350)	0.2 (34/20,353)
Related deaths[d]	0	0
AE leading to study discontinuation throughout the study	<0.1 (3/20,350)	<0.1 (1/20,353)

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Tables 14.3.1.2.1.f, 14.3.1.2.1.8.f, 14.3.2.1.1.f, and 14.3.2.1.1.5.f. Data cutoff: August 21, 2025.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; IRT, interactive response technology; MAAE, medically attended adverse event; n, number of exposed participants who reported the event; N, number of participants in the solicited safety subset or safety set; N1, number of participants who received a study intervention; QIV, quadrivalent influenza vaccine; SAE, serious adverse event; TIV, trivalent influenza vaccine
Numbers are based on actual vaccination group and percentages are based on the number of participants in the Solicited Safety Subset or Safety Set (N1). Any solicited local or systemic adverse reaction that meet the definition of an SAE is considered an AE.
[a] Solicited local reactions included pain, erythema (redness), swelling (hardness), axillary swelling or tenderness.
[b] Solicited systemic reactions included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills.
[c] Participants with at least one nonserious AE that was also severe/≥Grade 3.
[d] The event was considered related to study vaccination by the investigator.

Solicited Adverse Reactions

Solicited Local Adverse Reactions

Appendix B Table 19 shows the frequency of solicited local ARs by maximum severity grade in each group. Within 7 days of vaccination, solicited local ARs were reported by 67.5% of mRNA-1010 (TIV) recipients and 32.1% of SD comparator recipients. The most frequently reported local AR in both groups was injection site pain (65.8% in the mRNA-1010 [TIV] group and 29.8% in the SD comparator group). Most local ARs were Grade 1 in severity. Grade 3 local ARs were reported by 1.7% of mRNA-1010 (TIV) recipients and 0.1% of SD comparator recipients. No Grade 4 local ARs were reported in either group. There were no notable differences in solicited local ARs between recipients of the TIV and QIV SD comparator formulations (data not shown).

Appendix B Table 19. Overall Frequency of Solicited Local Adverse Reactions Within 7 Days of Vaccination, Participants 50 Years of Age and Older, Solicited Safety Subset, Study P304

Event	mRNA-1010 (TIV) N1=3015 % (n)	SD Comparator (TIV + QIV) N1=2997 % (n)
Any local adverse reaction	--	--
Any	67.5 (2034)	32.1 (961)
Grade 3	1.7 (51)	0.1 (4)
Pain[a]	--	--
Any	65.8 (1985)	29.8 (894)
Grade 3	0.9 (27)	<0.1 (1)

Event	mRNA-1010 (TIV) N1=3015 % (n)	SD Comparator (TIV + QIV) N1=2997 % (n)
Erythema[b]	--	--
Any ≥25 mm	3.9 (117)	1.3 (38)
Grade 3	0.3 (10)	<0.1 (2)
Swelling[b]	--	--
Any ≥25 mm	5.7 (172)	1.5 (45)
Grade 3	0.3 (9)	0.1 (4)
Axillary swelling or tenderness[a]	--	--
Any	17.2 (520)	6.1 (184)
Grade 3	0.3 (10)	<0.1 (1)

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Tables 14.3.1.2.1.f and 14.3.1.2.1.8.f. Data cutoff: August 21, 2025.
Abbreviations: Any, Grade 1 or higher; G1, Grade 1; G2, Grade 2; G3, Grade 3, G4, Grade 4; IRT, interactive response technology; n, number of exposed participants who reported the event; N1, number of exposed participants in the solicited safety subset
There were no Grade 4 solicited systemic adverse reactions reported.
Numbers are based on actual vaccination group and percentages are based on the number of exposed participants the Solicited Safety Subset.
The toxicity grade is the maximum toxicity grade reported on any day from Baseline. Assessments by investigator are used in analysis if occurred on the same day as participant's assessments.
[a] Toxicity grade for injection site pain, axillary swelling or tenderness ipsilateral to the side of injection are defined as: G1=no interference with activity; G2=some interference with activity; G3=prevent daily activity; G4=requires emergency room visit or hospitalization.
[b] Toxicity grade for injection site erythema (redness) or injection site swelling/induration (hardness) are defined as: G1=25-50 mm; G2=51-100 mm; G3≥100 mm; G4=necrosis (injection site erythema) or exfoliative dermatitis (injection site swelling/induration).

The median day of onset for solicited local ARs was 2 days postvaccination in both groups. The median duration was 2 days in the mRNA-1010 (TIV) group and 1 day in the SD comparator group. A slightly higher proportion of local ARs persisted beyond 7 days in the mRNA-1010 (TIV) group compared with the SD comparator group (0.6% versus 0.3%).

Solicited Systemic Adverse Reactions

Appendix B Table 20 shows the frequency of solicited systemic ARs by maximum severity grade. Within 7 days of vaccination, any systemic AR was reported by 58.0% of mRNA-1010 (TIV) recipients and 32.4% of SD comparator recipients. The most frequently reported systemic ARs among mRNA-1010 (TIV) recipients were fatigue (45.1%), headache (37.8%), and myalgia (35.4%). Most systemic ARs were Grade 1 or 2 in severity. Grade 3 systemic ARs were reported by 5.5% of mRNA-1010 (TIV) recipients and 0.9% of SD comparator recipients. No Grade 4 systemic ARs were reported in either group. There were no notable differences in solicited systemic ARs between TIV and QIV SD comparator recipients (data not shown).

Consistent with the higher reactogenicity in the mRNA-1010 (TIV) group, a higher proportion of mRNA-1010 (TIV) recipients reported use of antipyretic or pain medication compared with SD comparator recipients (28.5% versus 9.1%).

Appendix B Table 20. Overall Frequency of Solicited Systemic Adverse Reactions Within 7 Days of Vaccination, Participants 50 Years of Age and Older, Solicited Safety Subset, Study P304

Event	mRNA-1010 (TIV) N1=3015 % (n)	SD Comparator (TIV + QIV) N1=2997 % (n)
Any systemic adverse reaction	--	--
Any	58.0 (1750)	32.4 (970)
Grade 3	5.5 (167)	0.9 (27)

Event	mRNA-1010 (TIV) N1=3015 % (n)	SD Comparator (TIV + QIV) N1=2997 % (n)
Fever[a]	--	--
Any	5.8 (174)	0.9 (26)
Grade 3	0.6 (17)	0.1 (3)
Headache[b]	--	--
Any	37.8 (1140)	18.0 (538)
Grade 3	2.0 (59)	0.3 (10)
Fatigue[b]	--	--
Any	45.1 (1360)	20.3 (609)
Grade 3	3.2 (97)	0.4 (13)
Myalgia[b]	--	--
Any	35.4 (1067)	11.6 (348)
Grade 3	2.5 (76)	0.2 (7)
Arthralgia[b]	--	--
Any	27.8 (839)	10.6 (317)
Grade 3	1.9 (57)	0.2 (6)
Nausea/vomiting[c]	--	--
Any	8.6 (259)	3.4 (102)
Grade 3	0.2 (5)	<0.1 (2)
Chills[b]	--	--
Any	22.8 (688)	4.3 (129)
Grade 3	2.1 (62)	0.1 (4)
Use of antipyretic or pain medication	28.5 (860)	9.1 (272)

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Tables 14.3.1.2.1.f, 14.3.1.2.1.8.f, 14.1.3.3.4.f, and 14.1.3.3.4.1.f. Data cutoff: August 21, 2025.
Abbreviations: Any, Grade 1 or higher; G1, Grade 1; G2, Grade 2; G3, Grade 3, G4, Grade 4; IRT, interactive response technology; n, number of exposed participants who reported the event; N1, number of exposed participants in the solicited safety subset
Numbers are based on actual vaccination group and percentages are based on the number of exposed participants the Solicited Safety Subset.
There were no Grade 4 solicited systemic adverse reactions reported.
The toxicity grade is the maximum toxicity grade reported on any day from Baseline. Assessments by investigator are used in analysis if occurred on the same day as participant's assessments.
[a] Toxicity grade for fever (oral) is defined as: G1=38.0-38.4°C or 100.4-101.1°F; G2=38.5-38.9°C or 101.2-102.0°F; G3=39.0-40.0°C or 102.1-104.0°F; G4: ≥40.0°C or >104.0°F.
[b] Toxicity grade for headache, fatigue, myalgia (muscle aches all over body), arthralgia (joint aches in several joints), and chills are defined as: G1=no interference with activity; G2=some interference with activity; G3=prevent daily activity; G4, requires emergency room visit or hospitalization.
[c] Toxicity grade for nausea/vomiting are defined as: G1=no interference with activity or 1-2 episodes/24 hours; G2=some interference with activity or >2 episodes/24 hours; G3=prevent daily activity or requires outpatient intravenous hydration; G4=requires emergency room visit or hospitalization for hypotensive shock.

The median day of onset for solicited systemic ARs was 2 days postvaccination in both groups. The median duration was 2 days in both groups. A slightly higher proportion of systemic ARs persisted beyond 7 days in the mRNA-1010 (TIV) group compared with the SD comparator group (1.0% versus 0.7%).

Subgroup Analyses for Solicited Adverse Reactions

Solicited ARs were examined across multiple subgroups, including age, race, sex, baseline high-risk classification, prior influenza vaccination status, SD comparator type (TIV or QIV), and geographic region. Across all subgroups, solicited ARs occurred at a higher frequency in mRNA-1010 (TIV) recipients compared with SD comparator recipients. Within the mRNA-1010 (TIV) group, the solicited AR profile was generally consistent across subgroups, with the exception of age, as described below.

Age

Rates of solicited local and systemic ARs by age subgroup are shown in Appendix B Table 21. The magnitude of increased reactogenicity for mRNA-1010 (TIV) relative to the SD comparator was comparable across age subgroups. Among mRNA-1010 (TIV) recipients, the frequency of solicited ARs was slightly lower in participants ≥65 yoa compared with those 50 to 64 yoa. This trend of decreasing reactogenicity with increasing age was also observed when the ≥65 years subgroup was further divided into 65 to 74 years and ≥75 years age groups.

Appendix B Table 21. Frequency of Solicited Adverse Reactions Within 7 Days of Vaccination, Solicited Safety Subset, By Age Subgroup, Study P304

Event	50-64 Years mRNA-1010 (TIV) N1=1510 % (n)	50-64 Years SD Comparator (TIV+QIV) N1=1502 % (n)	≥65 Years mRNA-1010 (TIV) N1=1505 % (n)	≥65 Years SD Comparator (TIV+QIV) N1=1495 % (n)
Any local adverse reaction	--	--	--	--
Any	70.0 (1057)	36.3 (545)	64.9 (977)	27.8 (416)
Grade 3	1.9 (28)	0.1 (2)	1.5 (23)	0.1 (2)
Pain[a]	--	--	--	--
Any	68.7 (1038)	34.4 (517)	62.9 (947)	25.2 (377)
Grade 3	1.1 (17)	<0.1 (1)	0.7 (10)	0
Erythema[b]	--	--	--	--
Any ≥25 mm	4.4 (66)	1.3 (19)	3.4 (51)	1.3 (19)
Grade 3	0.3 (4)	<0.1 (1)	0.4 (6)	<0.1 (1)
Swelling[b]	--	--	--	--
Any ≥25 mm	6.4 (96)	1.2 (18)	5.0 (76)	1.8 (27)
Grade 3	0.3 (4)	0.1 (2)	0.3 (5)	0.1 (2)
Axillary swelling or tenderness[a]	--	--	--	--
Any	20.3 (306)	6.9 (104)	14.2 (214)	5.4 (80)
Grade 3	0.3 (4)	<0.1 (1)	0.4 (6)	0
Any systemic adverse reaction	--	--	--	--
Any	61.4 (927)	33.7 (506)	54.7 (823)	31.0 (464)
Grade 3	6.5 (98)	1.1 (16)	4.6 (69)	0.7 (11)
Fever[c]	--	--	--	--
Any	6.0 (90)	0.9 (13)	5.6 (84)	0.9 (13)
Grade 3	0.7 (11)	0.1 (2)	0.4 (6)	<0.1 (1)
Headache[a]	--	--	--	--
Any	41.9 (633)	20.1 (302)	33.7 (507)	15.8 (236)
Grade 3	2.2 (33)	0.4 (6)	1.7 (26)	0.3 (4)
Fatigue[a]	--	--	--	--
Any	48.1 (727)	20.6 (309)	42.1 (633)	20.1 (300)
Grade 3	3.9 (59)	0.6 (9)	2.5 (38)	0.3 (4)
Myalgia[a]	--	--	--	--
Any	40.6 (613)	13.0 (196)	30.2 (454)	10.2 (152)
Grade 3	2.9 (44)	0.3 (4)	2.1 (32)	0.2 (3)
Arthralgia[a]	--	--	--	--
Any	31.5 (476)	11.1 (167)	24.1 (363)	10.0 (150)
Grade 3	2.3 (34)	0.2 (3)	1.5 (23)	0.2 (3)

