BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA)
STN	125869/0
CBER Received Date	December 5, 2025
PDUFA Goal Date	August 5, 2026
Division / Office	(b) (6) OVRR
Priority Review (Yes/No)	Yes (Priority Review Voucher)
Reviewer Names	(b) (6) OVRR (b) (6) VRR
Review Completion Date / Stamped Date	August 5, 2026
Supervisory Concurrence	(b) (6) OVRR
Applicant	Moderna TX, Inc.
Established Name	mRNA-1010
Proposed Trade Name	mFlusiva
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each 0.38 mL dose contains three nucleoside mRNAs (12.5 micrograms of each RNA; 37.5 micrograms of total RNA), each encoding one of the following seasonal influenza strain hemagglutinin (HA) glycoproteins: A/Missouri/11/2025 (H1N1) pdm09-like virus; A/Michigan/105/2025, an A/Darwin/1415/2025 (H3N2)-like virus; and B/Pennsylvania/19/2025, a B/Pennsylvania/14/2025-like virus, encapsulated in lipid nanoparticles.
Dosage Form and Route of Administration	Suspension for intramuscular injection (IM)
Dosing Regimen	Single 0.38 mL dose
Indication and Intended Population	Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine. mFlusiva is approved for use in persons 50 years of age and older. The indication for persons 65 years of age and older is approved under accelerated approval based on immune responses. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
Orphan Designated (Yes/No)	No

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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
CLIA	Clinical Laboratory Improvement Amendments
CoP	correlate of protection
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CoR	correlate of risk
DBL	database lock
DMG	dimyristoyl glycerol
DSPC	1,2-distearoyl-sn-glycero-3 phosphocholine
eDiary	electronic diary
EOS	end-of-study
FDA	U.S. Food and Drug Administration
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutinin inhibition
HD	high dose
ILI	influenza-like illness
IM	intramuscular
ISS	Integrated Summary of Safety
IST	internal safety team
LB	lower bound
LGE	late gadolinium enhancement
LL	lower limit
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
mRNA-LNP	messenger RNA liquid nanoparticle
NH	Northern Hemisphere
NI	noninferiority
NP	nasopharyngeal
PEG2000	polyethylene glycol 2000
PFS	pre-filled syringe
PPIS	per-protocol immunogenicity subset
PT	MedDRA preferred term
QIV	quadrivalent influenza vaccine
RD	risk difference

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
TEAE	treatment emergent adverse event
TIV	trivalent influenza vaccine
U.S.	United States
UTI	urinary tract infection
WHO	World Health Organization

1.Executive Summary

On December 5, 2025, Moderna TX, Inc. (the Applicant) submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) to support licensure of mRNA-1010 (trade name mFlusiva), with a proposed indication of active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine in persons 50 years of age and older. mRNA-1010 is an mRNA vaccine encoding the full-length, membrane-bound influenza hemagglutinin (HA) glycoproteins of the seasonal influenza subtypes A/H1N1 and A/H3N2 and type B/Victoria-lineage encapsulated in lipid particles.

The Applicant has proposed licensure via dual regulatory pathways:

1) Traditional Approval in adults 50 through 64 years of age based on relative vaccine efficacy (rVE) compared with a standard dose (SD) influenza vaccine comparator against reverse transcriptase polymerase chain reaction (RT-PCR)–confirmed influenza-like illness (ILI) from a Phase 3 efficacy trial in adults 50 years of age and older (Study P304), and

2) Accelerated Approval in adults 65 years of age and older based on immunogenicity comparison against high dose (HD) influenza vaccine, a Centers for Disease Control and Prevention (CDC)-preferentially recommended vaccine in this age group, using hemagglutination inhibition (HAI) as a surrogate endpoint reasonably likely to predict clinical benefit. This immunogenicity comparison was conducted in Study P303 Part C, a Phase 3 immunogenicity trial in adults 65 years of age and older. Because the SD comparator used in Study P304 is not a CDC-preferentially recommended influenza vaccine for adults 65 years of age and older, and therefore not considered the standard-of-care in this population, rVE data from Study P304 in this age group were insufficient to serve as the primary basis for approval, but provided supportive evidence for the clinical benefit of mRNA-1010 in this age group. As a condition of Accelerated Approval, the Applicant has proposed a Phase 4 confirmatory efficacy study to verify and describe the clinical benefit of mRNA-1010 in adults 65 years of age and older.

The Applicant submitted safety and effectiveness data from the two primary Phase 3 studies (Study P304 and Study P303 Part C), along with supportive data from additional studies evaluating earlier formulations of mRNA-1010 (Study P101, P301, P302, P303 Parts A and B), in support of the BLA.

Key Findings

1. **Clinical Efficacy from Study P304 (Primary Basis for Traditional Approval in Adults 50 Through 64 Years of Age)**

Study P304 was a Phase 3, randomized, observer-blinded, active-controlled relative vaccine efficacy trial, in which 40,805 participants ≥50 years of age were randomized to receive a single dose of mRNA-1010 (trivalent influenza vaccine; TIV) (N=20,402) or a SD influenza vaccine comparator (Fluarix TIV or Fluarix quadrivalent influenza vaccine [QIV]; hereafter referred to as SD comparator) (N=20,403). Submission of the BLA followed a successful protocol-specified interim analysis (considered the primary analysis) that evaluated the primary efficacy endpoint of RT-PCR confirmed protocol-defined ILI with onset at least 14 days after vaccination. As of the April 30, 2025 data cutoff, representing the end of the influenza season, the median duration of follow-up for efficacy was approximately 6 months. rVE in preventing RT-PCR confirmed ILI was

26.6% (95% confidence interval [CI]: 16.7, 35.4) compared with the active comparator. The absolute vaccine efficacy compared with no vaccination would be expected to be higher. Supportive analyses of strain-specific rVE demonstrated consistent point estimates across the three influenza strain subtypes, although the confidence interval around the rVE for influenza B/Victoria was wide due to the small number of cases accrued. Subgroup analyses of the primary endpoint by age showed consistent rVE point estimates across all age subgroups, with rVE of 26.1% (95% CI: 12.3, 37.7) in adults 50 through 64 years of age and rVE of 27.4% (95% CI: 12.1, 40.0) in adults 65 years of age and older; however, interpretation of the rVE results in adults ≥65 years is limited by the use of a non-CDC preferentially recommended SD comparator vaccine.

2. Clinical Effectiveness from Study P303 Part C (Primary Basis for Accelerated Approval in Adults ≥65 Years of Age)

For Accelerated Approval, the Applicant used Day 29 HAI titers from Study P303 Part C as the surrogate endpoint reasonably likely to predict clinical benefit. This was supported by a Correlate of Risk (CoR) analysis conducted in Study P304, which examined the correlation between HAI titers and RT-PCR–confirmed, protocol-defined influenza-like illness (ILI). Study P303 Part C was a Phase 3 randomized, observer-blind, active-controlled immunogenicity study in which 3,003 participants ≥65 years of age were randomized to receive mRNA-1010 (quadrivalent influenza vaccine; QIV) (n=1,507) or HD influenza vaccine comparator (Fluzone HD [QIV]) (n=1,496). The pre-specified success criteria for the primary immunogenicity endpoint of noninferiority, followed by superiority, of mRNA-1010 (QIV) compared with Fluzone HD (QIV) based on both geometric mean titer (GMT) and the proportion of participants reaching seroconversion as measured by HAI antibody responses at Day 29, were met against all four vaccine-matched influenza strains. GMTs and proportion of participants with seroconversion remained higher in the mRNA-1010 (QIV) group compared with the Fluzone HD (QIV) group at the end of study (EOS)/Day 181 in the subset of participants evaluated.

Vaccine effectiveness in this age group will be confirmed with the planned Postmarketing Requirement (PMR) study designed to verify and describe the clinical benefit of mRNA-1010 in individuals 65 years of age and older.

3. Safety Profile

In both Study P304 and Study P303 Part C, solicited local and systemic adverse reactions (ARs) through 7 days postvaccination, including Grade 3 ARs, were reported more frequently in the mRNA-1010 groups compared with the active comparator groups; however, reported ARs were predominantly mild to moderate in severity and of short duration (median of 2 days). In Study P304, the most commonly reported solicited ARs among mRNA-1010 (TIV) recipients in both the 50 through 64 years of age group and 65 years of age and older group were injection site pain (68.7% and 62.9%, respectively), fatigue (48.1% and 42.1%, respectively), and headache (41.9% and 33.7%, respectively). Unsolicited adverse events (AEs) through 28 days postvaccination were balanced between groups in both studies. Across both studies, only one SAE was assessed by the clinical review team as likely related to study vaccine, an event of syncope on Day 2 in a mRNA-1010 (TIV) recipient in Study P304.

The Integrated Summary of Safety (ISS) consisted of pooled analyses of all SAEs, deaths, and adverse events of special interest (AESIs) reported in participants 50 years of age and older across Moderna's four Phase 3 clinical studies of mRNA-1010 (Studies P301, P302, P303, and P304). The analyses included 35,965 participants exposed to mRNA-1010 and 35,951

participants exposed to the SD comparator (Fluarix [TIV or QIV]) or HD comparator (Fluzone HD [QIV]) (hereafter referred to as SD/HD comparator). Overall, rates of SAEs and AESIs were balanced between study groups. No cases of myocarditis or pericarditis were reported within 42 days postvaccination in the mRNA-1010 group. Beyond the 42-day risk window and through the completion of all four Phase 3 studies, 10 (<0.1%) cases of myocarditis, pericarditis, or myopericarditis were reported in the mRNA-1010 group compared with 7 (<0.1%) cases in the SD/HD comparator group. Cardiac Event Adjudication Committee (CEAC)-confirmed cases were balanced across groups (4 in each group). Based on review of event narratives, latency of onset postvaccination, and presence of plausible alternative etiologies, none of these events were assessed as related to mRNA-1010 by the review team.

Deaths

In the ISS, a numerical imbalance was observed for deaths coded to the MedDRA preferred term (PT) “death (without further specification)”: 23 events in the mRNA-1010 group versus 9 events in the SD/HD comparator group. When pooled with the related PTs of “sudden death” and “sudden cardiac death,” this imbalance was more pronounced: 29 events in the mRNA-1010 group versus 12 in the SD/HD comparator group. All-cause mortality through study completion was balanced across groups [102 (0.3%) vs. 97 (0.3%)], indicating that the imbalance in unspecified-cause deaths is not reflected in total mortality. Based on review of event narratives, temporal distribution of events across the study period, the absence of clustering within the 28-day postvaccination window (3 unspecified deaths in the mRNA-1010 group vs. 2 in the SD/HD comparator within 28 days), balance in all-cause mortality, and the high prevalence of serious comorbidities among decedents, the review team assesses a causal relationship between mRNA-1010 and the observed excess of unspecified-cause deaths as unlikely. Nevertheless, definitive causal assessment is precluded by the absence of autopsies in all 29 affected mRNA-1010 recipients and lack of systematic cause-of-death adjudication. These limitations represent residual uncertainty that cannot be resolved from existing trial data. Accordingly, the Applicant has committed, as part of the approval, to conduct active postmarketing surveillance for deaths — both unspecified and all-cause — in addition to myocarditis/pericarditis (a safety event of interest in mRNA vaccines) and Guillain-Barre syndrome (a safety event of interest in influenza vaccines) in a proposed Postmarketing Commitment (PMC) study.

4. Uncertainties/ Evidence Gaps

In Study P304, the influenza B/Victoria-specific rVE point estimate (29.1%) was consistent with those for the other influenza strains; however, the confidence interval crossed zero (95% CI: −18.5, 57.5) due to the limited number of B/Victoria cases accrued, introducing uncertainty regarding vaccine effectiveness against this strain. Although immunogenicity responses to influenza B/Victoria were higher in the mRNA-1010 group relative to both the SD comparator (Study P304) and the HD comparator (Study P303 Part C), the B/Victoria-specific correlate of risk (CoR) analysis, conducted to support the use of HAI as a surrogate marker reasonably likely to predict clinical benefit, was inconclusive. Given the residual uncertainty surrounding B/Victoria strain-specific effectiveness, the Applicant will evaluate strain-specific rVE as a secondary endpoint in the PMR confirmatory efficacy study.

5. Limitations of the Available Data

Clinical efficacy data are available for one influenza season only. Efficacy has not been established in immunocompromised individuals or very frail older adults, the populations at the

highest risk of severe influenza-related complications. Data on concomitant administration with routinely co-administered vaccines (e.g., coronavirus disease 2019 [COVID-19], respiratory syncytial virus [RSV], pneumococcal vaccines) are also unavailable.

Conclusion

mRNA-1010 met the protocol-defined success criteria for superior rVE versus the SD comparator in adults ≥50 years of age and superior immunogenicity versus a CDC-preferentially recommended HD comparator in adults ≥65 years of age. The reactogenicity profile, while elevated relative to comparators, was predominantly mild to moderate and resolved within 2 days. Overall rates of SAEs, deaths, and AESIs were balanced between groups, with no safety concerns identified. Data from this BLA submission was discussed at a Vaccine and Related Biological Products Advisory Committee (VRBPAC) meeting on June 18, 2026, and the VRBPAC members unanimously voted in agreement that the benefits of mRNA-1010 outweighed its risks for the prevention of influenza disease in both adults 50 through 64 years of age and adults 65 years of age and older.

The available data therefore support a favorable benefit-risk assessment for mRNA-1010 and support its approval for the indication of prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine under the following pathways: 1) Traditional Approval in individuals 50 through 64 years of age, and 2) Accelerated Approval in individuals 65 years of age and older, with a postmarketing requirement (PMR) study planned to verify and describe the benefit of mRNA-1010 in this age group.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed.

Effectiveness

Study P304 was conducted in multiple regions and countries. In descriptive analyses, rVE point estimates were generally consistent across demographics and baseline characteristic subgroups, including age, sex, race, region, and baseline protocol-defined high-risk factor. For some subgroups, rVE could not be estimated due to small sample sizes and insufficient case counts.

In Study P303 Part C, immunogenicity responses were similar across subgroups, although analyses were limited by small numbers of participants in some subgroups.

Safety

In Study P304, slightly higher rates of solicited adverse reactions were reported among mRNA-1010 (TIV) recipients 50 through 64 years of age compared with those ≥65 years of age, with differences ranging from less than 1% to approximately 10%. In both Study P304 and Study P303 Part C, no notable differences in the occurrence of unsolicited AEs or SAEs were observed across the subgroups by demographic and baseline characteristics.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Influenza is responsible for 3 to 5 million cases of severe disease and up to 650,000 deaths annually worldwide (WHO 2025). In the United States, adults ≥65 years of age account for approximately three-quarters of influenza-associated deaths (CDC 2024a). Seasonal influenza disproportionately affects older adults, young children, pregnant women, and individuals with underlying cardiac, immunocompromising, metabolic, or respiratory conditions (CDC 2024b). 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 (CDC 2024b). The cumulative public health burden is substantial, encompassing direct healthcare costs, lost productivity, and excess mortality, particularly during seasons with high antigenic mismatch.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/ Intervention(s) for the Proposed Indication(s)

Six U.S. licensed antiviral agents are available for prophylaxis and treatment of influenza disease – amantadine, ramantadine, oseltamivir, zanamivir, peramivir (treatment only), and baloxavir. Amantadine and ramantadine are no longer recommended by the CDC due to high levels of resistance among circulating influenza A. Antivirals are not considered substitutes for early influenza vaccination on an annual basis as recommended by the CDC Advisory Committee on Immunization Practices (ACIP). Antivirals are pharmacologically unrelated to mRNA-1010 and are not comparators for the purpose of the mRNA-1010 benefit-risk assessment (see TAMIFLU, RELENZA, and XOFLUZA).

2.3 Safety and Efficacy of Pharmacologically Related Products

Seasonal Influenza Vaccines

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 years of age and older. Currently licensed influenza vaccines are generally considered to achieve up to 60% effectiveness under conditions of optimal antigenic match (Osterholm et al. 2012; Demicheli et al. 2018), 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 and Russell 2018). Vaccines with improved effectiveness, particularly in older adults, are needed (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.

mRNA Vaccines

Four FDA-approved mRNA vaccines – Spikevax, Comirnaty, mNexspike, and mResvia – share similar mRNA platform technology as mRNA-1010, three of which are manufactured by the Applicant. Spikevax, Comirnaty, and mNexspike are COVID-19 vaccines indicated for the prevention of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). mResvia is an RSV vaccine indicated for the prevention lower respiratory tract disease

(LRTD) caused by RSV. High rates of reactogenicity have been observed across the approved mRNA vaccines, most commonly injection-site pain, fatigue, headache, and myalgia. Myocarditis/pericarditis, has been identified as a key safety signal for all mRNA COVID-19 vaccines, typically occurring within the first week following vaccination, and is most frequently reported in young males. Reported rates from postmarketing surveillance are approximately 27 cases/million doses in males 12 through 24 years of age (see Section 5.2 of Spikevax USPI).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Currently, mRNA-1010 is not licensed in any country. mCombriax, the Applicant's mRNA-based seasonal influenza and COVID-19 combination vaccine, containing mRNA-1010 as its influenza component, received marketing authorization from the European Commission on April 20, 2026, for active immunization for the prevention of influenza disease and COVID-19 caused by SARS-CoV-2 in individuals 50 years of age and older.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

The following timeline includes a list of major regulatory activities associated with the submission of this BLA (including under IND 27460).

- On August 22, 2025, a pre-BLA meeting was held with the Applicant. Because of the use of a non-preferentially recommended comparator vaccine in Study P304 in adults 65 years of age and older, CBER requested that the Applicant provide a comprehensive benefit-risk assessment for use of mRNA-1010 in individuals 50 through 64 years of age and in individuals ≥65 years of age, with justification on the relevance of the rVE results in these age groups, and how these data provide substantial evidence of vaccine effectiveness. An integrated analysis of safety was requested to allow for a more comprehensive review and assessment of more rare adverse events in the study.
- On December 5, 2025, the Applicant submitted the BLA package under STN 125869/0 to seek Traditional Approval of mRNA-1010 for individuals 50 years of age and older based on data from Study P304.
- On February 3, 2026, CBER issued a Refusal to File Letter (RTF) to the Applicant.
- On February 17, 2026, a Type A meeting teleconference was held in which Moderna proposed a revised regulatory approach: 1) Traditional approval for adults 50 through 64 years of age, and 2) Accelerated approval for adults ≥65 years of age.
- On February 17, 2026, CBER granted Priority Review for this BLA and issued a Filing Notification Letter with Deficiencies Identified, outlining the following potential review issues:
  - Study P304's use of a SD comparator vaccine in participants ≥65 years of age, rather than a vaccine preferentially recommended by the CDC for use in older adults (e.g., Fluzone HD, Flublok)
  - Absence of a validated surrogate endpoint accepted by CBER as evidence of clinical benefit, raising questions of whether a favorable immunogenicity comparison of mRNA-1010 against a CDC-preferentially recommended vaccine for adults 65 years of age and older is sufficient to demonstrate substantial evidence of effectiveness to support Traditional Approval in this population.

- On April 6, 2026, a MidCycle Teleconference was held with the Applicant.
- On June 5, 2026, a LateCycle Teleconference was held with the Applicant.
- On June 18, 2026, data from this BLA was discussed at a VRBPAC meeting. The committee unanimously voted in agreement that the benefits of mRNA-1010 outweighed its risks for the prevention of influenza disease in both adults 50 through 64 years of age and adults 65 years of age and older.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review. Please see review memorandum by Data Standards reviewer for additional details regarding the quality of the study datasets.

3.2 Compliance With Good Clinical Practices and Submission Integrity

All clinical trials submitted to the BLA were conducted in accordance with the International Council on Harmonization's Good Clinical Practice (GCP) guidelines [E6(R2)]. The informed, written consent was obtained from all participants as per GCP guidelines and contained all the essential elements of informed consent as stated in 21 CFR 50.25.

(b) (6) inspections were issued for three clinical investigators, conducting Study mRNA-1010-P304, including two clinical investigators in the U.S. and one foreign clinical investigator in Estonia. No deficiencies have been identified that would impact the integrity of the clinical trial data submitted to this BLA.

3.3 Financial Disclosures

Studies P304 and P303
Was a list of clinical investigators provided? ☑ Yes ☐ No
Total number of investigators identified: 354
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The CBER Chemistry, Manufacturing, and Controls (CMC) reviewer identified one issue that may impact the conclusions of the clinical review, to be further evaluated in the PMR study. Studies P304 and P303C measured serum GMTs and SCR rates using the HAI assay with viruses propagated in mammalian cells (MDCK cells). Use of cell-derived rather than egg-derived viruses is considered more biologically relevant as they are expected to better represent

naturally circulating viruses; however, this may introduce a systematic bias favoring mFlusiva in immunogenicity comparisons with the egg-based comparator vaccines used in the clinical trials (Fluarix and Fluzone HD). FDA has requested that the Applicant further evaluate immune responses using both egg- and cell-derived assays in parallel in a planned PMC study (see Section 11.6 and CMC memo for further details).

The CMC reviewer also reviewed the CMC data on the 2026 - 2027 Northern Hemisphere formula of mRNA-1010 with no concerns identified.

4.2 Assay Validation

The submitted data for the assays used in the clinical studies, including the HAI assay and microneutralization (MN) assays used to measure serum antibody levels as well as RT-PCR testing used for detection of influenza infection, have been adequately validated and found to be analytically suitable for their intended purposes. See clinical memorandum from CBER assay reviewer for additional details regarding the assays used in the clinical studies.

4.3 Nonclinical pharmacology/Toxicology

Please refer to the Toxicology Reviewer Memorandum. No clinically relevant toxicology issues were identified.

4.4 Statistical

CBER statistical reviewers verified the key statistical analyses for safety, immunogenicity, and efficacy and identified a concern in the Study P304 Correlate of Risk (CoR) analysis regarding a non-statistically significant magnitude of correlation between HAI titers and RT-PCR confirmed protocol defined ILI caused by B/Victoria. mRNA-1010's clinical protection against B/Victoria will be further characterized in the Applicant's PMR study to be conducted over two influenza seasons. Please see Sections 6.1.11.9, Section 6.2.11.1 and the Statistical Review Memo for further details.

4.5 Pharmacovigilance

The CBER Pharmacovigilance (PV) reviewer had no safety concerns and agrees with the Applicant's proposed pharmacovigilance plans to 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 vaccines. The Applicant also 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 post-approval:

- Thrombocytopenia
- Guillain-Barré syndrome (GBS)
- 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, and myopericarditis

The Applicant has additionally proposed a PMC study using the same study population as that of the PMR confirmatory study to conduct active surveillance for deaths (unspecified and all-cause), myocarditis/pericarditis, and GBS. Please see the Pharmacovigilance Review memo for further details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This BLA submission contains data from 5 clinical studies.

Traditional Approval of mRNA-1010 in adults 50 through 64 years of age is based on relative vaccine efficacy data from Study P304, in which mRNA-1010 (TIV) was compared to a SD influenza vaccine.

