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STN	125869/0
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Consultation	(b) (6)
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Applicant	ModernaTX, Inc.
Established Name	Influenza Vaccine
(Proposed) Trade Name	MFLUSIVA
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	37.5 µg of mRNAs (12.5 µg each) encoding the hemagglutinin HA glycoproteins of three seasonal influenza strains (A/H1N1, A/H3N2, B/Victoria-lineage), encapsulated in lipid particles
Dosage Form(s) and Route(s) of Administration	Single-dose prefilled syringe administered intramuscularly
Dosing Regimen	Single 0.38 mL dose
Indication(s) and Intended Population(s)	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

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GLOSSARY

Abbreviation	Full Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
BLA	Biologics License Application
BMI	Body Mass Index
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
CoP	Correlate of Protection
CoR	Correlate of Risk
CSR	Clinical Study Report
eDiary	Electronic Diary
EFS	Edmonton Frail Scale
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLSM	Geometric Least Square Mean
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GMR	Geometric Mean Titer Ratio
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
HD	High Dose
HR	Hazard Ratio
ILI	Influenza-like Illness
IM	Intramuscular
IND	Investigational New Drug
IPS	Inverse Probability of Sampling
IR	Information Request
IRT	Interactive Response Technology
ISS	Integrated Summary of Safety
LB	Lower Bound
LLOQ	Lower Limit of Quantification
MAAE	Medically Attended Adverse Event
m-CDC definition	Modified CDC Definition
mL	Millilitre
MN	Microneutralization
MN ₅₀	Microneutralization Assay with inhibitory dilution concentration of 50%
mRNA	Messenger Ribonucleic Acid
NA	North America
NC	Not Calculated

Abbreviation	Full Term
NH	Northern Hemisphere
NI	Noninferiority
PCA	Principal Component Analysis
PDUFA	Prescription Drug User Fee Act
PMR	Postmarketing Requirement
PP	Per-Protocol
PPCAS	Per-Protocol Correlate Analysis Set
PPIS	Per-Protocol Immunogenicity Set
QIV	Quadrivalent Influenza Vaccine
RoW	Rest of the World
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
rVE	Relative Vaccine Efficacy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate
SD	Standard Dose
STD	Standard Deviation
STN	Submission Tracking Number
TIV	Trivalent Influenza Vaccine
U.S.	United States
UK	United Kingdom
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1. Executive Summary

ModernaTX, Inc. submitted a Biologics License Application (BLA) to seek licensure of MFLUSIVA (mRNA-1010) for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine in adults 50 years of age and older, via: (1) traditional approval in adults 50-64 years of age based on direct demonstration of clinical efficacy and safety from the Phase 3 Study mRNA-1010-P304 (hereafter referred to as P304), and (2) accelerated approval in adults ≥ 65 years of age based on immunogenicity measured by the hemagglutination inhibition (HAI) assay from studies mRNA-1010-P303 Part C (hereafter referred to as P303 Part C) and P304, supported by analyses evaluating HAI titer as a surrogate marker reasonably likely to predict clinical benefit and efficacy from the subgroup of adults ≥ 65 years of age from Study P304. mRNA-1010 encodes the hemagglutinin (HA) glycoproteins of three seasonal influenza strains (A/H1N1, A/H3N2, and B/Victoria lineage).

This statistical review focuses on Studies P304 and P303 Part C. Additional studies supporting the integrated summary of safety (ISS) of mRNA-1010 include Phase 3 Studies mRNA-1010-P301 (P301), mRNA-1010-P302 (P302), and P303 Parts A and B.

P304 was a Phase 3, randomized, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 compared with a licensed standard dose (SD) comparator in adults ≥ 50 years of age. The primary objective was to demonstrate the relative vaccine efficacy (rVE) of mRNA-1010 versus the SD comparator, via a -10% noninferiority margin, to prevent the first episode of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed protocol-defined influenza-like illness (ILI) due to any influenza virus A or B strain from 14 days after vaccination through the end of the influenza season.

A total of 40,805 participants were randomized (1:1) to receive mRNA-1010 ($n=20,402$) or the SD comparator ($n=20,403$), stratified by age group (50-64 years or ≥ 65 years) and previous year influenza vaccination status. The study accumulated 968 cases in the 2024-2025 influenza season resulting in an rVE of 26.6% (95% CI: 16.7%, 35.4%), which met the pre-specified noninferiority (lower bound [LB] of 95% CI $> -10\%$), superiority (LB of 95% CI $> 0\%$), and super-superiority (LB of 95% CI $> 9.1\%$) criteria. The rVE point estimates were consistent across influenza A and B and across age groups (50-64 years: 26.1% [95% CI: 12.3%, 37.7%]; ≥ 65 years: 27.4% [95% CI: 12.1%, 40%]).

The applicant conducted a correlation of risk (CoR) analysis to evaluate the relationship between strain-specific influenza disease risk and Day 29 HAI titer. Data showed statistically significant negative correlation between Day 29 titer and protocol-defined ILI for A/H1N1 and A/H3N2. No meaningful association between Day 29 titer and disease risk was observed for B/Victoria. Data also suggested that the relationship between the Day 29 titer and disease risk may differ across vaccine groups for A/H1N1. These conclusions were consistent across age groups (50-64 years and ≥ 65 years).

P303 Part C was a Phase 3, randomized, observer-blind, active-controlled study to evaluate the immunogenicity and safety of mRNA-1010 vs. Fluzone High-Dose (HD) Quadrivalent Influenza Vaccine (QIV; also referred to as HD comparator) in adults ≥ 65 years old. A total of 3,003 participants were randomized 1:1 to receive mRNA-1010 (n=1,507) or HD comparator (n=1,496), stratified by previous influenza season vaccination status.

The primary and secondary immunogenicity objectives of demonstrating noninferiority and superiority in terms of the Day 29 HAI geometric mean titer (GMT) and seroconversion rate (SCR) were met for all four strains. The GMT ratio (GMR) comparing mRNA-1010 to HD comparator for A/H1N1, A/H3N2, B/Victoria, and B/Yamagata were, respectively, 1.34 (97.5% CI: 1.24, 1.45), 1.21 (97.5% CI: 1.12, 1.32), 1.25 (97.5% CI: 1.18, 1.33), and 1.14 (97.5% CI: 1.08, 1.21). SCR differences were, respectively, 13.42% (97.5% CI: 9.27%, 17.52%), 8.59% (97.5% CI: 4.38, 12.76), 9.67% (97.5% CI: 6.04%, 13.29%), and 5.88% (97.5% CI: 2.33%, 9.42%).

In both studies and age groups, rates of solicited local and systemic adverse reactions (ARs) were higher in the mRNA-1010 group compared with the SD or HD comparator. In both age groups, the most frequently reported local reaction after study vaccination was pain at the injection site, and the most frequently reported systemic adverse reaction was fatigue. Among mRNA-1010 recipients, the median onset and median duration of local and systemic adverse reactions were two days. Furthermore, in both studies, within 28 days of study vaccination, there were no notable differences in rates of unsolicited adverse events (AEs), serious adverse events (SAEs), deaths, medically attended adverse events (MAAEs), and adverse events of special interest (AESIs) between mRNA-1010 and SD or HD comparator recipients. There were no deaths related to study vaccination per investigator throughout either study. Similar observations were made in the (ISS). There was one death due to natural causes in the mRNA-1010 group in Study P303 Part A assessed as related to the study vaccination by the investigator.

Overall, the data support the efficacy of mRNA-1010 against influenza disease caused by any influenza strain present in the vaccine and by A/H1N1 and A/H3N2 in adults 50-64 years of age. However, due to the smaller number of cases accrued for B/Victoria and the lack of meaningful association between B/Victoria-specific Day 29 HAI titer and disease risk, the efficacy of mRNA-1010 against B/Victoria remains uncertain in this age group. Similarly, the immunogenicity data, together with the CoR analysis results, support the effectiveness of mRNA-1010 against A/H1N1 and A/H3N2 among adults ≥ 65 years of age; however, effectiveness against B/Victoria similarly remains uncertain.

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was held on June 18, 2026, where 9 committee members voted yes and 0 voted no on each of the following voting questions: "Do the benefits of MFLUSIVA outweigh its risks for the prevention of influenza disease in adults 50 through 64 years of age?" and "Do the benefits of MFLUSIVA outweigh its risks for the prevention of influenza disease in adults 65 years of age and older?"

2. CLINICAL AND REGULATORY BACKGROUND

The applicant submitted STN 125869 on December 5, 2025, to seek licensure of MFLUSIVA (mRNA-1010) with the 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.

The applicant proposed two different regulatory pathways for the licensure of the vaccine across two age groups:

- Traditional approval for adults 50-64 years of age based on direct demonstration of clinical efficacy and safety from the pivotal Phase 3 Study P304.
- Accelerated approval for adults 65 years of age and older based on immunogenicity from studies P303C and P304, in combination with analyses evaluating HAI titer as a surrogate biomarker reasonably likely to predict clinical benefit and efficacy from the subgroup of adults ≥ 65 years of age from Study P304. Study mRNA-1010-P910 is planned as a postmarketing requirement (PMR) to confirm clinical benefit and is reviewed under IND 27460.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized to conduct a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

No substantial issues were found during the review of this BLA.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to the review memos from other review disciplines.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This statistical review focuses on the relative efficacy, immunogenicity, and safety data from studies P304 and P303C, as well as the integrated summary of safety (ISS) based on studies P304, P303C, P301, P302, and P303 Parts A and B.

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

STN 125869/0 (Submitted on December 5, 2025)

Module 5: Datasets and Clinical Study Report for Study P304; datasets and Clinical Study Report for Study P303 Part C; datasets and Integrated Summary of Safety; Correlation of Protection Report for Study P304

STN 125869/0.1 (Submitted on January 9, 2026)

Module 5: R codes for mRNA-1010-P304 Correlate of Protection Report

STN 125869/0.2 (Submitted on January 13, 2026)

Module 1: Clinical Information Amendment

Response to the IR comment regarding the datasets used for CoR analysis.

STN 125869/0.11 (Submitted on March 9, 2026)

Module 5: Partial set of datasets for mRNA-1010-P304 Interim Analysis

STN 125869/0.22 (Submitted on March 23, 2026)

Module 5: mRNA-1010-P304 Correlate of Protection Report Annex 28 Jan 2026

STN 125869/0.24 (Submitted on March 24, 2026)

Module 1: Clinical Information Amendment

Response to IR comments regarding Correlation Protection Report submitted under IND 27460.

STN 125869/0.32 (Submitted on April 13, 2026)

Module 1: Clinical Information Amendment

Response to the IR comment regarding the comparison of immunogenicity of mRNA-1010 QIV vs mRNA-1010 TIV

STN 125869/0.34 (Submitted on April 16, 2026)

Module 1: Clinical Information Amendment

Module 5: Concept Protocol for PMR study mRNA-1010-P910

STN 125869/0.37 (Submitted on April 23, 2026)

Module 1: Clinical Information Amendment

Response to information request regarding Correlate of Protection report

STN 125869/0.43 (Submitted on May 1, 2026)

Module 1: Clinical Information Amendment

Response to information request regarding Correlate of Protection report

STN 125869/0.53 (Submitted on May 15, 2026)

Module 1: Clinical Information Amendment

Response to information request regarding PMR study mRNA-1010-P910

- STN 125869/0.54 (Submitted on May 15, 2026)
Module 1: Clinical Information Amendment
Response to information request using evaluation of MN titer as a CoR for B/Victoria ILI endpoint
- STN 125869/0.58 (Submitted on May 20, 2026)
Module 1: Clinical Information Amendment
Codes related to the comparison of mRNA-1010 TIV and mRNA-1010 QIV
- STN 125869/0.63 (Submitted on May 26, 2026)
Module 1: Clinical Information Amendment
Module 5: Concept Protocol for PMR study mRNA-1010-P910
- STN 125869/0.75 (Submitted on June 12, 2026)
Module 1: Clinical Information Amendment
Response to IR comments regarding the statistically significant interaction between A/H1N1 HAI titer and vaccine group.
- STN 125869/0.94 (Submitted on July 15, 2026)
Module 1: Clinical Information Amendment
Response to IR comments regarding CoR analysis for different clinical endpoints.
- STN 125869/0.97 (Submitted on July 17, 2026)
Module 1: Cover Letter
Cross reference to IR comments regarding PMR submitted to IND 27460.
- STN 125869/0.108 (Submitted on July 28, 2026)
Module 1: Clinical Information Amendment and Package Insert.
- STN 125869/0.116 (Submitted on August 3, 2026)
Module 1: Updated Package Insert.

5.3 Table of Studies/Clinical Trials

Five clinical studies were conducted to support this BLA and are summarized in Table 1.

Table 1. Clinical Studies Supporting the Safety and Efficacy of mRNA-1010

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	<u>Part A*</u> : mRNA-1010 (QIV): N=1220 SD comparator (QIV): N=1180 <u>Part B*</u> : mRNA-1010 (QIV): N=1492 SD comparator (QIV): N=1488 <u>Part C</u> : mRNA-1010 (QIV): N=1502 Fluzone HD (QIV): N=1490	<u>Part A*</u> : mRNA-1010.6 [#] (QIV) 50 μg <u>Part B*</u> : mRNA-1010.4 (QIV) 50 μg <u>Part C</u> : 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

Study Number (Country); Study Dates	Study Design	Total mRNA-1010 Recipients Total Comparator Recipients	Formulation and Dose Levels of mRNA-1010 Evaluated
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 μ g
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 μ g

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.

mRNA-1010.4 and mRNA1010.6 are identical, with the only difference being the scale of manufacturing. They both include optimized influenza B antigen(s) encoding 2 stabilizing point mutations in non-surface exposed regions that do not impact antigenic epitopes.

Source: Summarized by the reviewer from STN 125869/0, Clinical Overview.

5.4 Consultations

A VRBPAC meeting was held on June 18, 2026, where 9 committee members voted yes and 0 voted no on each of the following voting questions: "Do the benefits of MFLUSIVA outweigh its risks for the prevention of influenza disease in adults 50 through 64 years of age?" and "Do the benefits of MFLUSIVA outweigh its risks for the prevention of influenza disease in adults 65 years of age and older?"