Event	50-64 Years mRNA-1010 (TIV) N1=1510 % (n)	50-64 Years SD Comparator (TIV+QIV) N1=1502 % (n)	≥65 Years mRNA-1010 (TIV) N1=1505 % (n)	≥65 Years SD Comparator (TIV+QIV) N1=1495 % (n)
Nausea/vomiting[d]	--	--	--	--
Any	9.7 (147)	4.1 (61)	7.4 (112)	2.7 (41)
Grade 3	0.2 (3)	<0.1 (1)	0.1 (2)	<0.1 (1)
Chills[a]	--	--	--	--
Any	27.5 (415)	4.7 (71)	18.1 (273)	3.9 (58)
Grade 3	2.8 (42)	0.2 (3)	1.3 (20)	<0.1 (1)
Use of antipyretic or pain medication	33.2 (501)	10.5 (157)	23.9 (359)	7.7 (115)

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Tables 14.1.3.3.4.2.f, 14.1.3.3.4.4.f, 14.3.1.2.1.1.f 14.3.1.2.1.9.f., 14.3.1.2.1.1.f, and 14.3.1.2.1.9.f. Data cutoff: August 21, 2025.
Abbreviations: Any, Grade 1 or higher; G1, Grade 1; G2, Grade 2; G3, Grade 3, G4, Grade 4; 50-64; IRT, interactive response technology; N1, number of exposed participants in the Solicited Safety Subset; n, number of exposed participants who reported the event
There were no Grade 4 solicited systemic adverse reactions reported.
Numbers are based on actual vaccination group and percentages are based on the number of exposed participants the Solicited Safety Subset.
The toxicity grade is the maximum toxicity grade reported on any day from Baseline. Assessments by the investigator are used in analysis if occurred on the same day as participant's assessments.
[a] Toxicity grade for injection site pain, axillary (underarm) swelling or tenderness ipsilateral to the side of injection, headache, fatigue, myalgia (muscle aches all over body), arthralgia (joint aches in several joints), and chills are defined as: G1=no interference with activity; G2=some interference with activity; G3=prevent daily activity; G4=requires emergency room visit or hospitalization.
[b] Toxicity grade for injection site erythema (redness) or injection site swelling/induration (hardness) are defined as: G1=25-50 mm; G2=51-100 mm; G3≥100 mm; G4=necrosis (injection site erythema) or exfoliative dermatitis (injection site swelling/induration).
[c] Toxicity grade for fever (oral) is defined as: G1=38.0-38.4°C or 100.4-101.1°F; G2=38.5-38.9°C or 101.2 102.0°F; G3=39.0-40.0°C or 102.1-104.0°F; G4≥40.0°C or >104.0°F.
[d] Toxicity grade for nausea/vomiting are defined as: G1=no interference with activity or 1-2 episodes/24 hours; G2=some interference with activity or >2 episodes/24 hours; G3=prevent daily activity or requires outpatient intravenous hydration; G4=requires emergency room visit or hospitalization for hypotensive shock.

Unsolicited Adverse Events

Unsolicited Adverse Events Through 28 Days After Vaccination

The rates of unsolicited AEs within 28 days of vaccination were balanced: 5.9% of mRNA-1010 (TIV) recipients and 5.7% of SD comparator recipients. Unsolicited AEs were most commonly reported under the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of infections and infestations (1.4% in both groups). Unsolicited AEs within 28 days assessed as related to study vaccine by the investigator were reported in 0.5% of mRNA-1010 (TIV) recipients and 0.2% of SD comparator recipients; this difference was largely attributable to AEs overlapping with protocol-specified solicited ARs, which also occurred more frequently in the mRNA-1010 (TIV) group. Rates of unsolicited AEs were generally similar across subgroups based on age, sex, race, and high-risk status.

Medically Attended Adverse Events (MAAEs)

MAAEs within 28 days of vaccination were reported in 3.8% of participants in both groups. Through study completion (median follow-up of approximately 6 months), 12.3% of mRNA-1010 (TIV) recipients and 12.0% of SD comparator recipients reported at least one MAAE. MAAEs were most frequently reported under the MedDRA SOC of infections and infestations (3.6% in the mRNA-1010 [TIV] group and 3.3% in the SD comparator group). MAAEs assessed as related to study vaccine by the investigator were reported in 23 (0.1%) mRNA-1010 (TIV) recipients and 14 (<0.1%) SD comparator recipients. The most commonly reported related MAAEs were under the SOCs of skin and subcutaneous tissue disorders (5 mRNA-1010 [TIV] recipients and 4 SD comparator recipients)

and cardiac disorders (6 mRNA-1010 [TIV] recipients and 2 SD comparator recipients). No individual preferred term under cardiac disorders was reported by more than one participant, and no clear pattern emerged to suggest a specific safety concern.

Deaths

Within 28 days of vaccination, 7 deaths (<0.1%) were reported in the mRNA-1010 (TIV) group and 9 (<0.1%) in the SD comparator group. Through study completion on August 21, 2025, there were 40 deaths (0.2%) in the mRNA-1010 (TIV) group and 34 deaths (0.2%) in the SD comparator group. No deaths in either group were assessed as related to study vaccine by the investigator. Based on independent review of event narratives, FDA agrees with the investigators' assessments that these deaths were unlikely to be related to study vaccine. In general, the causes of death are representative of common causes of death among older adults and the general U.S. population (e.g., heart disease, motor vehicle accident, cancer).

Serious Adverse Events (SAEs)

SAEs within 28 days of vaccination were reported in 0.5% (n=92) of mRNA-1010 (TIV) recipients and 0.5% (n=92) of SD comparator recipients. Through study completion (median follow-up of approximately 6 months), SAEs were reported in 2.2% (n=455) of mRNA-1010 (TIV) recipients and 1.9% (n=392) of SD comparator recipients. SAEs were most frequently reported under the MedDRA SOCs of infections and infestations (0.4% in each group) and cardiac disorders (0.3% in each group). Through the entire study duration, 4 participants (<0.1%) in the mRNA-1010 (TIV) group and 2 participants (<0.1%) in the SD comparator group reported at least one SAE assessed as related to study vaccine by the investigator. The four SAEs in the mRNA-1010 (TIV) group are described below.

SAEs Assessed as Related to mRNA-1010 (TIV) by the Investigator

Syncope: A 62-year-old female with a history of hypercholesterolemia, hypothyroidism, and insomnia (on trazodone) experienced syncope on Study Day 2. Emergency medical technicians (EMTs) evaluated her at the scene and noted possible dehydration and a temperature of 101.3°F. She also reported body aches, chills, and headache, all of which resolved by Day 3. She declined an ER visit and recovered at home with rest and fluids. The event of syncope was recorded as resolved on Day 2. The Applicant agreed with the investigator's assessment that this event was related to study vaccine.

> **FDA Assessment:** FDA agrees with the investigator's assessment that this SAE of syncope is likely related to study vaccine, given the timing of onset postvaccination and the concurrent documented fever and solicited ARs. However, concurrent trazodone use may also have contributed.

Hypotension: A 67-year-old male with hypertension (pre-dose blood pressure 112/71 mmHg; post-dose 136/90 mmHg on Day 1), type 2 diabetes mellitus, gout, and benign prostatic hyperplasia (on gabapentin, metoprolol, and tamsulosin) reported hypotension on Study Day 2 requiring hospitalization for further evaluation. He reported headache and low blood pressure readings at home that prompted his medical visit. All tests were negative and he was discharged home on Day 4 with hypotension recorded as resolved. On Day 8, he withdrew consent and refused release of further medical information. The Applicant assessed this event as not related to study vaccine.

> **FDA Assessment:** Although the timing of onset is consistent with a possible contribution from study vaccine, the participant reported no reactogenicity during the 7-day postvaccination period. Moderate-to-severe reactogenicity (e.g., fever or nausea/vomiting leading to

dehydration and subsequent hypotension) would have provided additional support for a causal association. Concurrent antihypertensive medications may also have independently contributed.

Myopericarditis and Congestive Cardiomyopathy: A 54-year-old female current smoker with a history of hypertension, hypothyroidism, type 2 diabetes mellitus, and ADHD (on methylphenidate) presented to the ER on Study Day 95 with dyspnea and left-sided chest pain radiating to the neck and arm. She was diagnosed with uncontrolled diabetes mellitus, dilated cardiomyopathy, and myopericarditis, and concurrently reported cough, sputum production, rhinorrhea, and fatigue. Workup demonstrated severely reduced left ventricular ejection fraction, global hypokinesis, third-degree diastolic dysfunction, early dilated cardiomyopathy with signs of past perimyocarditis, and mild mitral valve insufficiency without significant coronary stenoses. She was discharged on Day 103 with dilated cardiomyopathy and myopericarditis ongoing; uncontrolled diabetes was considered resolved. The CEAC concluded that the event did not meet criteria for confirmed or probable myocarditis, acute pericarditis, or myopericarditis. The Applicant assessed these events as unrelated to study vaccine.

> **FDA Assessment:** These events are unlikely to be related to study vaccine. The long latency period, significant medical history, and concurrent symptoms of recent respiratory illness suggest more plausible alternative etiologies.

Myocarditis: A 64-year-old male former smoker with no significant medical history reported an SAE of myocarditis on Study Day 183. On Day 33, he presented with persistent upper respiratory symptoms; nasal swabs were positive for rhinovirus/enterovirus. Over the following months, he developed worsening dyspnea, lower extremity edema, orthopnea, and lethargy. On Day 183, he presented to the ER in atrial fibrillation with markedly elevated brain natriuretic peptide (BNP) and CT evidence of fluid overload. Echocardiography demonstrated severely impaired biventricular systolic function, biventricular and biatrial dilation, and significant valvular regurgitation. He was discharged on Day 191 with a diagnosis of heart failure with reduced ejection fraction, likely secondary to myocarditis. Cardiac MRI on Day 199 showed late gadolinium enhancement (LGE) at the right ventricular insertion point, possible biatrial wall and circumferential pericardial LGE, and severely impaired biventricular function, which the cardiologist assessed as possibly consistent with myocarditis/pericarditis or cardiomyopathy. The CEAC determined the event met criteria for confirmed myopericarditis. The Applicant assessed this event as unrelated to study vaccine.

> **FDA Assessment:** This event is unlikely to be related to study vaccine given the long latency (well outside the typical onset window of within the first week postvaccination observed with mRNA COVID-19 vaccines) and the preceding rhinovirus/enterovirus infection immediately before symptom onset, suggesting a more plausible alternative etiology.

Adverse Events of Special Interest (AESIs)

Protocol-defined AESIs are listed in Appendix A. Through Day 28 postvaccination, AESIs were reported in 4 participants (<0.1%) in the mRNA-1010 (TIV) group and 3 participants (<0.1%) in the SD comparator group. Through study completion (median approximately 6 months of follow-up), 17 participants (<0.1%) in the mRNA-1010 (TIV) group and 15 participants (<0.1%) in the SD comparator group reported AESIs. Of these, 5 were assessed as related by the investigator: 3 in the mRNA-1010 (TIV) group and 2 in the SD comparator group. The investigator-assessed related AESIs in the mRNA-1010 (TIV) group are described below.

AESIs Assessed as Related by the Investigator in the mRNA-1010 (TIV) Group

Thrombocytopenia: A 51-year-old male with a history of regular alcohol use and concomitant meloxicam use experienced a mild event of thrombocytopenia on Day 84 in the context of a concurrent upper respiratory tract infection. The event resolved without intervention.

> **FDA Assessment:** This event is unlikely to be related to study vaccine given the long latency from vaccination. The concurrent respiratory tract infection represents a more plausible alternative etiology.

Myocarditis: A 64-year-old male experienced myocarditis on Day 183 in the context of a concurrent rhinovirus/enterovirus infection. This case and the FDA assessment are described above under SAEs Assessed as Related to mRNA-1010 (TIV) by the Investigator.

Myopericarditis: A 54-year-old female experienced myopericarditis on Day 95 in the context of concurrent SAEs of uncontrolled type 2 diabetes mellitus and congestive cardiomyopathy. This case and the FDA assessment are described above under SAEs Assessed as Related to mRNA-1010 (TIV) by the Investigator.

Pregnancies

No pregnancies were reported throughout the study.

Dropouts and/or Discontinuations

Through study completion on August 21, 2025, deaths led to study discontinuation in 0.2% of participants in each group. Additionally, 3 participants in the mRNA-1010 (TIV) group and 2 in the SD comparator group had AEs leading to study discontinuation. None of the AEs that led to discontinuation in either group were considered related to study vaccine by the investigator or upon FDA assessment.