Accelerated approval of mRNA-1010 in adults 65 years of age and older is based on immunogenicity data from Study P303 Part C, in which mRNA-1010 (QIV) was compared to a HD influenza vaccine preferentially recommended by CDC for this age group. Relative vaccine efficacy (rVE) data from the ≥65 years of age subgroup of Study P304 were considered supportive, with the key limitation that the comparator vaccine in Study P304 was not preferentially recommended for this age group. Accelerated approval criteria were met based on the following:

1. Serious or Life-Threatening Condition: Influenza disproportionately burdens older adults, who account for 70–85% of influenza-related deaths and 50–70% of hospitalizations in the U.S. Hospitalization and mortality rates in adults ≥65 years of age are more than double those of adults 50–64 years of age (CDC 2024a).

2. Meaningful Therapeutic Benefit Over Available Therapy: mRNA manufacturing may provide greater antigenic fidelity of the vaccine relative to circulating strains by avoiding egg-adaptive HA mutations inherent to egg-based manufacturing and could provide shorter timelines from formula update recommendations to vaccine availability. The clinical meaningfulness of these manufacturing technology differences over available licensed vaccines remains to be fully characterized.

3. Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit: The Applicant proposes Day 29 HAI titers as the surrogate endpoint. While HAI titers have historically served as a surrogate endpoint in influenza vaccine development, prior supporting evidence was derived from studies of inactivated, egg-adapted vaccines. Given that the mRNA platform may elicit a distinct immune response profile, the Applicant conducted a pre-specified correlate of risk (CoR) analysis in Study P304 evaluating the association between Day 29 HAI titers and RT-PCR-confirmed, protocol-defined ILI (see Section 6.1.11.9). The CoR analysis demonstrated a statistically significant association between HAI titers and ILI caused by influenza A/H1N1 and A/H3N2. Results were inconclusive for B/Victoria due to low case accrual and a non-statistically significant magnitude of correlation, leaving residual uncertainty regarding protection against this strain. Notwithstanding this uncertainty, HAI

titers, along with the totality of available clinical data, support the clinical benefit of this vaccine based on: (1) the biological plausibility of HAI as a mechanism of protection against influenza, reinforced by the observed correlation between HAI and rVE for both influenza A strains in the Study P304 CoR analysis for mRNA-1010; (2) superior immunogenicity of mRNA-1010 (QIV) relative to Fluzone HD (QIV) in Study P303 Part C, with potential improved effectiveness against influenza A strains alone carrying substantial public health significance for this high-risk population; (3) a directionally consistent and robust B/Victoria-specific rVE point estimate of 29.1% from Study P304, with the wide confidence interval attributable to low case accrual rather than absence of effect; (4) an overall rVE of 27.4% (95% CI: 12.1, 40.0) in adults ≥65 years of age (Study P304), comparable in magnitude to rVE estimates observed in CDC-preferentially recommended influenza vaccines in this age group (i.e., Fluzone HD and Flublok) when compared to SD vaccines; and (5) the Applicant's plan to further characterize B/Victoria effectiveness through the postmarketing requirement (PMR) study.

4. Postmarketing Confirmatory Study: The Applicant will conduct a pragmatic, cluster-randomized clinical trial comparing the effectiveness of mRNA-1010 against an approved CDC-preferentially recommended influenza vaccine in individuals ≥65 years of age to confirm clinical benefit post-approval (see Section 11.4).

Safety of mRNA-1010 in adults 50 years of age and older is supported by safety data from studies P301, P302, P303, and P304. Studies P301 and P302 used an earlier formulation of mRNA-1010 prior to modification[1] of the B antigen and failed their primary objectives; therefore, their results will not be discussed in detail in this BLA clinical review.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following amendments were reviewed by the clinical review team in support of this application:

Table 1. Amendments Reviewed for BLA 125869

Amendment Number	Date Submitted	Module (s)
7	February 18, 2026	1, 5
9	February 27, 2026	1
12	March 10, 2026	1
15	March 17, 2026	1
16	March 18, 2026	1
17	March 18, 2026	1
19	March 20, 2026	1
23	March 23, 2026	1, 5
25	March 25, 2026	1
28	March 31, 2026	1
32	April 13, 2026	1
33	April 14, 2026	1
34	April 16, 2026	1

1 "Modified" mRNA-1010 formula includes 2 non-surface-exposed amino acid residues in the B antigens to increase the stability of the antigen and elicit improved immune response against influenza B strains.

Amendment Number	Date Submitted	Module (s)
35	April 21, 2026	1, 5
39	April 27, 2026	1
40	April 28, 2026	1
41	May 1, 2026	1
45	May 4, 2026	1
46	May 5, 2026	1
48	May 12, 2026	1
53	May 15, 2026	1
55	May 15, 2026	1
56	May 19, 2026	1
58	May 20, 2026	1
62	May 26, 2026	1
64	May 27, 2026	1, 5
73	June 11, 2026	1
76	June 15, 2026	1
94	July 15, 2026	1
96	July 17, 2026	1, 5
105	July 24, 2026	1, 5
108	July 28, 2026	1
109	July 29, 2026	1
110	July 30, 2026	1
112	July 31, 2026	1, 5
113	July 31, 2026	1
114	July 31, 2026	1, 5
115	July 31, 2026	1
116	August 3, 2026	1
117	August 4, 2026	1
118	August 4, 2026	1
119	August 5, 2026	1
120	August 5, 2026	1

Source: FDA-generated table.

The amendments satisfactorily addressed all clinical requests sent during the review period, and salient responses from the amendments were incorporated into this memorandum.

5.3 Overview of Clinical Studies

The clinical development program for mRNA-1010 comprises five studies (see). Early-phase dose-selection data were generated in Study P101 (Phase 1/2). Study P101, along with Studies P301 and P302, evaluated an earlier formulation with pre-modified influenza B antigens (mRNA-1010 [Original QIV]). Studies P301 and P302 contribute safety data to the ISS only. Study P303 Parts A and B evaluated the modified quadrivalent formulation (mRNA-1010.6 and 1010.4, respectively) in adults ≥18 years of age and 18 through 64 years of age, 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 years of age, and Study P303 Part C, providing immunogenicity and safety data for mRNA-1010 (QIV) compared with Fluzone HD (QIV) in adults ≥65 years of age.

Table 2. 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

Study Number (Country); Study Dates	Study Design	Total mRNA-1010 Recipients Total Comparator Recipients	Formulation and Dose Levels of mRNA-1010 Evaluated
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.
^original refers to an earlier formulation of mRNA-1010 with influenza B antigens manufactured differently than those in the formulation intended for licensure
mRNA-1010.4 and mRNA1010.6 are identical, with the only difference being the scale of manufacturing. They both include modified influenza B antigen(s) encoding 2 stabilizing point mutations in non-surface exposed regions that do not impact antigenic epitopes.

5.4 Advisory Committee Meeting

The Vaccine and Related Biological Products Advisory Committee convened on June 18, 2026, to discuss and vote on whether the available efficacy and safety data support licensure of mRNA-1010 (mFlusiva) for the prevention of influenza in individuals 50 years of age and older. The Applicant proposed a bifurcated regulatory pathway with (1) Traditional Approval requested for use in adults 50 through 64 years of age, based on safety, immunogenicity, and clinical efficacy data, and (2) Accelerated Approval requested for use in adults ≥65 years of age, based on comparative immunogenicity data, as well as supportive evidence (e.g., rVE against a SD comparator), and a postmarketing Phase 4 randomized confirmatory study requirement. Nine out of the nine committee members voted yes to both voting questions posed:

1. Do the benefits of mFlusiva outweigh its risks for the prevention of influenza disease in adults 50 through 64 years of age?
2. Do the benefits of mFlusiva outweigh its risks for the prevention of influenza disease in adults 65 years of age and older?

The committee expressed general concerns regarding recent increases in vaccine hesitancy and poor vaccine uptake for the influenza vaccine in some populations. They signaled a need to effectively communicate the potential benefits of this vaccine while also being transparent about the increased reactogenicity seen with this and other mRNA-based vaccines. The committee also acknowledged the review team's discussion of an observed imbalance in deaths due to an unspecified cause in the review of the Applicant's Integrated Summary of Safety (ISS). Although our review determined this imbalance does not represent a safety signal for mFlusiva (see Section 8.4.1), the committee recommended using the proposed Phase 4 PMR study to gather additional mortality data.

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 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 years of age.

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.

6.1.1 Objectives

Primary Objectives

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.

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 Table 3 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%).

Clinical Reviewer Comment: *The terminology and thresholds used for the primary endpoint sequentially tested success criteria of superiority and "super-superiority" were defined by the Applicant. In April 2024, the review team advised the Applicant that the rVE success criterion of lower bound (LB) >0% would not support a claim of superiority and recommended that the LB of the CI be >10% to demonstrate superiority. Given that the Applicant ultimately evaluated a higher level of superiority of LB >9.1%, the review team considered this acceptable. The expectation of superior rVE against a standard dose influenza vaccine comparator, especially among participants ≥65 years of age and older, aligns with the previously demonstrated superiority by two other influenza vaccines preferentially recommended for use in adults ≥65 years of age: Fluzone HD and Flublok. In the PMR efficacy study to confirm the clinical benefit of Fluzone HD in adults ≥65 years of age, Fluzone HD demonstrated a rVE of 24.2% (95% CI: 9.7; 36.5) compared with standard dose Fluzone (Fluzone HD U.S. Prescribing Information [USPI]). Similarly, in the PMR efficacy study to confirm the clinical benefit of Flublok in adults ≥50 years of age, Flublok demonstrated a rVE of 30% (95% CI: 10, 47) compared with Fluarix (Flublok USPI). The Applicant's proposed LB of the 95% CI of >9.1% for superiority is consistent with the LBs of the 95% CIs for rVE observed in the efficacy studies supporting Fluzone HD and Flublok.*

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 Table 3 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 and 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

Exploratory Objectives (Descriptive Analyses; No Hypothesis Testing)

- To evaluate rVE of mRNA-1010 (TIV) versus the SD comparator against various ILI case definitions including: RT-PCR–confirmed CDC-defined ILI, World Health Organization (WHO)-defined ILI, ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302), and RT-PCR-confirmed influenza infection regardless of whether clinical symptoms meet ILI case definitions (see Table 3 for case definitions) caused by any influenza A or B strain.

  Endpoints

  First episode of each respective RT-PCR–confirmed ILI definition (or RT-PCR-confirmed influenza infection regardless of 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.

- 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.

6.1.2. Design Overview

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 years of age or ≥65 years of age) 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.

6.1.3 Population

Key Inclusion Criteria

- Medically stable adult participants ≥50 years of age.

Key Exclusion Criteria

- Any history of a diagnosis or condition that was clinically unstable or could affect participant safety, assessment of study endpoints including immune response, or adherence to study procedures**.** Clinically unstable was defined as requiring changes in management or medication within 60 days prior to Screening and including ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
- History of congenital or acquired immunodeficiency, immunosuppressive condition, asplenia, or recurrent severe infections disease. HIV positive participants on antiretroviral therapy with CD4 count ≥500 cells/mm3 and HIV RNA ≤500 copies/mL within the past 365 days are allowed. Certain immune-mediated conditions that are stable and well-controlled (e.g., Hashimoto's thyroiditis), as well as those that do not require systemic immunosuppressants may be allowed
- Tested positive for influenza within 180 days prior to Day 1
- Malignancy within 2 years prior to Day 1, with the exception of adequately treated basal cell carcinoma and squamous cell carcinoma
- History of Guillain-Barre syndrome after any influenza vaccine.
- History of myocarditis, pericarditis, or myopericarditis within 180 days prior to Day 1
- Receipt of corticosteroids at ≥10 mg/day of prednisone or equivalent for >14 days in total within 90 days prior to Day 1 or anticipating the need for corticosteroids during the study.
- Receipt of systemic immunosuppressive treatment, including long-acting biological therapies that affect immune responses (e.g., infliximab), within 180 days prior to Day 1 or plans to do so during the study.
- Treatment with antiviral therapies for influenza within 180 days prior to Day 1

- Receipt of a licensed seasonal influenza vaccine within 180 days (or planned anytime during study) or any vaccine approved by a local health agency within 28 days prior to Day 1 (Baseline) or any planned vaccine within 14 days of Day 1, or those unsure if they received a licensed or investigational seasonal influenza vaccine within 1 year prior to Day 1.

6.1.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1010 (mRNA-1010.4; TIV)

- Dose and route of administration: 0.5 mL intramuscular (IM)
- Formulation: 37.5 µg total mRNA (12.5 µg mRNA per strain), consisting of equal amount of mRNA encoding for HA from influenza A/H1N1, A/H3N2, and B/Victoria, formulated in lipid nanoparticles composed of SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000-dimyristoyl glycerol(DMG)
- Presentation: Frozen liquid suspension in glass vial
- Lots: Y000011938, Y000012381, Y000012382, Y000013836, Y000013834, Y000013835, Y000013838, Y000013837, Y000017535, Y000017536

Fluarix (TIV)

- Dose and route of administration: 0.5mL IM
- Formulation: 45 µg, 15 µg each of HA from the following three influenza strains: A/Victoria/4897/2022 (H1N1) IVR-238, A/Thailand/8/2022 (H3N2) IVR-237 and, B/Austria/1359417/2021 BVR-26 (B-Victoria lineage).
- Presentation: Liquid suspension in PFS (pre-filled syringe)
- Lots:
  - **U.S.:** T7245, 745P4, K9XL5, 72RF2, KM5GK, G7CY7, 37AK2
  - **Canada:** 83398.4

Fluarix (QIV)

- Dose and route of administration: 0.5 mL IM
- Formulation: 15µg each of HA from the following four influenza strains: A/Victoria/4897/2022 (H1N1)pdm09-like virus, A/Thailand/8/2022 (H3N2)-like virus, B/Austria/1359417/2021-like virus, B/Phuket/3073/2013-like virus
- Presentation: suspension for injection in PFS
- Lots:
  - Fluarix Tetra (Asia-Pacific): ZT240001, ZT240002
  - Influsplit Tetra (European Union): 38739.3, 38739.4, 23506.9, 23506.8, AFLBA800AA *, AFLBA796AA *, AFLBA803AE *, AFLBA801AB *, AFLBA804AB *
  - Alpharix Tetra (European Union): Lot: Y37264 *

  * Asterisk denotes a lot that was sourced directly by the clinical site for use within the study.

  Clinical Reviewer Comments: *In October 2023, the Vaccines and Related Biologic Products Advisory Committee voted to exclude the B/Yamagata lineage antigen component from licensed influenza vaccines, in alignment with the WHO Influenza Vaccine Composition Advisory Committee recommendations and based on data showing that B/Yamagata*

lineage viruses had not been detected in >3 years. Therefore, the Applicant was requested to use a U.S.-licensed trivalent vaccine comparator in Study P304. However, due to variability in global availability of trivalent influenza vaccines during the initiation of this study, an agreement was reached with the Applicant that in the case of unavailability, a comparison to a U.S.-licensed quadrivalent influenza vaccine would be acceptable.

Noninferiority of Fluarix Quadrivalent to Fluarix TIV-1 (Containing B/Victoria) and Fluarix TIV-2 (containing B/Yamagata) was previously demonstrated, with no evidence that the addition of the second B strain resulted in immune interference to the other strains contained in the vaccine (see Fluarix Quadrivalent USPI, Table 10). Therefore, the comparison of mRNA-1010 (TIV) to combined data from both Fluarix Quadrivalent and Fluarix (TIV) was considered acceptable for Study P304 given the logistical constraints of procuring and administering Fluarix (TIV) during this time at non-U.S. sites.

The volume of mRNA-1010 (TIV) administered in Study P304 was 0.5 mL, whereas the formulation proposed for commercial use is a volume of 0.38 mL. The Applicant clarified under Amendment 40 of this BLA submission that the difference in dosing volume is due to an increase in drug product concentration for the proposed commercial presentation, while maintaining the same delivered dose. This was assessed to be acceptable by the CMC review team. The 0.5mL volume used in Study P304 allowed blinding by maintaining the same volume as the active comparator. The lower dose volume proposed for licensure would likely result in similar or lower local reactogenicity compared with the higher dose volume used in the clinical trial.

6.1.5 Directions for Use

A single IM injection of either mRNA-1010 or SD comparator in the deltoid muscle.

6.1.6 Sites and Centers

Study P304 was conducted at 301 sites in 11 countries in North America (Canada, United States), Europe (Belgium, Bulgaria, Estonia, Finland, Georgia, Germany, United Kingdom), and East Asia (South Korea, Taiwan).

6.1.7 Surveillance/Monitoring

Study oversight included Institutional Review Board or Independent Ethics Committee review and approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents.

An independent Data Safety Monitoring Board (DSMB) reviewed blinded and unblinded safety data on a routine basis and could convene ad hoc as needed. The DSMB made recommendations to the Applicant based on prespecified rules in the DSMB charter. The DSMB also reviewed the results of the interim analysis (IA).

An independent Cardiac Event Adjudication Committee (CEAC) which included cardiologists reviewed Investigator-reported suspected cases of myocarditis, pericarditis, or myopericarditis to determine if they met CDC criteria (see Appendix B) of “probable” or “confirmed” event, and to assess severity. The CEAC operated under the rules of an approved charter that was written and reviewed at the organizational meeting of the CEAC.

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. The end of the influenza season was defined as April 30, 2025, based on epidemiological data.

Safety Monitoring

A subset of approximately 6,000 participants reported solicited local and systemic ARs in a Reactogenicity electronic diary (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 (see Appendix A), and MAAEs were recorded through Month 6 (Day 181) and followed at least monthly until resolution, stabilization, the event was otherwise explained, or the participant was lost to follow-up.

Efficacy Monitoring

All participants completed the symptom eDiary twice weekly from Day 1 through the end of the influenza season 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 3) underwent an unscheduled illness visit, with 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[2]). Swabs could be performed at home by qualified personnel. If an NP swab could not be obtained, any available influenza test results performed outside of the study were captured in the electronic Case Report Form (eCRF). Results from specimens obtained using a local diagnostic test at a healthcare visit external to the study were accepted if the results were obtained using 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/B and other respiratory viruses. Influenza-positive samples underwent additional characterization (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.

Evaluation of Immunogenicity

All participants provided a blood sample on Day 1 (baseline, prior to study intervention) and on Day 29. Of these, samples from a prespecified subset of approximately 2,400 participants from North America where Fluarix (trivalent formulation) was used were analyzed for HAI titers at

[2] Study sites were instructed to collect samples for participants meeting protocol-defined respiratory illness within 5 days after symptom onset; however, the protocol-defined ILI case definition used a longer time frame (within 7 days of symptom onset) from the positive PCR test to increase sensitivity for case detection.

Day 1 (Baseline) and Day 29 to assess humoral immunogenicity endpoints. A subset of approximately 200 participants provided an additional blood sample on Day 1 (Baseline) and on Day 29 to support cellular immunogenicity objectives.

Serum antibody levels were measured by HAI assay and/or MN assay. Serum antibody levels were measured by validated HAI assay (b) (4) and/or validated MN assay ((b) (4) for each influenza strain. RT-PCR testing was performed at either the central laboratory (b) (4)) or a local certified laboratory (CLIA-certified or CLIA-equivalent). Antigenic typing was performed at (b) (4) . Genetic sequencing of RT-PCR sample assays was validated at (b) (4)).

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1 above and Section 6.1.9 below.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The study protocol was designed to enroll participants across up to two Northern Hemisphere influenza seasons (NH 2024/2025 and NH 2025/2026). An interim analysis was planned at the end of the first influenza season, when approximately 70% of target cases were expected to have accrued. The final analysis was planned when all participants had completed the Month 6 Visit or End of Influenza Season Visit, whichever was later. High influenza transmission in the 2024/2025 NH influenza season resulted in 968 cases accrued at the end of the influenza season, which exceeded the study target of 836 cases, and thus did not necessitate study continuation 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 formed the primary efficacy analysis for this study. Additional descriptive analyses were conducted when all participants completed the study.

The study employed a hierarchical sequential testing strategy across nine null hypotheses, tested in a pre-specified order to control the type I error. Testing progressed through three tiers in sequence: first, rVE against protocol-defined ILIs caused by any strain; second, rVE against modified CDC-defined ILIs caused by any strain; and third, rVE against protocol-defined ILIs with antigenic match. Within each tier, testing further progressed through three successive statistical hypotheses – non-inferiority, superiority, and super-superiority – in that order. Advancement to the next hypothesis at any stage was contingent on rejection of the preceding one.

> ***Reviewer Comment:*** *Single-season efficacy data are inherently limited in generalizability, as the circulating strain composition and antigenic match vary substantially across influenza seasons. The rVE estimates from Study P304 reflect the 2024–2025 Northern Hemisphere season and may not be representative of performance in future seasons. Accordingly, the confirmatory PMR study is designed to characterize rVE across two additional influenza seasons under real-world conditions. Single-season efficacy studies are consistent with regulatory precedent for influenza vaccine licensure; the PMR study will address the limitation of single season data for mRNA-1010.*

Methods

Efficacy

Primary Efficacy Endpoint

The primary objective was to evaluate rVE of mRNA-1010 versus SD comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strain. Cases were counted starting 14 days after study intervention.

The following null hypothesis was tested first: the rVE of mRNA-1010 versus SD comparator is inferior, using a 10% noninferiority margin:

- H_0^1: rVE ≤-10% (rVE is defined as the percent reduction in the hazard of the primary endpoint; H_0^1 is equivalent to HR ≥1.1)

NI is met if the p-value for rejecting HR ≥1.1 was less than the adjusted 1-sided significance level based on the Pocock alpha-spending function on the PP Set.

Once NI was demonstrated, rVE was evaluated using the same endpoint for superiority. The following null hypothesis was tested:

- H_0^2: rVE ≤0 (Equivalent to HR ≥1)

Superiority is met if the p-value for rejecting HR ≥1 was less than the adjusted 1-sided significance level.

Once superiority was demonstrated, rVE was further evaluated using the same endpoint for super-superiority. The following null hypothesis was tested:

- H_0^3: rVE ≤9.1% (Equivalent to HR ≥0.909)

Super-superiority is met if the p-value for rejecting HR ≥0.909 was less than the adjusted 1-sided significance level.

Secondary Efficacy Endpoints

If NI, superiority and super-superiority were demonstrated for the primary efficacy endpoint, then the following secondary efficacy endpoints were evaluated for NI, superiority and super-superiority.

1. rVE of mRNA-1010 versus SD comparator against **modified CDC-defined ILI** caused by any influenza A or B strains, where rVE is the percent reduction in the hazards of RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains (mRNA-1010 versus Fluarix).
    - Null hypothesis for NI: H_0^4: rVE ≤-10% (equivalent to HR ≥1.1)
    - Null hypothesis for superiority: H_0^5: rVE ≤0 (equivalent to HR ≥1)
    - Null hypothesis for super-superiority: H_0^6: rVE ≤9.1% (equivalent to HR ≥0.909)

2. rVE of mRNA-1010 versus SD comparator against protocol-defined ILI caused by influenza A or B strains with **antigenic match to the vaccine strains**, where rVE is the percent reduction in the hazards of RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains (mRNA-1010 versus Fluarix).
    - Null hypothesis for NI: H_0^7: rVE ≤-10% (HR ≥1.1)

- Null hypothesis for superiority: H_0[8]: rVE ≤0 (HR ≥1)
- Null hypothesis for super-superiority: H_0[9]: rVE ≤9.1% (HR ≥0.909)

***Reviewer Comment**: The thresholds and terminology for both superiority and "super superiority" were defined by the Applicant. Because the rVE represents the additional benefit of mRNA-1010 beyond what the SD comparator provides, the "super-superiority" threshold is considered a more clinically meaningful margin for assessing the relative benefit of mRNA-1010 to a SD comparator, which is not a CDC preferentially recommended influenza vaccine in adults 65 years of age and older, who make up nearly half of the overall study population (see Table 5 and Table 6).*

Case Definitions

The case definitions for the efficacy endpoints for Study P304 are shown in Table 3.