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 mRNA-1010-P304

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

6.1.1 Objectives

Primary Objectives

1. To evaluate the safety and reactogenicity of mRNA-1010.

2. To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains.

Secondary Objectives

1. To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed modified Center of Disease Control and Prevention (CDC)-defined ILI caused by any influenza A or B strains.
2. To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI or RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains with antigenic match to the vaccine strains.
3. To evaluate the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains in a subset of approximately 2400 participants.
4. To evaluate HAI titers as a surrogate of risk and protection against RT-PCR-confirmed protocol-defined ILI (CoR and CoP) for mRNA-1010 and an active comparator.

6.1.2 Design Overview

Study P304 was a Phase 3, randomized, observer-blind (participant- and assessor-blind), active-controlled study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 vs. a licensed SD comparator in adults ≥ 50 years of age.

A trivalent influenza vaccine (TIV) formulation of mRNA-1010 was used in this study in accordance with recent WHO recommendations. The SD comparator administered in this study was a licensed SD inactivated seasonal influenza vaccine, administered as a single IM injection. While a licensed TIV was the preferred SD comparator, a licensed quadrivalent influenza vaccine (QIV) was used in participating countries where a licensed TIV was unavailable.

Participants were randomized in a 1:1 ratio to receive a single injection of mRNA-1010 or an SD comparator. Randomization was stratified by age category (≥ 50 to 64 years or ≥ 65 years) at screening and by influenza vaccine status in the previous influenza season (received or not received). Approximately 50% of enrolled participants were to be ≥ 65 years of age, including approximately 10% who were ≥ 75 years of age.

Solicited ARs were collected in a Reactogenicity Subset of approximately 6000 participants from Day 1 through Day 7 via eDiary. Unsolicited AEs were recorded throughout the study per protocol-defined timeframes. Blood samples were collected from all participants on Day 1 (Baseline) and Day 29 for immunogenicity assessments. Immunogenicity endpoints based on HAI titers were planned to be assessed in a prespecified subset of 2400

participants from North America where TIV SD comparator was used. A stratified random subset of approximately 500 participants from the Per-Protocol Immunogenicity Subset (PPIS) was selected to perform exploratory MN immunogenicity analyses. For the CoR/CoP analyses, in addition to these 2400 participants, a random subset of 800 participants from Rest of the World (Europe and East Asia) and all RT-PCR-confirmed protocol-defined ILI cases were assessed for HAI titers.

6.1.3 Population

Healthy male and female adults ≥ 50 years of age were enrolled.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study interventions are outlined in Table 2. mRNA-1010 was administered as a single IM injection at a total mRNA dose level of 37.5 μg (TIV, 12.5 μg per strain). The comparator administered in this study was an SD licensed inactivated seasonal influenza vaccine administered as a single IM injection. Study interventions were administered such that TIV/QIV comparator use was dictated by region, with TIV used in North America and QIV in the Rest of the World (Europe and East Asia).

Table 2: Study Interventions Administered

Intervention Name	mRNA-1010	Fluarix, Fluarix Tetra, Influsplit® Tetra, Alpharix® Tetra
Unit Dose Strength	37.5 μg of mRNA	45 μg (TIV) or 60 μg (QIV) of protein
Dosage Volume	Single dose of 0.5 mL	Single dose of 0.5 mL
Route of Administration	IM	IM

Abbreviations: IM = intramuscular; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine.

Source: Table 3 of mRNA-1010-P304 CSR submitted to STN 125869/0.

6.1.6 Sites and Centers

This study was conducted at 301 sites in 11 countries in North America, Europe, and East Asia.

6.1.7 Surveillance/Monitoring

Please refer to the clinical reviewer's memo.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

- First episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.

Primary Safety Endpoints

- Solicited local and systemic ARs from Day 1 to Day 7 in a subset of approximately 6000 participants.
- All unsolicited AEs from Day 1 to Day 28.
- MAAEs from Day 1 to Month 6 (Day 181).
- AEs leading to discontinuation from Day 1 to Month 6 (Day 181).
- SAEs from Day 1 to Month 6 (Day 181).
- AESIs from Day 1 to Month 6 (Day 181).

Secondary Endpoints

- First episode of RT-PCR-confirmed modified CDC-defined ILI that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
- First episode of RT-PCR-confirmed protocol-defined ILI or modified CDC-defined ILI that begins 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.
- GMT at Day 29 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI, defined as the proportion of participants with either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer $\geq$ 1:40 or a pre-vaccination HAI titer $\geq$ 1:10 and a minimum 4-fold rise in post-vaccination HAI titer.
- Frequency of participants with an HAI titer $\geq$ 1:40 at Day 29.
- GMFR comparing Day 29 to Day 1 as measured by HAI.

The applicant defined each efficacy endpoint as follows.

RT-PCR-confirmed protocol-defined ILI:

- The participant has a positive influenza RT-PCR result performed at the global central laboratory or a local certified laboratory, AND
- The participant experienced at least 1 systemic symptom (temperature $> 37.2^{\circ}\text{C}$ [$> 99.0^{\circ}\text{F}$], chills, feverish, tiredness, headaches, or myalgia) AND at least 1 respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) with onset within ± 7 days from the sample collection date of the positive RT-PCR result.

RT-PCR-confirmed modified CDC (m-CDC)-defined ILI:

- The definition of RT-PCR-confirmed protocol-defined ILI is met, AND
- The participant experienced body temperature $> 37.2^{\circ}\text{C}$ ($> 99.0^{\circ}\text{F}$) accompanied by cough and/or sore throat with onset within ± 7 days of the sample collection date of the positive RT-PCR result.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

The applicant defined the following analysis populations:

- Randomization Set: all participants who were randomized, regardless of the participants' intervention status in the study. Participants were analyzed according to the group to which they were randomized.
- Full Analysis Set (FAS): all randomized participants who received any study vaccination. Participants were analyzed according to the group to which they were randomized.
- Safety Analysis Set: all randomized participants who received any study vaccination. The Safety Set was used for all analyses of safety except for solicited ARs. Participants were analyzed according to the study vaccination they actually received.
- Solicited Safety Subset: all randomized participants in the subset of approximately 6000 participants who received any study vaccination and contributed any solicited AR data in the eDiary. The Solicited Safety Subset was used for all analyses of solicited ARs. Participants were analyzed according to the study vaccination they actually received.
- 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 a suboptimal response to study vaccination). The PP Set was used as the primary analysis set for efficacy endpoints. The protocol deviations were decided blindly by the blinded study team before database lock for the analysis. Participants were analyzed according to the study vaccination group to which they were randomized.
- Immunogenicity Subset: a prespecified subset of participants in the FAS who received TIV and had Day 1 and Day 29 humoral immunogenicity samples. Participants were analyzed according to the study vaccination group to which they were randomized.
- Per-Protocol Immunogenicity Subset (PPIS): all participants in the Immunogenicity Subset who received the planned dose of study vaccination and had no important protocol deviations that impacted the immunogenicity assessment. Participants with RT-PCR-confirmed influenza infection between Day 1 and Day 29 were removed from the PPIS. Protocol deviations were decided blindly by the blinded study team before database lock for the analysis.

Sampling of Immunogenicity Subset

A stratified random subcohort of 3200 participants was to be selected among participants in the FAS who had both Day 1 and Day 29 immunogenicity samples. In North America, 300 participants were to be sampled within each of eight strata defined by age group (50 through 64 years and ≥ 65 years), influenza vaccination status in the previous season (received or not received), and vaccine group (mRNA-1010 or active comparator), totaling 2400 participants. Similarly, in Rest of the World, 100 participants were to be sampled within each of the eight strata, totaling 800 participants.

Analysis of Efficacy Endpoints

The stratified Cox proportional hazards regression model was used to estimate the HR and rVE for each efficacy endpoint, defined as $1 - \text{HR}$ and expressed as a percentage. The same stratification factors at randomization were to be applied as the strata variables. Similar methods were used for subgroup analyses.

Interim Analysis

The target number of cases for the primary analysis was 836. A formal interim analysis based on the Pocock boundary was to be carried out when 70% of the target number (586) of cases were accumulated. Due to the high incidence rate, 968 cases were accrued at the end of the 2024-2025 influenza season. Thus, no interim analysis was performed, and an end-of-season analysis was performed with the full one-sided alpha of 2.5%.

Hypotheses and Multiplicity Adjustment

The hypotheses for noninferiority were $H_0: \text{rVE} < -10\%$ vs. $H_1: \text{rVE} > -10\%$, the hypotheses for superiority were $H_0: \text{rVE} \leq 0\%$ vs. $H_1: \text{rVE} > 0\%$, and the hypotheses for super-superiority were $H_0: \text{rVE} \leq 9.1\%$ vs. $H_1: \text{rVE} > 9.1\%$. Of note, this statistical review focuses on the statistical superiority and super-superiority defined by the applicant. Please refer to the clinical review memo regarding the clinical interpretation of superior efficacy.

Adjustments for multiplicity to control the overall study Type 1 error were handled by hierarchical testing of statistical hypotheses as follows. For each efficacy endpoint, non-inferiority, superiority, and super-superiority were assessed in a fixed sequence.

1. NI of rVE against RT-PCR-confirmed protocol-defined ILIs caused by any strain.
2. Superiority of rVE against RT-PCR-confirmed protocol-defined ILIs caused by any strain.
3. Super-superiority of rVE against RT-PCR-confirmed protocol-defined ILIs caused by any strain.

4. NI of rVE against RT-PCR-confirmed modified CDC-defined ILIs caused by any strain.
5. Superiority of rVE against RT-PCR-confirmed modified CDC-defined ILIs caused by any strain.
6. Super-superiority of rVE against RT-PCR-confirmed modified CDC-defined ILIs caused by any strain.
7. NI of rVE against RT-PCR-confirmed protocol-defined ILIs with antigenic match caused by any strain.
8. Superiority of rVE against RT-PCR-confirmed protocol-defined ILIs with antigenic match caused by any strain.
9. Super-superiority of rVE against RT-PCR-confirmed protocol-defined ILIs with antigenic match caused by any strain.

Sample Size

The sample size was driven by the total number of cases needed to demonstrate NI for the primary efficacy endpoint. A total of 836 cases in the PP Set would provide at least 80% power to establish NI at a margin of -10%, assuming a true rVE of 10%, using a log-rank test statistic with an overall 1-sided Type I error rate of 2.5%. With an attack rate of 1.5% in the mRNA-1010 group and a non-evaluable rate of 10%, approximately 56,000 participants across two seasons were planned to accrue 836 cases.

Analysis of Immunogenicity

A descriptive analysis of covariance (ANCOVA) model was carried out with the log-transformed HAI titer on Day 29 as the dependent variable, and vaccination group, log-transformed baseline HAI titer, and the stratification factors (age group and previous year vaccination status) as independent variables. The geometric least square mean (GLSM) and its corresponding 95% CI in log-transformed scale estimated from the model were back-transformed to the original scale to obtain the GMT and its 95% CI. The GMR (mRNA-1010 vs. active comparator) and its 95% CI were estimated by back-transforming the ratio of GLSMs and the corresponding 95% CI from the ANCOVA model.

The numbers and percentages of participants with seroconversion or HAI titer $\geq 1:40$ on Day 29 were computed along with the Clopper-Pearson 95% CIs. Differences in seroconversion rates between vaccine groups were computed along with 95% CIs based on Miettinen-Nurminen's method.

Analysis of Safety

The proportion of participants reporting each safety event was descriptively summarized.

Statistical Methods for CoR Analysis

Analyses were adjusted for baseline risk factors, which included randomization strata and synthetic baseline risk scores derived from a set of baseline covariates: age, sex, BMI, BMI group ($< 30 \text{ kg/m}^2$ or $\geq 30 \text{ kg/m}^2$), region (North America, Europe, Rest of the World), high risk status, ethnicity, and race. Due to potential correlation and high dimension of the baseline covariates, the applicant performed a principal component analysis (PCA) and the first two PCAs were used as the synthetic baseline risk scores. Each continuous variable was normalized to have a mean of 0 and standard deviation of 1. Missing values were imputed using a k-nearest neighbor algorithm.

The analysis was based on the Per-Protocol Correlate Analysis Set (PPCAS), consisting of the stratified random subcohort, augmented with all participants with RT-PCR-confirmed protocol-defined ILI in the study.

In order to ensure that the analysis set was representative of the study population, inverse probability of sampling (IPS) weights were calculated within each of the following 18 strata: 1) mRNA-1010 ILI cases; 2) active comparator vaccine ILI cases; 3) eight baseline strata defined by age group, influenza vaccine status in the previous season, and region for the mRNA-1010 non-cases; and 4) eight baseline strata for the active comparator vaccine non-cases. The IPS weight was calculated for each stratum by $w_i(x) = N_x/n_x$, where $w_i(x)$ was the weight for subject i within stratum x , N_x was the total sample size of stratum x in the study population, and n_x was the sample size of stratum x in the PPCAS.

The CoR analysis was performed for each of the three strains separately to evaluate whether the strain-specific HAI titer correlated with strain-specific disease. The applicant fitted three IPS-weighted Cox proportional hazards models for each strain. All HAI titers were $\log_2$ -transformed for analyses.

Model 1 evaluated the relationship between the vaccine group and the disease endpoint, adjusted for age group (50 – 64 years vs. ≥ 65 years), prior influenza vaccination status (received vs. not received), and synthetic baseline risk scores.

Model 2 included the strain-specific Day 29 HAI titer in addition to all covariates from Model 1. A statistically significant HR of < 1 for the Day 29 HAI titer suggested that the strain-specific Day 29 HAI titer may be a CoR for that disease endpoint. Additionally, if the HR corresponding to the vaccine group in Model 2 was closer to 1 compared to Model 1, this may suggest a potential mediation of protection via the HAI titer.

Model 3 included an interaction between the vaccine group and the Day 29 HAI titer in addition to all covariates in Model 2. A statistically significant interaction suggested that the disease-titer relationship may differ across vaccines.

The relationship between the strain-specific Day 29 HAI titer and the disease endpoint was further evaluated in each subgroup. For the subgroup analysis, an IPS-weighted Cox PH model was fitted in each subgroup in each arm separately with Day 29 HAI titer as the only covariate. The HR was estimated from the estimated coefficient. The following subgroups were considered:

- Age group (50-64 years; ≥ 65 years).
- Prior influenza vaccination status (Received; Not received).
- Region (North America; Rest of the World).
- High risk status (High risk [≥ 1 risk factor]; Not high risk).
- Sex (Male; Female).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 40,805 participants ≥ 50 years of age were randomized, including 19,519 (47.8%) participants ≥ 65 years of age and 4,729 (11.6%) participants ≥ 75 years of age. The demographic characteristics of the Safety Analysis Set are shown in Table 3. Demographic and baseline characteristics were generally balanced between the vaccine groups. There were more female participants than male participants. Approximately 82.6% of the participants were White and 13.2% of the participants were Black or African American. Approximately 47% of the participants received seasonal influenza vaccine in the previous influenza season. Demographic characteristics were similar in the Per-Protocol Set.