Appendix C – Study P303 Part C: Efficacy and Safety

NCT05827978

Title: "A Phase 3, Randomized, Stratified, Observer-Blind, Active-Controlled Study to Evaluate the Immunogenicity, Reactogenicity, and Safety of mRNA-1010 Seasonal Influenza Vaccine in Adults 18 Years of Age and Older"

Study Overview

Study mRNA-1010-P303 (P303) was a Phase 3, multicenter, randomized, stratified, observer-blind, active-controlled study evaluating the immunogenicity, reactogenicity, and safety of the quadrivalent mRNA-1010 seasonal influenza vaccine (mRNA-1010 [QIV]). This briefing document focuses on Part C of Study P303, which compared immunogenicity and safety of mRNA-1010 (QIV) to Fluzone High-Dose (QIV) (Fluzone HD [QIV]) in adults 65 yoa and older. Fluzone HD (QIV) is one of three influenza vaccines preferentially recommended by the CDC for this age group.

Data from Study P303 Part C support the immunogenicity assessment of mRNA-1010 relative to a high-dose active comparator in adults 65 yoa and older. This assessment involves two key considerations: (1) an evaluation of the use of hemagglutination inhibition (HAI) as a surrogate endpoint reasonably likely to predict clinical benefit (addressed separately) and (2) an assessment of whether immunogenicity data from the quadrivalent formulation (QIV) can support the effectiveness of the trivalent formulation (TIV) (see Section 3.1.3.4).

The study was initiated on November 13, 2023, and completed on June 24, 2024. The final database lock date was July 22, 2024.

Objectives

Primary Objectives

Primary Immunogenicity Objective

To evaluate the humoral immunogenicity of mRNA-1010 (QIV) for noninferiority relative to Fluzone HD (QIV) against four vaccine-matched influenza A and B strains at Day 29 in adults ≥65 yoa, as measured by HAI.

Endpoints:

- Geometric mean titer (GMT) at Day 29
- Seroconversion rate (SCR) at Day 29

There were eight coprimary endpoints based on GMT ratio and SCR difference for the four vaccine-matched strains. Each endpoint was evaluated for noninferiority of mRNA-1010 (QIV) versus Fluzone HD (QIV) at a two-sided alpha level of 0.05. Study success required all eight coprimary endpoints to meet the noninferiority criteria.

Statistical Criterion for Noninferiority

Noninferiority at Day 29 was demonstrated if, for all four influenza strains:

- Lower limit (LL) of the 95% CI of the GMT ratio (mRNA-1010 [QIV] / Fluzone HD [QIV]) was >0.667.
- LL of the 95% CI of the SCR difference (mRNA-1010 [QIV] − Fluzone HD [QIV]) was >−10%.

Primary Safety Objective

To evaluate the safety and reactogenicity of mRNA-1010 (QIV), including: frequency and severity of solicited local and systemic adverse reactions (ARs) through Day 7; frequency and severity of unsolicited adverse events (AEs) through Day 28; and serious adverse events (SAEs), medically attended adverse events (MAAEs), adverse events of special interest (AESIs), and AEs leading to study discontinuation through Day 181/end of study (EOS).

Secondary Objectives

Secondary Immunogenicity Objectives

To evaluate the humoral immunogenicity of mRNA-1010 (QIV) for superiority relative to Fluzone HD (QIV) against vaccine-matched influenza A and B strains at Day 29, as measured by HAI.

Endpoints:

- GMT at Day 29
- SCR at Day 29

Superiority testing was conducted upon successful demonstration of noninferiority for all eight coprimary endpoints.

Statistical Criterion for Superiority

Superiority at Day 29 was demonstrated if, for each of the four influenza strains:

- LL of the 97.5% CI of the GMT ratio (mRNA-1010 [QIV] / Fluzone HD [QIV]) was >1.
- LL of the 97.5% CI of the SCR difference (mRNA-1010 [QIV] − Fluzone HD [QIV]) was >0.

Descriptive secondary endpoints (no hypothesis testing):

- Proportion of participants with HAI titer ≥1:40 at Day 29
- Geometric mean fold rise (GMFR) from Baseline to Day 29 as measured by HAI

Select Exploratory Objectives (Descriptive; No Hypothesis Testing)

To evaluate the humoral immunogenicity of mRNA-1010 (QIV) relative to Fluzone HD (QIV) against vaccine-matched influenza A and B strains at Day 181/EOS in a participant subset, as measured by HAI.

Endpoints:

- GMT at Day 181
- SCR at Day 181

Design

A total of 3,003 participants were enrolled at 96 centers in the United States and randomized 1:1 to receive a single intramuscular injection of either mRNA-1010 (QIV) or Fluzone HD (QIV). The influenza strains encoded in mRNA-1010 (QIV) were aligned with FDA recommendations for the 2023/2024 Northern Hemisphere (NH) influenza vaccine for cell- or recombinant-based vaccines. The strains in Fluzone HD (QIV) were aligned with FDA recommendations for 2023/2024 NH egg-based vaccines.

Randomization was stratified by prior influenza season vaccination status (received or not received; if received, whether from prior participation in Study P302). Total study duration, including screening, was up to 7 months per participant.

Medically stable adults ≥65 yoa were enrolled. Key exclusion criteria were similar to those in Study P304 (see Appendix B). After the screening visit, participants completed up to two clinic visits (Day 1 and Day 29) and three telephone visits (Day 8, Day 91, and Day 181/EOS). The first 1,000 participants enrolled also attended a clinic visit on Day 181 (Month 6)/EOS for immunogenicity blood sampling; remaining participants were contacted by telephone.

Evaluation of Immunogenicity

Blood samples for HAI antibody assessment were collected at Day 1 (Baseline), Day 29, and Day 181/EOS (in a subset of participants). Microneutralization (MN) immunogenicity analyses were performed on a randomly selected subset of 500 participants (250 per vaccination group) from the per-protocol immunogenicity set (PPIS).

Evaluation of Safety

Study oversight and safety monitoring—including solicited and unsolicited AEs, MAAEs, AESIs, SAEs, and AEs leading to study discontinuation—were conducted as described for Study P304 (see Appendix B).

Analysis Populations

Appendix C Table 1. Analysis Sets

Analysis Set	Description
Randomization Set	All participants who were randomly assigned to the study injection, regardless of the participants' study intervention status in the study.
FAS	All participants in the Randomization Set who received any study injection. Participants were analyzed according to the group to which they were randomized.
Immunogenicity Subset	All participants in the FAS who had Baseline and Day 29 antibody assessment via HAI assay. Participants were analyzed according to the group to which they were randomized.
PPIS	The PPIS included all participants in the Immunogenicity Set who received the planned dose of study intervention, complied with the immunogenicity testing schedule for Baseline and Day 29[4], and had no significant protocol deviations that impacted key or critical data. Participants with RT-PCR–confirmed influenza between Days 1 and 29 were removed from the PPIS. The PPIS was used for all analyses of immunogenicity unless otherwise specified. Participants were analyzed according to the group to which they were randomized.
PPIS microneutralization (MN) Subset	Participants randomly selected from PPIS for MN analyses with MN values on Day 1 and Day 29.
Solicited Safety Set	All participants in the FAS who contributed any solicited AR data. The Solicited Safety Set was used for the analyses of solicited ARs. Participants were included in the group corresponding to the study intervention that they actually received.
Safety Set	All participants in the FAS. The Safety Set was used for all analyses of safety except for the solicited ARs. Participants were included in the group corresponding to the study intervention that they actually received.

Source: Adapted from STN 125869/0, mmRNA-1010-P303 Part B and C CSR Table 8.
Abbreviations: AR, adverse reaction; FAS, full analysis set; HAI, hemagglutination inhibition; PPIS, per-protocol immunogenicity set; RT-

[4] Compliance with the immunogenicity testing schedule for Baseline and Day 29 is defined as having immunogenicity samples collected before the study intervention administration and between Day 22 and Day 43 (i.e., −7/+14 days of Day 29).

PCR, reverse transcription polymerase chain reaction

Subgroup Analyses

Immunogenicity subgroup analyses were conducted for the following subgroups: age (65 to <75 years; ≥75 years), prior influenza vaccination status (received, received from Study P302, not received), race, sex, and BMI category (<30 kg/m² or ≥30 kg/m²). Unsolicited AE analyses were conducted for all subgroups except prior influenza vaccination status and BMI.

Post Hoc Analyses

Post hoc analyses of immunogenicity and safety were performed in high-risk participants, defined as those with a significant comorbidity based on medical history, including autoimmune and immune-mediated disorders; chronic obstructive pulmonary disease; diabetes; cardiac disorders; blood, renal, and hepatic disorders; mental impairment; and neurologic disorders.

The Applicant also conducted a post hoc analysis comparing Day 29 HAI GMTs between the PPISs of Study P303 Part C and Study P304, restricted to participants 65 yoa and older, to support the use of immunogenicity data from mRNA-1010 (QIV) to support licensure of mRNA-1010 (TIV).

Study Population and Disposition

Participant disposition in the immunogenicity populations is shown in Appendix C Table 2. The percentages of participants excluded from the PPIS were similar between groups: 2.3% in the mRNA-1010 (QIV) group and 1.9% in the Fluzone HD (QIV) group. The most common reasons for exclusion were significant protocol deviations (1.0% in each group) and noncompliance with immunogenicity blood sampling timing (1.2% and 0.8%, respectively).

Appendix C Table 2. Participant Disposition, Adults 65 Years of Age and Older, Immunogenicity Populations, Study P303 Part C

Population	mRNA-1010 N=1507 n (%)	Fluzone HD (QIV) N=1496 n (%)
FAS[a]	1504 (99.8)	1492 (99.7)
Immunogenicity Set	1458 (96.7)	1437 (96.1)
PPIS	1425 (94.6)	1409 (94.2)
Excluded from PPIS	33 (2.3)	28 (1.9)
Reason for exclusion from PPIS	--	--
Major dosing error	1 (<0.1)	1 (<0.1)
Did not comply with timing of immunogenicity blood sampling	14 (1.0)	15 (1.0)
Had significant protocol deviations that impact key or critical data	18 (1.2)	12 (0.8)

Source: Adapted from STN 125869/0, mRNA-1010-P303 Part B and Part C Clinical Study Report, Table 14.1.2.2.1.c, and Table 14.1.3.1.c. Data cutoff: June 24, 2024.
Abbreviations: FAS, full analysis set; HD, high dose; N, number of participants in the Randomization Set; n, number of participants in a given subpopulation or category; PPIS, per-protocol immunogenicity set
[a] Numbers are based on the planned vaccination group and percentages are based on the number of participants in the Randomization Set.

Participant disposition in the Safety Set is shown in Appendix C Table 3. Overall study discontinuation was slightly lower in the mRNA-1010 (QIV) group (1.3%) than in the Fluzone HD (QIV) group (2.4%). The most common reasons for discontinuation were lost to follow-up (0.7% vs. 1.7%) and withdrawal

of consent by the participant (0.5% vs. 0.7%). No participant discontinued due to an adverse event. The median duration of follow-up after vaccination was 171 days in both groups.

Appendix C Table 3. Participant Disposition, Adults 65 Years of Age and Older, Safety Populations, Study P303 Part C

Population	mRNA-1010 (QIV) N=1502 n (%)	Fluzone HD (QIV) N=1490 n (%)
Received injection	1502 (100)	1490 (100)
Completed the study[a]	1482 (98.7)	1454 (97.6)
Discontinued from the study	20 (1.3)	36 (2.4)
Reason for discontinuation	--	--
Adverse event	0	0
Death	3 (0.2)	1 (<0.1)
Lost to follow-up	10 (0.7)	25 (1.7)
Withdrawal of consent by participant	7 (0.5)	10 (0.7)
Median follow-up (days) (min, max)	171.0 (1, 207)	171.0 (1, 204)

Source: Adapted from STN 125869/0, mRNA-1010-P303 Part B and Part C Clinical Study Report, Table 14.1.1.1.2.c, Table 14.1.4.3.4.c. Data cutoff: June 24, 2024.
Abbreviations: HD, high dose; max, maximum; min, minimum; N, number of participants in the Safety Set; n, number of participants in a given subpopulation or category; QIV, quadrivalent influenza vaccine
[a] Participants are considered completed the study if they completed the final visit on Day 181 (Month 6).