Table 3. 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.

***Clinical Reviewer Comment:** Protocol-defined respiratory illness was not a study endpoint; it served as the broadest case definition, used to identify participants for increased surveillance and monitoring (see Section 6.1.7). Protocol-defined ILI required at least one systemic symptom, but unlike the CDC and WHO case definitions, did not require fever. Additional case definitions were used to assess secondary and exploratory endpoints.*

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 C). 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.

Immunogenicity

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, with 95% CIs calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale. The GMFR with 95% CI was reported at Day 29 relative to Baseline. An ANCOVA model, adjusting for 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 SD comparator. The seroconversion rates and the proportion of participants with HAI titers ≥1:40 at Day 29 were reported and the corresponding 95% CIs were calculated using Clopper-Pearson method. Seroconversion rate (SCR) differences between groups were reported, and the corresponding 95% CIs were calculated using Miettinen-Nurminen method.

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

The analysis of HAI as a correlate of risk/protection (CoR/CoP) used a case-cohort study design. The analysis was done on per-protocol correlate analysis set (PPCAS). Please refer to the Statistical Review Memorandum for details.

Protocol Amendments and Changes to Planned Analyses

The Original Protocol was dated March 14, 2024.

Amendment KOR-1 (September 25, 2024) incorporated non-substantial changes to the original protocol requested from the South Korean Ministry of Food and Drug Safety.

Global Amendment 1 (February 12, 2025) included the IA decision rules for sample size reassessments and updates to the projected information fraction for the IA, including sample size reassessment to allow for an increase in the second season to accrue up to a maximum of 1.5 times the planned number of cases, if any of the prespecified criteria for NI, superiority, or super-superiority were not met at IA. Revised the criteria for conducting an IA (when approximately 70% are expected to have accrued).

6.1.10 Study Population and Disposition

A total of 40,805 participants were randomized in the study: 20,402 to the mRNA-1010 group and 20,403 to the Fluarix group. The first participant, first visit took place on September 16, 2024, and the last participant, last contact took place on August 21, 2025.

6.1.10.1 Populations Enrolled/Analyzed

The analysis populations used in Study P304 are defined in Table 4. Efficacy analyses were performed using the Per-protocol (PP) Set, unless otherwise noted. The immunogenicity endpoints were analyzed using the Per-protocol Immunogenicity Subset (PPIS).

Table 4. Analysis Sets

Analysis Set	Description
Randomization Set	All randomized participants, 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.
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

6.1.10.2 Demographics

The demographics and baseline characteristics of participants in the Safety Set are shown in 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 through 97 years). Across both groups, 52.2% of participants were 50 to <65 years of age, 47.8% were ≥65 years of age, and 11.6% were ≥75

years of age. 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 protocol-defined high-risk condition (Table 5) was reported by 57.0% of participants, with baseline BMI ≥30 kg/m² being the most common. Among participants ≥65 years of age, 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 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%).

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)
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)

Characteristic	mRNA-1010 (TIV) N=20,350	SD Comparator (TIV + QIV) N=20,353
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
Protocol-defined 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.

> ***Reviewer Comment:*** *Demographic differences in the SD comparator vaccine are likely attributable to geographic differences in the study populations (TIV used in North America; QIV used in Europe and East Asia). Study P304's North American study population receiving TIV is most representative of the U.S. population. The primary endpoint is analyzed separately for this population in a subgroup analysis and the PPIS also is specific to participants receiving TIV.*

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). No notable differences were observed 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.

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)
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.

Reviewer Comments: *Generalizability of the study findings to many individuals at highest-risk for serious complications from influenza may be limited, for the following reasons:*

- *The protocol-defined high-risk conditions encompassed a heterogenous group of baseline medical conditions. They do not align directly with the CDC's list of People at Increased Risk for Flu Complications (CDC 2024b). For example, the CDC uses a BMI cutoff of ≥40 kg/m^2, whereas Study P304 uses 30 g/m^2. In addition, many high-risk participants were excluded based on the study's exclusion criteria (e.g., those who were immunocompromised or taking immunosuppressive medications).The percentage of participants with a high-risk condition in Study P304 was lower than that previously reported for the general U.S. population (78% among adults 35 to 64 years of age and 93% among adults ≥65 years of age (Watson et al. 2025)). This may reflect differences in how high-risk conditions were defined, as well as the exclusion of certain high-risk participants.*

- *Overall, only <1% of study participants 65 years of age and older were considered moderately frail or severely frail (≥10) based on the Edmonton Frail Scale (EFS). EFS scoring varies across practices and the Applicant's scoring thresholds of 0-3 (fit), 4-5 (vulnerable) and ≥6 (frail) are more conservative than other scoring conventions, which classify scores of 6-7 as vulnerable and 8-9 as mild frailty. The study also did not collect data on nursing home or assisted living residence.*

- *The percentage of participants with prior seasonal influenza vaccination was lower than national rates (44.9% among adults 50 through 64 years of age and 67.1% among adults ≥65 years of age (NCHS 2024)). Lower prior vaccination rates observed in this*

study may reflect the exclusion criteria that exclude high-risk individuals who may be more likely to be vaccinated. Given the antigenic variability between influenza seasons and the waning nature of influenza vaccine-induced immunity, the impact of this difference on observed immunogenicity and efficacy results may be limited; however, subgroup analyses were conducted for both efficacy and immunogenicity based on prior vaccination status.

6.1.10.3 Participant Disposition

Participant disposition by analysis population is presented in Table 7 (efficacy and immunogenicity populations) and Table 8 (safety population).

The percentage 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 percentage 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. No notable differences were observed when comparing the PP Set exclusions with the SD comparator (TIV) and SD comparator (QIV) recipients.

The percentage 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).

Table 7. 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)

Population	mRNA-1010 (TIV) N=20,402 n (%)	SD Comparator (TIV + QIV)* N=20,403 n (%)
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 who 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).

Table 8. 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
One more participant is in the active comparator group and one fewer participant is 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.

***Clinical Reviewer Comment**: Rates and reasons for discontinuation were generally balanced across study groups.*

6.1.11 Analyses of Vaccine Effectiveness

6.1.11.1 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 Table 9, mRNA-1010 (TIV) demonstrated an rVE of 26.6% (95% CI: 16.7, 35.4) in all participants ≥50 years of age, 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.

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 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.

6.1.11.2 Supportive Analyses of the Primary Efficacy Endpoint

Analysis by Influenza Strain Type

Table 10 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.

Table 10. 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.

Reviewer Comment: *Influenza A strains made up 94.0% of influenza cases across both groups, and over half of cases observed in the study were due to Influenza A/H1N1. Thus, the strain-specific rVE for any Influenza A strain and for the Influenza A/H1N1 strain were consistent with the primary endpoint of rVE against any influenza strain. Strain-specific rVE against Influenza A/H3N2 was slightly lower: 22.2% (95% CI 4.3, 36.9), though the LB remained >0%.*

Influenza B/Victoria cases represented the smallest percentage of cases; 6.1% in the mRNA-1010 (TIV) group and 6.3% in the SD Comparator group. While the B/Victoria strain-specific rVE point estimate of 29.1% was consistent with those against other strains, the confidence interval was wide and crossed zero (95% CI: −18.5, 57.5), likely due to the limited number of cases, introducing uncertainty about vaccine effectiveness against influenza B/Victoria. Although the study was not powered to assess strain-specific rVE as this would require an impracticably large sample size, the planned Phase 4 confirmatory PMR study will include descriptive secondary objectives to assess strain-specific rVE over two influenza seasons, providing an opportunity to further characterize B/Victoria-specific effectiveness (see Section 11.4).

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).

Reviewer Comment: *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 significantly affect the efficacy estimates.*

Analyses of Co-Infection

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 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.

6.1.11.3 Subpopulation Analyses

Subgroup Analyses by Age

Descriptive analyses of rVE by age subgroup are shown in Table 11. The rVE point estimate for each age subgroup was consistent with the overall study population.

Table 11. 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.

***Clinical Reviewer Comment**: The use of a non-preferentially recommended SD comparator limits interpretation of rVE in participants ≥65 years of age. Nonetheless, the observed rVE of 27.4% (95% CI: 12.1%, 40.0%) provides supportive evidence for a robust immune response in this subgroup, with a LB of the 95% CI well above zero. 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 through 64 years of age and those ≥65 years of age (data not shown).*

Additional Subgroup Analyses

The Applicant also conducted subgroup analyses of rVE (shown in Table 12) in the PP Set by influenza vaccine status in the previous season, sex, race, BMI, SD comparator type (Fluarix TIV versus QIV), region, baseline frailty score, and protocol-defined 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.

Table 12. 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)

Subgroup	mRNA-1010 (TIV) % (Case/N)	SD Comparator % (Case/N)	rVE (%) (95% CI[a])
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)
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. No cases were observed 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 ILI 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.

Reviewer Comment: *rVE was similar when comparing participants who had or had not received an influenza vaccine in the previous season. 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.*

No cases were observed in East Asia, which comprised Taiwan and South Korea and contributed 353 participants to the study. In Amendment 48 to the BLA, the Applicant stated that participants in East Asia were enrolled later compared to the other regions (from November 25, 2024, through March 7, 2025) which contributed to the absence of protocol-defined ILI cases in this region.

6.1.11.4 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 3 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 Table 13, 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 years of age, 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."

Table 13. 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.

> ***Reviewer Comment****: The modified CDC-defined ILI requires a temperature above 37.2°C, cough and/or sore throat. This case definition is more stringent compared with the protocol-defined ILI case definition and resulted in fewer cases across both mRNA-1010 and Fluarix groups. The more stringent fever requirement and the lower likelihood of fever during influenza illness in adults ≥65 years of age (Smith et al. 2020) may have 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 years of age.*

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 Table 14. Overall, rVE remained consistent when limited to antigenically matched cases for both case definitions.

Table 14. Analyses of rVE for mRNA-1010 (TIV) Versus 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.

Reviewer Comment: *Overall, rVE remained consistent when analyzed against antigenically matched cases of both RT- PCR confirmed Protocol-Defined ILI and Modified CDC-defined ILI. For influenza A/H3N2, which had the highest percentage 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.*

6.1.11.5 Analysis of Exploratory Efficacy Endpoints

rVE for mRNA-1010 Compared With SD Comparator Across Case Definitions

Table 15 shows rVE of mRNA-1010 (TIV) compared with the SD comparator across additional ILI case definitions. rVE was consistent across all case definitions with no notable differences.

Table 15. 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

Table 16 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).

Table 16. 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.

Reviewer Comment: *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 years of age (seven 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 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).*

6.1.11.6 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.

Table 17 shows Day 29 HAI GMTs in the mRNA-1010 (TIV) and SD comparator (TIV) groups for each vaccine-matched influenza strain. Day 29 GMTs were higher in the mRNA-1010 (TIV) group compared with the SD comparator (TIV) group for all three strains.

Table 17. 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 (TIV) 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.

Table 18 shows Day 29 HAI SCRs in the mRNA-1010 (TIV) and SD comparator (TIV) 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 end-of-study were consistent with end-of-season results.

Table 18. 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 (TIV) 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.

Reviewer Comment: *The GMT ratio and SCR descriptive analyses support the higher immune responses to mRNA-1010 (TIV) as compared with SD Comparator (TIV) as measured by HAI. Although not powered to do so, all analyses would have met the conventional success criteria for noninferiority (lower bound of the 95% CI >0.67 for GMT ratio and >-10% for SRR percentage difference), superiority (LB of the 95% CI >1.0 for GMT ratio and >0% for SRR percentage difference), and the CBER recommended higher level of superiority (LB of the 95% CI >1.5 for GMT ratio and >10% for SRR percentage difference) of mRNA-1010 (TIV) versus the SD comparator (TIV).*

The low case accrual for B/Victoria resulted in a wide 95% CI for the rVE point estimate, raising uncertainty about clinical protection for this strain. Immunogenicity data would typically provide supportive evidence of effectiveness in this setting; however, the Applicant's pre-specified CoR analysis demonstrated an inconclusive association between HAI titers and clinical protection against B/Victoria (see Section 6.1.11.9), limiting the interpretation of immunogenicity data as corroborating evidence of vaccine effectiveness for this strain.

6.1.11.7 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 (TIV) recipients across all subgroups evaluated.

6.1.11.8 Exploratory Immunogenicity Endpoints

The Applicant assessed neutralizing antibody responses by microneutralization (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 Table 19, Day 29 MN antibody responses were higher in the mRNA-1010 (TIV) group compared with the SD comparator (TIV) group for all three influenza strains. Results were similar in participants 50 through 64 years of age and ≥65 years of age.

Table 19. 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]	SD Comparator (TIV) 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.

> ***Reviewer Comment:*** *MN assay results show consistently higher immune responses in mRNA-1010 (TIV) versus SD Comparator (TIV) recipients across all three influenza strains, consistent with the immunogenicity results based on HAI. The Applicant also conducted a correlation analysis which found MN titers were positively correlated with HAI titers (see Statistical Review Memo).*

6.1.11.9 Correlate of Risk (CoR) Analysis

In seasonal influenza vaccine studies, immunogenicity analyses have historically relied on measurement of HAI antibody titers as the primary endpoint. The use of HAI antibody titers as a surrogate endpoint is based on the historical association of an HAI titer of ≥1:40 with approximately 50% protection against influenza infection in adults, established through human challenge studies and field trials. HAI assays measure antibodies that inhibit hemagglutinin binding to sialic acid receptors on erythrocytes, a mechanism that mimics inhibition of influenza viral attachment to and entry into respiratory epithelial cells. Because this receptor-binding step is essential for initiating infection, vaccine-induced HAI antibodies represent a biologically plausible mechanism of protection (Hobson et al. 1972; Couch and Kasel 1983; de Jong et al. 2003). However, an important limitation of the existing evidentiary framework is that the foundational studies underpinning the use of HAI as an appropriate immune marker for seasonal influenza vaccines were conducted with inactivated, egg-adapted influenza vaccines. These conventional platforms may differ from mRNA-based vaccines in the magnitude, breadth, and character of the elicited immune response; therefore, it cannot be assumed that HAI retains the same predictive value in the context of a novel vaccine platform.

To address this uncertainty and to provide evidence that HAI is a fit-for-purpose surrogate endpoint for mRNA-1010, Moderna conducted a prospectively-designed, statistically tested correlate of risk (CoR) analysis evaluating the correlation between HAI titers and RT-PCR-confirmed protocol-defined ILI from Study P304. The CoR analysis demonstrated a correlation between HAI titers and RT-PCR-confirmed, protocol-defined ILI caused by Influenza A/H1N1 and A/H3N2. However, the CoR analysis was inconclusive for B/Victoria due to low case

accrual combined with low, non-statistically significant magnitude of correlation, leaving residual uncertainty about the clinical protection conferred by HAI titer responses against this strain. See the Statistical Review Memo for full review of the correlation analyses.

Reviewer Comments:

- *The Applicant's CoR analysis has several important limitations, as detailed in the Statistical Review Memo, including potential residual confounding given that HAI titers were not randomized, reliance on data from a single study and influenza season, and modeling assumptions that may not fully reflect the true titer-protection relationship.*
- *Residual uncertainty exists regarding mRNA-1010 effectiveness against B/Victoria, based on 1) B/Victoria specific rVE which although directionally consistent, had a wide 95% CI that crossed zero, and 2) HAI titers, which although higher in participants receiving mRNA-1010 (TIV) compared with the SD comparator, did not demonstrate a statistically significant correlation with PCR-confirmed protocol defined ILI caused by B/Victoria. To address this residual uncertainty, the Applicant was requested to assess strain-specific rVE data as part of the planned Phase 4 confirmatory PMR study designed to verify and describe the clinical benefit of mRNA-1010 in adults 65 years of age and older. The large study size (up to 800,000 participants) over two influenza seasons may be able to provide additional data supporting vaccine effectiveness against B/Victoria. Given the inherent variability in circulating strain composition across influenza seasons, it is not feasible to power a study for assessment of strain-specific rVE; therefore, the PMR study is expected to generate descriptive analysis of strain-specific rVE that will depend on the epidemiologic conditions and circulating strains at the time of study conduct.*
- *Given this mRNA manufacturing technology represents a novel seasonal influenza vaccine technology, it is possible that an immune marker other than HAI may be more suitable and fit-for-purpose as a surrogate endpoint for mRNA-1010. In light of the inconclusive correlation observed between HAI titers and relative vaccine efficacy against influenza B/Victoria, the Applicant was requested to perform a similar CoR analysis using microneutralization (MN) antibody titers to determine whether this alternative immune marker may be more appropriate surrogate immune marker for mRNA-1010. The Applicant has committed to perform this analysis as a PMC study (see Section 11.6).*
- *For detailed discussion of how results from this CoR analysis are interpreted to inform the context of the use of HAI as a surrogate endpoint reasonably likely to predict clinical benefit to support Accelerated Approval in individuals 65 years of age and older, please see Section 6.2.11 and Section 10.*

6.1.12 Safety Analyses

The safety set included 40,703 participants, 20,350 participants in the mRNA-1010.4 group and 20,353 participants in the Fluarix group. As of the September 16, 2025, data cutoff, the median duration of safety follow-up was 184 days for both groups.

6.1.12.1 Methods

Please see Section 6.1.7,

6.1.12.2 Overview of Adverse Events

Table 20 provides an overview of the rates of solicited adverse reactions (ARs) and unsolicited adverse events (AEs) in the mRNA-1010 (TIV) group compared with the SD comparator. Solicited adverse reactions through 7 days were more frequently reported among participants who received mRNA-1010 (TIV) compared with those who received SD comparator. Rates of unsolicited AEs through 28 days, and SAEs and AESIs through study completion were similar across the mRNA-1010 (TIV) and SD comparator groups.

No notable differences were observed in the rates of solicited ARs through 7 days, unsolicited AEs through 28 days, and SAEs or AESIs through study completion when comparing the two age subgroups (50 through 64 years, 65 years of age and older) with the overall population of 50 years of age and older. Additionally, no notable differences were identified in the safety profile of participants who received a QIV active comparator and those who received a TIV active comparator.

Table 20. 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)
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)

Event Type	mRNA-1010 (TIV) % (n/N1)	SD Comparator (TIV + QIV) % (n/N1)
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.

6.1.12.3 Solicited Adverse Reactions

Solicited local and systemic ARs occurring within 7 days postvaccination were assessed using the Solicited Safety Set, which included all randomized participants who received any study vaccine and contributed any solicited AR data. Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling/induration, and axillary swelling/tenderness) and systemic reactions (headache, fatigue, myalgia, arthralgia, nausea/vomiting, fever, and chills), as described above in Section 6.1.7.

Solicited Local Adverse Reactions

Table 21 includes the percentages of mRNA-1010 (TIV) and SD comparator vaccine recipients who reported any solicited local AR, by maximum severity. Within 7 days postvaccination, the percentage of participants reporting any local AR was higher in the mRNA-1010 (TIV) group (67.5%) compared with the SD comparator vaccine group (32.1%). The most frequently reported local reaction in both groups was pain at the injection site, reported by 65.8% of participants in the mRNA-1010 (TIV) group and 29.8% of participants in the SD comparator vaccine group. Most solicited local ARs were Grade 1 in severity. Severe (Grade 3) solicited local reactions were reported by 1.7% and 0.1% of participants in the mRNA-1010 (TIV) and SD comparator vaccine groups, respectively. No Grade 4 local ARs were reported in either group. No notable differences in solicited local ARs were observed between participants who received a TIV versus QIV SD comparator (data not shown).

Table 21. 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)
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; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine.
No Grade 4 solicited systemic adverse reactions were 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 to 50 mm; G2=51 to 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 the mRNA-1010 (TIV) and SD comparator vaccine groups. Solicited local ARs had a median duration of 2 days in the mRNA-1010 (TIV) group and 1 day in the SD comparator vaccine group, with a higher percentage persisting beyond 7 days in the mRNA-1010 (TIV) group compared with the SD comparator vaccine group (0.6% mRNA-1010 [TIV] and 0.3% SD comparator).

Solicited Systemic Adverse Reactions

Table 22 includes the percentages of mRNA-1010 (TIV) and SD comparator vaccine recipients who reported any solicited systemic AR, by maximum severity. Within 7 days postvaccination, the percentages of participants reporting any systemic AR was higher in the mRNA-1010 (TIV) group (58.0%) compared with the SD comparator vaccine group (32.4%). The most frequently reported systemic reactions among mRNA-1010 (TIV) recipients were fatigue (45.1%), headache (37.8%), and myalgia (35.4%). While the majority of solicited systemic ARs were Grade 1 or 2 in severity, Grade 3 systemic ARs were reported in 5.5% of mRNA-1010 (TIV) recipients compared with 0.9% of SD comparator vaccine recipients. No Grade 4 systemic ARs were reported in either group. No notable differences in solicited systemic ARs were observed between participants who received a TIV versus a QIV SD comparator (data not shown).

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

Table 22. 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[f] % (n)	SD Comparator (TIV + QIV) N1=2997[f] % (n)
Any systemic adverse reaction	--	--
Any	58.0 (1750)	32.4 (970)
Grade 3	5.5 (167)	0.9 (27)
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; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine.
Numbers are based on actual vaccination group and percentages are based on the number of exposed participants the Solicited Safety Subset.
No Grade 4 solicited systemic adverse reactions were 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 to 38.4°C or 100.4 to 101.1°F; G2=38.5 to 38.9°C or 101.2 to 102.0°F; G3=39.0-40.0°C or 102.1 to 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 to 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.
[f] Except for fever, which had N1=3001 (mRNA-1010 [TIV]), N1=2997 (SD Comparator)

The median day of onset for solicited systemic ARs was 2 days postvaccination in both the mRNA-1010 (TIV) and SD comparator groups. Solicited systemic ARs had a median duration of 2 days in both the mRNA-1010 (TIV) group and SD comparator vaccine group, with a slightly higher percentage persisting beyond 7 days in the mRNA-1010 (TIV) group compared with the SD comparator vaccine group (1.0% for mRNA-1010 [TIV] and 0.7% for SD comparator).

Subgroup Analyses for Solicited Adverse Reactions

Solicited adverse reactions were examined across multiple subgroups, including age, race, sex, protocol-defined baseline high-risk classification, prior receipt of influenza vaccination, type of SD comparator vaccine used (TIV or QIV), and region (North America, Europe, and East Asia). Across all subgroups examined, solicited ARs occurred at a higher frequency among mRNA-1010 (TIV) recipients compared with SD comparator recipients. Within the mRNA-1010 (TIV) group, solicited AR profiles were generally consistent across subgroups, with the exception of age, as noted below.