Table 3: Demographic and Baseline Characteristics (Safety Set^a)

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, n (%)	--	--
Median age, years (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)

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

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

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

Percentages are based on the number of participants in the Safety Set.

^a The Safety Set 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/m², 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 reported a participant with a BMI of 139.0. After an information request, the applicant clarified 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.

Source: Adapted from STN 125869/0.48, mRNA-1010-P304 CSR, Tables 14.1.3.1.3.f and 14.1.3.1.8.f.

Participant disposition is summarized in Table 4. The percentages of participants discontinuing the study were similar between vaccine arms. Most discontinuations were due to lost-to-follow-up.

Table 4. Participant Disposition

Population	mRNA-1010 n (%)	SD Comparator n (%)
Randomization Set, N	20,402	20,403
Safety Set, N	20,350	20,353
Solicited Safety Subset	3015 (14.8)	2997 (14.7)
Excluded from Solicited Safety Subset	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	19,569 (96.2)	19,621 (96.4)
Discontinued the study	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)

Population	mRNA-1010 n (%)	SD Comparator n (%)
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)

Percentages are based on the number of participants in the Safety Set.

^a 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.

Source: Adapted from STN 125869/0, mRNA-1010-P304 CSR, Tables 8, 14.1.1.1.2.f, 14.1.1.1.6.f, 14.1.2.2.1.f, 14.1.3.4.1.f, and 14.1.3.4.3.f.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

A total of 968 participants (411 [2.0%] in the mRNA-1010 group and 557 [2.8%] in the SD comparator group) had RT-PCR-confirmed protocol-defined ILI in the PP Set at the end of the 2024/2025 influenza season (Data Cutoff Date: April 30, 2025). This comprised of 908 participants testing positive for any influenza A strain (538 participants with A/H1N1, 360 participants with A/H3N2, and 10 participants with A unknown) and 60 participants testing positive for influenza B strain (Table 5). Since the total number of primary cases exceeded the total planned for the entire study, the full 1-sided alpha of 2.5% was used for the end-of-season analysis. The rVE was 26.6% (95% CI: 16.7%, 35.4%), which met the prespecified success criteria for noninferiority (LB of 95% CI >-10%), superiority (LB of 95% CI >0%), and super-superiority (LB of 95% CI >9.1%).

Descriptive estimates of strain-specific rVEs were similar across each strain and consistent with the overall rVE: rVE against RT-PCR-confirmed protocol-defined ILI associated with any influenza A, influenza A/H1N1, A/H3N2, and B/Victoria was 26.5% (95% CI: 16.1%, 35.5%), 29.6% (95% CI: 16.4%, 40.7%), 22.2% (95% CI: 4.3%, 36.9%), and 29.1% (95% CI: -18.5%, 57.5%), respectively (Table 11).

Supportive analyses of the primary efficacy endpoint at the end-of-study (EOS) with a cutoff date of September 16, 2025 resulted in an rVE of 26.5% (95% CI: 16.5%, 35.3%), consistent with that observed at the end of the 2024/2025 influenza season. In the supportive analysis, three participants (one mRNA-1010 and two SD active comparator recipients) who experienced RT-PCR-confirmed protocol-defined ILI were later found to have had prohibited medications leading to subsequent removal from the Per-Protocol Set.

Table 5 summarizes rVE by age group and strain. The rVE point estimates were similar across age groups and for all three strains.

Table 5: Relative Vaccine Efficacy of mRNA-1010 Against RT-PCR-Confirmed Protocol-Defined ILI (PP Set)

-	mRNA-1010 n (%)	SD Comparator n (%)	rVE % (95% CI)
Overall	N=20,179	N=20,124	--
Any Type / Subtype	411 (2.0)	557 (2.8)	26.6 (16.7, 35.4)
Influenza A	386 (1.9)	522 (2.6)	26.5 (16.1, 35.5)
A/H1N1	223 (1.1)	315 (1.6)	29.6 (16.4, 40.7)
A/H3N2	158 (0.8)	202 (1.0)	22.2 (4.3, 36.9)
A (Unknown)	5 (<0.1)	5 (<0.1)	-
B/Victoria	25 (0.1)	35 (0.2)	29.1 (-18.5, 57.5)
50-64 Years of Age	N=10,542	N=10,501	-
Any Type / Subtype	229 (2.2)	307 (2.9)	26.1 (12.3, 37.7)
A/H1N1	123 (1.2)	170 (1.6)	28.3 (9.5, 43.1)
A/H3N2	90 (0.9)	115 (1.1)	22.4 (-2.2, 41.1)
A (Unknown)	2 (<0.1)	4 (<0.1)	NC
B/Victoria	14 (0.1)	18 (0.2)	23.0 (-54.8, 61.7)
≥ 65 Years of Age	N=9,637	N=9,623	-
Any Type / Subtype	182 (1.9)	250 (2.6)	27.4 (12.1, 40.0)
A/H1N1	100 (1.0)	145 (1.5)	31.2 (11.2, 46.7)
A/H3N2	68 (0.7)	87 (0.9)	22.0 (-7.1, 43.2)
A (Unknown)	3 (<0.1)	1 (<0.1)	NC
B/Victoria	11 (0.1)	17 (0.2)	35.5 (-37.7, 69.8)

n: number of cases; *N*: number of participants in the PP Set; NC: not calculated.

Source: Adapted from Tables 10 and 11 of mRNA-1010-P304 CSR and calculated by the reviewer.

6.1.11.2 Analyses of Secondary Endpoints

Efficacy

Since the primary endpoint achieved all prespecified success criteria, rVE based on the secondary endpoint of RT-PCR-confirmed modified CDC-defined ILI was subsequently evaluated for noninferiority, superiority, and super-superiority. A total of 223 (1.1%) cases were reported in the mRNA-1010 group and 290 (1.4%) in the SD comparator group, resulting in an rVE of 23.5% (95% CI: 9.0%, 35.8%). Prespecified criterion for superiority was met; however, the criterion for super-superiority was not met. Results of supportive analyses of RT-PCR-confirmed modified CDC-defined ILI at EOS were consistent with those observed at the end of the 2024/2025 influenza season.

Table 6 summarizes rVE by age group and strain. The rVE point estimates were similar across age groups and for all three strains.

Table 6: Relative Vaccine Efficacy of mRNA-1010 Against RT-PCR-Confirmed Modified CDC-Defined ILI (PP Set)

-	mRNA-1010 n (%)	SD Comparator n (%)	rVE % (95% CI)
Overall	N=20,179	N=20,124	--

-	mRNA-1010 n (%)	SD Comparator n (%)	rVE % (95% CI)
Any Type / Subtype	223 (1.1)	290 (1.4)	23.5 (9.0, 35.8)
Influenza A	211 (1.0)	276 (1.4)	24.0 (9.1, 36.5)
A/H1N1	125 (0.6)	172 (0.9)	27.7 (9.0, 42.6)
A/H3N2	83 (0.4)	102 (0.5)	19.1 (-8.1, 39.5)
A (Unknown)	3 (<0.1)	2 (<0.1)	-
B/Victoria	12 (<0.1)	14 (<0.1)	14.8 (-84.3, 60.6)
50-64 Years of Age	N=10,542	N=10,501	-
Any Type / Subtype	129 (1.2)	162 (1.5)	22.2 (1.9, 38.4)
A/H1N1	70 (0.7)	97 (0.9)	28.5 (2.7, 47.4)
A/H3N2	54 (0.5)	57 (0.5)	6.1 (-36.3, 35.3)
A (Unknown)	0 (0)	1 (<0.1)	NC
B/Victoria	5 (<0.1)	7 (0.1)	29.3 (-123.0, 77.6)
≥ 65 Years of Age	N=9,637	N=9,623	-
Any Type / Subtype	94 (1.0)	128 (1.3)	25.2 (2.5, 42.6)
A/H1N1	55 (0.6)	75 (0.8)	26.8 (-3.6, 48.3)
A/H3N2	29 (0.3)	45 (0.5)	35.7 (-2.5, 59.7)
A (Unknown)	3 (<0.1)	1 (<0.1)	NC
B/Victoria	7 (0.1)	7 (0.1)	0.3 (-184.0, 65.0)

n: number of cases; *N*: number of participants in the PP Set; NC: not calculated.

Source: Adapted from Tables 14 and 15 of mRNA-1010-P304 CSR and calculated by the reviewer.

Efficacy Against Antigenically Matched Strains

Table 7 summarizes rVE against RT-PCR-confirmed protocol-defined ILI with antigenic match by age group and strain at EOS. Overall, age group- and strain-specific rVE were similar to those observed for the primary endpoint.

Table 7: Relative Vaccine Efficacy of mRNA-1010 Against RT-PCR-Confirmed Protocol-Defined ILI with Antigenic Match at EOS (PP Set)

-	mRNA-1010 n (%)	SD Comparator n (%)	rVE % (95% CI)
Overall	N=20,178	N=20,122	-
Any Type / Subtype	261 (1.3)	364 (1.8)	28.7 (16.4, 39.2)
Influenza A	246 (1.2)	345 (1.7)	29.1 (16.5, 39.8)
A/H1N1	181 (0.9)	252 (1.3)	28.5 (13.5, 41.0)
A/H3N2	65 (0.3)	93 (0.5)	30.5 (4.6, 49.4)
B/Victoria	15 (<0.1)	19 (<0.1)	21.6 (-54.3, 60.2)
50-64 Years of Age	N=10,541	N=10,500	-
Any Type / Subtype	140 (1.3)	209 (2.0)	33.6 (17.7, 46.4)
Influenza A	131 (1.2)	199 (1.9)	34.7 (18.6, 47.6)
A/H1N1	93 (0.9)	145 (1.4)	36.4 (17.5, 51.0)
A/H3N2	38 (0.4)	54 (0.5)	30.2 (-5.7, 53.9)
B/Victoria	9 (<0.1)	10 (<0.1)	10.9 (-119.0, 63.8)
≥ 65 Years of Age	N=9,637	N=9,622	-
Any Type / Subtype	121 (1.3)	155 (1.6)	22.1 (1.2, 38.6)
Influenza A	115 (1.2)	146 (1.5)	21.4 (-0.4, 38.4)

-	mRNA-1010 n (%)	SD Comparator n (%)	rVE % (95% CI)
A/H1N1	88 (0.9)	107 (1.1)	17.9 (-8.8, 38.1)
A/H3N2	27 (0.3)	39 (0.4)	30.9 (-12.8, 57.7)
B/Victoria	6 (<0.1)	9 (<0.1)	33.5 (-86.7, 76.3)

n: number of cases; *N*: number of participants in the PP Set.

Source: Adapted from Tables in Clinical Information Amendment submitted to STN 125869/0.40 and calculated by the reviewer.

Immunogenicity

The secondary immunogenicity objective was to describe HAI titers at Day 1 and Day 29 in terms of model-based GMTs (Table 8) and seroconversion rates (Table 9) in a subset of participants ≥ 50 years of age in the PPIS in North America. All participants in the PPIS received a TIV formulation. Overall, HAI titers and seroconversion rates were higher in the mRNA-1010 group compared to the SD comparator group.

Table 8. GMTs as Measured by HAI at Day 1 and Day 29 (PPIS)

Endpoint	mRNA-1010 (TIV) N=1167 GMT (95% CI)	SD Comparator (TIV) N=1175 GMT (95% CI)	GMR (95% CI)
A/H1N1	-	-	-
Day 1	35.91 (34.07, 37.86)	35.80 (33.86, 37.86)	-
Day 29	146.34 (138.71, 154.40)	80.23 (76.06, 84.63)	1.82 (1.69, 1.97)
A/H3N2	-	-	-
Day 1	31.83 (30.12, 33.65)	31.06 (29.37, 32.84)	-
Day 29	148.48 (140.90, 156.47)	93.44 (88.68, 98.45)	1.59 (1.48, 1.71)
B/Victoria	-	-	-
Day 1	79.79 (75.92, 83.85)	79.46 (75.70, 83.41)	-
Day 29	250.88 (240.28, 261.94)	149.96 (143.65, 156.55)	1.67 (1.57, 1.78)

Source: Table 19 of mRNA-1010-P304 CSR submitted to STN 125869/0.

Table 9. Seroconversion Rates and Rate Differences for HAI titers (PPIS)

Endpoint	mRNA-1010 (TIV) N=1167 % (95% CI)	SD Comparator (TIV) N=1175 % (95% CI)	SCR Difference (95% CI)
A/H1N1	55.0 (52.11, 57.89)	27.1 (24.54, 29.70)	27.95 (24.09, 31.73)
A/H3N2	60.8 (57.97, 63.65)	40.9 (38.02, 43.72)	19.99 (15.99, 23.92)
B/Victoria	45.1 (42.19, 47.98)	19.7 (17.50, 22.14)	25.33 (21.65, 28.95)

Source: Table 19 of mRNA-1010-P304 CSR submitted to STN 125869/0.

Exploratory analyses of neutralizing antibody responses by the microneutralization (MN) assay for each influenza strain in a subset of the PPIS are presented in Table 10. Overall, responses as measured by MN were consistent with those measured by HAI.

Table 10. GMTs as Measured by MN at Day 29 (PPIS Subset)

Endpoint	mRNA-1010 (TIV) N=247 GMT (95% CI)	SD Comparator (TIV) N=253 GMT (95% CI)	GMR (95% CI)
A/H1N1	527.19 (447.53, 621.03)	187.67 (159.63, 220.63)	2.81 (2.23, 3.54)
A/H3N2	434.42 (397.15, 475.19)	317.55 (290.63, 346.97)	1.37 (1.21, 1.55)
B/Victoria	1263.26 (1115.89, 1430.08)	600.83 (531.54, 679.14)	2.10 (1.77, 2.50)

Source: Table 20 of mRNA-1010-P304 CSR submitted to STN 125869/0.