Demographics and Other Baseline Characteristics

Demographic and baseline characteristics of participants in the Safety Set are shown in Appendix C Table 4. Characteristics were similar across the mRNA-1010 (QIV) and Fluzone HD (QIV) groups and were comparable to those in the PPIS. The median age was 70 years (range: 64–93 years). The majority of participants were 65 to <75 yoa; 22.1% were ≥75 years. Most participants were White (82.7%) and female (57.8%). Over half (52.6%) had received a seasonal influenza vaccine in the prior season.

High-risk comorbidities were present in 37.7% of mRNA-1010 (QIV) participants and 40.7% of Fluzone HD (QIV) participants. Diabetes mellitus was the most prevalent condition in both groups (20.4% and 24.1%, respectively). The overall prevalence of high-risk conditions in this study population was lower than population-level estimates, which indicate that 93% of U.S. adults 65 yoa and older have at least one high-risk condition (Watson et al., 2025). As in Study P304, this difference in prevalence likely reflects differences in how high-risk conditions were defined as well as the exclusion of certain high-risk participants (e.g., those who were immunocompromised or taking immunosuppressive medications)..

The prevalence of obesity (BMI ≥30 kg/m²) in Study P303 Part C was higher than reported in the general U.S. population (29.5% of U.S. adults ≥65 yoa), with regional variation noted in the Midwest and South (America's Health Rankings, 2025). The proportion of participants who received an influenza vaccine in the prior season (52.6%) was lower than the national estimate of 71.3% reported by the CDC National Health Interview Survey (NCHS, 2024).

Appendix C Table 4. Demographic and Baseline Characteristics, Adults 65 Years of Age and Older, Safety Set, Study P303 Part C

Characteristic	mRNA-1010 (QIV) N=1502	Fluzone HD (QIV) N=1490
Sex, n (%)	--	--
Male	624 (41.5)	638 (42.8)
Female	878 (58.5)	852 (57.2)
Age, years	--	--
Median age (min, max)	70.0 (65, 93)	70.0 (64, 93)
65 to <75 years of age	1176 (78.3)	1154 (77.4)
≥75 years of age	326 (21.7)	335 (22.5)
Race, n (%)	--	--
African American/Black	224 (14.9)	235 (15.8)
American Indian or Alaska Native	4 (0.3)	9 (0.6)
Asian	10 (0.7)	10 (0.7)
Native Hawaiian or other Pacific Islander	2 (0.1)	0
White	1255 (83.6)	1220 (81.9)
Multiracial	2 (0.1)	6 (0.4)
Other	1 (<0.1)	4 (0.3)
Unknown	1 (<0.1)	4 (0.3)
Not reported	3 (0.2)	2 (0.1)
Ethnicity, n (%)	--	--
Hispanic/Latino	450 (30.0)	454 (30.5)
Not Hispanic/Latino	1037 (69.0)	1021 (68.5)
Not reported	14 (0.9)	14 (0.9)
Unknown	1 (<0.1)	1 (<0.1)
Body mass index (kg/m^2)	--	--
Median (min, max)	28.90 (10.3, 61.9)	28.90 (7.6, 58.2)
<30 kg/m^2	865 (57.6)	845 (56.7)
≥30 kg/m^2	637 (42.4)	645 (43.3)
≥40 kg/m^2	113 (7.5)	99 (6.6)
Influenza vaccine status, n (%)	--	--
Received seasonal flu vaccine	787 (52.4)	787 (52.8)
Did not receive previous seasonal flu vaccine	715 (47.6)	703 (47.2)
High-risk condition*	567 (37.7)	607 (40.7)
Autoimmune/immune mediated disease	50 (3.3)	45 (3.0)
Blood disorders	3 (0.2)	4 (0.3)
Cardiac disorders	171 (11.4)	177 (11.9)
Diabetes mellitus	307 (20.4)	359 (24.1)
Hepatic disorders	22 (1.5)	28 (1.9)
Mental impairment disorders	0 (0)	2 (0.1)
Nervous system disorders	7 (0.5)	5 (0.3)
Pulmonary disorders	141 (9.4)	169 (11.3)
Renal disorders	20 (1.3)	22 (1.5)
No high-risk condition	935 (62.3)	883 (59.3)

Source: Adapted from STN 125869/0, mRNA-1010-P303 Part B and Part C Clinical Study Report, Table 14.1.4.1.3.c; Table 14.1.4.1.7.c; and Table 14.1.2.2.5.c. Data cutoff: June 24, 2024.

Abbreviations: BMI, body mass index: (body weight in kilograms)/(height in meters)^2; HD, high dose; max, maximum; min, minimum; N, number of participants in safety set; n, number of participants in the safety set in the given subpopulation/category; QIV, quadrivalent influenza vaccine

Baseline values for height, weight, and BMI were defined as the most recent nonmissing measurement (scheduled or unscheduled) collected on or before the study injection.

Numbers were based on the actual vaccination group, and percentages were based on the number of participants in the Safety Set.

* Defined post hoc.

Analyses of Vaccine Effectiveness

Analysis of the Primary Objective

Analyses of the primary immunogenicity endpoints, as measured by HAI for vaccine-matched influenza strains at Day 29 postvaccination, are shown in Appendix C Table 5 (GMTs and GMT ratios) and Appendix C Table 6 (SCRs and SCR differences). Baseline GMTs were similar across groups. Day 29 GMTs and SCRs were higher in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group for all four influenza strains.

Noninferiority of mRNA-1010 (QIV) compared with Fluzone HD (QIV) was demonstrated for all four strains based on GMT ratio (LL of the 95% CI >0.667) and SCR difference (LL of the 95% CI >−10%). Protocol-defined superiority was also demonstrated for all four strains based on GMT ratio (LL of the 97.5% CI >1) and SCR difference (LL of the 97.5% CI >0%).

Appendix C Table 5. Analyses of Primary Immunogenicity Endpoint of GMTs as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29 Postvaccination, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Endpoint	mRNA-1010 (QIV) N=1425 GMT (95% CI)	Fluzone HD (QIV) N=1409 GMT (95% CI)	GMT Ratio (mRNA-1010 [QIV] / Fluzone HD [QIV]) (95% CI) (97.5% CI)
Influenza A/H1N1	168.3 (160.4, 176.7)	125.7 (119.7, 131.9)	1.3 (1.3, 1.4) (1.2, 1.4)
Influenza A/H3N2	137.9 (130.9, 145.4)	113.8 (107.9, 120)	1.2 (1.1, 1.3) (1.1, 1.3)
Influenza B/Victoria	242.1 (232.9, 251.6)	193.7 (186.3, 201.3)	1.3 (1.2, 1.3) (1.2, 1.3)
Influenza B/Yamagata	102.7 (99.2, 106.2)	89.8 (86.8, 92.9)	1.1 (1.1, 1.2) (1.1, 1.2)

Source: Adapted from STN 125869/0, mRNA-1010 P303 Clinical Study Report, Table 14.2.1.1.c. Data cutoff: June 24, 2024.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GMT, geometric mean titer; HAI, hemagglutination inhibition; HD, high dose; LLOQ, lower limit of quantification; N, number of participants with nonmissing HAI data at corresponding visit; PPIS, per protocol immunogenicity set; QIV, quadrivalent; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
The log-transformed antibody levels are 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: Influenza Vaccine Status Since September 2022 to 6 Months Ago (not received seasonal flu vaccine, received seasonal flu vaccine from non mRNA-1010-P302, and received seasonal flu vaccine from mRNA-1010-P302).
The model based GMT and GMT ratio, and its corresponding 95% CI and/or 97.5% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Appendix C Table 6. Analyses of Primary Immunogenicity Endpoint of SCRs as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29 Postvaccination, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Endpoint	mRNA-1010 (QIV) N=1425 SCR%[a] (95% CI)	Fluzone HD (QIV) N=1409 SCR%[a] (95% CI)	Difference in SCR (mRNA-1010 [QIV]−Fluzone HD [QIV]) (95% CI)[b] (97.5%CI)[c]
Influenza A/H1N1	49.7 (47.1, 52.3)	36.3 (33.8, 38.8)	13.4 (9.8, 17) (9.3, 17.5)
Influenza A/H3N2	56.4 (53.8, 59)	47.8 (45.2, 50.5)	8.6 (4.9, 12.2) (4.4, 12.8)
Influenza B/Victoria	29.8 (27.5, 32.3)	20.2 (18.1, 22.4)	9.7 (6.5, 12.8) (6, 13.3)
Influenza B/Yamagata	26.0 (23.8, 28.4)	20.2 (18.1, 22.4)	5.9 (2.8, 8.9) (2.3, 9.4)

Source: Adapted from STN 125869/0, mRNA-1010 P303 Clinical Study Report, Table 14.2.1.1.c. Data cutoff: June 24, 2024
Abbreviations: CI, confidence interval; HAI, hemagglutination inhibition; HD, high dose; LLOQ, lower limit of quantification; N, number of participants with nonmissing HAI data at baseline (Day 1) and the corresponding visit; PPIS, per protocol immunogenicity set; QIV, quadrivalent influenza vaccine; SCR, seroconversion rate; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
[a] Rate of seroconversion is defined as the proportion of participants with either a baseline HAI titer <1:10 and a postbaseline titer ≥1:40 or a baseline HAI titer ≥1:10 and a minimum 4-fold rise in postbaseline HAI antibody titer.
[b] 95% CI is calculated using the Clopper-Pearson method.
[c] 95% CI, 97.5% CI are calculated using the Miettinen-Nurminen (score) method.

Post Hoc Analysis of mRNA-1010 (QIV) and mRNA-1010 (TIV)

To support the use of immunogenicity data from the quadrivalent formulation (evaluated in Study P303 Part C) for licensure of the trivalent formulation in adults 65 yoa and older, the Applicant conducted a post hoc analysis comparing Day 29 HAI GMTs between the PPISs of Study P303 Part C and Study P304, restricted to participants ≥65 yoa, shown in Appendix C Table 7.

Although this was a descriptive post hoc analysis, the LL of the 95% CI of the Day 29 HAI GMT ratio (mRNA-1010 [QIV] / mRNA-1010 [TIV]) for each of the three shared strains was >0.667, which would have met the conventional success criteria for noninferiority.

Appendix C Table 7. Supportive Post-hoc Analyses of Day 29 HAI Antibody Levels for Seasonal Influenza Strains Comparing mRNA-1010 QIV (Study P303 Part C) and TIV (Study P304) in Adults ≥65 Years of Age (PPIS)

Influenza Subtype	Model	mRNA-1010 (QIV) Study P303 Part C N=1425 Model-based GMT (95% CI)	mRNA-1010 (TIV) Study P304 N=586 Model-based GMT (95% CI)	Model-based GMT Ratio (QIV / TIV) (95% CI)
A/H1N1	Model 1: ANCOVA with 6 PCA factors	161.13 (153.80, 168.81)	159.36 (148.08, 171.50)	1.011 (0.926, 1.104)
A/H1N1	Model 2: ANCOVA with 4 PCA factors	160.96 (153.61, 168.67)	159.77 (148.41, 171.99)	1.007 (0.923, 1.100)
A/H3N2	Model 1: ANCOVA with 6 PCA factors	138.85 (132.12, 145.92)	158.13 (146.26, 170.95)	0.878 (0.800, 0.964)

A/H3N2	Model 2: ANCOVA with 4 PCA factors	138.83 (132.09, 145.91)	158.19 (146.29, 171.04)	0.878 (0.800, 0.963)
B/Victoria	Model 1: ANCOVA with 6 PCA factors	234.78 (225.85, 244.07)	289.93 (272.69, 308.25)	0.810 (0.753, 0.871)
B/Victoria	Model 2: ANCOVA with 4 PCA factors	234.58 (225.65, 243.87)	290.55 (273.26, 308.94)	0.807 (0.750, 0.869)

Source: Adapated Adapted from STN 125869/0, Amendment 32, Response to IR Database lock/data extraction dates: 22 Jul 2024 (P303 Part C) and 03 Jun 2025 (P304).
The ANCOVA model includes vaccine (mRNA-1010 QIV in P303C or mRNA-1010 TIV in P304) as a fixed factor, log-transformed baseline HAI titer as a fixed covariate, adjusted for the selected top principal components from the PCA of the demographic and baseline characteristics. Model 1 incorporates 6 PCA factors which explained 82% of the total variance and Model 2 incorporates 4 PCA factors which explained 62% of the total variance.

This analysis has several limitations:

- Studies P303 Part C and P304 were conducted in different influenza seasons using different WHO-recommended strains.
- Participants were not randomized between studies; although baseline demographics were adjusted for, residual confounding may remain.