Age

Reported rates of solicited local and systemic ARs by age subgroup are shown in Table 23. The magnitude of increased reactogenicity observed for mRNA-1010 (TIV) compared with the SD comparator was comparable across age subgroups.

Among mRNA-1010 (TIV) recipients, the frequency of solicited ARs was slightly lower among participants ≥65 years of age compared with participants 50 through 64 years of age. This trend of decreasing reactogenicity with increasing age was also noted when the ≥65 years age subgroup was further parsed into 65 through 74 years of age and 75 years of age and older.

> ***Reviewer Comment:*** *Decreased reactogenicity with increasing age in older adults is a finding that has been commonly observed with vaccines.*

Table 23. 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[e] % (n)	50-64 Years SD Comparator (TIV+QIV) N1=1502[e] % (n)	≥65 Years mRNA-1010 (TIV) N1=1505[e] % (n)	≥65 Years SD Comparator (TIV+QIV) N1=1495[e] % (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

Event	50-64 Years mRNA-1010 (TIV) N1=1510[e] % (n)	50-64 Years SD Comparator (TIV+QIV) N1=1502[e] % (n)	≥65 Years mRNA-1010 (TIV) N1=1505[e] % (n)	≥65 Years SD Comparator (TIV+QIV) N1=1495[e] % (n)
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)
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 to 64; IRT, interactive response technology; N1, number of exposed participants in the Solicited Safety Subset; n, number of exposed participants who reported the event; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine.

No Grade 4 solicited systemic adverse reactions were 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 to 50 mm; G2=51 to 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 to 38.4°C or 100.4 to 101.1°F; G2=38.5 to 38.9°C or 101.2 102.0°F; G3=39.0 to 40.0°C or 102.1 to 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 to 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.

[e] Except for fever, which had N1=1505 (mRNA-1010 [TIV] 50 through 64 years), N1=1501 (SD Comparator 50 to 64 years), N1=1496 (mRNA-1010 [TIV] ≥65 years), N1=1491 (SD Comparator ≥65 years)

6.1.12.4 Unsolicited Adverse Events

Overall, the percentages of unsolicited AEs within 28 days postvaccination were balanced among mRNA-1010 (TIV) recipients (5.9%) and SD comparator recipients (5.7%). Unsolicited AEs were most commonly reported under the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) infections and infestations (1.4% in both groups). Unsolicited AEs within 28 days assessed as related to the 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 that represented events associated with vaccine reactogenicity, which also occurred more frequently in the mRNA-1010 (TIV) group.

Subgroup Analyses for Unsolicited Adverse Events

Rates of unsolicited AEs were generally similar across subgroups based on age, sex, and race, and high-risk status.

6.1.12.5 Medically Attended Adverse Events (MAAEs)

MAAEs occurring within 28 days following vaccination were reported in 3.8% of participants in both the mRNA-1010 (TIV) and SD comparator groups. Through the study completion date of August 21, 2025, with a median follow-up of 6 months, 12.3% of participants in the mRNA-1010 (TIV) group and 12.0% of participants in the SD comparator group reported at least one MAAE. MAAEs were most frequency 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 by the study Investigator were reported in 23 (0.1%) participants in the mRNA-1010 (TIV) group and 14 (<0.1%) participants in the SD comparator group. The most commonly reported MAAEs assessed as related were under the SOCs of skin and subcutaneous tissue disorders (five mRNA-1010 [TIV] recipients and four SD comparator recipients) and cardiac disorders (six mRNA-1010 [TIV] recipients and two SD comparator recipients). Of the MAAEs assessed as related by the investigator under the SOC cardiac disorders, no PT was reported by more than one participant, and at the PT level there was no clear pattern suggesting a safety concern.

> ***Clinical Reviewer Comment****: For those related MAAEs occurring within 28 days following vaccination, most events were also classified as either SAEs or AESIs and are further discussed in Sections 6.1.12.7 and 6.1.12.8, respectively. The remaining MAAEs have either plausible alternative non-vaccine contributors, including pre-existing cardiovascular and metabolic diseases, or increased reactogenicity that may have contributed to the MAAEs. The balanced overall MAAE rate provides reassurance that mRNA-1010 (TIV) did not produce an overall meaningful increase in healthcare utilization compared with the SD comparator.*

6.1.12.6 Deaths

Through study completion, with a median follow-up of 6 months, 40 deaths (0.2%) were reported in the mRNA-1010 (TIV) group and 34 deaths (0.2%) in the SD comparator group. None of the reported deaths in either group were assessed as related to the study vaccination by the investigator.

Within 28 days following study injection, seven deaths were reported in the mRNA-1010 (TIV) group (<0.1%) and nine deaths reported in the SD comparator group (<0.1%) (Table 24).

Clinical Reviewer Comment: *In general, the causes of death among study participants are representative of common causes of death among older adults and in the general U.S. population (e.g., heart disease, motor vehicle accident, cancer). Based on independent review of event narratives, FDA agrees with the investigators' assessments that these deaths were unlikely to be related to study vaccine.*

Table 24. **Deaths Through 28 Days Postvaccination, Safety Set, Study P304**

Vaccine Received	Preferred Term / Verbatim Term[a]	Sex / Age (Years)	Study Day of Event Onset
mRNA-1010 (TIV)	Cardiovascular disorder/Sudden death due to suspected or probable complications due to cardiovascular disease	Male / 54	4
mRNA-1010 (TIV)	Hypovolemic shock	Male / 75	9
mRNA-1010 (TIV)	Road traffic accident/ Car accident injury	Male / 73	16
mRNA-1010 (TIV)	Road traffic accident/ Motor vehicle accident	Female / 66	16
mRNA-1010 (TIV)	Subdural hemorrhage/Subdural hemorrhage due to blunt trauma due to a fall	Male / 54	20
mRNA-1010 (TIV)	Cardiac arrest	Female / 72	24
mRNA-1010 (TIV)	Death/ Death unknown cause	Male / 67	24
SD Comparator	Malignant neoplasm of unknown primary site/ Malignant neoplasm, primary site unknown, so stated	Female / 80	2
SD Comparator	Death/ Death unknown cause	Female / 52	9
SD Comparator	Acute leukemia	Male / 72	12
SD Comparator	Cardiac arrest	Male / 75	22
SD Comparator	Suicide attempt	Male / 82	23
SD Comparator	Road traffic accident/Traumatic motor vehicle accident	Male / 54	25
SD Comparator	Toxicity to various agents/ Combined toxic effects of cocaine and ethanol	Male / 62	26
SD Comparator	Myocardial infarction	Female / 53	26
SD Comparator	Death/ Unknown cause of death	Female / 83	27

Source: Adapted from STN 125869/0, mRNA-1010-P304 Clinical Study Report, Listing 16.2.7.17.f Data cutoff September 16, 2025.
a. Verbatim term is only applicable when it differs from Preferred Term

Narratives of Deaths in the mRNA-1010 (TIV) Group Through 28 Days Postvaccination

Only cases involving potentially cardiac related causes of death or cases where an unknown cause of death was specified will be discussed below. All other cases have clear alternative etiology and lack biological plausibility for relationship to study vaccine.

Cardiovascular disorder: A 54-year-old male with a history of obesity, cardiovascular disease, hypertension, type 2 diabetes mellitus, obstructive sleep apnea, and attention deficit hyperactivity disorder treated with lisdexamfetamine and bupropion, experienced a cardiovascular disorder and died at home on Day 4. On the morning of the fatal event, the participant reported feeling well overall but experiencing fatigue. The participant described the vaccine as having "kicked his butt" and mentioned taking ibuprofen. No cardiac symptoms such as chest pain or breathing difficulties were reported. The participant was found deceased approximately 1-1.5 hours later. No autopsy was conducted. The death certificate classified the death as natural.

Clinical Reviewer Comment*: The participant's significant cardiovascular comorbidities and stimulant medication use (lisdexamphetamine) represent plausible alternative etiologies for*

sudden cardiac death. The absence of autopsy data precludes definitive assessment of whether post-vaccination systemic inflammation contributed to the acute cardiac event. Electronic diary data showing decreased solicited reactogenicity in the days before death are consistent with resolution of the acute post-vaccination inflammatory response but do not exclude an ongoing subclinical systemic post-vaccination inflammatory response. Because subclinical cardiovascular effects cannot be excluded on the basis of symptom reporting alone, residual uncertainty remains regarding the contribution of vaccination-related systemic inflammation to the acute cardiac event.

Cardiac arrest: A 72-year-old female with a history significant for Factor V Leiden deficiency, bilateral deep vein thrombosis (DVT), and tobacco dependency (one pack per week), experienced a cardiac arrest on Study Day 23 that resulted in death on Study Day 24. Briefly, she experienced cardiac arrest at home, was resuscitated by emergency medical services (EMS), and brought to the hospital. CT chest/abdomen/pelvis obtained on admission revealed extensive bilateral reticular nodular lung infiltrates with basal consolidation, an echocardiogram revealed severe global left ventricular dysfunction, moderately reduced right ventricular systolic function, and a venous ultrasound that revealed deep vein thrombosis. One day after admission, the participant died from cardiac arrest. An autopsy was not performed.

Clinical Reviewer Comment: *Given the participant's significant comorbidities and the imaging findings on admission, the clinical reviewer agrees with the investigator's assessment that this death is unlikely to be related to the study vaccine.*

Death: A 67-year-old male with a relevant medical history of hypertension, on amlodipine and clonidine, was reported to have died of an unknown cause on Study Day 24. The participant's death was reported by a friend who was also enrolled in the trial. The cause of death could not be determined. A death certificate was not provided, and it is unknown whether an autopsy was conducted. Attempts to obtain additional information were unsuccessful. No other AEs were reported by the participant before this event.

Clinical Reviewer Comment: *Given the paucity of information regarding the circumstances surrounding the participant's death, it is not possible to assess causality with respect to the study vaccine.*

6.1.12.7 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, with a median follow-up of 6 months, SAEs were reported by 2.2% (n=455) of mRNA-1010 (TIV) recipients and 1.9% (n=392) of SD comparator recipients. SAEs were most frequently reported in the SOCs of infections and infestations (0.4% in each group) and cardiac disorders (0.3% in each group). Of the SAEs reported through the entire study duration, four participants (<0.1%) in the mRNA-1010 (TIV) group and two participants (<0.1%) in the SD comparator group reported at least one SAE assessed as related to study vaccination by the Investigator. The four SAEs in the mRNA-1010 (TIV) group are described in further detail 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.

> ***Clinical Reviewer Comment:*** *The clinical reviewer 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.

> ***Clinical Reviewer Comment:*** *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.

> ***Clinical Reviewer Comment:*** *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.

> ***Clinical Reviewer Comment:*** *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.*

6.1.12.8 Adverse Events of Special Interest (AESIs)

Protocol-defined AESIs are listed in Appendix A. Through 28 days postvaccination, AESIs were reported in four participants (<0.1%) in the mRNA-1010 (TIV) group and three (<0.1%) in the SD comparator group. Through study completion, with a median follow up of 6 months, 17 participants (<0.1%) in the mRNA-1010 (TIV) group and 15 participants (<0.1%) in the SD comparator group reported AESIs (Table 25).

Table 25. Participant Incidence of Unsolicited AEs of Special Interest as Assessed by Investigator Throughout the Study by SOC and PT, Study P304 (Safety Set)

System Organ Class Preferred Term	mRNA-1010 (TIV) N=20,350 n (%)	SD Comparator N=20,353 n (%)
Number of participants with AESIs	17 (<0.1)	15 (<0.1)
Number of AESIs	19	16
Infections and infestations	1 (<0.1)	0
Herpes zoster oticus	1 (<0.1)	0
Blood and lymphatic system disorders	5 (<0.1)	3 (<0.1)
Thrombocytopenia	5 (<0.1)	3 (<0.1)
Thrombotic thrombocytopenic purpura	0	1 (<0.1)
Nervous system disorders	5 (<0.1)	9 (<0.1)
Seizure	2 (<0.1)	6 (<0.1)
Alcoholic seizure	1 (<0.1)	0
Demyelinating polyneuropathy	1 (<0.1)	0
Facial paresis	1 (<0.1)	0
Focal dyscognitive seizures	1 (<0.1)	0
Bell's palsy	0	2 (<0.1)
Epilepsy	0	1 (<0.1)
Cardiac disorders	6 (<0.1)	3 (<0.1)
Myocarditis	3 (<0.1)	1 (<0.1)
Pericarditis	2 (<0.1)	2 (<0.1)
Myopericarditis	1 (<0.1)	0

Source:
Abbreviations: AESI, adverse event of special interest; PT, preferred term; SOC, system organ class

AESIs Assessed as Related by the Investigator

Two events in the SD comparator group were assessed as related by the investigator: an event of Bell's palsy on Day 18 and an event of pericarditis on Day 60. Details for the three investigator-assessed related AESIs in the mRNA-1010 (TIV) group are further described below.

mRNA-1010

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.

> ***Clinical Reviewer Comment*** *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 in Section 6.1.12.7.

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 in Section 6.1.12.7.

6.1.12.9 Pregnancies

No pregnancies were reported throughout the study.

6.1.12.10 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, three participants in the mRNA-1010 (TIV) group and two in the SD comparator group reported AEs leading to discontinuation from the study. None of the AEs that led to study discontinuation in either group were considered related to the study vaccination by the study investigator or on FDA assessment.

6.1.13 Study Summary and Conclusions

Study P304 was the primary study submitted to support the safety, efficacy, and immunogenicity of mRNA-1010 (TIV) in individuals 50 through 64 years of age. For individuals ≥65 years of age, rVE data from Study P304 were considered supportive, given that the comparator vaccine used was not preferentially recommended for this age group.

The primary objective for the demonstration of noninferior rVE against the SD comparator was met, and protocol-specified sequentially tested criteria for superiority and higher level of superiority were also met. Although the study was not powered for rVE in specific age groups, subgroup analyses showed similar rVE for age subgroups 50 through 64 years of age and 65 years of age and older, both with LB of the 95% CI >10. Descriptive analyses of strain-specific rVE were consistent with the primary endpoint, with the exception of rVE against B/Victoria, for which the rVE point estimate was directionally consistent but the 95% CI was wide and crossed zero due to low case accrual.

mRNA-1010 (TIV) was generally well tolerated. Solicited local and systemic ARs were more frequent in the mRNA-1010 group than in the SD comparator group, but were predominantly Grade 1 to 2 in severity, with rapid onset (within 2 days) and short duration (median 2-day resolution). Unsolicited AEs through 28 days postvaccination, and SAEs and deaths through study completion were balanced between groups. No cases of myocarditis or pericarditis occurred within the 42-day risk window in the mRNA-1010 (TIV) group, and no cases of myocarditis or pericarditis irrespective of time-to-occurrence were assessed as related to

mRNA-1010 (TIV) by the review team. Review of protocol-defined AESIs and programmatic standard MedDRA query (SMQ) analyses identified no safety concerns. Subgroup analyses by age, sex, race, and baseline risk status revealed no notable differences in safety.

Overall, the totality of safety and efficacy data from Study P304 support a favorable benefit-risk profile for mRNA-1010 (TIV) in adults 50 years of age and older.

6.2 Study mRNA-1010-P303C

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 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 formulation of mRNA-1010 (mRNA-1010 [QIV]). This clinical review memo focuses on Part C of Study P303, which compared immunogenicity and safety of mRNA-1010 (QIV) to Fluzone High Dose Quadrivalent (Fluzone HD [QIV]) in adults 65 years of age and older. Fluzone HD (QIV) is one of three influenza vaccines preferentially recommended by the CDC for this age group.

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

> ***Reviewer Comment****: Data from Study P303 Part C support the immunogenicity assessment of mRNA-1010 relative to a high dose active comparator in adults 65 years of age 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 (see Statistical Review Memo and Section 6.1.11.9) and (2) an assessment of whether immunogenicity data from the quadrivalent formulation (QIV) can support the effectiveness of the trivalent formulation (TIV) (see Section 6.2.11.5).*

6.2.1 Objectives

Primary Objectives

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).

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 years of age, as measured by HAI.

  Endpoints

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

The Applicant prespecified eight coprimary endpoints that were 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%.

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.

Exploratory Objectives (Descriptive; No Hypothesis Testing)

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

Endpoints

- GMT at Day 181 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 181 as measured by HAI.

- To evaluate the humoral immunogenicity of mRNA-1010 (QIV) relative to Fluzone HD (QIV) against vaccine-matched or vaccine-mismatched A and B strains.

  Endpoints

  - GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched/mismatched strains on Day 29 compared with Day 1 (Baseline)
  - GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline)

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

6.2.2 Design Overview

A total of 3,003 participants randomized 1:1 to receive a single intramuscular injection of either mRNA-1010 (QIV) or Fluzone HD (QIV). 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.

6.2.3 Population

Key Inclusion Criteria

- Medically stable adults ≥65 years of age

Key Exclusion Criteria

Exclusion criteria were overall similar to those in Study P304 (Section 6.1.3), with the following notable differences in exclusion for P303 Part C:

- Participants who are HIV positive and on antiviral therapy with CD4 count ≥350 cells/mm³ and HIV RNA ≤500 copies/mL within the past 12 months are permitted at the discretion of the investigator (Study P304 allowed participants with CD4 counts ≥500 cells/mm³)
- Participants who have received systemic immunosuppressants for more than 14 days within 180 days prior to Day 1 are excluded (Study P304 excludes immunosuppressant use to within 90 days prior to Day 1)
- Participants who have received any vaccine authorized or approved by local health agency ≤28 days prior to study intervention dosing (Day 1) or plan to receive a vaccine within 28 days before or after study intervention dosing (P304 excludes within ≤14 days)
- Participants previously enrolled in mRNA-1010-P303 Part A are not eligible to participate in Part C

6.2.4 Study Treatments or Agents Mandated by the Protocol

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.

mRNA-1010 (QIV)

- Dose and route of administration: 0.5 mL administered IM
- Formulation: 50 µg mRNA, consisting of 12.5 µg mRNA each encoding the HA from the four influenza strains [A/Wisconsin/67/2022 (A/H1N1) virus, A/Darwin/6/2021 (A/H3N2) virus, B/Austria/1359417/2021 (B/Victoria lineage) virus, B/Phuket/3073/2013 (B/Yamagata lineage)] formulated in LNPs composed of SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 – dimyristoyl glycerol (DMG).
- Presentation: Frozen liquid suspension in glass vial
- Lots: 7068923001

Fluzone HD (QIV)

- Dose and route of administration: 0.7 mL IM
- Formulation: 240 µg, 60 µg each of HA from the four influenza strains [A/Victoria/4897/2022 IVR-238 (H1N1), A/Darwin/9/2021 SAN-010 (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Michigan/01/2021 (a B/Austria/1359417/2021-like virus, B Victoria lineage)].
- Presentation: Liquid suspension in PFS
- Lots: U8130CA, U8138CA, UT8079BA

6.2.5 Directions for Use

A single IM injection of either mRNA-1010 or Fluzone HD administered in the deltoid muscle.

6.2.6 Sites and Centers

Study P303 Part C enrolled participants at 96 centers in the U.S.

6.2.7 Surveillance/Monitoring

Study oversight including Institutional Review Board or Independent Ethics Committee approval, internal safety team (IST) conduct, and CEAC operation was as described by Study P304 (Section 6.1.7).

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.

Safety Monitoring

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 Section 6.1.7).

Immunogenicity Monitoring

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).

6.2.8 Endpoints and Criteria for Study Success

See Section 6.2.1 above and 6.2.9 below.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

Of the 3,000 randomized participants, approximately 15% were expected to be excluded from the PP Immunogenicity Set, leaving 2,550 participants (1,275 per group). Assuming an underlying GMT ratio of 0.90 (mRNA-1010 [QIV] versus Fluzone HD [QIV]) and a standard deviation of 1.5 for log-transformed titers, the study had ≥99% power to meet GMT noninferiority criteria for all 4 strains (1-sided α=0.025; NI margin =1.5). Assuming SCRs of 58% (mRNA-1010 [QIV]) versus 60%/50% (Fluzone HD [QIV], A/B strains), the study had ≥93% power to meet SCR noninferiority criteria for all 4 strains (1-sided α=0.025; NI margin =10%).

Strain-specific power estimates were:

- GMT superiority (individual strain, GMR =1.2): 79.5%
- SCR superiority, A strain (assumes 64% versus 60%): 43%
- SCR superiority, B strain (assumes 54% versus 50%): 41%

Superiority tests were conducted at 2-sided α=0.025 with multiplicity adjustment.

Methods

Immunogenicity

The primary immunogenicity objective was to demonstrate noninferiority of mRNA-1010 (QIV) versus Fluzone HD (QIV) for GMT and SCR at Day 29 by HAI assay across all 4 vaccine-matched strains. All 8 coprimary endpoints were tested at 1-sided α=0.025; success required all 8 to meet noninferiority criteria. For each of the 4- vaccine matched strains, the following noninferiority hypotheses were tested:

- GMT ($\mathbf{H_0^1}$): GMT Ratio ≤0.667; noninferiority demonstrated if the LB of the 95% CI of the GMT Ratio >0.667 (NI margin =1.5).
- SCR ($\mathbf{H_0^2}$): SCR difference ≤−10%; noninferiority demonstrated if the LB of the 95% CI of the SCR difference >−10% (NI margin =10%).

Upon successful demonstration of noninferiority, the following superiority hypotheses were tested:

- GMT: ($\mathbf{H_0^3}$): GMT Ratio =1, superiority demonstrated if the LB of the 95% CI of the GMT Ratio >1.
- SCR: ($\mathbf{H_0^4}$): SCR difference =0, superiority demonstrated if LB of the 95% CI of the SCR difference >0%.

Subgroup Analyses

Immunogenicity subgroup analyses were conducted for the following subgroups: age (65 to <75 years of age; ≥75 years of age), 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 participants classified as high-risk based on significant comorbidity in their 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 P304 and Study P303 Part C, restricted to participants 65 years of age and older, to justify the use of immunogenicity data from mRNA-1010 (QIV) to support licensure of mRNA-1010 (TIV).

Protocol Amendments and Changes to Planned Analyses

The original protocol was approved on February 28, 2023.

Protocol Amendment 1 (dated October 10, 2023) added Parts B and C.

Protocol Amendment 2 (dated December 11, 2023) amended the immunogenicity objectives and endpoint in Part B.

6.2.10 Study Population and Disposition

3,003 participants were randomized: 1,507 participants to the mRNA-1010 (QIV) group and 1496 participants to the Fluzone HD (QIV) group. The first participant, first visit was on November 13, 2023, and the last participant, last visit was on June 24, 2024.