CoR Analyses

As a secondary endpoint, the applicant performed a CoR analysis using a case-cohort sampling design (Prentice 1986, Self and Prentice 1988). The purpose of the analysis was to evaluate the utility of the strain-specific Day 29 HAI titer as a surrogate endpoint for the strain-specific disease endpoint. The analysis was performed based on the EOS data. The CoR analyses were performed on the Per-Protocol Correlate Analysis Set (PPCAS). The case-cohort immunogenicity subset is the union of two components: stratified random subcohort and RT-PCR confirmed ILI cases.

Stratified Random Subcohort

A total of 3,109 participants were sampled into the random subcohort for immunogenicity testing. The numbers of sampled participants in each stratum are provided in Table 11. Demographic characteristics were generally similar to the P304 study population.

Table 11: Number of Participants Included in Each Stratum

Stratum	Region, Age Group, Influenza Vaccination in Previous Season	mRNA-1010 n	SD Comparator n	Total n
S1	NA, 50–64 years, Received	287	294	581
S2	NA, 50–64 years, Not Received	285	293	578
S3	NA, ≥65 years, Received	300	299	599
S4	NA, ≥65 years, Not Received	279	281	560
S5	RoW, 50–64 years, Received	96	99	195
S6	RoW, 50–64 years, Not Received	100	101	201
S7	RoW, ≥65 years, Received	102	102	204
S8	RoW, ≥65 years, Not Received	97	94	191
Total	-	1546	1563	3109

NA: North America; RoW: Rest of the World.

Source: Computed by the statistical reviewer.

RT-PCR-Confirmed ILI Cases

All participants in the study with at least one RT-PCR-confirmed, protocol-defined ILI caused by any influenza A or B strain, with ILI onset at least 7 days after the Day 29 visit, were additionally included in the PPCAS. The purpose of including only cases occurring

at least 7 days after the Day 29 visit was to ensure that the HAI titer measured was induced by the vaccine only, not by an infection. A total of 900 (504 A/H1N1 [208 in mRNA-1010, 296 in SD comparator], 337 A/H3N2 [150 in mRNA-1010, 187 in SD comparator], and 59 B/Victoria [25 in mRNA-1010, 34 in SD comparator]) cases were included in the analyses.

CoR Analysis Results for A/H1N1

The results of the CoR analysis for A/H1N1 are summarized in Table 12. In Model 1, the HR corresponding to the vaccine group (mRNA-1010/SD comparator) was statistically significant (HR = 0.70 with 95% CI: 0.58, 0.85). After the A/H1N1 Day 29 HAI titer was introduced in Model 2, the HR for the vaccine group became 1.00 (95% CI: 0.81, 1.24) with a statistically significant HR for the Day 29 HAI titer of 0.48 (95% CI: 0.43, 0.54), suggesting that the Day 29 HAI titer may be a CoR for the A/H1N1 disease endpoint. In Model 3, the interaction term between the A/H1N1 HAI titer and the vaccine group was statistically significant with a p-value of 0.002 (HR: 0.71 [95% CI: 0.57, 0.88]), suggesting that the disease-titer relationship may differ across vaccines.

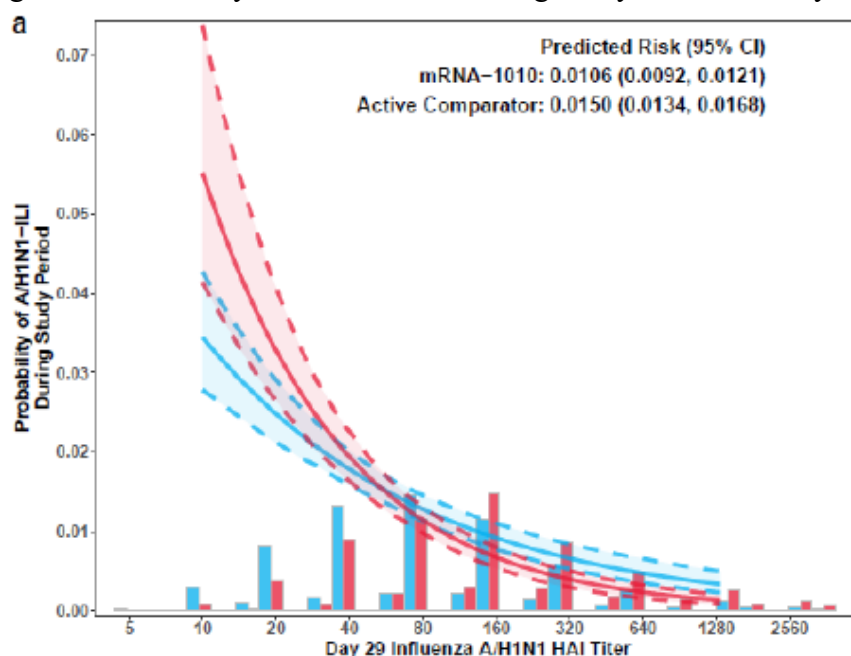
Table 12: Cox PH Model Summary for A/H1N1

Model	Vaccine Group HR (95% CI)	Day 29 HAI titer HR (95% CI)	Vaccine Group x Day 29 HAI titer (95% CI)
Model 1	0.70 (0.58, 0.85)	-	-
Model 2	1.00 (0.81, 1.24)	0.48 (0.43, 0.54)	-
Model 3	0.84 (0.68, 1.05)	0.56 (0.49, 0.64)	0.71 (0.57, 0.88)

Source: Figure 3 of the CoP report Version 2 submitted in STN 125869/0 and calculated by the reviewer.

Figure 1 depicts the estimated risk of A/H1N1 ILI at a given Day 29 titer during the study period for each vaccine group. The estimated risk curves intersect at a titer between 1:40 and 1:80, consistent with the statistically significant interaction term. The plot suggests that at titers below the intersection, the risk of A/H1N1-associated disease is higher in the mRNA-1010 group compared to the active comparator. However, at titers above the intersection, the disease risk appears lower in the mRNA-1010 group. These results further suggest that the disease-titer relationship may differ across vaccines. As a result, the Day 29 A/H1N1 HAI titer alone may not be sufficient to predict disease risk without information on the actual vaccine received.

Figure 1: Probability of A/H1N1 ILI During Study Period vs. Day 29 Titer



Solid red (mRNA-1010) and blue (the active comparator) curves represent the marginalized covariate-adjusted cumulative incidence of A/H1N1 ILI during the study period across a range of assigned HAI titers (within 2.5th to 97.5th percentiles of observed Day 29 HAI titers in both the mRNA-1010 and the active comparator vaccine groups). Dashed red and blue curves along with the shades represent the bootstrap pointwise 95% CIs.

Source: Figure 5a of mRNA-1010-P304 Correlate of Protection Report Version 2.

Table 13 summarizes the HR of HAI titer in each subgroup for each arm. CoR analysis results across subgroups defined by age group, prior influenza vaccination status, region, high-risk status, and sex within each vaccine group. An inverse association between disease risk and HAI titer was observed across all evaluated subgroups in both vaccine groups.

Table 13: Subgroup CoR Analysis for A/H1N1

Subgroup	mRNA-1010 HR for Day 29 Titer (95% CI)	Active Comparator HR for Day 29 Titer (95% CI)
Overall — All Vaccinees	0.40 (0.34, 0.47)	0.55 (0.48, 0.62)
Age Group	-	-
50 to <65 Years	0.37 (0.29, 0.47)	0.47 (0.39, 0.57)
≥65 Years	0.42 (0.33, 0.52)	0.64 (0.54, 0.76)
Prior Influenza Vaccination Status	-	-
Received	0.43 (0.35, 0.53)	0.65 (0.56, 0.76)
Not Received	0.39 (0.30, 0.51)	0.51 (0.41, 0.63)
Region	-	-
North America	0.34 (0.28, 0.42)	0.56 (0.48, 0.64)
Rest of World	0.50 (0.38, 0.66)	0.53 (0.41, 0.69)
High-Risk Status	-	-
High-Risk (≥1 Risk Factor)	0.37 (0.29, 0.46)	0.54 (0.46, 0.63)
Not High Risk	0.44 (0.35, 0.55)	0.57 (0.47, 0.70)

Subgroup	mRNA-1010 HR for Day 29 Titer (95% CI)	Active Comparator HR for Day 29 Titer (95% CI)
Sex	-	-
Female	0.38 (0.31, 0.47)	0.58 (0.49, 0.68)
Male	0.42 (0.32, 0.55)	0.50 (0.41, 0.62)

Source: Figure S6 of the CoP report Version 2, submitted to STN 125869/0.

Reviewer's Comment:

- For all CoR analyses, I observed similar results in my independent analyses.
- Due to the statistically significant interaction between the Day 29 HAI titer and vaccine group, suggesting differences in the disease-titer relationship, inferences on the disease risk for A/H1N1 need to take into consideration both the vaccine group and the magnitude of the HAI titer.
- Observations were consistent across age groups (50-64 years and ≥ 65 years).
- Figure 1 indicates that the disease risk corresponding to A/H1N1 is lower in the mRNA-1010 group compared to the SD comparator when the titer is greater than 1:80. Of note, in the PPCAS, there were 54.5% subjects in the mRNA-1010 group and 33.1% subjects in the SD comparator group with titer higher than 1:80. These results suggest that the relative effectiveness trends slightly higher at higher titers than at lower titers.

CoR Analysis Results for A/H3N2

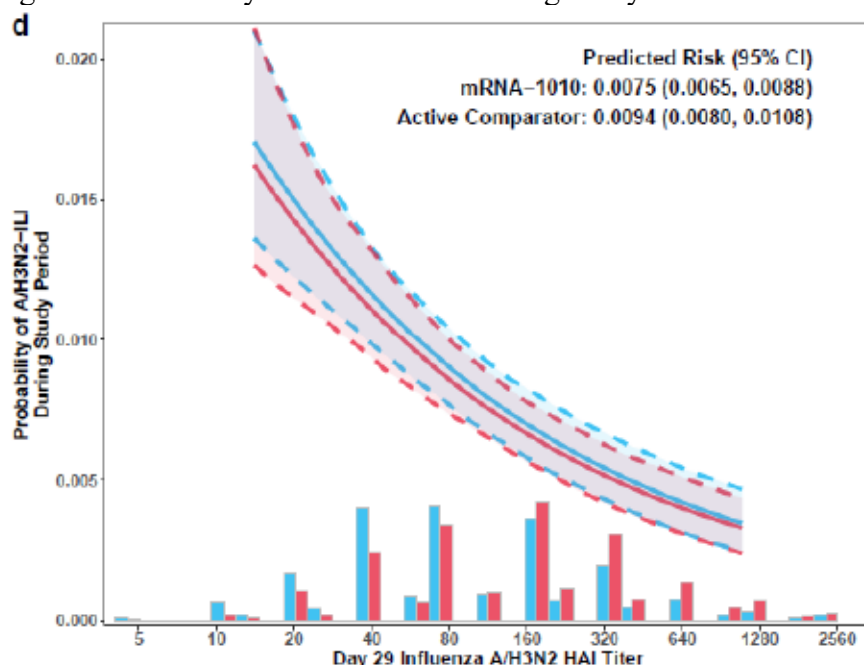
Similar methods as described for A/H1N1 were applied for the A/H3N2-ILI endpoint. The results of Models 1 to 3 are summarized in Table 14. In Model 2, the estimated HR for the A/H3N2 HAI titer was 0.66 (95% CI: 0.58, 0.74; $p < 0.001$), while the HR for vaccine group was attenuated to 0.95 (95% CI: 0.75, 1.20; $p = 0.659$), suggesting some mediation of the vaccine effect through the Day 29 A/H3N2 HAI titer. No statistically significant interaction between the Day 29 A/H3N2 HAI titer and vaccine group was observed in Model 3 (HR: 0.95 [95% CI: 0.75, 1.21]; $p = 0.676$), as suggested in Figure 2.

Table 14: Cox PH Model Summary for A/H3N2

Model	Vaccine Group HR (95% CI)	Day 29 HAI titer HR (95% CI)	Vaccine Group x Day 29 HAI titer (95% CI)
Model 1	0.80 (0.64, 1.00)	-	-
Model 2	0.95 (0.75, 1.20)	0.66 (0.58, 0.74)	-
Model 3	0.93 (0.73, 1.19)	0.67 (0.57, 0.80)	0.95 (0.75, 1.21)

Source: Figure 3 of the CoP report Version 2 submitted in STN 125869/0 and calculated by the reviewer.

Figure 2: Probability of A/H3N2 ILI During Study Period



Solid red (mRNA-1010) and blue (the active comparator) curves represent the marginalized covariate-adjusted cumulative incidence of A/H3N2 ILI during the study period across a range of assigned HAI titers (within 2.5th to 97.5th percentiles of observed Day 29 HAI titers in both the mRNA-1010 and the active comparator vaccine groups). Dashed red and blue curves along with the shades represent the bootstrap pointwise 95% CIs.

Source: Figure 5d of the CoP Report Version 2, submitted to STN 125869/0.

Table 15 summarizes the CoR analysis results across subgroups defined by age group, prior influenza vaccination status, region, high-risk status, and sex within each vaccine group. Findings were generally consistent in direction across all evaluated subgroups in both vaccine groups, with the exception of the active comparator in the Rest of the World, where the estimated HR corresponding to the A/H3N2 HAI titer was 0.95 (95% CI: 0.72, 1.26), which was not statistically significant.

Table 15: Subgroup CoR Analysis for A/H3N2

Subgroup	mRNA-1010 HR (95% CI)	SD Comparator HR (95% CI)
Overall — All Vaccinees	0.63 (0.53, 0.75)	0.67 (0.57, 0.79)
Age Group	-	-
50 to <65 Years	0.62 (0.50, 0.78)	0.71 (0.56, 0.90)
≥65 Years	0.64 (0.50, 0.83)	0.60 (0.48, 0.75)
Prior Influenza Vaccination Status	-	-
Received	0.75 (0.60, 0.93)	0.65 (0.53, 0.79)
Not Received	0.53 (0.41, 0.68)	0.70 (0.54, 0.91)
Region	-	-
North America	0.62 (0.51, 0.75)	0.55 (0.45, 0.66)
Rest of World	0.65 (0.47, 0.90)	0.95 (0.72, 1.26)
High-Risk Status	-	-

Subgroup	mRNA-1010 HR (95% CI)	SD Comparator HR (95% CI)
High-Risk (≥ 1 Risk Factor)	0.67 (0.54, 0.83)	0.58 (0.45, 0.74)
Not High Risk	0.56 (0.42, 0.74)	0.77 (0.62, 0.96)
Sex	-	-
Female	0.63 (0.49, 0.79)	0.60 (0.48, 0.76)
Male	0.64 (0.50, 0.81)	0.76 (0.60, 0.96)

Source: Figure S6 of the CoP report Version 2 submitted to STN 125869/0 and calculated by the reviewer.