For Influenza A/H1N1, a GMT ratio of 1.0 indicates no meaningful difference between mRNA-1010 (QIV) and mRNA-1010 (TIV). For Influenza A/H3N2 and B/Victoria, mRNA-1010 (QIV) elicited slightly lower antibody responses than mRNA-1010 (TIV) (point estimate and upper bound of the 95% CI both <1.0), although the noninferiority threshold was met for both strains (data not shown). This suggests that inclusion of B/Yamagata may have reduced immune responses to A/H3N2 and B/Victoria in mRNA-1010 (QIV). Because this potential reduction biases results against mRNA-1010 (QIV) rather than the comparator, mRNA-1010 (TIV) would be expected to generate equal or higher immune responses to these two strains compared with mRNA-1010 (QIV). Notwithstanding the limitations of this analysis, FDA's preliminary assessment is that mRNA-1010 (QIV) immunogenicity data may be used to support the effectiveness of mRNA-1010 (TIV) in adults 65 yoa and older.

Subpopulation Immunogenicity Analyses

The Applicant conducted subgroup analyses for the primary immunogenicity endpoints. The noninferiority criteria based on GMT ratio and SCR difference would have been met across all four strains in every subgroup with a sufficient sample size for meaningful interpretation.

Analysis of the Secondary Immunogenicity Endpoint

Secondary immunogenicity results demonstrating superiority of mRNA-1010 (QIV) compared with Fluzone HD (QIV) against vaccine-matched influenza A and B strains at Day 29 are shown in Appendix C Table 5 and Table 6. The study met prespecified superiority criteria for all eight endpoints (LL of the 97.5% CI >1 for GMT ratio and >0 for SCR difference for each strain).

Descriptive secondary endpoints showed that both the proportion of participants with HAI titer ≥1:40 and the GMFR from Baseline to Day 29 were higher in mRNA-1010 (QIV) recipients than in Fluzone HD (QIV) recipients across all four influenza strains (Appendix C Table 8).

Appendix C Table 8. Analyses of Secondary Immunogenicity Endpoint of Anti-HA Antibody Titers ≥1:40 and GMFR at Day 29 for Vaccine-Matched Influenza Strains, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Endpoint	mRNA-1010 (QIV) N=1425 Titer ≥1:40 n (%)[a] (95% CI)[b]	Fluzone HD (QIV) N=1409 Titer ≥1:40 n (%)[a] (95% CI)[b]	mRNA-1010 (QIV) N=1425 GMFR (95% CI)[c]	Fluzone HD (QIV) N=1409 GMFR (95% CI)[c]
Influenza A/H1N1	1375 (96.5) (95.4, 97.4)	1301 (92.3) (90.8, 93.7)	3.5 (3.3, 3.7)	2.6 (2.5, 2.7)
Influenza A/H3N2	1323 (92.8) (91.4, 94.1)	1252 (88.9) (87.1, 90.5)	4.1 (3.9, 4.4)	3.4 (3.2, 3.6)
Influenza B/Victoria	1425 (100) (99.7, 100)	1402 (99.5) (98.9, 99.8)	2.4 (2.3, 2.5)	1.9 (1.8, 1.9)
Influenza B/Yamagata	1370 (96.1) (95, 97.1)	1320 (93.7) (92.3, 94.9)	2.2 (2.1, 2.3)	1.9 (1.9, 2)

Source: Adapted from STN 125869/0, mRNA-1010 P303 Clinical Study Report, Table 14.2.2.1.c. Data cutoff: June 24, 2024.
Abbreviations: CI, confidence interval; GMFR, geometric mean of fold rise; HA, hemagglutinin; HD, high dose; LLOQ, lower limit of quantification; N, number of participants with nonmissing HAI data at baseline (Day 1) and the corresponding visit; PPIS, per-protocol Immunogenicity Set; QIV, quadrivalent; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
[a] Number of participants meeting the criterion at the corresponding visit. Percentage is based on N.
[b] 95% CI is calculated using the Clopper-Pearson method

Exploratory Immunogenicity Objectives

GMT and SCR at EOS/Day 181

Appendix C Table 9 shows GMTs measured by HAI at EOS/Day 181 in participants with Day 181 data. GMTs remained higher in the mRNA-1010 (QIV) group compared with the Fluzone HD (QIV) group for all four influenza strains, although confidence intervals overlapped for all strains except A/H3N2.

Appendix C Table 9. Analysis of GMTs as Measured by HAI for Vaccine-Matched Influenza Strains at EOS/Day 181, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Strain	mRNA-1010 (QIV) N=462 GMT (95% CI)[a]	Fluzone HD (QIV) 240 µg N=459 GMT (95% CI)[a]	GMT Ratio (mRNA-1010 [QIV] / Fluzone HD [QIV]) (95% CI)[b]
Influenza A/H1N1	78.2 (72.1, 84.8)	68.3 (62.9, 74.1)	1.1 (1.0, 1.3)
Influenza A/H3N2	65.8 (60.4, 71.9)	54.7 (50.2, 59.6)	1.2 (1.1, 1.4)
Influenza B/Victoria	132.8 (124.7, 141.5)	122.8 (115.3, 130.9)	1.1 (0.9, 1.2)
Influenza B/Yamagata	55.9 (52.6, 59.5)	53.9 (50.7, 57.3)	1.0 (0.9, 1.1)

Source: Adapted from STN 125869/0, mRNA-1010 P303 Clinical Study Report, Table 14.2.2.9.c., from Amendment 55 Response to IR #43 dated May 15, 2026. Data cutoff: June 24, 2024.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EOS, end of study; GMT, geometric mean titer; HAI, hemagglutination inhibition; HD, high dose; IR, information request; LLOQ, lower limit of quantification; PPIS, per-protocol immunogenicity set; QIV, quadrivalent influenza vaccine; ULOQ, upper limit of quantification
Antibody values reported as below the LLOQ are replaced by 0.5× LLOQ. Values greater than the ULOQ are converted to the ULOQ.
[a] The log-transformed antibody levels are 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: Influenza Vaccine

Appendix C Table 10 shows the percentage of participants with seroconversion at EOS/Day 181. The proportion of participants with seroconversion was higher in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group for all four strains, although confidence intervals overlapped for all strains except A/H1N1.

Appendix C Table 10. Analysis of SCR as Measured by HAI for Vaccine-Matched Influenza Strains at EOS/Day 181, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Strain	mRNA-1010 (QIV) N=462 SCR%[a] (95% CI)[b]	Fluzone HD (QIV) N=459 SCR%[a] (95% CI)[b]	Difference in SCR (mRNA 1010 [QIV] − Fluzone HD [QIV]) (95% CI)[c]
Influenza A/H1N1	28.6 (24.5, 32.9)	19.4 (15.9, 23.3)	9.2 (3.7, 14.7)
Influenza A/H3N2	31.4 (27.2, 35.8)	23.3 (19.5, 27.5)	8.1 (2.3, 13.8)
Influenza B/Victoria	12.1 (9.3, 15.5)	9.4 (6.9, 12.4)	2.8 (-1.3, 6.8)
Influenza B/Yamagata	9.1 (6.6, 12.1)	7.8 (5.5, 10.7)	1.3 (-2.4, 4.9)

Source: Adapted from STN 125869/0, mRNA-1010 P303 Clinical Study Report, Table 14.2.2.1.c. Data cutoff: June 24, 2024.
Abbreviations: CI, confidence interval; EOS, end of study; HAI, hemagglutination inhibition; HD, high dose; PPIS, per protocol immunogenicity set; QIV, quadrivalent influenza vaccine; SCR, seroconversion rate
[a] Rate of seroconversion is defined as the percentage of participants with either a baseline HAI titer <1:10 and a postbaseline titer ≥1:40 or a baseline HAI titer ≥1:10 and a minimum 4-fold rise in postbaseline HAI antibody titer.
[b] 95% CI is calculated using the Clopper-Pearson method.
[c] 95% CI is calculated using the Miettinen-Nurminen (score) method.

Anti-HA Antibody Titers ≥1:40 and GMFRs at EOS/Day 181

At Day 181, the percentage of participants with HAI titers ≥1:40 was slightly higher in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group for Influenza A/H1N1 (84.9% vs. 79.1%), A/H3N2 (75.3% vs. 69.9%), and B/Yamagata (83.2% vs. 80.4%), and similar for B/Victoria (98.7% vs. 99.3%); 95% CIs overlapped between groups for all four strains. GMFR from Baseline to Day 181 was higher in the mRNA-1010 (QIV) group for both influenza A strains and similar between groups for both influenza B strains.

MN Titers at Day 29

Day 29 MN titers were evaluated in 250 participants per vaccination group in the PPIS MN Subset. Day 29 GMT levels and GMFRs from Baseline were higher in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group for all four influenza strains. For A/H1N1, 95% CIs did not overlap; for A/H3N2 and both influenza B strains, 95% CIs overlapped. Subgroup analyses of MN data showed GMT ratios were similar across subgroups by age and prior influenza vaccine status. MN titers were positively correlated with HAI titers for each influenza strain.

Safety Analyses

The Safety Set included 2,993 participants: 1,502 in the mRNA-1010 (QIV) group and 1,490 in the Fluzone HD (QIV) group. The median duration of safety follow-up was 171 days in both groups (database lock: July 22, 2024).

Overview of Adverse Events

Appendix C Table 11 summarizes the rates of solicited ARs and unsolicited AEs. Solicited AR rates through Day 7 were higher in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group. Rates of unsolicited AEs through Day 28, and MAAEs, SAEs, and AESIs through study completion, were similar between groups.

Appendix C Table 11. Number and Percentage of Participants 65 Years of Age and Older Reporting at Least One Safety Event, Safety Set and Solicited Safety Set, Study P303 Part C

Event Type	mRNA-1010 (QIV) % (n/N1)	Fluzone HD (QIV) % (n/N1)
Solicited adverse reactions within 7 days	--	--
Any solicited adverse reaction	75.3 (1131/1502)	49.3 (734/1490)
Solicited local adverse reaction[a]	66.1 (993/1502)	38.9 (580/1490)
Grade 3 or above solicited local adverse reaction	2.4 (36/1502)	0.8 (12/1490)
Solicited systemic adverse reaction[b]	61.3 (920/1502)	32.9 (490/1489)
Grade 3 or above solicited systemic adverse reaction	6.9 (103/1502)	1.7 (25/1489)
Unsolicited adverse events	--	--
Unsolicited adverse event through 28 days after vaccination	10.3 (155/1502)	9.2 (137/1490)
Nonserious unsolicited adverse event[c]	9.9 (149/1502)	9.1 (135/1490)
Severe nonserious unsolicited AE	<0.1 (1/1502)	0
Medically attended adverse events throughout the study	17.1 (257/1502)	16.6 (248/1490)
Related MAAE[d]	0.3 (4/1502)	<0.1 (1/1490)
SAE throughout the study	2.7 (41/1502)	2.6 (38/1490)
Related SAE[d]	0	<0.1 (1/1490)
AESI throughout the study	0.1 (2/1502)	<0.1 (1/1490)
Related AESI[d]	<0.1 (1/1502)	0
Deaths throughout the study	0.2 (3/1502)	<0.1 (1/1490)
Related deaths[d]	0	0
AE leading to study discontinuation throughout the study	0	0

Source: Adapted from STN 125869/0, mRNA-1010-P303 Part B and Part C Clinical Study Report, Table 14.3.1.2.1.c and Table 14.3.2.1.1.c. Data cutoff: June 24, 2024.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; MAAE, medically attended adverse event; n, number of exposed participants who reported the event; N1, number of exposed participants who submitted any data for the event; SAE, serious adverse event
Any solicited local or systemic adverse reactions that meet the definition of an SAE are considered as AE.
Numbers are based on actual vaccination group and percentages are based on the number of participants in the Safety Set.
[a] Solicited local reactions included pain, erythema (redness), swelling (hardness), axillary swelling or tenderness.
[b] Solicited systemic reactions included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills.
[c] Participants with at least one nonserious AE that was also severe/≥grade 3.
[d] The event was considered related to study vaccination by the investigator.

Solicited Adverse Reactions

Solicited ARs were generally higher in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group, consistent with findings from Study P304. The rates and severity of solicited ARs among mRNA-1010 (QIV) recipients in Study P303 Part C were comparable to those among mRNA-1010 (TIV) recipients in the same age subgroup in Study P304.

Solicited Local Adverse Reactions

Appendix C Table 12 shows the percentages of participants reporting solicited local ARs, by maximum severity. Solicited local ARs were reported by 66.1% of mRNA-1010 (QIV) recipients and 38.9% of Fluzone HD (QIV) recipients. The most frequently reported local AR was injection site pain (64.6% vs. 36.7%). The majority of local ARs were Grade 1 or 2. Grade 3 ARs were reported in 2.4% of mRNA-1010 (QIV) recipients versus 0.8% of Fluzone HD (QIV) recipients. No Grade 4 solicited local ARs were reported in either group.