> ***Clinical Reviewer Comment:*** *One participant in the Fluzone HD (QIV) group was 64 years of age at the time of vaccination. This participant was excluded from the PPIS and did not contribute to the analyses of immunogenicity. This participant has been removed from the analyses of solicited adverse reactions in Section 6.2.1; however, the participant is included in the total N for the demographics and disposition tables and the analyses of unsolicited safety in Study P303 Part C and in the ISS. Given the large size of this study, the addition of this single participant in the comparator group is not expected to affect the overall study conclusions.*

6.2.10.1 Populations Enrolled/Analyzed

Populations used in the study analyses are defined in Table 26. Immunogenicity analyses were based on the PPIS, which included all participants in the Immunogenicity subset who received the planned dose of study intervention, complied with the immunogenicity testing schedule for Baseline and Day 29, had no significant protocol deviations, and did not have RT-PCR-confirmed influenza between Days 1 to 29.

Table 26. 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[3], 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, mRNA-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-PCR, reverse transcription polymerase chain reaction

6.2.10.2 Demographics

Demographic and baseline characteristics of participants in the Safety Set are shown in Table 27. 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 to 93 years). A majority of participants were 65 to <75 years of age; 22.1% were ≥75 years of age. Most participants were White (82.7%) and female (57.8%). Over half (52.6%) had received a seasonal influenza vaccine in the prior season. Protocol-defined 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).

3 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).

Table 27. 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.
[#]N for Fluzone HD (QIV) includes 1 participant who was 64 years of age at time of study vaccination
* Defined post hoc.

***Reviewer Comment**: The overall prevalence of protocol-defined high-risk conditions in this study population was lower than population-level estimates, which indicate that 93% of U.S. adults 65 years of age 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 years of age), with regional variation noted in the Midwest and South (America's Health Rankings, 2025). The percentage 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).*

6.2.10.3 Participant Disposition

Participant disposition in the immunogenicity populations is shown in Table 28. 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).

Table 28. 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; QIV, quadrivalent influenza vaccine
[#]N for Fluzone HD includes 1 participant who was 64 years of age at time of study vaccination
[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 Table 29. 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% versus 1.7%) and withdrawal of consent by the participant (0.5% versus 0.7%). No participant discontinued due to an adverse event. The median duration of follow-up after vaccination was 171 days in both groups.

Table 29. 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
[#]N for Fluzone HD includes 1 participant who was 64 years of age at time of study vaccination.
[a] Participants are considered completed the study if they completed the final visit on Day 181 (Month 6).

6.2.11 Analyses of Vaccine Effectiveness

6.2.11.1 Analysis of Primary Objective

Analyses of the primary immunogenicity endpoints, as measured by HAI for vaccine-matched influenza strains at Day 29 postvaccination, are shown in Table 30 (GMTs and GMT ratios) and Table 31 (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%).

Table 30. 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)

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 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 31. 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, 59.0)	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.

Reviewer Comments:

1. *The Applicant's proposed Accelerated Approval for mRNA-1010 in adults ≥ 65 years of age is based on immunogenicity data from Study P303 Part C, using HAI titers as a surrogate endpoint reasonably likely to predict clinical benefit in this population. The CoR analysis (see Section 6.1.11.9) supported the use of HAI as a surrogate endpoint*

reasonably likely to predict clinical benefit for the influenza A/H1N1 and A/H3N2 strains, but introduced uncertainty regarding the use of HAI as a surrogate endpoint for the B/Victoria strain. While the primary immunogenicity analyses from Study P303 Part C demonstrated the noninferiority and protocol-defined superiority of mRNA-1010 (QIV) compared to Fluzone HD (QIV), a vaccine preferentially recommended by CDC for use in this age group, interpretation of B/Victoria-specific immunogenicity results is limited. Nonetheless, based on the totality of the available evidence, the review team concludes that the Applicant has provided substantial evidence of effectiveness to support the Accelerated Approval of mRNA-1010 in individuals ≥65 years of age. The basis for this conclusion is discussed in full in Section 10.

Sensitivity Analysis

Results of the sensitivity analyses based on adjustment for actual stratification factors in the PPIS (Part C) were similar to the primary analyses results.

6.2.11.2 Subpopulation Immunogenicity Analyses

The Applicant conducted the following subgroup analyses for the primary immunogenicity endpoints. No notable differences were observed based on demographics and baseline characteristics, except those noted below.

- ***Age:*** GMT ratios were lower in adults ≥75 years of age compared with the 65 through 74 years age group across all 4 strains; however, the LB of the 95% CI of the GMT ratio remained >0.667 for each strain. The LB of the 95% CI for the SCR difference was >0 for all strains in adults 65 through 74 years of age; in adults ≥75 years of age, the LB was <0 but >-10% for all strains.
- ***Previous Year Seasonal Influenza Vaccine Status:*** Among participants who received a previous year influenza vaccine and those who had not, the LB of the 95% of the CI for GMT ratio was >1 for all four strains. For SCR differences, the LB of the 95% was >0 for all four strains in those who had received a previous influenza vaccine, but in those who had not, the LB was <0% but >-10% for all four strains.
- ***Race:*** The LB of the 95% CIs were >1 for GMR and >0 for SCR difference for all 4 strains in White participants. For Black or African American participants, the LB was <1 but >0.667 for GMR and <0 but >-10% for SCR difference for all strains. Other racial subgroups had small sample sizes and analysis was limited.

  Reviewer Comment: *It is reasonable to conclude that 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 by High-Risk Status

The Applicant performed a post hoc analysis of immunogenicity by baseline status for high-risk of severe influenza disease. Table 32 shows that GMT ratios across all 4 strains were higher in participants with at least one high-risk condition compared with those without. Table 33 shows that SCR differences were greater in high-risk participants compared with those considered not high-risk, for influenza A/H3N2, B/Victoria, and B/Yamagata. For Influenza A/H1N1, SCR differences were similar across high-risk and non-high-risk participants.

Table 32. Post Hoc Analyses of Geometric Mean Titer Ratios of Anti-HA Antibody Levels for Vaccine-Matched Seasonal Influenza A and B Strains Measured by HAI Assay on Day 29, by High-risk Status, PPIS, Study P303 Part C

Strain	mRNA-1010 (QIV) GMT (95% CI)	Fluzone HD (QIV) GMT (95% CI)	GMT Ratio (mRNA-1010 [QIV] / Fluzone [HD]) (95% CI)
High Risk, n	540	572	--
Influenza A/H1N1	164.79 (152.69, 177.84)	118.64 (110.12, 127.82)	1.389 (1.252, 1.541)
Influenza A/H3N2	147.22 (135.34, 160.14)	103.12 (94.98, 111.96)	1.428 (1.273, 1.601)
Influenza B/Victoria	253.71 (238.69, 269.67)	188.59 (177.66, 200.19)	1.345 (1.238, 1.462)
Influenza B/Yamagata	108.75 (102.80, 115.05)	89.97 (85.15, 95.06)	1.209 (1.119, 1.305)
Not high risk, n	885	837	--
Influenza A/H1N1	171.27 (160.98, 182.23)	131.06 (123.02, 139.62)	1.307 (1.200, 1.424)
Influenza A/H3N2	132.76 (124.16, 141.96)	121.52 (113.48, 130.12)	1.093 (0.996, 1.198)
Influenza B/Victoria	234.76 (223.47, 246.62)	197.20 (187.52, 207.38)	1.190 (1.112, 1.274)
Influenza B/Yamagata	99.21 (95.07, 103.53)	90.03 (86.19, 94.03)	1.102 (1.039, 1.169)

Source: Adapted from STN 125869/0, Amendment 45 Tables 14.2.1.1.6.c and 14.2.2.1.1.6c, Data extraction date: February 14, 2025.
Abbreviations: ANCOVA, Analysis of Covariance; CI, Confidence Interval; GLSM, Geometric Least Squares Mean; GMT, Geometric Mean Titer, estimated by GLSM; HA, Hemagglutinin; HAI, Hemagglutination Inhibition; HD, high dose; LLOQ, Lower Limit of Quantification; PPIS, Per-protocol immunization Set; QIV, quadrivalent; ULOQ, Upper Limit of Quantification.
n, number of participants with non-missing anti-HA antibody data at the corresponding timepoint.
Antibody values reported as below the LLOQ are replaced by 0.5 x 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 are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Table 33. Post Hoc Analyses of SCR as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29, by High-Risk Status, PPIS, Study P303 Part C

Endpoint	mRNA-1010 (QIV) SCR[a] (95%CI)[b]	Fluzone HD (QIV) SCR[a] (95%CI)[b]	Difference in SCR (mRNA-1010 [QIV] - Fluzone HD [QIV]) (95%CI)[c]
High Risk, n	540	572	--
Influenza A/H1N1	51.1 (46.81, 55.40)	37.8 (33.77, 41.88)	13.35 (7.52, 19.09)
Influenza A/H3N2	58.7 (54.42, 62.89)	45.5 (41.32, 49.64)	13.25 (7.39, 19.02)
Influenza B/Victoria	32.0 (28.12, 36.16)	18.4 (15.27, 21.78)	13.68 (8.61, 18.73)
Influenza B/Yamagata	27.6 (23.86, 31.57)	20.8 (17.55, 24.36)	6.79 (1.76, 11.83)
Not high risk, n	885	837	--
Influenza A/H1N1	48.8 (45.47, 52.16)	35.2 (32.01, 38.59)	13.57 (8.92, 18.15)
Influenza A/H3N2	55.0 (51.68, 58.34)	49.5 (46.02, 52.91)	5.57 (0.84, 10.26)
Influenza B/Victoria	28.5 (25.52, 31.57)	21.4 (18.65, 24.32)	7.09 (3.01, 11.15)
Influenza B/Yamagata	25.1 (22.26, 28.08)	19.7 (17.07, 22.57)	5.37 (1.43, 9.29)

Source: Adapted from STN 125869/0, Amendment 45 Tables 14.2.1.1.6.c and 14.2.2.1.1.6c, Data extraction date: February 14, 2025.
Abbreviations: ANCOVA, Analysis of Covariance; CI, Confidence Interval; GLSM, Geometric Least Squares Mean; GMT, Geometric Mean Titer, estimated by GLSM; HAI, Hemagglutination Inhibition; HD, high dose; LLOQ, Lower Limit of Quantification; ULOQ, Upper Limit of Quantification.
[a] SCR is defined as the proportion of participants with either a baseline HAI titer <1:10 and a post-baseline titer ≥1:40 or a baseline HAI titer ≥1:10 and a minimum 4-fold rise in post-baseline HAI antibody titer.
[b] 95% CI is calculated using the Clopper-Pearson method.

Reviewer Comment: *The high-risk population used for this post hoc analysis was generated based on medical history and includes a heterogeneous group of medical conditions. Generalization to other populations, including to frail older adults, may be limited.*

6.2.11.3 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 Table 34. 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 percentage of participants with HAI titer ≥1:40 and the GMT Ratio from Baseline to Day 29 were higher in mRNA-1010 (QIV) recipients than in Fluzone HD (QIV) recipients across all four influenza strains (Table 34).

Table 34. 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.

6.2.11.4 Exploratory Immunogenicity Objectives

GMT and SCR by HAI at EOS/Day 181

Table 35 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.

Table 35. 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 status

Table 36 shows the percentage of participants with seroconversion at EOS/Day 181. The percentage 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.

Table 36. 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% versus 79.1%), A/H3N2 (75.3% versus 69.9%), and B/Yamagata (83.2% versus 80.4%), and similar for B/Victoria (98.7% versus 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.

Reviewer Comment: *EOS/Day 181 immunogenicity results suggest persistence of immune response after vaccination with mRNA-1010 (QIV).*

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.

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

To justify the use of immunogenicity data from the quadrivalent formulation of mRNA-1010 evaluated in Study P303 Part C to support licensure of the trivalent formulation of mRNA-1010 in adults 65 years of age and older, the Applicant conducted a post hoc analysis comparing Day 29 HAI GMTs between the PPISs of Study P304 and Study P303 Part C, restricted to participants ≥65 years of age, shown in Table 37, using an ANCOVA model that accounted for differences in baseline demographic factors between the two groups, including age, race, sex, ethnicity, baseline BMI group, previous influenza vaccine status, and baseline high-risk status.

Table 37. Day 29 HAI for Vaccine-Matched Strains Comparing mRNA-1010 TIV (Study P304) and QIV (Study P303 Part C) in Adults ≥65 Years of Age, Model 1: ANCOVA With 6 PCA Factors

Influenza Type	Model-Based GMT (95% CI) mRNA-1010 (TIV) Study P304 N=586	Model-Based GMT (95% CI) mRNA-1010 (QIV) Study P303 Part C N=1425	Model-based GMT Ratio (TIV/QIV) (95% CI)
Influenza A/H1N1	159.36 (148.08, 171.50)	161.13 (153.80, 168.81)	0.989 (0.906, 1.080)
Influenza A/H3N2	158.13 (146.26, 170.95)	138.85 (132.12, 145.92)	1.139 (1.037, 1.250)
Influenza B/Victoria	289.93 (272.69, 308.25)	234.78 (225.85, 244.07)	1.235 (1.148,1.328)

Source: Adapted from STN 125869/0, Amendment 32, Response to IR Database lock/data extraction dates: July 22, 2024 (P303 Part C) and June 3, 2025 (P304).
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GMT, geometric mean titer; PCA, principal components analysis; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine
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

Clinical Reviewer Comment: *Although the analysis was not hypothesis tested, noninferiority of the TIV formulation compared with the QIV formulation of mRNA-1010 would have been demonstrated for all three shared strains using a threshold of the LL of the 95% CI for GMT ratio >0.667. For Influenza A/H1N1, the GMT ratio approaching 1.0 indicates no meaningful difference between TIV and QIV formulations. For Influenza A/H3N2 and B/Victoria, the TIV formulation elicited higher antibody responses compared with the QIV formulation, with GMT ratio point estimates and lower limits of the 95% CI both >1.0. Lower antibody responses from the quadrivalent formulation suggest that inclusion of B/Yamagata may have reduced immune responses to A/H3N2 and B/Victoria strains. 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).

This analysis has several limitations: the two studies were conducted in different influenza seasons with different strain selection and the potential for residual confounding remains despite adjustment for baseline demographics. Recognizing these limitations, FDA's assessment is that because the data supports noninferiority of mRNA-1010 TIV to QIV across the three shared strains, with any interference from B/Yamagata favoring TIV, the immunogenicity data from mRNA-1010 (QIV), which demonstrated superiority against a HD comparator, may be used to support the effectiveness of mRNA-1010 (TIV) in adults 65 years of age and older.

6.2.12 Safety Analyses

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

6.2.12.1 Methods

Please see Section 6.2.7.

6.2.12.2 Overview of Adverse Events

Table 38 provides an overview of the rates of solicited adverse reactions and unsolicited AEs in the mRNA-1010 (QIV) group compared with the Fluzone HD (QIV) group. The rates of solicited adverse reactions through 7 days were higher in participants who received mRNA-1010 (QIV) relative to those who received Fluzone HD (QIV). Overall, rates of unsolicited AEs through 28 days and MAAEs, SAEs, and AESIs through study completion were similar across the mRNA-1010 (QIV) and Fluzone HD (QIV) groups.

Table 38. 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)

Event Type	mRNA-1010 (QIV) % (n/N1)	Fluzone HD (QIV) % (n/N1)[#]
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; QIV, quadrivalent influenza vaccine
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.
[#]N1 for Fluzone HD includes 1 participant who was 64 years of age at time of study vaccination
[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.

6.2.12.3 Solicited Adverse Reactions

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

Solicited Local Adverse Reactions

Table 39 includes the percentages of mRNA-1010 (QIV) and Fluzone HD (QIV) recipients who reported any solicited local AR, by maximum severity. Solicited local ARs were reported by 66.1% of mRNA-1010 (QIV) recipients compared with 38.9% of Fluzone HD (QIV) recipients, with the most frequently reported ARs being injection site pain (64.6% in the mRNA-1010 [QIV] group versus 36.7% in the Fluzone HD [QIV] group). The majority of solicited ARs in both groups were Grade 1 or 2 in severity, with Grade 3 ARs reported in 2.4% of participants in the mRNA-1010 (QIV) group versus 0.8% of participants in the Fluzone HD (QIV) group. No Grade 4 solicited local ARs were reported in either group.

Table 39. 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=1488-1489 % (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 (546)
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)

Solicited Adverse Reaction Category, Grade	mRNA-1010 (QIV) N1=1502 % (n)	Fluzone HD (QIV) N1=1488-1489 % (n)
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., and Amendment 108 14.3.1.2.1.6.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
No Grade 4 solicited local ARs were 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 to 50 mm; G2=51 to 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).

The median onset of solicited local ARs was 2 days postvaccination in the mRNA-1010 (QIV) group and 1 day in the Fluzone HD (QIV) group. Solicited local ARs had a median duration of 2 days in both groups, with a higher percentage persisting beyond 7 days in the mRNA-1010 (QIV) group (1.2%) compared with the Fluzone HD (QIV) group (0.5%).

Solicited Systemic Adverse Reactions

Table 40 includes the percentages of mRNA-1010 (QIV) and Fluzone HD (QIV) recipients who reported any solicited systemic AR, by maximum severity. Solicited systemic ARs were reported by 61.3% of participants in the mRNA-1010 (QIV) group compared with 32.9% of participants in the Fluzone HD (QIV) group. 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 solicited ARs in both groups were Grade 1 or 2 in severity. Grade 3 ARs were reported in 6.7% of participants in the mRNA-1010 (QIV) group versus 1.7% in the Fluzone HD (QIV) group. Two Grade 4 solicited systemic ARs of fever were reported in the mRNA-1010 (QIV) group and are described below. Neither participant sought medical attention for their Grade 4 fever.

1. A 66-year-old female participant reported a fever of 104.9°F on Day 2. She did not take any medications for the fever. Besides Grade 1 injection site pain on Day 2, no other solicited ARs or unsolicited AEs were reported for the participant throughout the study.
2. A 70-year-old female participant reported a fever of 105°F on Day 3, for which she took acetaminophen. No fevers were reported in the previous or subsequent days. Within 7 days of vaccination, the participant also reported solicited ARs of headache, myalgia, arthralgia, and chills, all of which were Grade 1 to 2 in severity. No unsolicited AEs were reported for the participant throughout the study.

Table 40. 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=1487-1488 % (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 (529)	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[d]	--	--
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., , and Amendment 108 14.3.1.2.1.6.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 to 38.4°C or 100.4 to 101.1°F; G2=38.5 to 38.9°C or 101.2 to 102.0°F; G3=39.0 to 40.0°C or 102.1 to 104.0°F; G4: ≥40.0°C or >104.0°F.
[b] Toxicity grade for headache, fatigue, myalgia (muscle aches all over body), and arthralgia (joint aches in several joints) 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 to 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.
[d] Toxicity grade for chills was defined as: G1 = no interference with activity; G2 = some interference with activity not requiring medical intervention; G3 = prevents daily activity and requires medical intervention

The median day of onset for solicited systemic ARs was 2 days postvaccination in both the mRNA-1010 group and the Fluzone HD (QIV) group. Solicited systemic ARs had a median duration of two days in both groups, with a higher percentage persisting beyond seven days in the mRNA-1010 (QIV) group (1.7%) compared with the Fluzone HD (QIV) group (1.1%).

6.2.12.4 Unsolicited Adverse Events

Overall, the percentages of unsolicited AEs within 28 days postvaccination were balanced across mRNA-1010 (QIV) and Fluzone HD (QIV) recipients (10.3% and 9.2%, respectively). By MedDRA SOC, unsolicited AEs through 28 days were most frequently reported under infections and infestations (4.5% in the mRNA-1010 [QIV] group versus 4.4% in the Fluzone HD [QIV] group) and musculoskeletal and connective tissue disorders (1.1% in the mRNA-1010 [QIV] group versus 1.2% in the Fluzone HD [QIV] group).

Unsolicited AEs within 28 days assessed as related 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 based on age, sex, and race.

6.2.12.5 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. Throughout the study, MAAEs were reported by a similar percentage of mRNA-1010 (QIV) recipients (17.1%) and the Fluzone HD (QIV) recipients (16.6%). MAAEs were most frequently reported under the MedDRA SOC of infections and infestations (6.4% in the mRNA-1010 [QIV] group and 7.8% in the Fluzone HD [QIV] group).

MAAEs assessed as related by the Investigator to study vaccination were higher in the mRNA-1010 (QIV) group (0.3%, n=4) compared with the Fluzone HD (QIV) group (<0.1%, n=1). The four MAAEs assessed as related to mRNA-1010 (QIV) by the study Investigator were:

- An 80-year-old female with cough on the evening of the study 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, and concomitant medication of phentermine/topiramate, experienced chest discomfort on Day 2, which resolved in 1 hour. Concurrently, she reported MAAE of dizziness (reported as “lightheadedness – orthostatic – intermittent”), also with onset and resolution on Day 2, which was assessed as unrelated to study injection by the Investigator. No additional evaluation or treatment was reported for these events.
- A 72-year-old female with face swelling on Study Day 2. This event was also classified as an AESI and discussed in further detail in Section 6.2.12.8.

  Clinical Reviewer Comment: *Based on the temporal association with study vaccination and lack of clear alternative etiology, the clinical reviewer considers it plausible that the study vaccine contributed to these events; however, as the majority were mild to moderate in severity and resolved promptly without intervention, these events are not considered to represent clinically meaningful safety concerns.*

6.2.12.6 Deaths

Through study completion, with a median follow-up of 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, and none of the

reported deaths in either group were assessed as related to the study vaccination by the investigator.

Within 28 days following study injection, one death was reported in the mRNA-1010 (QIV) group (<0.1%) and zero deaths reported in the Fluzone HD (QIV) group. The one death in the mRNA-1010 (QIV) group is further described below.

> A 65-year-old male with hypertension, hyperlipidemia, history of prior myocardial infarction, type 2 diabetes mellitus (reported as pre-diabetes on screening), cigarette smoking (half a pack daily), and alcohol use (12 to 15 beers weekly), experienced acute myocardial infarction on Day 26. The participant complained of chest pain to a family member and was found unresponsive approximately 20 minutes later. Electrocardiogram performed by emergency medical services showed ST-elevation myocardial infarction. Resuscitation was unsuccessful and the patient was pronounced dead. Both the Investigator and Applicant assessed the event as not related to the study intervention.

Clinical Reviewer Comment: *The clinical reviewer agrees with the investigator that this event was unrelated to study vaccine. The participant's comorbid conditions combined with lifestyle risk factors provide a more plausible alternative etiology for the myocardial infarction.*

Based on independent review of narratives of all deaths reported in Study P303 Part C, the clinical reviewer agrees with the investigators' assessments that none of these deaths were related to study vaccine.

6.2.12.7 Serious Adverse Events (SAEs)

SAEs within 28 days of vaccination were reported in 0.6% (n=9) and 0.5% (n=7) of participants in the mRNA-1010 (QIV) and Fluzone HD (QIV) groups, respectively. Overall, 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 SOCs of infections and infestations (0.7% of participants in the mRNA-1010 [QIV] group versus 0.5% of participants in the Fluzone HD [QIV] group). No SAEs were assessed as related to mRNA-1010 (QIV) by the Investigator.