Reviewer's Comment: these results were similar across age groups (50-64 years and ≥ 65 years).

CoR Analysis Results for B/Victoria

Similar methods were applied for B/Victoria ILI. The results of Models 1 to 3 are summarized in Table 16. In Model 2, the estimated HR for the B/Victoria HAI titer was 0.93 (95% CI: 0.72, 1.21) and the HR for the vaccine group was 0.74 (95% CI: 0.43, 1.28), neither of which was statistically significant. Interaction between the Day 29 B/Victoria HAI titer and vaccine group in Model 3 was also not statistically significant (HR: 0.99 [95% CI: 0.59, 1.67]; $p = 0.992$). Similarly, no statistically significant correlation was observed between B/Victoria HAI titer and disease risk within either vaccine group.

Notably, given that the point estimate of the HR for the Day 29 B/Victoria HAI titer in Model 2 was close to 1, the lack of statistical significance may not be solely attributable to the limited number of B/Victoria-ILI cases ($n = 59$) available for the analysis.

The applicant stated that 46 (approximately 78%) of the cases for B/Victoria were from Bulgaria, a country that contributed only 9.4% of the overall study population. The applicant further stated that more than 80% of the participants enrolled in Bulgaria did not receive influenza vaccination in the prior season, which was substantially higher compared to most other participating countries.

To further assess the lack of statistically significant correlation, the applicant conducted a post-hoc subgroup analysis (Table 16) evaluating the B/Victoria HAI titer via Models 1 and 2 by Bulgaria and non-Bulgaria regions. In Bulgaria, the estimated HR for the Day 29 B/Victoria HAI titer in Model 2 was 0.96 (95% CI: 0.70, 1.30; $p = 0.774$), indicating no statistically significant association between the B/Victoria HAI titer and B/Victoria-ILI risk. In non-Bulgaria regions, there were only 13 B/Victoria-ILI cases available for the analysis (5 in the mRNA-1010 group and 8 in the active comparator group), and the estimated HR for the Day 29 B/Victoria HAI titer was 0.62 (95% CI: 0.37, 1.02; $p = 0.060$), which approached but did not reach statistical significance at the two-sided $\alpha = 0.05$ level. While a numerical attenuation of the vaccine group HR was observed upon conditioning on the Day 29 B/Victoria HAI titer in non-Bulgaria regions, the limited number of cases in this subgroup precludes any meaningful conclusion in the non-Bulgaria population.

Table 16: Cox PH Model Summary for B/Victoria

Model	Vaccine Group HR (95% CI)	Day 29 HAI titer HR (95% CI)	Vaccine Group x Day 29 HAI titer (95% CI)
Model 1 (Overall)	0.72 (0.42, 1.24)	-	-
Model 2 (Overall)	0.74 (0.43, 1.28)	0.93 (0.72, 1.21)	-
Model 3 (Overall)	0.74 (0.43, 1.28)	0.93 (0.66, 1.31)	0.99 (0.59, 1.67)
Model 1 (Non-Bulgaria)	0.60 (0.19, 1.89)	-	-
Model 2 (Non-Bulgaria)	0.79 (0.24, 2.58)	0.62 (0.37, 1.02)	-
Model 1 (Bulgaria)	0.79 (0.40, 1.57)	-	-
Model 2 (Bulgaria)	0.80 (0.40, 1.58)	0.96 (0.70, 1.30)	-

Source: Figure 9 of the CoP Report Version 2 submitted to STN 125869/0 and calculated by the reviewer.

Subgroup analyses by age group, prior influenza vaccination status, region, high-risk status, and sex within each vaccine group are summarized in Table 17. Similar to the overall analysis, there was no statistically significant inverse relationship between B/Victoria HAI titer and B/Victoria-ILI risk in any of the subgroups.

Table 17: Subgroup CoR Analysis for B/Victoria

Subgroup	mRNA-1010 HR (95% CI)	Active Comparator HR (95% CI)
All vaccinees	0.98 (0.65, 1.47)	1.16 (0.84, 1.62)
Age group	-	-
50 to <65 Years	1.00 (0.62, 1.61)	1.19 (0.71, 2.01)
≥ 65 Years	0.95 (0.47, 1.92)	1.13 (0.78, 1.66)
Vaccination in Previous Influenza Season	-	-
Received	0.84 (0.30, 2.32)	0.81 (0.44, 1.48)
Not Received	0.96 (0.63, 1.46)	1.15 (0.78, 1.68)
Region	-	-
North America	1.29 (1.22, 1.38)	0.66 (0.31, 1.45)
Rest of World	0.94 (0.61, 1.45)	1.14 (0.78, 1.66)
High Risk	-	-
≥1 High Risk	0.73 (0.34, 1.54)	0.95 (0.62, 1.46)
No High Risk	1.19 (0.77, 1.83)	1.38 (0.86, 2.19)
Sex	-	-
Female	1.12 (0.65, 1.93)	1.56 (1.02, 2.39)
Male	0.80 (0.44, 1.43)	0.85 (0.53, 1.36)

Source: Summarized by the reviewer based on information submitted to STN 125869/0.24.

Reviewer's Comments:

- These results were similar across age groups (50-64 years and ≥ 65 years).
- Similar conclusions were obtained for other case definitions (modified-CDC-defined ILI, CDC-defined ILI, WHO-defined ILI).
- The applicant previously performed a similar analysis to evaluate HAI as a CoR in the mRNA-1010-P301 (P301) study. The corresponding report was reviewed under STN 125836/0. In the P301 analysis, all three strain-specific HAI titers were

correlated with ILI risk, in contrast to the P304 analysis where HAI titer was not correlated with risk for B/Victoria. An information request (IR #23) was sent to the applicant to comment on this issue.

In response (IR #23), the applicant performed a pooled analysis by combining data from P301 and P304 to evaluate association between HAI titer and disease outcome for B/Victoria. While a statistically significant association was observed for B/Victoria, these analyses had notable shortcomings: 1) the B/Victoria formulation included in the vaccines were different between the two studies. Therefore, combining the results from these two studies may not be meaningful; 2) the results are primarily driven by the P301 study, which did not evaluate the formulation intended to be licensed under STN 125869.

Based on the totality of the data, the utility of the HAI titer as a CoR for B/Victoria in the context of STN 125869 remains uncertain.

- *The following considerations should be made when interpreting the CoR analysis results for all strains:*
 - a. *As HAI titers were not randomized, the potential impact of residual confounding on the observed disease-titer relationships, particularly by unmeasured factors, and the degree to which the HAI titers alone mediate protection is unknown.*
 - b. *Conclusions are based on data from a single study (P304) in a single season. As such, applicability of the findings to other age groups, influenza vaccines and formulations, influenza strains, and endpoint definitions have not been evaluated.*
 - c. *Analyses were data-driven and did not intend to adjust for multiple testing.*
 - d. *The Cox proportional hazards models assume that the log-hazard of disease is a monotone, linear function of the log-HAI titers, which may not be an exact representation of the true disease-titer relationship.*
 - e. *Lack of evidence indicating statistically significant interaction between vaccine group and HAI titers should not be interpreted as evidence demonstrating equivalence of disease-titer relationships between vaccines.*
 - f. *The biological mechanism of protection via the HAI titer should be considered in tandem with the CoR analysis findings, which I defer to the clinical and assay reviewers.*

6.1.11.3 Subpopulation Analyses

Table 18 summarizes subgroup analysis by past influenza season vaccination status, sex, and SD comparator used (TIV or QIV). The rVE point estimates were similar across these subgroups. In addition, no notable differences in rVE were observed across these subgroups within each age group.

Table 18: Relative Vaccine Efficacy of mRNA-1010 Against RT-PCR-Confirmed Protocol-Defined ILI by Subgroup (PP Set)

-	mRNA-1010 n/N (%)	SD Comparator n/N (%)	rVE (95% CI)
Influenza Vaccination in the Previous Influenza Season	-	-	-
Received	238/9,456 (2.5)	316/9,421 (3.4)	25.2 (11.5, 36.8)
Not Received	173/10,723 (1.6)	241/10,703 (2.3)	28.6 (13.2, 41.3)
Sex	-	-	-
Male	183/8,775 (2.1)	226/8,619 (2.6)	20.9 (3.9, 34.9)
Female	228/11,404 (2.0)	331/11,505 (2.9)	30.7 (17.9, 41.4)
Active Comparator Type	-	-	-
Countries using TIV comparator	253/14,176 (1.8)	353/14,162 (2.5)	28.5 (16.0, 39.2)
Countries using QIV comparator	158/6,003 (2.6)	204/5,962 (3.4)	23.0 (6.0, 37.9)

n: number of cases; *N*: number of participants in the PP Set.

Source: Table 14.2.1.1.4.1 of mRNA-1010-P304 CSR.

6.1.12 Safety Analyses

Solicited Local Adverse Reactions

Frequencies of solicited local adverse reactions by age and vaccine group are summarized in Table 19. The most frequently reported local reaction after study vaccination was pain at the injection site among both participants 50 to 64 years of age (68.7% and 34.4% of mRNA-1010 and SD comparator recipients, respectively) and participants ≥ 65 years of age (62.9% and 25.2% of mRNA-1010 and SD comparator recipients, respectively). In general, rates of solicited local adverse reactions were higher in the mRNA-1010 group compared to the SD comparator for each reaction. The same trend was observed for Grade 3 local reactions. The median onset of solicited local adverse reactions was 2 days in both vaccine groups. The median duration of reaction was 2 days in the mRNA-1010 group and 1 day in the SD comparator group.

Table 19: Solicited Local Adverse Reactions Within 7 Days After Injection by Maximum Toxicity Grade (Solicited Safety Set)

Event	50-64 Years mRNA-1010 N=1510 n (%)	50-64 Years SD Comparator N=1502 n (%)	≥ 65 Years mRNA-1010 N=1505 n (%)	≥ 65 Years SD Comparator N=1495 n (%)
Any local adverse reaction	-	-	-	-
Any	1057 (70.0%)	545 (36.3%)	977 (64.9%)	416 (27.8%)
Grade 3	28 (1.9%)	2 (0.1%)	23 (1.5%)	2 (0.1%)
Pain	-	-	-	-
Any	1038 (68.7%)	517 (34.4%)	947 (62.9%)	377 (25.2%)
Grade 3	17 (1.1%)	1 (<0.1%)	10 (0.7%)	0
Erythema	-	-	-	-
Any (≥ 25 mm)	66 (4.4%)	19 (1.3%)	51 (3.4%)	19 (1.3%)
Grade 3	4 (0.3%)	1 (<0.1%)	6 (0.4%)	1 (<0.1%)

Event	50-64 Years mRNA-1010 N=1510 n (%)	50-64 Years SD Comparator N=1502 n (%)	≥65 Years mRNA-1010 N=1505 n (%)	≥65 Years SD Comparator N=1495 n (%)
Swelling	--	--	--	--
Any (≥25 mm)	96 (6.4%)	18 (1.2%)	76 (5.0%)	27 (1.8%)
Grade 3	4 (0.3%)	2 (0.1%)	5 (0.3%)	2 (0.1%)
Axillary swelling or tenderness	-	-	-	-
Any	306 (20.3%)	104 (6.9%)	214 (14.2%)	80 (5.4%)
Grade 3	4 (0.3%)	1 (<0.1%)	6 (0.4%)	0

n = Number of participants experiencing reaction; N=Number of participants contributing data.

Source: Adapted from mRNA-1010-P304 CSR, 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, submitted to STN 125869/0.16.

Solicited Systemic Adverse Reactions

As shown in Table 20, the most frequently reported systemic adverse reaction was fatigue, reported by 48.1% and 20.6% of mRNA-1010 and SD comparator recipients 50 to 64 years of age and 42.1% and 20.1% of mRNA-1010 and SD comparator recipients ≥ 65 years of age, respectively. Across all systemic adverse reactions, proportions of mRNA-1010 recipients reporting reactions were at least two fold higher compared to SD comparator recipients. Similar trends were observed for Grade 3 solicited systemic adverse reactions. The median onset of systemic adverse reactions were 2 days in both groups and the median duration of these reactions were also 2 days in both groups.

Table 20: Solicited Systemic Adverse Reactions Within 7 Days After Injection by Maximum Toxicity Grade (Solicited Safety Set)

Event	50-64 Years mRNA-1010 N=1510 n (%)	50-64 Years SD Comparator N=1502 n (%)	≥65 Years mRNA-1010 N=1505 n (%)	≥65 Years SD Comparator N=1495 n (%)
Any systemic adverse reaction	-	-	-	-
Any	927 (61.4%)	506 (33.7%)	823 (54.7%)	464 (31.0%)
Grade 3	98 (6.5%)	16 (1.1%)	69 (4.6%)	11 (0.7%)
Fever*	-	-	-	-
Any	90 (6.0%)	13 (0.9%)	84 (5.6%)	13 (0.9%)
Grade 3	11 (0.7%)	2 (0.1%)	6 (0.4%)	1 (<0.1%)
Headache	-	-	-	-
Any	633 (41.9%)	302 (20.1%)	507 (33.7%)	236 (15.8%)
Grade 3	33 (2.2%)	6 (0.4%)	26 (1.7%)	4 (0.3%)
Fatigue	-	-	-	-
Any	727 (48.1%)	309 (20.6%)	633 (42.1%)	300 (20.1%)
Grade 3	59 (3.9%)	9 (0.6%)	38 (2.5%)	4 (0.3%)
Myalgia	-	-	-	-
Any	613 (40.6%)	196 (13.0%)	454 (30.2%)	152 (10.2%)

Event	50-64 Years mRNA-1010 N=1510 n (%)	50-64 Years SD Comparator N=1502 n (%)	≥65 Years mRNA-1010 N=1505 n (%)	≥65 Years SD Comparator N=1495 n (%)
Grade 3	44 (2.9%)	4 (0.3%)	32 (2.1%)	3 (0.2%)
Arthralgia	-	-	-	-
Any	476 (31.5%)	167 (11.1%)	363 (24.1%)	150 (10.0%)
Grade 3	34 (2.3%)	3 (0.2%)	23 (1.5%)	3 (0.2%)
Nausea/vomiting	-	-	-	-
Any	147 (9.7%)	61 (4.1%)	112 (7.4%)	41 (2.7%)
Grade 3	3 (0.2%)	1 (<0.1%)	2 (0.1%)	1 (<0.1%)
Chills	-	-	-	-
Any	415 (27.5%)	71 (4.7%)	273 (18.1%)	58 (3.9%)
Grade 3	42 (2.8%)	3 (0.2%)	20 (1.3%)	1 (<0.1%)

n = Number of participants experiencing reaction, N=Number of participants contributing data.