The median onset of solicited local ARs was Day 2 postvaccination in the mRNA-1010 (QIV) group and Day 1 in the Fluzone HD (QIV) group. Median duration was 2 days in both groups. A higher

percentage of solicited local ARs persisted beyond 7 days in the mRNA-1010 (QIV) group (1.2%) compared with the Fluzone HD (QIV) group (0.5%).

Appendix C Table 12. Summary of Participants with Solicited Local ARs Within 7 Days After Injection by Toxicity Grade, 65 Years of Age and Older, Solicited Safety Set, Study P303 Part C

Solicited Adverse Reaction Category, Grade	mRNA-1010 (QIV) N1=1502 % (n)	Fluzone HD (QIV) N1=1490 % (n)
Any solicited local adverse reaction	--	--
Any	66.1 (993)	38.9 (580)
Grade 3	2.4 (36)	0.8 (12)
Injection site pain[a]	--	--
Any	64.6 (971)	36.7 (547)
Grade 3	1.5 (23)	0.4 (6)
Erythema (redness)[b]	--	--
Any	2.8 (42)	1.3 (20)
Grade 3	0.4 (6)	0.2 (3)
Swelling (hardness)[b]	--	--
Any	4.5 (67)	1.7 (25)
Grade 3	0.4 (6)	0.1 (2)
Axillary swelling or tenderness[a]	--	--
Any	16.8 (252)	8.6 (128)
Grade 3	0.5 (8)	0.4 (6)

Source: Adapted from STN 125869/0, mRNA-1010-P303 Part B and Part C Clinical Study Report, Table 14.3.1.2.1.c. Data cutoff: June 24, 2024.
Abbreviations: Any, Grade 1 or higher; AR, adverse reaction; CI, confidence interval; G, grade; n, number of exposed participants who reported the event on any day within 7 days of study injection; N1, number of exposed participants in the Solicited Safety Subset; QIV, quadrivalent influenza vaccine
There were no Grade 4 solicited local ARs reported in either group.
The toxicity grade is the maximum toxicity grade reported on any day from Baseline. Assessments by investigator are used in analysis if occurred on the same day as participant's assessments.
[a] Toxicity grade for injection site pain, axillary swelling or tenderness ipsilateral to the side of injection are defined as: G1=no interference with activity; G2=some interference with activity; G3=prevent daily activity; G4=requires emergency room visit or hospitalization.
[b] Toxicity grade for injection site erythema (redness) or injection site swelling/induration (hardness) are defined as: G1=25-50 mm; G2=51-100 mm; G3≥100 mm; G4=necrosis (injection site erythema) or exfoliative dermatitis (injection site swelling/induration).
Numbers were based on actual group and percentages were based on the number of exposed participants who submitted any data for the event(s).

Solicited Systemic Adverse Reactions

Appendix C Table 13 shows the percentages of participants reporting solicited systemic ARs, by maximum severity. Solicited systemic ARs were reported by 61.3% of mRNA-1010 (QIV) recipients and 32.9% of Fluzone HD (QIV) recipients. The most frequently reported systemic ARs among mRNA-1010 (QIV) recipients were fatigue (44.5%), myalgia (41.7%), and headache (39.4%). The majority of systemic ARs were Grade 1 or 2. Grade 3 ARs were reported in 6.7% of mRNA-1010 (QIV) recipients versus 1.7% of Fluzone HD (QIV) recipients. Two Grade 4 solicited systemic ARs of fever were reported in the mRNA-1010 (QIV) group: one participant with a fever of 104.9°F on Day 2 and one participant with a fever of 105°F on Day 3. Neither participant sought medical attention for these events.

The median day of onset for solicited systemic ARs was Day 2 postvaccination in both groups. Median duration was 1 day in both groups. A higher percentage of systemic ARs persisted beyond 7 days in the mRNA-1010 (QIV) group (1.7%) compared with the Fluzone HD (QIV) group (1.1%).

Appendix C Table 13. Summary of Participants with Solicited Systemic ARs Within 7 Days After Injection by Toxicity Grade, 65 Years of Age and Older, Solicited Safety Set, Study P303 Part C

Solicited Adverse Reaction, Category, Grade	mRNA-1010 (QIV) N1=1502 % (n)	Fluzone HD (QIV) N1=1490 % (n)
Solicited systemic adverse reactions*	--	--
Any	61.3 (920)	32.9 (490)
Grade 3	6.7 (101)	1.7 (25)
Grade 4	0.1 (2)	0
Fever[a]	--	--
Any	8.5 (127)	1.4 (21)
Grade 3	0.6 (9)	<0.1 (1)
Grade 4	0.1 (2)	0
Headache[b]	--	--
Any	39.4 (592)	17.3 (258)
Grade 3	2.3 (35)	0.7 (10)
Fatigue[b]	--	--
Any	44.5 (669)	19.7 (293)
Grade 3	3.5 (52)	0.8 (12)
Myalgia[b]	--	--
Any	41.7 (626)	16.1 (239)
Grade 3	3.2 (48)	0.7 (11)
Arthralgia[b]	--	--
Any	35.2 (528)	14.1 (210)
Grade 3	2.3 (35)	0.7 (11)
Nausea/vomiting[c]	--	--
Any	12.8 (192)	4.2 (63)
Grade 3	0.3 (4)	0.2 (3)
Chills[b]	--	--
Any	29.5 (443)	7.7 (115)
Grade 3	1.2 (18)	0.3 (5)

Source: Adapted from STN 125869/0, mRNA-1010-P303 Part B and Part C Clinical Study Report, Table 14.3.1.2.1.c. Data cutoff: June 24, 2024.
Abbreviations: Any, Grade 1 or higher; AR, adverse reaction; CI, confidence interval; G, grade; N1, number of exposed participants in the Solicited Safety Subset; n, number of exposed participants who reported the event; QIV, quadrivalent influenza vaccine
* Absence of rows for Grade 4 reactions means no Grade 4 reactions were reported.
Numbers were based on actual group and percentages were based on the number of exposed participants who submitted any data for the event(s).
95% CI was calculated using the Clopper-Pearson method.
[a] Toxicity grade for fever (oral) is defined as: G1=38.0-38.4°C or 100.4-101.1°F; G2=38.5-38.9°C or 101.2-102.0°F; G3=39.0-40.0°C or 102.1-104.0°F; G4: ≥40.0°C or >104.0°F.
[b] Toxicity grade for headache, fatigue, myalgia (muscle aches all over body), arthralgia (joint aches in several joints), and chills are defined as: G1=no interference with activity; G2=some interference with activity; G3=prevent daily activity; G4=requires emergency room visit or hospitalization.
[c] Toxicity grade for nausea/vomiting are defined as: G1=no interference with activity or 1-2 episodes/24 hours; G2=some interference with activity or >2 episodes/24 hours; G3=prevent daily activity or requires outpatient intravenous hydration; G4=requires emergency room visit or hospitalization for hypotensive shock.

Unsolicited Adverse Events

Unsolicited Adverse Events Through 28 Days After Vaccination

The percentages of participants with unsolicited AEs within 28 days postvaccination were balanced between groups: 10.3% in the mRNA-1010 (QIV) group and 9.2% in the Fluzone HD (QIV) group. By MedDRA System Organ Class (SOC), unsolicited AEs were most frequently reported under infections and infestations (4.5% vs. 4.4%) and musculoskeletal and connective tissue disorders (1.1% vs. 1.2%). Unsolicited AEs assessed as related to study vaccination by the investigator were reported in

0.5% of mRNA-1010 (QIV) recipients and 0.2% of Fluzone HD (QIV) recipients; this difference was largely attributable to nonserious AEs related to vaccine reactogenicity. Rates of unsolicited AEs were generally similar across subgroups by age, sex, and race.

Medically Attended Adverse Events

Through 28 days postvaccination, MAAEs were reported by 5.9% of mRNA-1010 (QIV) recipients and 5.6% of Fluzone HD (QIV) recipients. Through study completion, MAAEs were reported by similar proportions in each group (17.1% vs. 16.6%). MAAEs were most frequently reported under the MedDRA SOC of infections and infestations (6.4% vs. 7.8%). MAAEs assessed as related to study vaccination were more common in the mRNA-1010 (QIV) group (0.3%, n=4) than in the Fluzone HD (QIV) group (<0.1%, n=1).

The four MAAEs assessed as related to mRNA-1010 (QIV) by the investigator were:

- An 80-year-old female with cough onset on the evening of the injection (Day 1), which resolved the following afternoon.
- A 72-year-old female with injection site pruritus on Study Day 4.
- A 67-year-old female with a medical history of seasonal allergies, obesity, iron deficiency, and vitamin D deficiency (concomitant use of phentermine/topiramate) who experienced chest discomfort on Day 2 that resolved within 1 hour. Concurrently, she reported dizziness (described as 'lightheadedness – orthostatic – intermittent') also with onset and resolution on Day 2, which the investigator assessed as unrelated to study injection. No additional evaluation or treatment was reported for either event.
- A 72-year-old female with face swelling on Study Day 2. This event was also classified as an AESI and is discussed further in the Adverse Events of Special Interest section below.

Based on the temporal association with study vaccination and the absence of a clear alternative etiology, FDA considers it plausible that the study vaccine contributed to these events. Because the majority were mild to moderate in severity and resolved promptly without intervention, these events are not considered to represent clinically meaningful safety concerns.

Deaths

Within 28 days of vaccination, one death was reported in the mRNA-1010 (QIV) group (<0.1%) and none in the Fluzone HD (QIV) group. Through study completion (median follow-up approximately 6 months), three deaths (0.2%) were reported in the mRNA-1010 (QIV) group and one death (<0.1%) in the Fluzone HD (QIV) group. All four participants had extensive underlying medical conditions. None of the deaths in either group were assessed as related to study vaccination by the investigator. Based on independent review of event narratives, FDA agrees that these deaths were unlikely to be related to the study vaccine.

Serious Adverse Events (SAEs)

SAEs within 28 days of vaccination were reported in 0.6% (n=9) of mRNA-1010 (QIV) recipients and 0.5% (n=7) of Fluzone HD (QIV) recipients. Through study completion, 2.7% of mRNA-1010 (QIV) recipients and 2.6% of Fluzone HD (QIV) recipients reported SAEs. SAEs were most commonly reported under the SOC of infections and infestations (0.7% vs. 0.5%). No SAEs were assessed as related to mRNA-1010 (QIV) by the investigator or by FDA.

Adverse Events of Special Interest (AESIs)

Protocol-defined AESIs are listed in Appendix A. Through 28 days after vaccination, one AESI (<0.1%) was reported in the mRNA-1010 (QIV) group and none in the Fluzone HD (QIV) group. Through study completion, two AESIs were reported in the mRNA-1010 (QIV) group and one in the Fluzone HD (QIV) group.

One AESI in the mRNA-1010 (QIV) group was a partial seizure occurring on Day 51, which the investigator assessed as unrelated to study vaccine. The second AESI was an event of face swelling (also classified as an MAAE), which the investigator assessed as related to the study vaccine. This event is described below.

Swelling face: A 72-year-old female with a history of asthma, coronary artery disease, and obesity experienced face swelling on Study Day 2. She was evaluated in the emergency department and treated with prednisone and diphenhydramine; the event resolved by Day 10. She denied any other concurrent symptoms, and no additional unsolicited AEs were reported around this time. The Applicant, in agreement with the investigator, assessed this event as related to the study vaccine. FDA agrees that this event of face swelling is possibly related to the vaccine, given the temporal relationship to vaccination and the absence of alternative etiologies.

Pregnancies

No pregnancies were reported in either group.

Dropouts and/or Discontinuations

Aside from study discontinuations due to death (discussed in the Deaths section above), no additional discontinuations due to adverse events were reported in either group.

Appendix D – Integrated Overview of Safety

Safety Assessment Methods

The Applicant conducted an Integrated Summary of Safety (ISS) to provide a cross-study evaluation of the safety profile of mRNA-1010 in adults 50 yoa and older. The ISS pooled safety data from all four Phase 3 studies (P301, P302, P303, and P304) in participants 50 yoa and older, with analyses focused on serious adverse events (SAEs), adverse events of special interest (AESIs), and deaths. The pooled mRNA-1010 group (trivalent [TIV] and quadrivalent [QIV] formulations), referred to hereafter as 'mRNA-1010,' was compared with pooled standard-dose and high-dose comparator vaccines (Fluarix [TIV and QIV]; Fluzone HD [QIV]), referred to hereafter as 'SD/HD comparator.'

The Applicant also conducted a focused safety meta-analysis evaluating two specific neurological AESIs — Bell's palsy and Guillain-Barré syndrome (GBS) — both of which have been inconsistently associated with licensed influenza vaccines.