Clinical Reviewer Comment*: Based on independent review of event narratives, the clinical reviewer agrees with the investigators' assessments that none of the SAEs were related to mRNA-1010 (QIV).*

6.2.12.8 Adverse Events of Special Interest (AESIs)

Protocol-defined AESIs are listed in Appendix A. Through 28 days after vaccination, an AESI was reported by one (<0.1%) mRNA-1010 (QIV) recipient and no Fluzone HD (QIV) recipients. Through study completion, two AESIs were reported in the mRNA-1010 (QIV) group and one AESI reported in the Fluzone HD (QIV) group. One AESI in the mRNA-1010 (QIV) group was a partial seizure occurring on Day 51, which was assessed as unrelated to study vaccine by the investigator. The other AESI in the mRNA-1010 (QIV) group was an event of swelling face, also classified as an MAAE, which was assessed as related to the vaccine by the study investigator. This event is further described below.

- Face swelling: A 72-year-old female with history of asthma, environmental allergies (cat dander, dust), and obesity experienced a moderate AE of face swelling on Study Day 2. She

was seen in the emergency department and given prednisone and diphenhydramine; the event was reported as resolved on Day 10. She denied any other symptoms and no other unsolicited AEs were reported around this time. The Investigator assessed this event as a possible symptom of angioedema and reported it as an AESI. However, the event was not a protocol-specified AESI and did not meet the protocol-defined definition of anaphylaxis of sudden onset, rapidly progressing, and involving 2 or more major organ systems. The Applicant, in agreement with the investigator, assessed this event as related to the study vaccine.

Clinical Reviewer Comment: *The clinical reviewer agrees with the investigator's assessment that this event of face swelling is possibly related to vaccine given the temporal relationship to study vaccination. However, the participant's environmental allergies represent a plausible alternative etiology. Although the investigator reported this event as an AESI, facial swelling in the absence of other signs and symptoms is not consistent with the protocol-defined AESI of anaphylaxis. This was a non-serious, non-severe, event of facial swelling that was not clinically concerning for anaphylaxis or severe hypersensitivity. As such, the clinical review team does not conclude that this isolated event represents a safety concern for mRNA-1010.*

6.2.12.9 Pregnancies
No participants reported pregnancies in either group.

6.2.12.10 Dropouts and/or Discontinuations
Besides the study discontinuations due to death (discussed in Section 6.2.12.6), no additional discontinuations due to AEs were reported in either group.

6.2.13 Study Summary and Conclusions

Study mRNA-1010-P303 Part C evaluated the safety and immunogenicity of mRNA-1010 (QIV) compared with Fluzone HD (QIV) in adults 65 years of age and older. The study met prespecified criterion for noninferiority and superiority of HAI antibody responses as measured by GMT ratio and SCR differences at Day 29 as elicited by mRNA-1010 (QIV) as compared with Fluzone HD (QIV) for all four influenza strains. A post hoc analysis comparing Day 29 HAI GMTs between the PPISs of Study P304 and Study P303 Part C, restricted to participants ≥65 years of age supported the noninferiority of mRNA-1010 (TIV) to mRNA-1010 (QIV) across the three shared strains and therefore, the use of immunogenicity data from mRNA-1010 (QIV) to support the approval of mRNA-1010 (TIV).

mRNA-1010 (QIV) was generally well tolerated. Solicited local and systemic ARs were more frequent in the mRNA-1010 (QIV) group than in the Fluzone HD (QIV) group, but were predominantly Grade 1 to 2 in severity, with short duration (median 2 days). Unsolicited AEs through 28 days postvaccination, and SAEs and deaths through study completion were balanced between groups. No cases of myocarditis or pericarditis occurred within the 42-day risk window in the mRNA-1010 (QIV) group.

Overall, the totality of safety and immunogenicity data from Study P303 Part C support a favorable benefit-risk profile for mRNA-1010 (QIV) in adults 65 years of age and older.

6.3 Study mRNA-1010-P101

NCT04956575

Title: "A Phase 1/2, Randomized, Stratified, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1010 Seasonal Influenza Vaccine in Healthy Adults 18 Years and Older"

Overview: Study mRNA-1010-P101 (P101) was a Phase 1/2, randomized, stratified, observer-blind, dose-ranging trial evaluating the safety, reactogenicity, and immunogenicity of the original quadrivalent (QIV) formulation of the mRNA-1010 (hereafter referred to as mRNA-1010 [Original QIV]) in adults 18 years of age and older. The study was designed to determine the optimal dose level of mRNA-1010. The Study was organized into 3 parts, Phase 1/2, Phase 2 Northern Hemisphere (NH), and Phase 2 Extension, with the Phase 1/2 part being placebo-controlled and the Phase 2 NH and Phase 2 Extension parts being active-controlled. The study was initiated in June 2021 and completed in September 2022.

6.3.1 Objectives

Primary Objectives (Phase 1/2)

Primary Safety Objective

- To evaluate the safety and reactogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 (Original QIV) administered as a single dose

  Endpoints

  - Frequency and severity of solicited local and systemic ARs through 7 days after each vaccination
  - Frequency and severity of unsolicited AEs through 28 days after each vaccination
  - Frequency of SAEs, AESIs, and MAAEs through Day 181/End of Study (EoS)
  - Safety laboratory abnormalities through 7 days after each vaccination

Primary Immunogenicity Objective

- To evaluate the humoral immunogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 (Original QIV) administered as a single dose against vaccine-matched Influenza A and B strains at Day 29

  Endpoint

  - GMT and GMFR at Day 29 compared with Day 1 (baseline) and percentage of participants with seroconversion, defined as a Day 29 titer ≥1:40 if baseline is <1:10 or a 4-fold or greater rise if baseline is ≥1:10 in anti-HA antibodies measured by HAI assay

Secondary Objective (Phase 1/2)

Secondary Immunogenicity Objective

- To evaluate the humoral immunogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 (Original QIV) administered as a single dose against vaccine-matched Influenza A and B strains at all evaluable humoral immunogenicity timepoints.

Endpoint

- GMT and GMFR of anti-HA antibodies as measured by HAI or MN assays at all evaluable humoral immunogenicity timepoints compared with Day 1 (baseline)

Primary Objectives (Phase 2 NH and Phase 2 Extension)

Primary Safety Objective:

- To evaluate the safety and reactogenicity of mRNA-1010 (Original QIV)

Endpoints

- Frequency and severity of solicited local and systemic ARs through 7 days after each vaccination
- Frequency and severity of unsolicited AEs through 28 days after each vaccination
- Frequency of SAEs, AESIs, and MAAEs through Day 181/EoS

Primary Immunogenicity Objective

- To evaluate the humoral immunogenicity of mRNA-1010 (Original QIV) relative to that of an active comparator against vaccine-matched Influenza A and B strains at Day 29.

Endpoints

- GMT at Day 29 as measured by HAI
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI

Secondary Objective (Phase 2 NH and Phase 2 Extension)

Secondary Immunogenicity Objective

- To evaluate the humoral immunogenicity of each vaccine group against vaccine-matched Influenza A and B strains at Day 29.

Endpoints

- The frequency of participants with HAI seroconversion and the frequency of participants with an HAI titer ≥1:40 at Day 29
- GMFR comparing Day 29 to Day 1 (baseline) as measured by HAI

6.3.2 Design Overview

The Phase 1/2 portion (N=180) used a dose-ranging design evaluating three dose levels (50 µg, 100 µg, and 200 µg) and placebo. An internal safety team (IST) conducted a blinded review of safety data through 7 days postvaccination collected from 36 participants in an initial stage, prior dosing of 144 participants in the expansion stage. Randomization in the expansion stage was stratified by age (18 through 49 years, 50 years and older).

In the Phase 2 NH portion, 500 participants were randomized in parallel across three dose levels (25, 50, and 100 µg) and an active comparator (Afluria Quadrivalent). Randomization was stratified by three age categories (18 through 49, 50 through 64, and 65 years and older) as well as by whether participants had received an influenza vaccine during the prior season.

In the Phase 2 Extension portion, 200 additional participants were similarly randomized in parallel across three lower dose levels (6.25, 12.5, and 25 µg) and an active comparator (Afluria

Quadrivalent). Randomization was stratified by two age categories (18 through 49 years, 50 years and older).

Each participant across all study parts followed the same overall timeline: a screening period of up to one month, followed by a six-month study period that included a single vaccine dose administered on Day 1, with a final study visit occurring on Day 181. The EOS was defined as the completion of the last visit or last scheduled procedure for the final participant enrolled in the Phase 2 Extension portion.

6.3.3 Population

Healthy (Phase 1/2) and medically stable (Phase 2 NH and Phase 2 Extension) adults 18 years of age and older were enrolled.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The Phase 1/2 portion of the study used the 2021 Southern Hemisphere influenza vaccine formulation, while the Phase 2 Northern Hemisphere (NH) and Phase 2 Extension portions used the 2021/2022 Northern Hemisphere formulation. The key difference between these two formulations was the substitution of the A/Hong Kong/45/2019 (H3N2) strain with the A/Cambodia/e0826360/2020 (H3N2) strain.

Phase 1/2

- mRNA-1010 (Original QIV) at 50 µg, 100 µg, or 200 µg
  - Dose and route of administration: 0.5 mL IM
  - Description: mRNA-based quadrivalent seasonal influenza vaccine, encoding the hemagglutinin (HA) antigens of four influenza strains recommended for the 2021 Southern Hemisphere (SH) (A/Wisconsin/588/2019(H1N1)pdm09, A/Hong Kong/45/2019(H3N2), B/Washington/02/2019, and B/Phuket/3073/2013) formulated in lipid nanoparticles composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG)
  - Presentation: dispersion for intramuscular injection
  - Lot numbers: 7003721001, 7003721002, 7008721001

- Placebo
  - Dose and route of administration: 0.5 mL IM
  - Description: 0.9% sodium chloride (normal saline)
  - Lot numbers: 6021478, 6022015, 6021570, 21077DK

Phase 2 NH and Phase 2 Extension

mRNA-1010 (Original QIV) at

- Phase 2 NH: 25 µg, 50 µg, or 100 µg
- Phase 2 Extension: 6.25 µg, 12.5 µg, or 25 µg

  - Dose and route of administration: 0.5 mL IM
  - Description: mRNA-based quadrivalent seasonal influenza vaccine, encoding the hemagglutinin (HA) antigens of four influenza strains recommended for the 2021/2022

Northern Hemisphere (NH) (A/Victoria/2570/2019 (H1N1)pdm09, A/Cambodia/e0826360/2020 (H3N2), B/Washington/02/2019, and B/Phuket/3073/2013) formulated in lipid nanoparticles composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG)

  - Presentation: dispersion for intramuscular injection
  - Lot numbers: 7003721001, 7003721002, 7008721001

- Afluria Quadrivalent 60 µg
  - Dose and route: 0.5mL IM
  - Description: Inactivated influenza vaccine, containing 60 µg hemagglutinin (HA) (15 µg per HA) for each of the four influenza strains recommended for the 2021-2022 Northern Hemisphere influenza season: A/Victoria/2570/2019 (H1N1)pdm09, A/Cambodia/e0826360/2020 (H3N2), B/Washington/02/2019, and B/Phuket/3073/2013
  - Presentation: sterile suspension in 0.5 mL pre-filled syringe (PFS) or 5 mL multidose vials.
  - Lot number: P100365584

6.3.5 Directions for Use

A single IM injection of either mRNA-1010 (Original QIV), placebo (Phase 1/2), or active comparator (Phase 2 NH and Phase 2 Extension) administered in the deltoid muscle.

6.3.6 Sites and Centers

The study was conducted at 20 clinical sites in the U.S. (Phase 1/2: 4 sites; Phase 2 NH: 18 sites; Phase 2 Extension: 5 sites).

6.3.7 Surveillance/Monitoring

Safety

Solicited ARs through Day 7 were collected via eDiary. Unsolicited AEs were monitored through Day 29. SAEs, MAAEs, and AESIs were continuously monitored from Day 1 through Day 181/EoS. Safety telephone calls were conducted on Days 8 and 15 during the Phase 2 NH and Phase 2 Extension parts. An IST performed blinded safety reviews; an independent, unblinded DSMB conducted safety oversight throughout the study.

Immunogenicity

Blood samples were collected at baseline (Day 1, pre-vaccination) and at post-baseline timepoints (Days 8, 29, and 181/EoS for Phase 1/2; Days 29, 91, and 181/EoS for Phase 2 NH and Phase 2 Extension) to assess anti-HA antibody titers via the cell-based HAI assay. An ICS assay was used to evaluate T-cell responses in the Phase 1/2 part.

6.3.8 Endpoints and Criteria for Study Success

See Section 6.3.1.

6.3.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive without formal hypothesis testing.

6.3.10 Study Population and Disposition

A total of 885 participants were randomized across all three study parts (180 in Phase 1/2, 503 in Phase 2 NH, and 202 in Phase 2 Extension). Most participants completed the study and reasons for discontinuation from the study were balanced across groups. The median age was 51 years (range: 18 to 90) in Phase 1/2, 52 years (range: 18 to 86) in Phase 2 NH, and 38 years (range: 18 to 76) in Phase 2 Extension. The median duration of follow-up was 175 days for the ≥50 µg mRNA-1010 (Original QIV) groups, 169.5-174 for the lower dose mRNA-1010 (Original QIV) groups, and 173 days for the Afluria and placebo group.

6.3.11 Analyses of Vaccine Effectiveness

All immunogenicity analyses were performed on the Per-Protocol (PP) Set. Baseline anti-HA antibody GMTs were similar across all vaccination groups and all four vaccine strains at the start of each study part.

Phase 1/2 Part, Humoral Immunogenicity

At Day 29, GMFRs in the mRNA-1010 (Original QIV) groups were approximately 7.5 to 11-fold for A/H1N1, 6 to 7-fold for A/H3N2, 2-fold for B/Victoria-lineage, and 3 to 4-fold for B/Yamagata-lineage. GMTs were highest in the 200-µg group but were generally comparable between the 50-µg and 100-µg groups. Among mRNA-1010 (Original QIV) recipients, seroconversion at Day 29 was observed in 67.4%-90.2% of participants against A/H1N1, 75.0%-81.4% of participants against A/H3N2, 14.0%-25.0% of participants against B/Victoria, and 41.9%-51.2% of participants against B/Yamagata. A dose response pattern was observed for A/H1N1, B/Victoria, and B/Yamagata, but not for A/H3N2.

At Day 181/EoS, GMTs declined from Day 29 peaks but remained above baseline for H1N1 and H3N2. Victoria-lineage and Yamagata-lineage GMTs returned to near-baseline levels.

Phase 1/2 Part, T-Cell Responses

Robust antigen-specific CD4+ T-cell responses, including CD40L expression and production of Th1 cytokines (IL-2, IFN-γ, TNF-α) with polyfunctional CD4+ T-cells, were detected among mRNA-1010 (Original QIV) recipients. Th2 cytokine responses (IL-4, IL-13) were also detected but at lower magnitude.

Phase 2 NH Part

The 95% CI lower bound of GMT Ratio of mRNA-1010 (Original QIV) at all dose levels versus Afluria Quadrivalent was >1 for A/H1N1 and A/H3N2, >0.67 but <1 for B/Yamagata, and 0.54-0.69 for B/Victoria. The SCR difference lower bound was >-10% for A/H1N1, A/H3N2, and B/Yamagata, but not B/Victoria. GMTs remained elevated above baseline through Day 181/EoS for Influenza A in all mRNA-1010 (Original QIV) groups. The immune responses were comparable between the 50-µg and 100-µg groups.

Phase 2 Extension Part

The 25-µg dose demonstrated the strongest immunogenic response. GMTs for Influenza B strains were lower compared with Afluria Quadrivalent across all mRNA-1010 (Original QIV)

dose groups, with lower bounds of the 95% CI for GMT ratio falling below 0.67 and lower bounds of the 95% CI for SCR difference falling below < -10% for both B/Victoria- and B/Yamagata-lineage.

Clinical Reviewer Comment: *The lower immune responses against Influenza B strains, notably B/Victoria, was similarly observed in subsequent Phase 3 studies P301 and P302, prompting the Applicant to modify the mRNA-1010 formulation by incorporating stabilizing point mutations in the B antigen to improve immunogenicity (mRNA-1010.4). The updated mRNA-1010.4 formulation was used in the pivotal Phase 3 studies P304 and P303 Part C submitted to support this BLA.*

6.3.12 Safety Analyses

Solicited Adverse Reactions

Solicited ARs were reported in a higher proportion of participants in mRNA-1010 (Original QIV) groups compared with Afluria Quadrivalent and placebo groups, with a clear dose-response relationship. All solicited ARs were Grade 1 or 2 in severity; no Grade 4 solicited ARs were reported.

Unsolicited Adverse Events

Unsolicited AEs within 28 days were higher in the mRNA-1010 (Original QIV) groups than in comparator groups. Most severe unsolicited AEs reflected solicited AR symptoms (headache, fatigue, arthralgia, myalgia, injection site pain/lymphadenopathy). The incidence of unsolicited MAAEs was similar across groups.

Deaths

Three participants died during the study; all events were assessed as unrelated to study vaccination by the Investigator, Applicant, and DSMB:

- 67-year-old in the 100-µg mRNA-1010 (Original QIV) group (Phase 2 NH): unwitnessed cardiac arrest on Day 16. Medical history of diabetes mellitus, hypertension, and obesity. No autopsy was performed.
- 54-year-old in the 6.25-µg mRNA-1010 (Original QIV) group (Phase 2 Extension): fatal road traffic accident on Day 57 with brain herniation.
- 84-year-old in the placebo group (Phase 1/2): Renal cancer on Day 176.

Clinical Reviewer Comment: *Based on independent review of event narratives, the clinical reviewer agrees with the investigators' assessments that these deaths were unlikely to be related to study vaccine. The 67-year-old participant who experienced an unwitnessed cardiac arrest had no other reported AEs post vaccination. The participant reported only Grade 1 injection site pain within the first 7 days postvaccination and no other solicited adverse reactions. The participant's underlying comorbidities are a more plausible alternative etiology for the death.*

Serious Adverse Events and AESIs

SAEs were reported by 2.1% of participants in the mRNA-1010 (Original QIV) group compared with 1.9% of participants in the Afluria Quadrivalent group and 4.4% of participants in the

placebo group. No SAEs were assessed by the investigator as related to study vaccine. No AESIs were reported during the study.

> ***Clinical Reviewer Comment:*** *Based on independent review of event narratives, the clinical reviewer agrees with the investigators' assessments that the SAEs were unlikely to be related to study vaccine.*

6.3.13 Study Summary and Conclusions

Study P101 was a first-in-human Phase 1/2 dose-ranging study in adults 18 years and older. A single dose of mRNA-1010 (Original QIV) was generally well-tolerated across all dose levels; however, the reactogenicity increased with increasing dose level and was higher in frequency and severity compared with the licensed active comparator Afluria Quadrivalent. mRNA-1010 (Original QIV) elicited higher immune responses compared with the active comparator against Influenza A strains; however, the responses against Influenza B strains were similar or lower. Based on the immunogenicity and safety data from Study P101, the Applicant selected the 50-µg dose to advance into further clinical development.

7. Integrated Overview of Efficacy

Study P304 was the only study with evaluation of clinical efficacy endpoints with the mRNA-1010 formulation intended for licensure. Therefore, an integrated overview of efficacy is not applicable to this review.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The Applicant conducted an ISS to provide a cross-study evaluation of the safety profile of mRNA-1010 in adults 50 years of age and older. The integrated safety review pooled safety data from participants 50 years of age and older across all four Phase 3 studies (P301, P302, P303, and P304), with analyses focused on SAEs, AESIs, and deaths. The pooled safety of mRNA-1010 (TIV and QIV), hereafter referred to as mRNA-1010 in this section, was compared with the pooled safety of the standard-dose and high-dose comparator vaccines (Fluarix [TIV and QIV], Fluzone HD [QIV]), hereafter referred to as SD/HD comparator.

The Applicant additionally provided 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.

8.2 Safety Database

The ISS Set comprised all randomized participants 50 years of age 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 since their injections were administered at least 10 months apart.

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Brief descriptions of the four Phase 3 studies contributing to the ISS analyses are presented in Section 5.3. Of note, due to small individual sample sizes, all three parts of Study P303 were combined and analyzed as a single study for the purposes of the ISS.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

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 to 449 days in the mRNA-1010 group and 1 to 445 days in the SD/HD comparator group). Study completion rates were high and comparable between groups, with 95.1% of mRNA-1010 participants and 95.2% of SD/HD comparator participants completing the study.

Demographic characteristics were well-balanced between the two study intervention groups. The median age was 64.0 years in both groups, with a range of 50 to 99 years in the mRNA-1010 group and 50 to 96 years in the SD/HD comparator group. Among mRNA-1010 recipients, 51.2% were between 50 through 64 years of age, 37.5% were 65 to 74 years of age, and 11.4% were ≥75 years of age. In the mRNA-1010 and SD/HD comparator groups, respectively, the majority of participants were female (56.5% versus 56.9%), White (79.4% versus 79.0%), not Hispanic or Latino (82.9% versus 83.2%), and did not receive an influenza vaccine in the previous season (55.8% versus 56.0%). Most participants were enrolled from North America (74.1% in both groups).

8.2.3 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 for all four studies. Participants with multiple occurrences of the same adverse event were counted once in the analysis of the number and percentage of participants with an event.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Several caveats should be considered when interpreting the pooled ISS data. The formulation of mRNA-1010 differed across the studies: Studies P301, P302, and P303 used a quadrivalent formulation while Study P304 used a trivalent formulation. Additionally, Studies P301 and P302 used the original formulation of mRNA-1010, while Studies P303 and P304 used the modified formulation of mRNA-1010 with the modified B antigen. This heterogeneity in the investigational product across studies may introduce variability in the safety profile that is not fully captured by pooled analyses alone. The comparator vaccines also differed across studies, including standard dose and high dose vaccines and trivalent and quadrivalent formulations, which may affect the interpretation of between-group comparisons. Follow-up durations varied across studies, ranging from approximately 6 months in Studies P303 and P304 to up to 12 months in Studies P301 and P302, which may influence the detection of late-onset adverse events. Furthermore, geographic and demographic differences across study sites may introduce population-level heterogeneity in background rates of adverse events.

8.4 Integrated Safety Results

8.4.1 Deaths

Within 28 days of vaccination, deaths were reported in 13 of 35,965 (<0.1%) participants in the mRNA-1010 group and 14 of 35,951 (<0.1%) participants in the SD/HD comparator group. The overall frequency of deaths throughout the studies was also balanced across groups, with death

reported in 102 (0.3%) of mRNA-1010 recipients and 97 (0.3%) SD/HD comparator recipients. In both groups, death was most commonly reported under the MedDRA SOC of cardiac disorders, occurring in 24 (<0.1%) of participants in the mRNA-1010 group and 30 (<0.1%) of participants in the SD/HD comparator group. By PT, death was most commonly reported under death (without further specification) (23 versus 9), myocardial infarction (7 versus 7), cardiac arrest (6 versus 6), cerebrovascular accident (4 versus 5), and pneumonia (2 versus 5) in the mRNA-1010 and SD/HD comparator groups, respectively. To more comprehensively evaluate the numerical imbalance observed for the PT of death (without further specification), 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; these events are summarized in Appendix E. The median time to onset of these events was approximately 131 days (range: 2 to 319 days) in the mRNA-1010 group and 87 days (range: 9 to 343 days) in the SD/HD comparator group, with most events (70/102 in the mRNA-1010 group and 60/97 in the SD/HD comparator group) occurring more than 90 days post-vaccination. Deaths within 28 days of vaccination under these three PTs occurred at similar frequencies across the two groups (three events in the mRNA-1010 group and two in the SD/HD comparator group).