*The number of participants reporting temperature in the eDiary were 1505, 1501, 1496, and 1491 among mRNA-1010 50-64 year-old recipients, SD comparator 50-64 year-old recipients, mRNA-1010 ≥ 65 year-old recipients, and SD comparator ≥ 65 year-old recipients, respectively.

Source: Adapted from mRNA-1010-P304 CSR, 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, submitted to STN 125869/0.16.

Unsolicited Adverse Events

Rates of unsolicited AEs, including SAEs, MAAEs, and deaths, within 28 days post vaccination (Table 21) were similar across vaccine groups (5.9% in mRNA-1010 group and 5.7% in SD comparator group). Rates of unsolicited AEs up to day 28 post vaccination considered related to study vaccination per investigator were higher in the mRNA-1010 group (0.5%) compared to the SD comparator (0.2%). Of note, 2 mRNA-1010 recipients experienced SAEs related to the study vaccination compared to 1 SD comparator recipient. There were no deaths within 28 days of vaccination that were considered related to study vaccination per investigator.

Table 21: Unsolicited Adverse Events up to 28 Days Post Vaccination (Safety Set)

-	mRNA-1010 (N=20,350)	SD Comparator (N=20,353)
Unsolicited AEs up to 28 days after injection	-	-
All	1,204 (5.9)	1,167 (5.7)
Serious	92 (0.5)	92 (0.5)
Fatal	7 (<0.1)	9 (<0.1)
Medically attended	775 (3.8)	782 (3.8)
Leading to study discontinuation	1 (<0.1)	0
Severe/≥ Grade 3	75 (0.4)	77 (0.4)
AESI per Investigator assessment	4 (<0.1)	3 (<0.1)
Related to Study Vaccination	-	-
All	98 (0.5)	49 (0.2)
Serious	2 (<0.1)	1 (<0.1)
Fatal	0	0

-	mRNA-1010 (N=20,350)	SD Comparator (N=20,353)
Medically attended	18 (<0.1)	12 (<0.1)
Leading to study discontinuation	0	0
Severe/≥ Grade 3	1 (<0.1)	1 (<0.1)
AESI per Investigator assessment	0	1 (<0.1)

Source: Table 24 of P304 CSR submitted to STN 125869/0.

Rates of unsolicited AEs throughout the study meeting criteria for continued collection beyond Day 28 are presented in Table 22. There was a total of 40 (0.2%) deaths in the mRNA-1010 group and 34 (0.2%) deaths in the SD comparator group, none of which was assessed as related to study vaccination per investigator. Per investigator assessment, 4 (<0.1%) mRNA-1010 and 2 (<0.1%) SD comparator recipients reported SAEs related to study vaccination, and 3 (<0.1%) mRNA-1010 and 2 (<0.1%) SD comparator recipients reported AESIs related to study vaccination, respectively.

Table 22: Unsolicited Adverse Events Throughout the Study (Safety Set)

-	mRNA-1010 (N=20,350)	SD Comparator (N=20,353)
Unsolicited AEs throughout the study	-	-
Serious	455 (2.2)	392 (1.9)
Fatal	40 (0.2)	34 (0.2)
Medically attended	2,509 (12.3)	2,439 (12.0)
Leading to study discontinuation	3 (<0.1)	1 (<0.1)
AESI per Investigator assessment	17 (<0.1)	15 (<0.1)
Related to Study Vaccination	-	-
Serious	4 (<0.1)	2 (<0.1)
Fatal	0	0
Medically attended	23 (0.1)	14 (<0.1)
Leading to study discontinuation	0	0
AESI per investigator assessment	3 (<0.1)	2 (<0.1)

Source: Table 25 of P304 CSR submitted to STN 125869/0.

6.2 Study mRNA-1010-P303 Part C

Study P303 was a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 in adults 18 years and older. This study had three parts: Parts A, B, and C. All three parts evaluated the QIV formulation of mRNA-1010.

Part A compared mRNA-1010 to Fluarix Quadrivalent in adults ≥18 years old, Part B compared mRNA-1010 to Fluarix in adults ≥18 to 64 years old, and Part C compared mRNA-1010 to a licensed high dose (HD) seasonal influenza vaccine, Fluzone HD QIV, in adults ≥65 years old. Of note, the HD licensed comparator is one of three influenza vaccines that is preferentially recommended by the Centers for Disease Control and Prevention (CDC) for adults aged ≥65 years.

This review focuses on data from P303 Part C to support accelerated approval of mRNA-1010 in adults ≥ 65 years of age.

6.2.1 Objectives

Primary Immunogenicity Objectives

- To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD QIV) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults ≥ 65 years old.

Primary Safety Objectives

- To evaluate the safety, including reactogenicity, of mRNA-1010.

Secondary Objectives

- To evaluate the humoral immunogenicity of mRNA-1010 (for superiority) relative to a licensed HD seasonal influenza vaccine (Fluzone HD QIV) against vaccine-matched influenza A and B strains at Day 29.
- To further evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29.

6.2.2 Design Overview

Approximately 3,000 medically stable adults ≥ 65 years of age were to be randomized 1:1 to receive a single dose of mRNA-1010 or Fluzone HD QIV at Day 1. Randomization was stratified by previous influenza season vaccination status (received or not received; if received, was it from prior participation in the mRNA-1010-P302 study).

Blood samples for immunogenicity assessments were obtained from participants on Days 1, 29, and 181/EOS (in a subset of approximately 1,000 participants). Solicited ARs were collected from Day 1 to Day 8 via eDiary, unsolicited AEs were collected from Day 1 to Day 29, and collection of SAEs, MAAEs, AESIs, and AEs leading to discontinuation from study participation continued through EOS/Day 181.

6.2.3 Population

P303 Part C enrolled medically stable adults ≥ 65 years of age at the time of consent; female participants were eligible if they were postmenopausal or a person of nonchildbearing potential.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The mRNA-1010 vaccine contained four mRNAs in an equivalent mRNA mass ratio encoding four different influenza strains recommended by the World Health Organization (WHO) for 2023-2024 northern hemisphere (NH) cell- or recombinant-based vaccines,

administered as a single 0.5 mL intramuscular (IM) injection at an mRNA total dose level of 50 µg.

The Fluzone HD licensed QIV comparator is a quadrivalent inactivated influenza vaccine that contains the hemagglutinins from the strains recommended by the WHO for 2023-2024 NH egg-based vaccines, administered as a single 0.7 mL IM injection.

6.2.6 Sites and Centers

P303 Part C was conducted at 96 centers in the U.S.

6.2.7 Surveillance/Monitoring

Please refer to the clinical reviewer's memo.

6.2.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

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

Primary Safety Endpoints

- Frequency and severity of solicited local and systemic ARs during a 7-day follow-up period postinjection.
- Frequency and severity of any unsolicited AEs during the 28-day follow-up period postinjection.
- Frequency of any SAEs, MAAEs, AESIs, and AEs leading to discontinuation from Day 1 to Day 181/EOS.

Secondary Endpoints

- GMT at Day 29 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
- Proportion of participants with HAI titer $\geq 1:40$ at Day 29.
- GMFR comparing Day 29 to Day 1 as measured by HAI.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets

The analysis sets considered for P303 Part C analyses are summarized in Table 23.

Table 23: Summary of Analysis Sets for P303 Part C

Population	Description
Randomization Set	All participants who were randomly assigned, analyzed according to the group to which they were randomized.
Full Analysis Set (FAS)	All participants in Randomization Set who received any study vaccination, analyzed according to the group to which they were randomized.
Immunogenicity Set	All participants in the FAS who had Day 1 and Day 29 antibody assessment via HAI assay, analyzed according to the group to which they were randomized.
PP Immunogenicity Set	All participants in the Immunogenicity Set who received the planned dose of study intervention, complied with the immunogenicity testing schedule for Day 1 and Day 29, and had no significant protocol deviations that impact key or critical data. The PP Immunogenicity Set was used for all analyses of immunogenicity unless otherwise specified. Participants were analyzed according to the group to which they were randomized.
Solicited Safety Set	All participants in the FAS who contributed any solicited AR data, analyzed according to the study intervention received. The Solicited Safety Set was used for the analyses of solicited ARs.
Safety Set	All participants in the FAS, analyzed according to the study intervention received. The Safety Set was used for all analyses of safety except for solicited ARs.

Source: Summarized by the reviewer from the P303 C Statistical Analysis Plan (SAP) submitted to STN 125869/0.

Analysis of Immunogenicity and Safety

Analysis methods were similar to those performed for Study P304.

Statistical Hypothesis

The primary objective of P303 Part C was to demonstrate noninferiority of the immune response to mRNA-1010 QIV compared to Fluzone HD QIV, as measured by GMT and seroconversion rate at Day 29 using the HAI assay, for all four vaccine-matched influenza virus A and B strains.

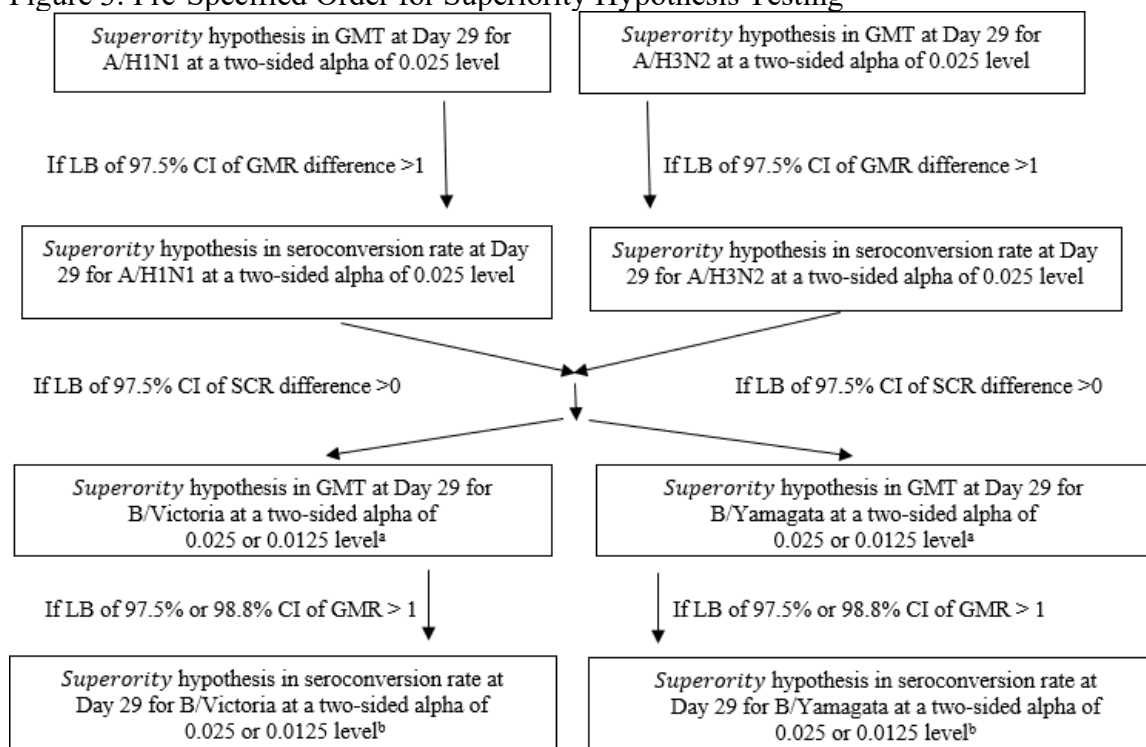
For each of the four vaccine-matched strains, the noninferiority hypothesis in terms of the GMT was $H_0^1: \text{GMR} \leq 0.667$ vs. $H_0^1: \text{GMR} > 0.667$, where the GMR was the ratio of the Day 29 GMTs in the mRNA-1010 group compared with the Fluzone HD QIV group. Superiority was additionally assessed with a margin of 1.

For each of the four vaccine-matched strains, the noninferiority hypothesis in terms of the SCR was $H_0^2: \text{SCR difference} \leq -10\%$ vs. $H_0^2: \text{SCR difference} > -10\%$, where the SCR difference was the difference in the SCR between the mRNA-1010 QIV group and the Fluzone HD QIV group. Superiority was additionally assessed with a margin of 0%.

Multiplicity Adjustment

Noninferiority was demonstrated if all eight noninferiority hypotheses for the GMT and SCR were rejected at a one-sided alpha of 0.025. Upon successful demonstration of noninferiority, the superiority hypotheses specified in Figure 3 were to be tested following the prespecified order.

Figure 3: Pre-Specified Order for Superiority Hypothesis Testing



^a.If both hypotheses at the previous step were successful, the hypothesis at the current step would be tested at a two-sided alpha of 0.025; if only one hypothesis at the previous step was successful, the current hypothesis would be tested at a two-sided alpha of 0.0125.

^b.The hypothesis would be tested at the same alpha level from the previous step (if success achieved at previous steps).

Source: Figure 1 of P303 Part C SAP.

Sample Size

A sample size of 3,000 randomized participants was expected to yield $\geq 99\%$ power to demonstrate NI of GMTs and $\geq 93\%$ power to demonstrate NI of SCRs for all four strains, assuming: 1) one-sided alpha of 0.025; 2) 15% non-evaluable rate; 3) GMR (mRNA-1010 vs. Fluzone HD QIV) of 0.90 for each strain; 4) standard deviation of 1.5 for the natural log-transformed titers; 5) SCRs of 58% for influenza A strains and 48% for influenza B strains in the mRNA-1010 group; and 6) SCRs of 60% for influenza A strains and 50% for influenza B strains in the Fluzone HD QIV group.