Safety Database

The ISS Set included all randomized participants 50 yoa and older who received at least one study injection across the four Phase 3 studies. Participants who enrolled in more than one study were counted separately in each study using unique participant identifiers, as their injections were administered at least 10 months apart.

Studies Contributing to the ISS

Brief descriptions of the four Phase 3 studies contributing to the ISS analyses are presented in Appendix A. Because of small individual sample sizes, all three parts of Study P303 were combined and analyzed as a single study for ISS purposes.

Overall Exposure and Demographics of the Pooled Safety Population

The ISS analysis included 35,965 participants exposed to mRNA-1010 and 35,951 participants exposed to SD/HD comparator. Median follow-up was 198 days in both groups (range: 1–449 days in the mRNA-1010 group; 1–445 days in the SD/HD comparator group). Study completion rates were high and comparable: 95.1% in the mRNA-1010 group and 95.2% in the SD/HD comparator group.

Demographic characteristics were well balanced between groups. Median age was 64.0 years in both groups (range: 50–99 years in the mRNA-1010 group; 50–96 years in the SD/HD comparator group). Among mRNA-1010 recipients, 51.2% were 50–64 yoa, 37.5% were 65–74 yoa, and 11.4% were ≥75 yoa. In both groups, the majority of participants were female (56.5% mRNA-1010; 56.9% SD/HD comparator), White (79.4% vs. 79.0%), non-Hispanic or non-Latino (82.9% vs. 83.2%), and had not received an influenza vaccine in the prior season (55.8% vs. 56.0%). Most participants were enrolled from North America (74.1% in both groups).

Categorization of Adverse Events

Adverse events in the ISS were summarized by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 25.0 across all four studies. Participants with multiple occurrences of the same adverse event were counted once per event category.

Caveats Introduced by Pooling Data Across Studies

The following caveats should be considered when interpreting the pooled ISS data:

- Formulation differences: Studies P301, P302, and P303 used a quadrivalent formulation; Study P304 used a trivalent formulation. Studies P301 and P302 used the original mRNA-1010 formulation; Studies P303 and P304 used the optimized formulation with a modified B

antigen. This heterogeneity may introduce variability in the safety profile not fully captured by pooled analyses.

- Comparator differences: Comparator vaccines varied across studies (standard-dose and high-dose; TIV and QIV formulations), which may affect the interpretation of between-group comparisons.
- Follow-up duration: Follow-up ranged from approximately 6 months in Studies P303 and P304 to approximately 12 months in Studies P301 and P302, which may influence the detection of late-onset adverse events.
- Population heterogeneity: Geographic and demographic differences across study sites may contribute to variation in background rates of adverse events.

Integrated Safety Results

Appendix D.1. Deaths

Within 28 days of vaccination, deaths were reported in 13 of 35,965 participants (<0.1%) in the mRNA-1010 group and 14 of 35,951 participants (<0.1%) in the SD/HD comparator group. Over the full study period, deaths were reported in 102 participants (0.3%) in the mRNA-1010 group and 97 participants (0.3%) in the SD/HD comparator group. In both groups, death was most commonly reported under the MedDRA SOC of cardiac disorders: 24 participants (<0.1%) in the mRNA-1010 group and 30 participants (<0.1%) in the SD/HD comparator group.

By PT, deaths occurring in more than 4 participants in either group included: death (unspecified) (23 vs. 9), myocardial infarction (7 vs. 7), cardiac arrest (6 vs. 6), cerebrovascular accident (4 vs. 5), and pneumonia (2 vs. 5) in the mRNA-1010 and SD/HD comparator groups, respectively.

To further evaluate the numerical imbalance in the PT of death (unspecified), SAEs coded to the PTs of death, sudden death, and sudden cardiac death were pooled for analysis. This combined analysis identified 29 participants in the mRNA-1010 group and 12 in the SD/HD comparator group with unspecified fatal events. Median time to onset was approximately 131 days (range: 2–319 days) in the mRNA-1010 group and 87 days (range: 9–343 days) in the SD/HD comparator group; most events occurred well beyond the acute postvaccination period. Deaths within 28 days of vaccination under these three PTs were few and similar across groups (3 in the mRNA-1010 group; 2 in the SD/HD comparator group).

Approximately 60% of participants with unspecified fatal events were ≥65 yoa, and nearly all had multiple pre-existing comorbidities, including hypertension, diabetes mellitus, chronic kidney disease, hyperlipidemia, coronary artery disease, atrial fibrillation, prior myocardial infarction, congestive heart failure, and chronic obstructive pulmonary disease (COPD). Causes of death were predominantly recorded as unknown or natural causes. No autopsies were conducted in the 29 mRNA-1010 group deaths; one autopsy in the SD/HD comparator group yielded no reported findings.

One death in the mRNA-1010 group — occurring on Day 2 in Study P303 Part A — was assessed as related to the study vaccine by the Investigator based on temporality and is described below. No other deaths in either group were assessed as vaccine-related.

Case Description: Death on Day 2 (Study P303 Part A)

A 76-year-old female with a history of coronary artery disease (prior coronary artery bypass graft [CABG] following myocardial infarction), atrial fibrillation, and type 2 diabetes mellitus was found unresponsive at home and confirmed deceased on Study Day 2 (PT: death). She reported no solicited adverse reactions on Study Day 1. Although solicited adverse reactions were not documented for Study Day 2, she reportedly told a friend that she felt unwell, tired, and nauseous earlier that day. Her most recent cardiology evaluation documented stable functional status with

mild exertional symptoms, sinus bradycardia with atrial fibrillation, and an incomplete right bundle branch block on ECG. No autopsy was performed; the death certificate attributed death to natural causes. The Applicant assessed this event as unrelated to the study vaccine.

FDA Assessment: Although the temporal relationship to study vaccination is notable and a contribution from a vaccine-related inflammatory response cannot be excluded, the participant's significant cardiac history — including prior myocardial infarction requiring CABG and atrial fibrillation — represents a more plausible alternative etiology. The numerical imbalance in unspecified deaths between the mRNA-1010 and SD/HD comparator groups was evaluated in the context of the totality of available evidence. Most of these deaths occurred in older participants with substantial underlying comorbidities, a population with elevated background mortality. The temporal distribution of events does not suggest a causal relationship to vaccination, and deaths of unspecified cause within 28 days of vaccination were few and similar across groups. The observed imbalance is not considered to represent a safety signal for mRNA-1010.

Appendix D.2. Serious Adverse Events (SAEs)

Within the first 28 days postvaccination, SAEs were reported by comparable proportions of participants: 0.5% (n=180) in the mRNA-1010 group and 0.5% (n=163) in the SD/HD comparator group. SAEs were most frequently reported under the SOC of infections and infestations (45 mRNA-1010 recipients vs. 34 SD/HD comparator recipients). The most frequent SAEs by PT were pneumonia (8 vs. 5) and acute myocardial infarction (4 vs. 6) in the mRNA-1010 and SD/HD comparator groups, respectively.

Over the full study periods, SAEs were reported in 3.1% of the mRNA-1010 group and 2.9% of the SD/HD comparator group. The most frequently reported SAEs were in the SOC of infections and infestations (0.7% vs. 0.6%). By PT, the most frequently reported SAEs were pneumonia (36 vs. 32), COPD (35 vs. 24), and cerebrovascular accident (32 vs. 29) in the mRNA-1010 and SD/HD comparator groups, respectively.

For SAEs occurring in at least four participants in each group, risk differences (RDs) with 95% confidence intervals (CIs) were calculated. Six PTs had 95% CIs that excluded zero:

- Higher in the mRNA-1010 group: anemia (9 vs. 2; RD: 0.02 [95% CI: >0, 0.04]); urinary tract infection (UTI) (25 vs. 12; RD: 0.04 [95% CI: >0, 0.07]); and death (unspecified) (23 vs. 9; RD: 0.04 [95% CI: 0.01, 0.07]).
- Higher in the SD/HD comparator group: chronic kidney disease (0 vs. 4), urinary retention (0 vs. 4), and hypertensive emergency (0 vs. 4).

The imbalance in deaths is reviewed in in Appendix D1. The anemia and UTI imbalances are reviewed below.

Anemia

A comprehensive review encompassing the additional PTs of anemia of chronic disease, blood loss anemia, hypochromic anemia, iron deficiency anemia, and normocytic anemia identified 14 participants in the mRNA-1010 group and 8 in the SD/HD comparator group. None were assessed as vaccine-related by the Investigator. Most events occurred more than 90 days after injection, with no temporal clustering. All participants in the mRNA-1010 group had plausible alternative etiologies, including iron deficiency, gastrointestinal bleeding, kidney or liver disease, serious infection, and concomitant medication use. A review of medically attended adverse events (MAAEs) of anemia in Study P304 identified a similar incidence between groups (31 in the mRNA-1010 [TIV] group vs. 30 in the SD comparator group). These data suggest that the numerical imbalance in SAEs of anemia is unlikely to reflect a causal association with mRNA-1010.

Urinary Tract Infection (UTI)

A comprehensive review encompassing the additional PTs of urinary tract infection bacterial, Escherichia urinary tract infection, cystitis, kidney infection, pyelonephritis, acute pyelonephritis, and urosepsis identified 38 participants in the mRNA-1010 group and 22 in the SD/HD comparator group. None were assessed as vaccine-related by the Investigator. There was no temporal clustering; median time to onset was 135 days in the mRNA-1010 group and 112.5 days in the SD/HD comparator group. The majority of participants in both groups had identifiable risk factors, including advanced age, female sex, postmenopausal status, diabetes mellitus, obstructive uropathies, chronic kidney disease, and use of concomitant medications known to increase UTI risk. A review of MAAEs of UTI in Study P304 identified a similar incidence between groups (153 in the mRNA-1010 [TIV] group vs. 158 in the SD comparator group). These data suggest that the numerical imbalance in SAEs of UTI is unlikely to reflect a causal association with mRNA-1010.

Investigator-Assessed Vaccine-Related SAEs

SAEs assessed as related to study vaccine by the Investigator were reported by 9 participants (<0.1%) with 11 events in the mRNA-1010 group and 3 participants (<0.1%) with 3 events in the SD/HD comparator group. Of the nine participants in the mRNA-1010 group, four were from Study P304 and are discussed in Appendix B SAEs Assessed as Vaccine-Related by the Investigator. The remaining five participants are described below.

Study P301 (mRNA-1010 [Original, QIV])

Acute coronary syndrome: A 53-year-old male current smoker with a history of obesity developed retrosternal chest pain on Day 3 and was subsequently hospitalized with a diagnosis of acute coronary syndrome. ECG showed ST-segment elevation; coronary angiography revealed mild stenoses and coronary artery spasms. Echocardiogram showed no wall motion abnormalities and a normal ejection fraction. The event resolved on Day 6. The Applicant assessed the event as unrelated to the study vaccine.

FDA Assessment: Although the temporal relationship to vaccination is notable and a vaccine contribution cannot be excluded, the participant's smoking history and obesity are significant risk factors for coronary artery disease, and the angiographic finding of stenosis is more consistent with a pre-existing condition, providing more plausible alternative etiologies.

Study P302 (mRNA-1010 [Original, QIV])

Angioedema: A 78-year-old female with a history of angioedema developed facial swelling on Study Day 5, which she described as less severe than her typical episodes. She self-treated with diphenhydramine and intramuscular (IM) epinephrine, and the event resolved the same day. The Applicant assessed the event as unrelated to the study vaccine.

FDA Assessment: Although the participant's history of angioedema could predispose her to a hypersensitivity reaction following vaccination, the delayed onset makes an alternative trigger also plausible. The participant's self-report that this episode was less severe than her typical episodes further limits concern that this event represents a clinically significant safety signal.

Pulmonary embolism: An 86-year-old female with a history of peripheral neuropathy, neuropathic pain, and hyperlipidemia developed chest pain and dyspnea on Study Day 9 and was hospitalized on Study Day 12 with an initial diagnosis of right lower lobe pneumonia. Chest CT revealed multiple bilateral pulmonary emboli in addition to the pneumonia. Venous duplex ultrasonography identified no deep vein thrombosis. The participant was discharged on oral edoxaban on Study Day 17, and the SAE of pulmonary embolism was considered resolved. The Applicant assessed the event as unrelated to study vaccine.

FDA Assessment: Although the event was temporally associated with vaccination, the participant's advanced age, hyperlipidemia, and concurrent pneumonia are all established risk factors for thromboembolic events and provide plausible alternative etiologies.

Study P303 Part A (mRNA-1010 [QIV])

Deep vein thrombosis and pulmonary embolism: A 57-year-old female current smoker with a history of severe varicose veins experienced deep vein thrombosis on Day 128 following an injury to the affected leg, and a subsequent pulmonary embolism on Day 132. The Applicant assessed both SAEs as unrelated to the study vaccine.