Approximately 60% of these participants with unspecified fatal events were ≥65 years of age, 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. No autopsy was conducted among the 29 deaths in the mRNA-1010 group; one autopsy was conducted in the SD/HD comparator group but yielded no reported findings.

> ***Clinical Reviewer Comment:*** *Based on the following three lines of evidence, a causal relationship between mRNA-1010 and this imbalance in deaths due to unspecified cause has been assessed as unlikely:*
>
> - *All-cause mortality balance: All-cause mortality through study completion (102 [0.3%] mRNA-1010 vs. 97 [0.3%] SD/HD comparator) and within 28 days of vaccination (13 [<0.1%] mRNA-1010 vs. 14 [<0.1%] SD/HD comparator) were balanced between groups, indicating the imbalance in unspecified-cause deaths is not reflected in overall mortality rates. Additionally, the observed rate of death in the mRNA-1010 and SD/HD comparator groups, 0.3%, is less than the estimated background annual mortality rate in the population of individuals 50 years of age and older, which is approximately 0.4% at around 50 years of age and increases to 13.8% at 85 years of age and older (Arias et al. 2025; CDC 2026a) .*
> - *Temporal distribution: Deaths of unspecified cause within 28 days of vaccination were few and similar across groups (3 in mRNA-1010 vs. 2 in SD/HD comparator), with no apparent temporal clustering in the acute postvaccination risk window nor across later time intervals. The median time to unspecified-cause death was longer in the mRNA-1010 group (approximately 131 days) compared with the SD/HD comparator group (approximately 87 days). The temporal distribution of deaths does not suggest clustering in the acute postvaccination period, which would be expected if a direct inflammatory or immunologic mechanism were responsible for the observed imbalance. However, the data do not formally exclude potential contributions from subacute or chronic biological processes to explain the observed imbalance.*

- *Comorbidity context: Because both study arms were well-balanced at baseline for known comorbidities, differential comorbidity burden does not fully explain the observed imbalance; however, most affected participants had significant underlying comorbidities that provided plausible alternative etiologies.*

Critical limitation affecting causal assessment: No autopsy was performed for any of the 29 mRNA-1010-group deaths of unspecified cause, compared with one autopsy in the SD/HD comparator group (which yielded no reported findings). The absence of pathological data in all deaths of unspecified causes means that the etiology of individual deaths and the collective pattern cannot be determined with certainty. This evidentiary limitation is the primary basis for requesting active postmarketing surveillance for deaths of unspecified cause.

Interpretation: While the totality of available circumstantial evidence— all-cause mortality balance, temporal distribution, and comorbidity prevalence—supports the assessment that vaccine-related causation is unlikely, the imbalance cannot be fully explained by available data, and residual uncertainty persists.

Active Postmarketing Surveillance: FDA initially requested that the Applicant incorporate active surveillance for deaths of unspecified cause into the planned PMR confirmatory efficacy study. The Applicant asserted that such monitoring would be logistically difficult to integrate into a study designed primarily to evaluate vaccine effectiveness, as the required safety data gathering would necessitate follow-up protocols not readily aligned with the proposed efficacy study design. Considering the Applicant's assertion of infeasibility, FDA accepted the Applicant's proposal for a separate postmarketing commitment (PMC) active surveillance study using the same target population as the planned PMR efficacy study (see Section 11.4). This PMC active surveillance study will monitor for:

- *Deaths of unspecified cause and all-cause mortality;*
- *Myocarditis and pericarditis (safety events of interest for mRNA vaccines); and*
- *Guillain-Barré syndrome (safety event of interest for influenza vaccines).*

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

- A 76-year-old female participant with a history of coronary artery disease (prior coronary artery bypass graft [CABG] after myocardial infarction), atrial fibrillation, and type 2 diabetes mellitus was found unresponsive at home and was confirmed deceased on Study Day 2 (PT: death). The participant reported no solicited ARs on Study Day 1. Solicited ARs were not documented for Study Day 2; however, she mentioned to her friend that she felt unwell, tired, and nauseous early in the day. Her most recent cardiology evaluation had 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, and the death was attributed to natural causes on the death certificate. The Applicant assessed this event as unrelated to study vaccine.

  ***Clinical Reviewer Comment:** While the temporal relationship to the study vaccination is notable and a contribution from vaccine-related inflammatory reaction cannot be excluded,*

the participant's significant cardiac history, including prior myocardial infarction requiring CABG and atrial fibrillation, represents a more likely alternative etiology.

8.4.2 SAEs

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

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

For SAEs occurring in at least four participants in each group, risk differences (RD) between the mRNA-1010 and SD/HD comparator groups were assessed. This analysis identified six PTs with 95% CIs for the risk difference that excluded zero. Rates were numerically higher in the mRNA-1010 group compared with the SD/HD comparator group for SAEs of anemia (9 versus 2, respectively; RD: 0.02 [95% CI: >0, 0.04]), urinary tract infection (UTI) (25 versus 12, respectively; RD: 0.04 [95% CI: >0, 0.07]) and death (without further specification) (23 versus 9, respectively; risk difference: 0.04 [95% CI: 0.01, 0.07]). Rates were numerically higher in the SD/HD comparator group compared with the mRNA-1010 group for chronic kidney disease (0 versus 4, respectively), urinary retention (0 versus 4, respectively), and hypertensive emergency (0 versus 4, respectively). See Section 8.4.1 for a review of the imbalance in deaths. Anemia and UTI imbalances are reviewed in more detail below.

For anemia, a comprehensive review, including the additional PTs of anemia of chronic disease, blood loss anemia, hypochromic anemia, iron deficiency anemia, and normocytic anemia, identified a total of 14 participants in the mRNA-1010 group and 8 in the SD/HD comparator group. None were assessed as related to study vaccine by the Investigator. Most events occurred more than 90 days after vaccination, with no temporal clustering. All participants with anemia events 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 MAAEs of anemia in Study P304 identified a similar overall incidence of anemia between groups (31 in in the mRNA-1010 [TIV] group versus 30 in the SD comparator group).

For UTI, a comprehensive review including the additional PTs of urinary tract infection bacterial, *Escherichia* urinary tract infection, cystitis, kidney infection, pyelonephritis, pyelonephritis acute, and urosepsis identified a total of 38 participants in the mRNA-1010 group and 22 in the SD/HD comparator group. None were assessed as related to study vaccine by the Investigator. No temporal clustering was observed, with a median time to onset of 135 days in the mRNA-1010 group and 112.5 days in the SD/HD comparator group. A majority of participants in both groups had identifiable risk factors, including advanced age, female sex, postmenopausal status, diabetes, 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 overall

incidence between groups (153 in the mRNA-1010 [TIV] group versus 158 in the SD comparator group).

> ***Clinical reviewer comment****: Overall, these data suggest that the numerical imbalances in SAEs of anemia and UTI are unlikely to reflect a causal association with mRNA-1010.*

SAEs assessed as related to study vaccine by the Investigator were reported by 9 (<0.1%) participants with 11 events in the mRNA-1010 group and 3 (<0.1%) participants with three events in the SD/HD comparator group. Of the nine participants in the mRNA-1010 group, four were from Study P304 and discussed in Section 6.1.12.7. The other five participants reporting at least one SAE assessed as related to mRNA-1010 by the investigator are described below.

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

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

> ***Clinical Reviewer Assessment:*** *While the temporal relationship to the study vaccine is notable and vaccine contribution cannot be excluded, the participant's existing comorbidities provide more plausible alternative etiologies for the event. 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 pre-existing condition.*

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

Angioedema: A 78-year-old female with a history of angioedema experienced angioedema on Study Day 5. The participant reported developing a swollen face, which she described as less severe than her typical angioedema episodes. She self-treated with her usual dose of diphenhydramine and IM epinephrine and the angioedema resolved the same day. The Applicant assessed the event as unrelated to the study vaccine.

> ***Clinical Reviewer Assessment:*** *While this event could be possibly related to study vaccine given the participant's history of angioedema which could predispose her to a hypersensitivity reaction, the delayed onset makes an alternative trigger other than vaccination also plausible. Notably, the participant described this episode as less severe than her typical episodes, further limiting concern for this event to represent a clinically concerning safety signal.*

Pulmonary embolism: An 86-year-old female with a history of peripheral neuropathy, neuropathic pain, and hyperlipidemia experienced pulmonary embolism on Study Day 9. She began experiencing 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 embolisms, in addition to the right lower lobe pneumonia. No deep vein thrombosis was identified on venous duplex ultrasonography. On Study Day 17, the participant was discharged from the hospital on oral edoxaban, and the SAE of pulmonary embolism was considered resolved. The Applicant assessed the event as unrelated to study vaccine.

Clinical Reviewer Assessment: *While the event was temporally associated with study vaccination, the participant also had risk factors for thromboembolic events, including advanced age and concurrent diagnosis of pneumonia, which could provide plausible alternative etiologies for development of pulmonary embolism.*

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 after an injury to the affected leg and a subsequent pulmonary embolism on Day 132. The Applicant assessed the SAEs as being unrelated to the study vaccine.

Clinical Reviewer Assessment: *The long latency between vaccination and the reported SAEs, along with the presence of more likely alternative etiologies, including recent injury, varicose veins, and smoking history, make a causal association with the study vaccine unlikely.*

Death in a 76-year-old participant on Study Day 2, as described in Section 8.4.1.

8.4.3 Protocol-Defined AESIs

Through 28 days after vaccination, AESIs were reported in seven (<0.1%) participants in the mRNA-1010 group and four (<0.1%) participants in the SD/HD comparator group. Throughout the study, AESIs were reported in 36 (0.1%) participants in the mRNA-1010 group and 37 (0.1%) participants in the SD/HD comparator group, with 5 and 2 participants, respectively, reporting AESIs assessed as related to study injection by the Investigator. The five AESIs assessed as related to mRNA-1010 by the Investigator were events of thrombocytopenia with onset on Day 84 (described in Section 6.1.12.8), swelling face with onset on Day 2 (described in Section 6.2.12.8), myopericarditis with onset on Day 95 (described in Section 6.1.12.7), myocarditis with onset on Day 183 (described in Section 6.1.12.7), and Bell's palsy with onset on Day 16 (described below in Section 8.4.3.2).

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

8.4.3.1 New Onset or Worsening of Specified Neurological Diseases

Across the ISS population, no events of Guillain-Barré syndrome (GBS) were reported in the SD/HD comparator group and one serious AESI of GBS was reported under the PT demyelinating polyneuropathy in the mRNA-1010 group. This event occurred in a 79-year-old female with history of hypothyroidism, COPD, hypertension, obesity, and dyslipidemia, with onset on Day 134. The participant initially presented on Day 129 with hypertension, feet tingling, and vomiting, and subsequently developed distal paresthesias and progressive lower extremity weakness, advancing to tetraparesis and respiratory failure by Day 134, and diagnosed with demyelinating polyneuropathy during hospitalization. This event was assessed as unrelated to study vaccine by the study Investigator.

Clinical Reviewer Comment*: The clinical reviewer agrees with the Investigator's assessment that this event was unrelated to study vaccine given the onset of neurological symptoms well outside of the typical 42-day risk window observed for vaccine-associated GBS.*

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

Bell's palsy (Study P303 Part B): A 59-year-old man with a history of obesity developed Bell's palsy on Study Day 16. The participant reported left upper lip induration and left cheek erythema of unknown etiology on Study Day 5, 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 of 176 mm Hg. He was diagnosed with hypertension, type 2 diabetes mellitus, and Bell's palsy. He was treated with valacyclovir and prednisone for the Bell's palsy and the event was considered resolved on Study Day 161. The Investigator assessed the event as related to the study vaccine, while the Applicant assessed the event as unrelated.

> ***Clinical Reviewer Assessment:*** *The reviewer agrees with the Investigator's assessment that this event of Bell's palsy is possibly related to study vaccine given the temporal relationship to vaccination; however, the participant's comorbidities of obesity, hypertension, and type 2 diabetes are all risk factors for Bell's palsy and could provide plausible alternative etiologies.*
>
> *The clinical reviewer also agrees with the Investigator's assessment of the SAE of facial paresis in the setting of herpes zoster as unrelated to vaccination.*

8.4.3.2 Myocarditis/Pericarditis

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

The incidence of Cardiac Event Adjudication Committee (CEAC)-confirmed cases was balanced across study intervention groups, with four confirmed cases in the mRNA-1010 group (one case of myopericarditis and three cases of acute pericarditis) and three 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 a case of myopericarditis, that was assessed as related to study vaccine by the Investigator; this case is described in Section 6.1.12.8. In the SD/HD comparator group, one participant from Study P304 had an AESI of pericarditis, adjudicated by the CEAC as a case of acute pericarditis, on Day 60 that was assessed as related by the Investigator.

8.5 Safety Conclusions

The pooled safety analysis across all four Phase 3 clinical studies in individuals 50 years of age and older did not identify a safety concern for mRNA-1010. However, a numerical imbalance in deaths of unspecified cause was observed (29 mRNA-1010 vs. 12 SD/HD comparator in the expanded PT analysis). This imbalance was assessed as unlikely vaccine-related based on: (1) balance in all-cause mortality, (2) absence of temporal clustering in the early post-vaccination period, and (3) high comorbidity burden in affected participants. Definitive causal assessment is precluded by the absence of autopsy data. The Applicant will conduct a PMC active surveillance study to further evaluate this imbalance.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnant women were excluded from enrollment in clinical studies of mRNA-1010. Female participants of childbearing potential were required to practice adequate contraception for ≥28 days prior to vaccination through 90 days following vaccination and to have a negative pregnancy test prior to receipt of study vaccine. Participants were followed for outcomes for all reported pregnancies that occurred after vaccination. No pregnancies were reported in Study P304 or Study P303 Part C, which enrolled participants ≥50 years of age and ≥65 years of age, respectively.

Pregnancies were reported infrequently in earlier studies of mRNA-1010 that evaluated the vaccine in participants down to 18 years of age.

- In Study P101, two pregnancies were reported among mRNA-1010 recipients; neither pregnancy had a recorded outcome at time of study completion.
- In Study P301, 25 pregnancies were reported: 12 among mRNA-1010 recipients and 13 among SD comparator recipients. Of the 12 pregnancies in the mRNA-1010 group, 6 were term births, 1 was a preterm birth (<37 weeks gestation), 4 were spontaneous abortions/miscarriages, and 1 was an ectopic pregnancy. Of the 13 pregnancies in the SD comparator group, 5 were term births, 1 was a preterm birth, 3 were spontaneous abortions/miscarriages, 1 was an elective termination, 2 had outcomes pending at the time of study completion, and 1 was lost to follow up.
- In Study P303 Part A, four pregnancies were reported: 2 in the mRNA-1010 group and 2 in the SD comparator group. In each group, one pregnancy had an outcome pending at the time of study completion and one resulted in spontaneous abortion.
- In Study P303 Part B, 3 pregnancies were reported: 1 in the mRNA-1010 group and 2 in the SD comparator group. The participant in the mRNA-1010 group had a pregnancy outcome of missed abortion at approximately 7 weeks gestation (Study Day 126). Both participants in the SD comparator group had pregnancy outcomes pending at the time of study completion.

The available data are insufficient to inform vaccine-associated risks in pregnancy.

9.1.2 Use During Lactation

Breastfeeding women were excluded from enrollment in clinical studies of mRNA-1010. Data are not available to assess the effects of mRNA-1010 on the breastfed infant or on milk production.

9.1.3 Pediatric Use and PREA Considerations

Safety and effectiveness of mRNA-1010 in individuals younger than 18 years of age have not been established.

To address requirements under the Pediatric Research Equity Act (PREA), the Applicant submitted a request for partial waiver for infants 0 to <6 months of age as necessary studies to support licensure in this age group are impossible or highly impracticable to conduct.

The Applicant has also proposed the following deferred studies in individuals 6 months to <18 years of age because the pediatric studies should be delayed until additional safety or effectiveness data have been collected:

- Deferred pediatric study under PREA to evaluate the safety, reactogenicity, and immunogenicity of MFLUSIVA in infants, children, and adolescents 6 months to <18 years of age.
- Deferred pediatric study under PREA to evaluate the safety and effectiveness of MFLUSIVA in healthy children and adolescents 9 years to <18 years of age.
- Deferred pediatric study under PREA to evaluate the safety and effectiveness of MFLUSIVA in children 3 years to <9 years of age.
- Deferred pediatric study under PREA to evaluate safety, efficacy, and immunogenicity of MFLUSIVA in healthy infants and children 6 months to <36 months of age.

The partial waiver and deferral requests and pediatric plans were accepted by FDA's (b) (6) on May 12, 2026.

9.1.4 Immunocompromised Individuals

The clinical studies of mRNA-1010 excluded enrollment of immunocompromised individuals. Data are not available on the safety and effectiveness of mRNA-1010 specifically in immunocompromised individuals.

9.1.5 Geriatric Use

In Study P304, 47.8% of mRNA-1010 (TIV) recipients were ≥ 65 years of age and 11.6% were ≥ 75 years of age. A descriptive subgroup analysis in adults ≥65 years resulted in rVE of 27.4% (95% CI: 12.1, 40.0) versus a SD comparator not preferentially recommended by CDC (see 6.1.11.3).

In Study P303 Part C, 1,502 participants ≥ 65 years of age received mRNA-1010 (QIV), of whom 21.7% were ≥ 75 years of age. In descriptive subgroup analyses, the GMT ratios and SCR differences compared with the HD comparator were observed to be lower among mRNA-1010 recipients ≥75 years of age versus mRNA-1010 recipients 65 through 74 years of age across all four strains, though the noninferiority criteria would still have been met in adults ≥75 years of age (see 6.2.11.2).

10. Conclusions

Based on the totality of available data and the risk-benefit considerations as described in Section 11, the clinical review team concludes that the clinical data submitted in this application support approval of mRNA-1010 for the proposed indication of prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine through Traditional Approval in individuals 50 through 64 years of age, based on relative efficacy data, and Accelerated Approval in individuals 65 years of age and older, based on immunogenicity data and supportive relative efficacy data. The following key issues were assessed as follows:

1. rVE Data in Adults 50 Through 64 Years of Age: Adequate to Support Traditional Approval: In Study P304, mRNA-1010 (TIV) demonstrated an rVE of 26.6% (95% CI: 16.7, 35.4) against RT-PCR–confirmed ILI compared with a SD comparator over one influenza season in adults ≥50 years of age, with consistent point estimates across all three strains and prespecified age subgroups, including in the subgroup of adults 50 through 64 years of age.

2. Immunogenicity Data in Adults ≥65 Years of Age: Adequate to Support Accelerated Approval: The FDA Accelerated Approval pathway allows for approval of a vaccine "for a serious or life-threatening disease or condition… upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit." The Applicant's proposed Accelerated Approval for mRNA-1010 in adults ≥ 65 years of age is based on immunogenicity data from Study P303 Part C, using HAI titers as a surrogate endpoint reasonably likely to predict clinical benefit in this population. The CoR analysis (see Section 6.1.11.9) supported the use of HAI as a surrogate endpoint reasonably likely to predict clinical benefit for the influenza A/H1N1 and A/H3N2 strains, but introduced uncertainty regarding the use of HAI as a surrogate endpoint for the B/Victoria strain. Accordingly, while the primary immunogenicity analyses from Study P303 Part C demonstrated the noninferiority and protocol-defined superiority of mRNA-1010 (QIV) compared to Fluzone HD (QIV), a vaccine preferentially recommended by the CDC for use in this age group, interpretation of B/Victoria-specific immunogenicity results is limited. Nonetheless, based on the totality of the available evidence, the review team concludes that the Applicant has provided substantial evidence of effectiveness to support the Accelerated Approval of mRNA-1010 in individuals ≥65 years of age, based on the following considerations:

i. The biological plausibility of immune response as measured by HAI as a mechanism of protection against influenza, supported by the observed correlation between HAI titers and relative vaccine efficacy for mRNA-1010 for both influenza A strains in the CoR analysis from Study P304.

ii. mRNA-1010 (QIV) elicited superior immune responses when compared with Fluzone HD (QIV) against all four influenza strains, indicating the potential for improved effectiveness relative to this CDC preferentially recommended vaccine for adults ≥65 years of age. Acknowledging the uncertainty surrounding interpretation of the influenza B/Victoria-specific immunogenicity results, meaningful improvements in effectiveness against influenza A/H1N1 and A/H3N2 alone would have substantial public health impact for this older adult population, which bears a disproportionate burden of influenza-related morbidity and mortality. Notably, influenza A strains have predominated in circulation over the past several influenza seasons (CDC 2026b).

iii. The B/Victoria-specific rVE point estimate from Study P304 (Table 10) was directionally consistent and robust (29.1%), with the wide confidence interval attributable to low case accrual, providing independent support that mRNA-1010 confers protection against B/Victoria.

iv. The rVE observed for the subgroup of participants ≥65 years of age (Table 11) from Study P304 was robust (rVE 27.4%; 95% CI: 12.1, 40.0) and consistent with that of the younger age cohort of participants 50 through 64 years of age. Although the comparator vaccine in Study P304 was a SD comparator not preferentially recommended for use in individuals ≥65 years of age, the magnitude of the observed rVE is comparable to that established in prior efficacy trials for vaccines preferentially recommended in this age group Specifically, Fluzone HD demonstrated an rVE of 24.2% (95% CI: 9.7; 36.5) compared with standard dose Fluzone in adults ≥65 years of age (Fluzone HD USPI) and Flublok demonstrated a rVE of 30% (95% CI: 10, 47) in adults ≥50 years of age, (Flublok USPI).

v. B/Victoria-specific clinical benefit will be further characterized through strain-specific rVE analyses included as a secondary objective in the Phase 4 confirmatory PMR study.

3. Safety Profile: Solicited adverse reactions were reported more frequently with mRNA-1010 than with comparator across Studies P304 and P303 Part C but were predominantly mild-to-moderate in severity and short in duration. In the pooled ISS from four Phase 3 studies (35,965 mRNA-1010 recipients and 35,951 SD/HD comparator recipients ≥50 years of age), SAEs, deaths, and AESIs were generally balanced between treatment groups. A numerical imbalance in deaths of unspecified cause was observed in the mRNA-1010 group; however, this imbalance was assessed as unlikely vaccine-related based on: (1) balance in all-cause mortality, (2) absence of temporal clustering in the early post-vaccination period, and (3) high comorbidity burden in affected participants. No cases of myocarditis or pericarditis were assessed as related to mRNA-1010. Overall, the pooled analysis did not identify adverse event patterns indicative of a definitive safety signal. Unspecified deaths, myocarditis/pericarditis, and GBS will be further evaluated through the Applicant's postmarketing commitment (PMC).