6.2.10 Study Population and Disposition

A total of 3,003 participants ≥ 65 years of age in the U.S. were enrolled and randomized to receive mRNA-1010 (n=1,507) or Fluzone HD QIV (n=1,496). Demographic and baseline characteristics in the Safety Set are summarized in Table 24. Baseline characteristics were balanced across arms and were similar in the PPIS.

Table 24: Baseline Demographics and Characteristics (Safety Set)

-	mRNA-1010 (N=1502)	Fluzone HD (N=1490)	Total (N=2993) ^a
Age (years)	-	-	-
n	1502	1490	2993
Mean (sd)	71.1 (4.92)	71.0 (4.95)	71.0 (4.93)
Median	70.0	70.0	70.0
Min, Max	65, 93	64, 93	64, 93
Age Group, n (%)	-	-	-
50 to <65 years	0	1 (<0.1)	1 (<0.1)
65 to <75 years	1176 (78.3)	1154 (77.4)	2331 (77.9)
75 years	326 (21.7)	335 (22.5)	661 (22.1)
Sex, n (%)	-	-	-
Male	624 (41.5)	638 (42.8)	1263 (42.2)
Female	878 (58.5)	852 (57.2)	1730 (57.8)
Race, n (%)	-	-	-
White	1255 (83.6)	1220 (81.9)	2476 (82.7)
Black or African American	224 (14.9)	235 (15.8)	459 (15.3)
Asian	10 (0.7)	10 (0.7)	20 (0.7)
American Indian or Alaska Native	4 (0.3)	9 (0.6)	13 (0.4)
Native Hawaiian or Other Pacific Islander	2 (0.1)	0	2 (<0.1)
Multiple	2 (0.1)	6 (0.4)	8 (0.3)
Other	1 (<0.1)	4 (0.3)	5 (0.2)
Not Reported	3 (0.2)	2 (0.1)	5 (0.2)
Unknown	1 (<0.1)	4 (0.3)	5 (0.2)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	450 (30.0)	454 (30.5)	904 (30.2)
Not Hispanic or Latino	1037 (69.0)	1021 (68.5)	2059 (68.8)
Not Reported	14 (0.9)	14 (0.9)	28 (0.9)
Unknown	1 (<0.1)	1 (<0.1)	2 (<0.1)
Weight (kg)	-	-	-
n	1502	1490	2993
Mean (standard deviation)	82.96 (19.74)	83.32 (19.03)	83.13 (19.39)
Median	80.15	81.55	80.90
Min, Max	25.6, 197.7	20.1, 170.3	20.1, 197.7
Height (cm)	-	-	-
n	1502	1490	2993
Mean (standard deviation)	166.64 (9.97)	167.00 (10.39)	166.82 (10.18)
Median	165.80	165.75	165.80
Min, Max	140.0, 196.0	122.5, 200.7	122.5, 200.7
Body mass index (kg/m ²)	-	-	-

-	mRNA-1010 (N=1502)	Fluzone HD (N=1490)	Total (N=2993) ^a
n	1502	1490	2993
Mean (standard deviation)	29.81 (6.31)	29.82 (6.03)	29.81 (6.17)
Median	28.90	28.90	28.90
Min, Max	10.3, 61.9	7.6, 58.2	7.6, 61.9
Influenza vaccination status, n (%) ^b	-	-	-
Not received seasonal Influenza vaccine	715 (47.6)	703 (47.2)	1418 (47.4)

Abbreviations: BMI = body mass index; HD = high dose; Max = maximum; Min = minimum; QIV = quadrivalent influenza vaccine. BMI = (body weight in kilograms)/(height in meters)². Baseline values for height, weight, and BMI were defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the study injection. Numbers were based on the actual group, and percentages were based on the number of participants in the Safety Set.

^a One participant in Part C was randomized into the injection group of 'Fluzone HD Quadrivalent 240 µg' but actually received 'Fluarix Quadrivalent 60 µg'. This participant is only included in the Total column.

^b Influenza vaccination status considered since previous influenza season (Sep 2022) and up to 6 months before screening per electronic case report form.

Source: Table 13 of P303 Part C CSR submitted to STN 125869/0.

The number of participants included in each analysis set is provided in Table 25. Non-evaluable rates were generally similar across the vaccine arms.

Table 25: Number of Participants in Analysis Sets

-	mRNA-1010 n (%)	Fluzone HD n (%)	Total n (%)
Randomization set	1507 (100)	1496 (100)	3003 (100)
Full analysis set	1504 (99.8)	1492 (99.7)	2996 (99.8)
Safety set	1502 (99.7)	1490 (99.6)	2993 (99.7)
Solicited safety set	1502 (99.7)	1490 (99.6)	2993 (99.7)
Immunogenicity set, n	1458 (96.7)	1437 (96.1)	2895 (96.4)
PP Immunogenicity set	1425 (94.6)	1409 (94.2)	2834 (94.4)

Source: Table 11 of P303 Part C CSR submitted to STN 125869/0.

6.2.11 Immunogenicity Analyses

Primary Endpoints

The primary immunogenicity endpoints are summarized in Tables 26 and 27 for the PPIS. Noninferiority criteria were met for all eight comparisons, with the lower bound of the 95% CI exceeding 0.667 for the GMR and -10% for the SCR difference for all four strains.

Table 26: Summary of Immunogenicity Results (PPIS)

Endpoint	mRNA-1010 (N=1425)	Fluzone HD (N=1409)
Influenza A H1N1 Wisconsin/67/2022	-	-
Baseline (Day 1)	-	-
GMT	50.08	50.00
95% CI	(47.68, 52.60)	(47.44, 52.70)
Day 29	-	-

Endpoint	mRNA-1010 (N=1425)	Fluzone HD (N=1409)
GMT	174.81	130.09
95% CI	(165.15, 185.04)	(122.86, 137.74)
Seroconversion, n (%)	708 (49.7)	511 (36.3)
95% CI	(47.06, 52.31)	(33.75, 38.84)
Influenza A H3N2 A/Darwin/6/2021	-	-
Baseline (Day 1)	-	-
GMT	34.35	34.17
95% CI	(32.59, 36.22)	(32.33, 36.10)
Day 29	-	-
GMT	141.62	116.24
95% CI	(133.29, 150.46)	(109.47, 123.44)
Seroconversion, n (%)	804 (56.4)	674 (47.8)
95% CI	(53.80, 59.02)	(45.20, 50.48)
Influenza B/Victoria-lineage	-	-
Baseline (Day 1)	-	-
GMT	105.50	103.52
95% CI	(101.49, 109.66)	(99.38, 107.82)
Day 29	-	-
GMT	248.03	195.97
95% CI	(237.34, 259.21)	(187.44, 204.89)
Seroconversion, n (%)	425 (29.8)	284 (20.2)
95% CI	(27.46, 32.27)	(18.09, 22.35)
Influenza B/Yamagata-lineage	-	-
Baseline (Day 1)	-	-
GMT	47.55	47.9
95% CI	(45.76, 49.41)	(46.08, 49.80)
Day 29	-	-
GMT	104.82	91.94
95% CI	(100.70, 109.11)	(88.33, 95.71)
Seroconversion, n (%)	371 (26.0)	284 (20.2)
95% CI	(23.77, 28.40)	(18.09, 22.35)

Source: Tables 18 and 19 of P303 Part C CSR submitted to STN 125869/0.

Table 27: Summary of Primary Immunogenicity Analyses (PPIS)

Endpoint	mRNA-1010 vs. Fluzone HD	95% CI	97.5 % CI
Influenza A H1N1 Wisconsin/67/2022	-	-	-
GMR	1.339	(1.254, 1.431)	(1.242, 1.445)
SCR Difference (%)	13.42	(9.79, 17.01)	(9.27, 17.52)
Influenza A H3N2 A/Darwin/6/2021	-	-	-
GMR	1.212	(1.128, 1.303)	(1.116, 1.317)
SCR Difference (%)	8.59	(4.91, 12.24)	(4.38, 12.76)
Influenza B/Victoria-lineage	-	-	-
GMR	1.25	(1.186, 1.318)	(1.177, 1.328)
SCR Difference (%)	9.67	(6.50, 12.83)	(6.04, 13.29)

Endpoint	mRNA-1010 vs. Fluzone HD	95% CI	97.5 % CI
Influenza B/Yamagata-lineage	-	-	-
GMR	1.143	(1.091, 1.198)	(1.083, 1.206)
SCR Difference (%)	5.88	(2.78, 8.97)	(2.33, 9.42)

Source: Table 18 and 14.2.1.1.c of P303 Part C CSR submitted to STN 125869/0.

Secondary Endpoints

GMFRs and percentages of participants with HAI titer $\geq 1:40$ at Day 29 were generally higher in the mRNA-1010 group compared with Fluzone HD QIV for all four strains (Table 28). In addition to meeting noninferiority criteria for both GMTs and SCRs for each strain, superiority criteria were met for both endpoints for all strains (Table 27).

Table 28: Summary of Secondary Immunogenicity endpoints (PPIS)

Endpoint	mRNA-1010 (N=1425)	Fluzone HD (N=1409)
Influenza A H1N1 Wisconsin/67/2022	-	-
GMFR	3.49	2.60
95% CI	(3.32, 3.67)	(2.47, 2.74)
Titer $\geq 1:40$, n (%)	1375 (96.5)	1301 (92.3)
95% CI	(95.40, 97.38)	(90.82, 93.67)
Influenza A H3N2 A/Darwin/6/2021	-	-
GMFR	4.12	3.40
95% CI	(3.90, 4.36)	(3.22, 3.60)
Titer $\geq 1:40$, n (%)	1323 (92.8)	1252 (88.9)
95% CI	(91.38, 94.13)	(87.10, 90.45)
Influenza B/Victoria-lineage	-	-
GMFR	2.35	1.89
95% CI	(2.26, 2.45)	(1.82, 1.97)
Titer $\geq 1:40$, n (%)	1425 (100)	1402 (99.5)
95% CI	(99.74, 100.00)	(98.98, 99.80)
Influenza B/Yamagata-lineage	-	-
GMFR	2.20	1.92
95% CI	(2.13, 2.28)	(1.85, 2.00)
Titer $\geq 1:40$, n (%)	1370 (96.1)	1320 (93.7)
95% CI	(95.01, 97.08)	(92.28, 94.90)

Source: Tables 22 and 23 of P303 Part C CSR submitted to STN 125869/0.

Reviewer's Comment: In the CoR analysis performed for P304, the disease risk associated with A/H1N1 at a given titer appeared lower in the mRNA-1010 group compared to the SD comparator when the titer was greater than 1:80, while the opposite was observed at lower titers. In the PPIS of P303 Part C, the majority (66.1% and 55.1%, respectively) of the participants had A/H1N1 titers above 1:80. Thus, the statistically significant difference in the disease-titer relationship between mRNA-1010 and the comparator vaccine observed in the CoR analysis is not expected to impact the immunogenicity conclusions.

Exploratory Post-Hoc Analyses

The applicant conducted a post-hoc analysis comparing the Day 29 HAI GMTs between the PPIS of Study P303 Part C and PPIS of Study P304, restricted to participants 65 years of age and older, to justify the use of immunogenicity derived from mRNA-1010 QIV in P303 Part C for the licensure of mRNA-1010 TIV. The mRNA-1010 strains were based on WHO recommendations for NH 2023-24 (P303 Part C) and 2024-25 (P304) cell-or recombinant based vaccines.

Day 29 log-transformed HAI titers were analyzed using an ANCOVA model with vaccine (mRNA-1010 QIV in P303 Part C or mRNA-1010 TIV in P304) and log transformed baseline HAI titers as independent variables, adjusted for demographic and baseline characteristics via the first five components of PCA. The model-based GMT and GMR and the corresponding 95% CIs were obtained by back-transforming the least squares means and least squares mean differences and corresponding 95% CIs to the original scale.

The following variables were considered for the PCA: age, race (White; African America; Asian; Others), sex (male; female), ethnicity (Hispanic; Not Hispanic), baseline BMI group ($<30 \text{ kg/m}^2$; $\geq 30 \text{ kg/m}^2$), baseline weight, previous influenza vaccine status (Received vs. Not received), and baseline high-risk factor (defined as having at least one of the following medical conditions: autoimmune/immune-mediated disease, blood disorders, cardiac disorders, diabetes mellitus, hepatic disorders, mental impairment disorders, nervous system disorders, pulmonary disorders, or renal disorders).

The results of the ANCOVA are summarized in Table 29. In this post-hoc analysis, the TIV formulation of mRNA-1010 elicited similar or higher HAI titers at Day 29 for the three strains assessed compared to the QIV formulation.

Table 29: Comparison of Day 29 HAI Titers Between mRNA-1010 QIV (Study P303 Part C) and TIV (Study P304) in Participants ≥ 65 Years of Age (PPIS)

Endpoint	mRNA-1010 TIV P304 (N=586)	mRNA-1010 QIV P303 Part C (N=1425)
A/H1N1	-	-
Baseline	-	-
GMT	36.50 (33.91, 39.29)	50.08 (47.68, 52.60)
Day 29	-	-
GMT	131.02 (119.14, 144.08)	174.81 (165.15, 185.04)
Model-based GMT	159.65(148.31, 171.86)	161.01 (153.66, 168.71)
Model-based GMR	0.992 (0.908, 1.083)	
A/H3N2	-	-
Baseline	-	-
GMT	32.79 (30.30, 35.47)	34.35(32.59, 36.22)
Day 29	-	-
GMT	150.27 (137.20, 164.47)	141.62 (133.29, 150.46)

Endpoint	mRNA-1010 TIV P304 (N=586)	mRNA-1010 QIV P303 Part C (N=1425)
Model-based GMT	158.30 (146.41, 171.16)	138.79 (132.05, 145.86)
Model-based GMR	1.14 (1.039, 1.25)	
B/Victoria	-	-
Baseline	-	-
GMT	80.10 (74.81, 85.78)	105.5 (101.49, 109.66)
Day 29	-	-
GMT	253.79 (235.39, 273.62)	248.03 (237.34, 259.21)
Model-based GMT	290.09 (272.84, 308.43)	234.73 (225.80, 244.02)
Model-based GMR	1.236 (1.148, 1.330)	

Source: Table 1 of Clinical Information Amendment submitted to STN 125869/0.32.