FDA Assessment: The long interval between vaccination and onset of these events, combined with the presence of more likely alternative etiologies — including recent leg injury, varicose veins, and smoking — makes a causal association with the study vaccine unlikely.

Death: A 76-year-old participant on Study Day 2, as described in Appendix D.1 Death

Appendix D.3. Protocol-Defined Adverse Events of Special Interest (AESIs)

Through 28 days after vaccination, AESIs were reported in 7 participants (<0.1%) in the mRNA-1010 group and 4 participants (<0.1%) in the SD/HD comparator group. Through the full study period, AESIs were reported in 36 participants (0.1%) in the mRNA-1010 group and 37 participants (0.1%) in the SD/HD comparator group; 5 and 2 participants, respectively, had AESIs assessed as related to study injection by the Investigator.

The five AESIs assessed as related to mRNA-1010 by the Investigator were: thrombocytopenia (onset Day 84; see Appendix B thrombocytopenia), facial swelling (onset Day 2; see Appendix C Facial Swelling), myopericarditis (onset Day 95; see Appendix B myopericarditis), myocarditis (onset Day 183; see Appendix B Myocarditis), and Bell's palsy (onset Day 16; see Appendix D.3.2 below).

Summaries of additional analyses for AESIs of myocarditis/pericarditis and new-onset or worsening neurological diseases are presented below. No meaningful differences were observed between the mRNA-1010 and SD/HD comparator groups in these analyses.

Appendix D.3.1. Myocarditis/Pericarditis

No AESIs of myocarditis, pericarditis, or myopericarditis were reported within 28 days of vaccination in either group. Through study completion, AESIs in the cardiac disorders SOC (myocarditis, pericarditis, and myopericarditis) were reported in 10 participants (<0.1%) in the mRNA-1010 group and 6 participants (<0.1%) in the SD/HD comparator group; one additional AESI of viral pericarditis in the SD/HD comparator group was not mapped to the cardiac disorders SOC.

Cardiac Event Adjudication Committee (CEAC)-confirmed cases were balanced across groups: 4 confirmed cases in the mRNA-1010 group (1 myopericarditis; 3 acute pericarditis) and 3 confirmed cases of acute pericarditis in the SD/HD comparator group. One additional CEAC-confirmed case of acute pericarditis in the SD/HD comparator group (Study P301) was adjudicated after database lock and therefore not captured in the study database.

In the mRNA-1010 group, one participant from Study P304 had an AESI of myocarditis on Day 183, adjudicated by the CEAC as myopericarditis and assessed as related to study vaccine by the Investigator; this case and the FDA assessment are described in Appendix B myopericarditis. In the SD/HD comparator group, one participant from Study P304 had an AESI of pericarditis, adjudicated as acute pericarditis, on Day 60 and assessed as related to the study vaccine by the Investigator.

Appendix D.3.2. New Onset or Worsening of Specified Neurological Diseases

Guillain-Barré Syndrome (GBS): Across the ISS population, no events of GBS were reported in the SD/HD comparator group. One serious AESI of GBS, coded under the PT of demyelinating polyneuropathy, was reported in the mRNA-1010 group in a 79-year-old female with a history of

hypothyroidism, COPD, hypertension, obesity, and dyslipidemia, with onset on Day 134. The participant initially presented on Day 129 with hypertension, foot tingling, and vomiting, and subsequently developed distal paresthesias and progressive lower extremity weakness, advancing to tetraparesis and respiratory failure by Day 134, with a diagnosis of demyelinating polyneuropathy made during hospitalization. The Investigator assessed this event as unrelated to the study vaccine.

FDA Assessment: FDA agrees that this event is unrelated to the study vaccine. Symptom onset occurred well outside the established 42-day risk window for vaccine-associated GBS.

Bell's Palsy: Across the ISS population, Bell's palsy (idiopathic peripheral facial nerve paralysis) was reported by 1 participant (<0.1%) in the mRNA-1010 group and 4 participants (<0.1%) in the SD/HD comparator group. Within the 42-day risk window, one event was reported in each group; both were assessed as related to the study vaccine by the respective study Investigators. The Bell's palsy event within the risk window in the mRNA-1010 group is described below. One additional mRNA-1010 recipient reported an AESI and concurrent SAE of facial paresis on Day 21 in the setting of concurrent herpes zoster; this event was assessed as unrelated to the study vaccine by the Investigator and by FDA.

Case Description: Bell's Palsy (Study P303 Part B)

A 59-year-old male with a history of obesity developed Bell's palsy on Study Day 16. On Study Day 5, he reported left upper lip induration and left cheek erythema of unknown etiology, followed by right-sided facial droop on Day 16. On Study Day 17, he presented to the emergency department with persistent right-sided facial droop and notably elevated systolic blood pressure (176 mmHg). He was diagnosed with hypertension, type 2 diabetes mellitus, and Bell's palsy. He was treated with valacyclovir and prednisone; the event was considered resolved on Study Day 161. The Investigator assessed the event as related to the study vaccine; the Applicant assessed it as unrelated.

FDA Assessment: FDA agrees with the Investigator's assessment that this event is possibly related to the study vaccine based on the temporal relationship to vaccination. However, the participant's comorbidities — obesity, hypertension, and type 2 diabetes — are established risk factors for Bell's palsy and represent plausible alternative etiologies.

Safety Conclusions

The pooled safety analysis across all four Phase 3 studies in individuals 50 yoa and older did not identify adverse event patterns indicative of a safety concern for mRNA-1010.

Appendix E – Adverse Events of Special Interest

Adverse Events of Special Interest Prespecified in Study Protocols of mRNA-1010

Medical Concept	Additional Notes
Thrombocytopenia:	• Platelet count <125×10^9/L. • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome.
New onset of or worsening of the following neurologic diseases:	• GBS. • ADEM. • Idiopathic peripheral facial nerve palsy (Bell's palsy). • Seizures, including but not limited to febrile seizures and/or generalized seizures/convulsions.
Anaphylaxis:	• Anaphylaxis associated with study intervention administration as defined in Section 8.3.1.4.1 of the protocol.
Myocarditis/pericarditis:	• Myocarditis. • Pericarditis. • Myopericarditis.

Source: Study P304 Protocol Table 5, Study P304 Part B/C Protocol Table 17.
Abbreviation: ADEM, acute disseminated encephalomyelitis; GBS, Guillain-Barré syndrome; HELLP, hemolysis, elevated liver enzymes, low platelets

Appendix F – CDC Criteria for Probable and Confirmed Cases of Myo, Peri, and Myopericarditis

CDC Criteria for Probable and Confirmed Cases of Myocarditis, Pericarditis, and Myopericarditis

Condition	Probable Case Definition	Confirmed Case Definition
Acute myocarditis	Presence of ≥1 new or worsening of the following clinical symptoms:[a] chest pain, pressure, or discomfort dyspnea, shortness of breath, or pain with breathing palpitations syncope OR infants and children <12 years of age might instead have ≥2 of the following symptoms: irritability vomiting poor feeding tachypnea lethargy AND ≥1 new finding of troponin level above upper limit of normal (any type of troponin) abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[b] abnormal cardiac function or wall motion abnormalities on echocardiogram cMRI findings consistent with myocarditis[c] AND No other identifiable cause of the symptoms and findings	Presence of ≥1 new or worsening of the following clinical symptoms:[a] chest pain, pressure, or discomfort dyspnea, shortness of breath, or pain with breathing palpitations syncope OR infants and children <12 years of age might instead have ≥2 of the following symptoms: irritability vomiting poor feeding tachypnea lethargy AND ≥1 new finding of histopathologic confirmation of myocarditis[d] cMRI findings consistent with myocarditis[c] in the presence of troponin level above upper limit of normal (any type of troponin) AND No other identifiable cause of the symptoms and findings
Acute pericarditis[e]	Presence of ≥2 new or worsening of the following clinical features: acute chest pain[f] pericardial rub on exam new ST-elevation or PR-depression on EKG new or worsening pericardial effusion on echocardiogram or MRI	-
Myo	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	-

Source: Adapted from STN 125869/0, mRNA-1010-P304 Protocol Amendment 1, Appendix 4.
Abbreviations: AV, atrioventricular; cMRI, cardiac magnetic resonance imaging; ECG/EKG, electrocardiogram; Myo, myopericarditis
An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al. 2021) and provide the assessment to the Applicant. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
[a] Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
[b] To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.
[c] Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).
[d] Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
[e] Adler et al 2015.
[f] Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur (Gargano et al. 2021).

Appendix G – Study P304 High-Risk Conditions

Participants were assigned to the high-risk group if their baseline BMI was ≥30 kg/m^2 or they had at least one high-risk factor in the medical history.

High-Risk Factors

High-Risk Factor	SMQ or HLT	Type	Detail
Autoimmune/immune-mediated disease	Immune-mediated/autoimmune disorders	SMQ	Narrow
Blood disorders	Coagulation disorders congenital	HLT	--
	Haemoglobinopathies congenital	HLT	--
Cardiac disorders	Cardiac conduction disorders	HLT	--
	Supraventricular arrhythmias	HLT	--
	Ventricular arrhythmias and cardiac arrest	HLT	--
	Cardiomyopathy	SMQ	Narrow
	Ischemic heart disease	SMQ	Narrow
Nervous system disorders	Cerebrovascular embolism and thrombosis	HLT	--
	Parkinson's disease and parkinsonism	HLT	--
	Paralysis and paresis (excl. cranial nerve)	HLT	--
	Demyelination	SMQ	Narrow
Diabetes mellitus	Diabetes mellitus (including subtypes)	HLT	--
Renal disorders	Chronic kidney disease	SMQ	Narrow
Hepatic disorders	Hepatocellular damage and hepatitis NEC	HLT	--
	Hepatic fibrosis and cirrhosis	HLT	--
Mental impairment disorders	Intellectual disabilities	HLT	--
	Dementia	SMQ	Narrow
Pulmonary disorders	Bronchospasm and obstruction	HLT	--
	Interstitial lung disease	SMQ	Narrow
	Pulmonary hypertension	SMQ	Narrow

Source: Study P304 SAP Appendix J. Derivation of High-Risk.
Abbreviations: HLT, high-level term; NEC, not elsewhere classified; SMQ, Standardized MedDRA Query

Appendix H – Phase 4 Confirmatory Study Protocol Synopsis

The Applicant proposed the following Phase 4 confirmatory study design as a postmarketing requirement (PMR) to support full approval of mFlusiva under Accelerated Approval pathway. The study protocol and proposed timeline are currently under review and are the subject of ongoing discussions between FDA and the Applicant.

STUDY OVERVIEW

Phase 4 pragmatic, cluster-randomized clinical trial to evaluate the relative vaccine effectiveness (rVE) of mRNA-1010 compared with agreed upon CDC-preferentially recommended vaccine in adults 65 yoa and older under real-world conditions.

RESEARCH QUESTION & OBJECTIVES

Is mRNA-1010 noninferior to agreed upon CDC-preferentially recommended vaccine in preventing laboratory-confirmed medically attended influenza in adults 65 yoa and older?

Secondary objectives include assessment of protection against influenza-associated emergency department, urgent care, or hospitalizations; influenza-associated hospitalization; and stratified analyses by strain type, if feasible.

STUDY DESIGN & POPULATION

Design: Vaccine clinics will be cluster-randomized, alternating weekly between mRNA-1010 and agreed upon CDC-preferentially recommended vaccine throughout the influenza season. This approach seeks to balance vaccine allocation and controls for confounding by calendar time and facility.

Enrollment: ~800,000 (~400,000 per season) adults 65 yoa and older in a 1:1 allocation (2 full seasons, 2027–2028 and 2028–2029).

OUTCOMES & STATISTICAL APPROACH

Primary endpoint: Laboratory-confirmed medically-attended influenza occurring ≥14 days postvaccination.

Noninferiority margin: -15% (H_0: rVE ≤ -15%; one-sided alpha = 0.025).

Sample size: 1,632 primary endpoint events provide ≥80% power to demonstrate noninferiority, assuming a true rVE of 0%.

Analysis: Cox proportional hazards regression, stratified by facility and conditioned on calendar date, adjusted for age, sex, race/ethnicity, and comorbidities.

DATA SOURCE & GOVERNANCE

Data source: Electronic medical records, capturing all vaccinations, laboratory results (PCR-confirmed influenza), medical encounters, and diagnoses.

Informed consent: A waiver of informed consent is anticipated, as the study reflects routine clinical practice and no specific vaccine selection is implied.

STUDY TIMELINE

Under Review

An interim analysis after Season 1 will assess adequacy of endpoint accrual; if sufficient, the study may conclude after one season.