4. Uncertainty Regarding B/Victoria Effectiveness: Acceptable in the Context of PMR Study: Despite the large sample size in Study P304, case accrual for RT-PCR–confirmed ILI caused by B/Victoria was insufficient to draw conclusions about strain-specific efficacy of mRNA-1010 (TIV). The CoR analysis introduced additional uncertainty regarding the correlation between HAI titers and protection specifically against influenza B/Victoria. Nevertheless, the totality of evidence, including the robust and directionally consistent B/Victoria-specific rVE point estimate from Study P304 and the biological plausibility of HAI-mediated protection against influenza support the conclusion that mRNA-1010 is reasonably likely to provide protection against B/Victoria-associated ILI. Effectiveness against B/Victoria will be further characterized through the Applicant's PMR study.

5. Limitations and Evidence Gaps: Acceptable and Typical for Initial BLA Submission: Identified limitations, including efficacy data from a single influenza season, absence of efficacy data in immunocompromised individuals or very frail older adults, and lack of data on concomitant administration with routinely co-administered vaccines, did not preclude a favorable benefit-risk determination (see Section 11). These limitations were considered

typical for an initial BLA submission and will be further characterized through the Applicant's PMR and future studies.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 41. STN 125869: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
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. (CDC 2024a). • 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 (CDC 2024b).	• Influenza is a serious, high-burden disease, particularly in high-risk groups such as older adults.
Unmet Medical Need	• Annual influenza vaccination is the primary preventive strategy. Currently licensed influenza vaccines have variable effectiveness, with up to 60% effectiveness under conditions of optimal antigenic match (Osterholm et al. 2012; Demicheli et al. 2018), and lower protection during mismatch seasons (Tricco et al. 2013). • Currently, CDC preferentially recommends HD (Fluzone HD), recombinant (FluBlok), or adjuvanted (Fluad) influenza vaccines for adults ≥65 years of age (CDC ACIP 2025). • Egg-based manufacturing — used by most licensed vaccines — introduces egg-adaptive mutations that can alter HA antigen conformation and may reduce vaccine immunogenicity (Petrova and Russell 2018). • The risk of substantial antigenic shift creates unmet need for vaccine manufacturing technologies capable of expedited vaccine development and deployment.	• In adults ≥65 years of age, a population at highest risk for influenza-related morbidity and mortality, there continues to be a need for vaccines with improved effectiveness, particularly when antigenically mismatched to circulating strains • Licensed influenza vaccines with high-volume manufacturing technologies capable of rapid strain reformulation, particularly to respond to antigenic shifts is an unmet medical need.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons

Clinical Benefits	• Study P304: rVE 26.6% [95% CI: 16.7, 35.4] versus SD comparator in adults ≥50 years of age. Consistent rVE across age subgroups (25.3% to 28.0%), including in adults ≥65 years of age [rVE 27.4%; 95% CI: 12.1, 40.0], and influenza strains (22.2% to 29.6%). Descriptive rVE against protocol-defined ILI requiring higher level of care (i.e., hospitalization, ER visit, urgent care visit) was 47.9% [95% CI: 12.8, 68.9].
	• Study P303 Part C: Met protocol-specified noninferiority and superiority success criteria for HAI GMT and SCR versus Fluzone HD (QIV) for all four vaccine-matched strains in adults ≥65 years of age; immune persistence at Day 181.
	• Uncertainties in clinical benefit include: vaccine effectiveness against influenza B/Victoria due to low case accrual in Study P304 and the inconclusive correlation between HAI titers and clinical efficacy for B/Victoria; rVE across multiple influenza seasons with different circulating strains; rVE in frail elderly individuals and immunocompromised individuals; concomitant administration with vaccines recommended for use in this population
		• The evidence for clinical benefit of mRNA-1010 meets the evidentiary standards for Traditional Approval in individuals 50 through 64 years of age, based on meeting all three sequentially tested prespecified success criteria (LL of the 95% CI >-10%, 0%, 9.1%) for relative vaccine efficacy compared with a SD seasonal influenza vaccine
		• The evidence for clinical benefit of mRNA-1010 meets the evidentiary standards for Accelerated Approval in individuals ≥65 years of age, based on:
		  • Meeting the sequentially tested prespecified success criteria for immunogenicity compared with a HD, CDC preferentially-recommended influenza vaccine for this age group based on HAI titers, considered a surrogate reasonably likely to predict clinical benefit, and
		  • Supportive efficacy data showing higher rVE compared with a standard-dose influenza vaccine in this age group
		• As a condition of Accelerated Approval, the Applicant will conduct a Phase 4 confirmatory PMR study to describe and verify the clinical benefit of mRNA-1010 in adults ≥65 years of age and older
		• Effectiveness against B/Victoria will be further evaluated in the confirmatory PMR study.
		• Residual uncertainties in clinical benefit over multiple seasons, in frail and immunocompromised individuals, and concomitant administration with other routine vaccines will be elucidated through future clinical and observational studies

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risks	• Solicited ARs were more frequent after mRNA-1010 compared with the SD/HC comparator vaccines, but were predominantly mild to moderate and of short duration (median of 2 days). • In an ISS population of 35,965 participants 50 years of age and older exposed to mRNA-1010, no safety concerns were identified; no myocarditis/pericarditis within 42 days. • Numerical imbalances in deaths of unspecified cause, anemia SAEs, and UTI SAEs in the ISS were assessed as unlikely to be vaccine-related. • Uncertainties: occurrence of more rare adverse events that can only be captured with a larger safety database.	• The data submitted adequately characterizes the reactogenicity of mRNA-1010 in adults 50 years of age and older. • The reactogenicity profile, while more reactogenic relative to comparators, appears generally acceptable. • Numerical imbalances in deaths of unspecified cause were assessed as unlikely to be vaccine related. However, the residual uncertainty will be assessed by the Applicant in their proposed PMC study. • The safety of mRNA-1010 is acceptable for its intended use.
Risk Management	• Risk mitigation proposed by Applicant: PMC study with active surveillance for deaths, myocarditis/pericarditis and GBS; routine pharmacovigilance per 21 CFR 600.80; aggregate AESI monitoring; VAERS reporting; VIS distribution.	• The safety data provided in the prescribing information adequately describes the risks • The Applicant's proposed plan for routine pharmacovigilance and active surveillance for deaths, myocarditis/pericarditis, and GBS in a proposed PMC study are adequate to manage risks

Source: Reviewer-generated table
Abbreviations: AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; CDC, Centers for Disease Control and Prevention; CI, confidence interval; GMT, geometric mean titer; HAI, hemagglutinin inhibition; HD, high dose; ISS, integrated summary of safety; PMR, postmarketing requirement; rVE, relative vaccine efficacyl; SAE, serious adverse event; SCR, seroconversion rate; SD, standard dose; UTI, urinary tract infection; VAERS, Vaccine Adverse Event Reporting System; VIS, Vaccine Information Statement

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of mRNA-1010 in preventing symptomatic influenza in individuals 50 years of age and older is favorable compared with the potential risks associated with vaccination. In Study P304, mRNA-1010 (TIV) demonstrated superior rVE against a U.S.-licensed SD comparator. Comparable rVE was observed across participants 50 through 64 years of age and 65 years of age and older; however, the active comparator in Study P304 was a SD influenza vaccine not preferentially-recommended by the CDC for adults 65 years of age and older. In Study P303 Part C, mRNA-1010 (QIV) elicited superior immune responses compared with a CDC preferentially-recommended comparator vaccine in participants 65 years of age and older.

Overall, the safety profile of mRNA-1010 is acceptable for its intended use. Solicited adverse reactions were reported at higher frequencies in mRNA-1010 groups relative to the active comparator groups but were predominantly mild to moderate and transient (median duration 2 days). No safety concerns were identified in an integrated safety population of 35,965 mRNA-1010 recipients ≥50 years of age. No events of myocarditis or pericarditis were observed within 42 days postvaccination. Numerical imbalance in deaths of unspecified cause, was assessed as unlikely to be vaccine-related based on: (1) absence of temporal clustering in the early post-vaccination period, (2) high comorbidity burden in affected participants, and (3) balance in overall all-cause mortality. As the imbalance in deaths of unspecified cause cannot be fully explained by the available data, and residual uncertainty remains, the Applicant will conduct active surveillance for deaths as part of a planned PMC study.

A Phase 4 confirmatory PMR study is planned to describe and verify the clinical benefit of mRNA-1010 in individuals ≥65 years of age. Residual uncertainties in effectiveness, including against B/Victoria lineage, across multiple seasons, and in frail elderly and immunocompromised individuals, will be addressed in future postmarketing studies or through observational data. The safety of mRNA-1010 is adequately described in the product's prescribing information and safety monitoring will be conducted through routine pharmacovigilance, as well as the planned PMC study mentioned above to evaluate for deaths, myocarditis/pericarditis, and GBS.

11.3 Discussion of Regulatory Options

The data submitted in the BLA indicate the safety and effectiveness of mRNA-1010 (mFlusiva) meet the statutory requirements to support its use for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine. The Applicant's proposed bifurcated licensure pathway of Traditional Approval in individuals 50 through 64 years of age, based on relative vaccine efficacy data against a SD comparator, and Accelerated Approval in individuals 65 years of age and older, based on immunogenicity data against a HD comparator, supported by relative efficacy data against a SD comparator in this age group, appear appropriate (see Section 5.1 for Accelerated Approval criteria and justification).

11.4 Recommendations on Regulatory Actions

Based on the totality of clinical data submitted, the clinical review team recommends approval of mFlusiva for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine, through Traditional Approval in individuals 50 through 64 years of age and through Accelerated Approval in individuals 65 years of age and older.

11.5 Labeling Review and Recommendations

The proprietary name mFlusiva was reviewed by the (b) (6) Branch and found acceptable. The mFlusiva U.S. Prescribing Information (USPI) was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.

Section 14 (Clinical Studies) of the USPI describes the totality of data supporting the substantial evidence of effectiveness for each approved age group (50 through 64 years of age and ≥65 years of age), including the residual uncertainties in effectiveness against influenza B/Victoria.

Section 6 (Adverse Reactions) describes the higher rates of solicited adverse reactions in the mFlusiva and mRNA-1010 (QIV) groups compared with the comparator groups in Study P304 and Study P303 Part C, respectively. The SAE of syncope on Study Day 2 in Study P304, assessed as related to mFlusiva by the review team, is briefly summarized in this section. The imbalance in deaths due to unspecified cause observed in the ISS (see 8.4.1) is not included in the Adverse Reactions section of the Prescribing Information because a causal relationship with mFlusiva has been assessed as unlikely. As per 21 CFR 201.57 (c) (7), “For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”

11.6 Recommendations on Postmarketing Actions

Under the accelerated approval regulations, 21 CFR 601.41 Subpart E, the Applicant is required to conduct a postmarketing requirement (PMR) confirmatory efficacy trial to verify and describe the clinical benefit of mFlusiva. The Applicant has proposed Study mRNA-1010-P910, a Phase 4, pragmatic, cluster-randomized, active-controlled study to evaluate the rVE of mFlusiva compared with Fluzone HD in adults 65 years of age and older. The study design includes vaccine clinics that will be cluster-randomized, alternating weekly between mFlusiva and the comparator vaccine throughout the influenza season. The study plans to enroll ~800,000 (400,000 per season) adults 65 years of age and older in a 1:1 allocation (two full seasons, 2027-2028 and 2028-2029). The study will include secondary efficacy endpoints to descriptively analyze strain-specific rVE.

1. A Pragmatic, Randomized Study to Evaluate Relative Vaccine Effectiveness of mRNA-1010 Versus High-Dose Influenza Vaccine in U.S. Adults ≥65 Years of Age (Study mRNA-1010-P910).
    - Final Protocol Submission: May 22, 2026 (Submitted)
    - Study Initiation: August 31, 2026
    - Interim Study Report 1 Submission: December 31, 2027
    - Interim Study Report 2 Submission: December 31, 2028
    - Interim Study Report 3 Submission: December 31, 2029
    - Study Completion: July 31, 2029
    - Final Report Submission: May 31, 2030

The Applicant has made the following postmarketing commitment subject to reporting requirements under Section 506B:

1. Post-Authorization Active Surveillance Safety Study to Monitor Real-World Safety of MFLUSIVA (mRNA-1010) Vaccine for the Prevention of Influenza Disease in the United States (Study mRNA-1010-P901). This study will be a safety study to evaluate deaths in a randomized population and an observational study for safety outcomes including myocarditis, pericarditis, myopericarditis, and Guillain-Barré syndrome after receipt of MFLUSIVA.
   - Final Protocol Submission: December 31, 2026
   - Study Completion: December 31, 2030
   - Final Report Submission: December 31, 2031

2. Exploratory Microneutralization Antibody Correlate of Risk Analysis for Influenza B/Victoria Lineage in Study mRNA-1010-P304.
   - Final Report Submission: December 31, 2026

3. A Phase 4, Randomized Study to Assess the Immunogenicity of an Updated mRNA Seasonal Influenza Vaccine Composition to evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed high-dose comparator in adults ≥65 years of age assessed with assays using both egg- and cell-based viruses.
   - Final Protocol Submission: September 14, 2026
   - Study Initiation: October 15, 2026
   - End of Season 1 Report: April 15, 2027
   - Study Completion: November 30, 2027
   - Final Report Submission: December 31, 2028

12. Appendices

12.1 Appendix A: Adverse Events of Special Interest (Study mRNA-1010-P304)

Table 42. 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
Myocarditis/pericarditis:	• Myocarditis • Pericarditis • Myopericarditis

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

12.2 Appendix B: CDC Criteria for Probable and Confirmed Cases of Myocarditis, Pericarditis, and Myopericarditis

Table 43. 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

Condition	Probable Case Definition	Confirmed Case Definition
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).

12.3 Appendix C: 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.

Table 44. 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	--
Blood disorders	Haemoglobinopathies congenital	HLT	--
Cardiac disorders	Cardiac conduction disorders	HLT	--
Cardiac disorders	Supraventricular arrhythmias	HLT	--
Cardiac disorders	Ventricular arrhythmias and cardiac arrest	HLT	--
Cardiac disorders	Cardiomyopathy	SMQ	Narrow
Cardiac disorders	Ischemic heart disease	SMQ	Narrow
Nervous system disorders	Cerebrovascular embolism and thrombosis	HLT	--
Nervous system disorders	Parkinson's disease and parkinsonism	HLT	--
Nervous system disorders	Paralysis and paresis (excl. cranial nerve)	HLT	--
Nervous system disorders	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 disorders	Hepatic fibrosis and cirrhosis	HLT	--
Mental impairment disorders	Intellectual disabilities	HLT	--
Mental impairment disorders	Dementia	SMQ	Narrow
Pulmonary disorders	Bronchospasm and obstruction	HLT	--
Pulmonary disorders	Interstitial lung disease	SMQ	Narrow
Pulmonary disorders	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

12.4 Appendix D: 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 is currently under review and is 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 mFlusiva compared with agreed upon CDC-preferentially recommended vaccine in adults 65 years of age and older under real-world conditions.

Research Question and Objectives

Is mRNA-1010 noninferior to agreed upon CDC-preferentially recommended vaccine in preventing laboratory-confirmed medically attended influenza in adults 65 years of age 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.

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 years of age and older in a 1:1 allocation (2 full seasons, 2027–2028 and 2028–2029).

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

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

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

12.5 Appendix E: Summary of Unspecified Deaths from ISS

Table 45. Deaths Reported Under the Preferred Terms Death (Unspecified), Sudden Death, or Sudden Cardiac Death Among Participants ≥50 Years of Age in the ISS

Number	Vaccine group	Study #	Verbatim Term	Age/ Sex	Event Onset (Study Day)	Relevant Medical History	Additional Information*
1	mRNA-1010	P301	Death from natural causes	76F	2	Coronary artery disease, type 2 diabetes mellitus (DM), hyperlipidemia (HLD), prior myocardial infarction (MI), atrial fibrillation, hypertension (HTN), hypothyroidism	Two recent ECGs documented: Sinus bradycardia, sinus arrhythmia, and Prolonged QT interval
2	mRNA-1010	P304	Death unknown cause	67M	24	HTN	None
3	mRNA-1010	P302	Death (NOS)	75F	27	HTN, HLD, arrhythmia, history of ischemic stroke	Participant reported dyspnea, presented to the emergency room (ER) and passed away while in ER
4	mRNA-1010	P304	Unknown cause of death	60F	37	Type I DM, obesity, HTN, HLD, hypothyroidism	AE of fall and foot fracture on Day 23
5	mRNA-1010	P304	Unspecified fatal event	61M	39	Type II DM, HTN, HLD, cardiac disorder, prior MI, prior pulmonary embolism, chronic obstructive pulmonary disease (COPD), emphysema, anxiety, major depression, obesity, polyneuropathy	Tobacco use (1 cigar daily)
6	mRNA-1010	P302	Unexpected death (no other inf [information])	52M	45	HTN	Event reported to have occurred outside of hospital setting. There was a toxicology report, but results could not be obtained.
7	mRNA-1010	P304	Unknown death	53F	48	Gastroesophageal reflux disease (GERD)	Medication addiction reported initially as suspected cause of death, but no history of addiction documented.

Number	Vaccine group	Study #	Verbatim Term	Age/ Sex	Event Onset (Study Day)	Relevant Medical History	Additional Information*
8	mRNA-1010	P302	Death unknown	71M	65	Type II DM	Participant died while abroad; participant's sibling reported death was due to "confirmed cardiovascular cause"
9	mRNA-1010	P303 Part C	Clinical death-natural causes, elderly	93F	68	HTN, HLD, osteoporosis	None
10	mRNA-1010	P304	Unspecified fatal event	70M	97	None	Tobacco use (10 cigarettes daily); Reported respiratory illness symptoms on Day 94, including wheezing and difficulty breathing.
11	mRNA-1010	P304	Sudden cardiac death	69F	98	None	Participant passed away while on vacation. Complained of dizziness prior to event.
12	mRNA-1010	P304	Death of unknown cause	54F	107	HTN	Participant's emergency contact reported participant received treatment for respiratory illness from Day 52 to Day 72.
13	mRNA-1010	P304	Unspecified fatal event	64F	121	Type II DM	Tobacco use (3 cigarettes daily)
14	mRNA-1010	P304	Unspecified fatal event	54F	127	Narcotic dependence, bipolar depression	Tobacco use (20 cigarettes daily)
15	mRNA-1010	P304	Unspecified fatal event	67M	131	None	None
16	mRNA-1010	P304	Sudden unwitnessed death-unknown cause	62M	135	None	Participant reported respiratory illness Day 95 through Day 101.
17	mRNA-1010	P302	Death (NOS)	79F	143	Cardiac failure, Basedow's disease	None
18	mRNA-1010	P304	Natural death	72M	147	HTN, atrial fibrillation, pacemaker insertion	Tobacco use (1 pack daily), alcohol use (10 ounces of wine daily)
19	mRNA-1010	P302	Death (unknown etiology)	65M	154	HTN, HLD	None

Number	Vaccine group	Study #	Verbatim Term	Age/ Sex	Event Onset (Study Day)	Relevant Medical History	Additional Information*
20	mRNA-1010	P303 Part A	Death from natural causes	80M	166	HTN, hypertriglyceridemia, hypercholesterolemia	None
21	mRNA-1010	P304	Unspecified fatal event	61M	173	Obesity	Per participant's partner, participant went to hospital for suspected bilateral lower extremity cellulitis, was provided with medication and procedure was performed, and participant died during hospital stay. Attempts to obtain information from participant's family and hospital unsuccessful.
22	mRNA-1010	P304	Unspecified fatal event	55F	194	Type II DM, depression	None
23	mRNA-1010	P302	Death unknown cause	51M	211	HTN	None
24	mRNA-1010	P301	Sudden cardiac death	68M	224	Type II DM	Participant reported to have gone to drink alcohol with friends on the morning of the event; was found unresponsive in the afternoon
25	mRNA-1010	P302	Death, unknown cause	71M	229	Type I DM, HLD	Participant reported to have missed recent visits with his primary care physician prior to the event
26	mRNA-1010	P302	Sudden death	70M	235	None	None
27	mRNA-1010	P302	Unknown cause of death	92F	283	Cardiac failure, HTN, dyslipidemia, type II DM	None
28	mRNA-1010	P302	Sudden death NOS	78M	299	HTN	None
29	mRNA-1010	P302	Death from unknown cause	77M	319	Non-small cell lung cancer with metastases to central nervous system, HTN, hypercholesterolemia, COPD	Diagnosis of lung cancer and metastases on Day 194; on palliative care at home

Number	Vaccine group	Study #	Verbatim Term	Age/ Sex	Event Onset (Study Day)	Relevant Medical History	Additional Information*
1	Comparator	P304	Death-unknown cause	52F	9	Type II DM, HTN, hypercholesterolemia	None
2	Comparator	P304	Unknown cause of death	83F	27	HTN	None
3	Comparator	P303 Part B	Death due to natural cause	62M	37	Type II DM, HTN, hypercholesterolemia, COPD, emphysema, sleep apnea	Death certificate noted death was due to natural causes, secondary to type II DM and heart disease
4	Comparator	P304	Sudden death (NOS)	65F	39	Congestive heart failure, HTN, hypercholesterolemia, type II DM, asthma	None
5	Comparator	P304	Sudden cardiac death	83M	57	Coronary artery disease, prior MI, HTN, HLD, COPD	History of tobacco use (1 pack daily)
6	Comparator	P304	Unspecified fatal event	65M	106	Aortic stenosis, HTN, HLD	Participant was hospitalized on Day 61 and passed away during hospitalization. No diagnosis or records were able to be obtained.
7	Comparator	P302	Death (unknown cause)	53F	113	Cardiac failure congestive, HTN, Hepatitis C, hepatic steatosis, depression	None
8	Comparator	P302	Death (NOS)	84F	150	HTN, osteoporosis	None
9	Comparator	P304	Death unknown cause	70M	172	Peripheral vascular disorder	Tobacco use (half pack daily)

Number	Vaccine group	Study #	Verbatim Term	Age/ Sex	Event Onset (Study Day)	Relevant Medical History	Additional Information*
10	Comparator	P302	Unknown cause of death	58M	232	HTN	Participant experienced cardiac arrest, was resuscitated, taken to the hospital and placed on life support; family decided to discontinue life support
11	Comparator	P302	Sudden death	87M	241	Arterial hypertension, atrial fibrillation, coronary arterial stent, chronic kidney disease, type II DM	None
12	Comparator	P302	Unknown cause of death	54F	343	Depression	Cause of death listed on death certificate was “atherosclerotic and hypertensive cardiovascular disease”

Source: Adapted from STN 125869/0, Study P304 CSR, Study P303 Part B-C CSR, Study P303 Part A CSR, Study P302 CSR, Study P301 CSR
Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECG, electrocardiogram; ER, emergency room; F, female; GERD, gastroesophageal reflux disease; HLD, hyperlipidemia; HTN, hypertension; M, male; MI, myocardial infarction; NOS, not otherwise specified
*An autopsy was not performed or results were not available for all of the listed events, with the exception of one death in the comparator group for which an autopsy was performed but yielded no findings.