Reviewer's Comment: The clinical review memo will address the adequacy of the mRNA-1010 QIV immunogenicity data to infer effectiveness of mRNA-1010 TIV in adults 65 years of age and older. The above analyses had the following limitations:

- *Studies P303 Part C and P304 were conducted in different influenza seasons using different WHO-recommended strains.*
- *Although this post-hoc analysis adjusted for baseline characteristics, participants were not randomized and thus there may be residual confounding.*

6.2.12 Safety Analyses

Solicited Local Adverse Reactions

Solicited local ARs are summarized in Table 30. The proportions of participants reporting a specific local AR within 7 days post vaccination were higher in the mRNA-1010 group compared to Fluzone HD QIV. Injection site pain was the most frequently reported solicited local AR (64.6% in mRNA-1010 group and 36.7% in Fluzone HD QIV group). The median onset of solicited local adverse reactions was 2 days in the mRNA-1010 group and 1 day in the Fluzone HD group. The median duration of reaction was 2 days in both groups.

Table 30. Summary of Solicited Local Adverse Reactions in ≥ 65 years of age (Solicited Safety Set)

Event	mRNA-1010 (N=1502) n (%)	Fluzone HD QIV (N=1488-89) ^a n (%)
Injection site pain	-	-
Any	971 (64.6)	547 (36.7)
Grade 3	23 (1.5)	6 (0.4)
Erythema (redness)	-	-
Any	42 (2.8)	20 (1.3)
Grade 3	6 (0.4)	3 (0.2)
Swelling (hardness)	-	-
Any	67 (4.5)	25 (1.7)
Grade 3	6 (0.4)	2 (0.1)

Event	mRNA-1010 (N=1502) n (%)	Fluzone HD QIV (N=1488-89) ^a n (%)
Axillary swelling or tenderness	-	-
Any	252 (16.8)	128 (8.6)
Grade 3	8 (0.5)	6 (0.4)

^aN is the number of vaccinated participants with available data for the adverse reactions listed.

Source: Table 14.3.1.2.1.6.c of the P303 Part C CSR submitted to STN 125869/0.108.

Solicited Systemic Adverse Reactions

Solicited systemic ARs are summarized in Table 31. Frequencies of systemic reactions within 7 days post vaccination were higher in the mRNA-1010 group compared to the Fluzone HD QIV group. Fatigue was the most frequently reported systemic AR (44.5% in the mRNA-1010 group and 19.7% in the Fluzone HD QIV group). Two (0.1%) participants in the mRNA-1010 group experienced Grade 4 fever. The median onset of solicited systemic adverse reactions was 2 days and the median duration of reaction was 2 days in both groups.

Table 31. Summary of Solicited Systemic Adverse Reactions in ≥ 65 years of age (Solicited Safety Set)

Event	mRNA-1010 (N=1502) n (%)	Fluzone HD QIV (N=1487-1488) ^a n (%)
Fever	-	-
Any	127 (8.5)	21 (1.4)
Grade 3	9 (0.6)	1 (<0.1)
Grade 4	2 (0.1)	0
Headache	-	-
Any	592 (39.4)	258 (17.3)
Grade 3	35 (2.3)	10 (0.7)
Fatigue	-	-
Any	669 (44.5)	293 (19.7)
Grade 3	52 (3.5)	12 (0.8)
Myalgia	-	-
Any	626 (41.7)	239 (16.1)
Grade 3	48 (3.2)	11 (0.7)
Arthralgia	-	-
Any	529 (35.2)	210 (14.1)
Grade 3	35 (2.3)	11 (0.7)
Nausea/vomiting	-	-
Any	192 (12.8)	63 (4.2)
Grade 3	4 (0.3)	3 (0.2)
Chills	-	-
Any	443 (29.5)	115 (7.7)
Grade 3	18 (1.2)	5 (0.3)

^aN is the number of vaccinated participants with available data for the adverse reactions listed.

Source: Table 14.3.1.2.1.6.c of the P303 Part C CSR submitted to STN 125869/0.108.

Unsolicited Adverse Events

Rates of unsolicited AEs through 28 days post vaccination are summarized in Table 32. The proportions of participants experiencing unsolicited AEs were 10.3% in the mRNA-1010 group compared to 9.2% in the Fluzone HD QIV group. Unsolicited AEs assessed as related to study vaccination per investigator were reported by 8 (0.5%) mRNA-1010 recipients and 3 (0.2%) Fluzone HD QIV recipients. There was one AESI of swelling face in the mRNA-1010 group that was assessed to be related to study vaccination by the investigator. One death due to acute myocardial infarction occurred in an mRNA-1010 recipient, which the investigator did not consider to be related to study vaccination.

Table 32: Unsolicited Adverse Events up to 28 days Post Vaccination (≥ 65 years of age) (Safety Set)

-	mRNA-1010 (N=1502) n (%)	Fluzone HD QIV (N=1489) n (%)
All	155 (10.3)	137 (9.2)
Serious	9 (0.6)	7 (0.5)
Fatal	1 (<0.1)	0
Medically attended	89 (5.9)	84 (5.6)
Leading to study discontinuation	0	0
Severe (Grade 3)	9 (0.6)	5 (0.3)
Non-serious	146 (9.7)	130 (8.7)
Severe (Grade 3)	1 (<0.1)	0
At least one non-serious event	149 (9.9)	135 (9.1)
Severe (Grade 3)	1 (<0.1)	0
AESI per Investigator Assessment	1 (<0.1)	0
Related to study injection	-	-
All	8 (0.5)	3 (0.2)
Serious	0	0
Fatal	0	0
Medically attended	4 (0.3)	0
Leading to study discontinuation	0	0
Severe (Grade 3)	0	0
Non-serious	8 (0.5)	3 (0.2)
Severe (Grade 3)	0	0
At least one non-serious event	8 (0.5)	3 (0.2)
Severe (Grade 3)	0	0
AESI per Investigator Assessment	1 (<0.1)	0

Source: Adapted from Table 32 of P303 Part C CSR submitted to STN 125869/0, and information submitted to STN 125869/0.108.

The summary of unsolicited AEs throughout the study is provided in Table 33. The proportions of participants experiencing SAEs were similar between the mRNA-1010 (2.7%) and Fluzone HD QIV groups (2.6%). Deaths were reported in 3 participants (0.2%) in the mRNA-1010 group vs. 1 participant (<0.1%) in the Fluzone HD QIV group.

Table 33: Unsolicited Adverse Events Throughout the Study (Safety Set)

-	mRNA-1010 (N=1502) n (%)	Fluzone HD QIV (N=1489) n (%)
All	309 (20.6)	290 (19.5)
Serious	41 (2.7)	38 (2.6)
Fatal	3 (0.2)	1 (<0.1)
Medically attended	257 (17.1)	248 (16.6)
Leading to study discontinuation	0	0
AESI per Investigator Assessment	2 (0.1)	1 (<0.1)
Related to study injection		
All	8 (0.5)	4 (0.3)
Serious	0	1 (<0.1)
Fatal	0	0
Medically attended	4 (0.3)	1 (<0.1)
Leading to study discontinuation	0	0
AESI per Investigator Assessment	1 (<0.1)	0

Source: Adapted from Table 36 of P303 Part C CSR submitted to STN 125869/0, and information submitted to STN 125869/0.108.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated overview of efficacy was submitted.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment methods

An ISS for mRNA-1010 was performed by the applicant by pooling safety data from participants ≥ 50 years of age who received any study injection from the following Phase 3 studies: P301, P302, P303 (Parts A, B, and C combined), and P304. Participants were analyzed according to the actual study vaccine received. Analyses were descriptive and focused on SAEs, AESIs, and deaths from each study. Analyses by age group (50-64 years and ≥ 65 years) were additionally performed.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The number of participants contributed by each study is summarized in Table 34. Since P304 was the largest of the four studies, it contributed the majority of the mRNA-1010 (56.58%) and Fluarix (59.06%) recipients. Among the four studies, P303 Part C was the only study that included Fluzone HD as a comparator.

Table 34: Safety Database by Study (ISS Set)

Study	mRNA-1010 n (%)	Fluarix SD n (%)	Fluzone HD n (%)
P301	1,539 (4.28)	1,552 (4.50)	-
P302	11,210 (31.17)	11,200 (32.50)	-
P303	2,866 (7.97)	1,356 (3.93)	1,490 (100)
P304	20,350 (56.58)	20,353 (59.06)	-
Total	35,965 (100)	34,461 (100)	1,490 (100)

Source: ISS Table 14.1.1.1 submitted to STN 125869/0.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Demographic characteristics of the ISS Set are summarized in Table 35. There were no notable differences in demographic characteristics between mRNA-1010 and active comparator recipients. The median (range) age of participants was 64 (50 to 99 years) years in the mRNA-1010 group, 64 (50 to 96 years) years in the Fluarix SD group, and 70 (64 to 93) years in the Fluzone HD group. The higher median age in the Fluzone HD group was due to P303 Part C enrolling only participants ≥ 65 years of age.

Table 35: Demographic and Baseline Characteristics (ISS Set)

Characteristic	mRNA-1010 N=35,965	Fluarix SD N=34,461	Fluzone HD N=1,490
Sex, n (%)	--	--	--
Male	15,630 (43.5)	14,869 (43.1)	638 (42.8)
Female	20,335 (56.5)	19,592 (56.9)	852 (57.2)
Age, years	--	--	--
Mean age (STD)	64.1 (8.34)	63.8 (8.38)	71.0 (4.95)
Median age (min, max)	64.0 (50, 99)	64.0 (50, 96)	70.0 (64, 93)
≥ 50 years	35,965 (100)	34,461 (100)	1,490 (100)
50 to 64 years	18,398 (51.2)	18,396 (53.4)	1 (<0.1)
≥ 65 years	17,567 (48.8)	16,065 (46.6)	1,489 (>99.9)
65 to <75 years	13,469 (37.5)	12,286 (35.7)	1,154 (77.4)
≥ 75 years	4,098 (11.4)	3,779 (11.0)	335 (22.5)
Race, n (%)	--	--	--
African American/Black	5,198 (14.5)	5,078 (14.7)	235 (15.8)
American Indian or Alaska Native	273 (0.8)	280 (0.8)	9 (0.6)
Asian	1,285 (3.6)	1,293 (3.8)	10 (0.7)
Native Hawaiian/other Pacific Islander	42 (0.1)	38 (0.1)	0
White	28,566 (79.4)	27,194 (78.9)	1,220 (81.9)
Other	89 (0.2)	87 (0.3)	4 (0.3)
Multiracial	337 (0.9)	318 (0.9)	6 (0.4)
Unknown	32 (<0.1)	38 (0.1)	4 (0.3)
Not reported	143 (0.4)	135 (0.4)	2 (0.1)
Ethnicity, n (%)	--	--	--
Hispanic/Latino	5,678 (15.8)	5,133 (14.9)	454 (30.5)
Not Hispanic/Latino	29,823 (82.9)	28,879 (83.8)	1,021 (68.5)
Not reported	464 (1.3)	449 (1.3)	15 (1.0)

Characteristic	mRNA-1010 N=35,965	Fluarix SD N=34,461	Fluzone HD N=1,490
Region	--	--	--
North America	26,665 (74.1)	25,148 (73.0)	1,490 (100)
Canada	1,230 (3.4)	1,200 (3.5)	0
United States	25,435 (70.7)	23,948 (69.5)	1,490 (100)
Europe	7,523 (20.9)	7,509 (21.8)	0
Belgium	512 (1.4)	461 (1.3)	0
Bulgaria	2,526 (7.0)	2,585 (7.5)	0
Denmark	7 (<0.1)	10 (<0.1)	0
Estonia	886 (2.5)	924 (2.7)	0
Finland	206 (0.6)	198 (0.6)	0
Georgia	176 (0.5)	178 (0.5)	0
Germany	1,743 (4.8)	1,714 (5.0)	0
Poland	199 (0.6)	194 (0.6)	0
Spain	65 (0.2)	63 (0.2)	0
United Kingdom	1,203 (3.3)	1,182 (3.4)	0
East Asia	238 (0.7)	252 (0.7)	0
South Korea	117 (0.3)	114 (0.3)	0
Taiwan	121 (0.3)	138 (0.4)	0
Rest of the World	1,539 (4.3)	1,552 (4.5)	0
Argentina	662 (1.8)	675 (2.0)	0
Australia	49 (0.1)	48 (0.1)	0
Colombia	298 (0.8)	297 (0.9)	0
Panama	21 (<0.1)	26 (<0.1)	0
Philippines	509 (1.4)	506 (1.5)	0
Body Mass Index (kg/m ²)	--	--	--
Mean (STD)	29.57 (6.42)	29.59 (6.49)	29.82 (6.03)
Median (min, max)	28.6 (10.3, 139.0)	28.0 (8.3, 84.0)	28.9 (7.6, 58.2)
Missing	37 (0.1)	32 (<0.1)	0
<30 kg/m ²	21,321 (59.3)	20,515 (59.5)	845 (56.7)
≥30 kg/m ²	14,607 (40.6)	13,914 (40.4)	645 (43.3)
≥40 kg/m ²	2,446 (6.8)	2,369 (6.9)	99 (6.6)
Influenza vaccine status, n (%)	--	--	--
Received seasonal flu vaccine ^a	15,895 (44.2)	15,036 (43.6)	787 (52.8)
Not received seasonal flu vaccine	20,070 (55.8)	19,425 (56.4)	703 (47.2)

BMI = Body Mass Index; HD = High Dose; ISS = Integrated Summary of Safety; Max = Maximum; Min = Minimum; QIV = Quadrivalent Trivalent Influenza Vaccine; SD = Standard Dose; STD = Standard Deviation; TIV = Trivalent Influenza Vaccine.

Numbers are based on actual vaccination group and percentages are based on the number of participants in the ISS Set. The active comparators consist of Fluarix TIV SD (U.S. and Canada sites in Study P304), Fluarix QIV SD (Studies P301, P302, P303 Parts A and B, and non-U.S./Canada sites in Study P304), and Fluzone QIV HD (Study P303 Part C). The investigational product, mRNA-1010, consists of mRNA-1010 TIV administered in Study P304, and mRNA-1010 QIV administered in Studies P301, P302, and P303.

^a For P303 Parts B and C, received from both P302 and non-P302 are included.

Source: Adapted from ISS Table 14.1.2.1, Table 14.1.2.4, Table 14.1.2.5, and Table 14.1.4.1, , submitted to STN 125869/0.23.

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

There are no additional caveats to be noted for this analysis.

8.4 Safety Results

Table 36 summarizes the rates of SAEs, deaths, and AESIs in the ISS Set by study vaccine. Up to 28 days after injection, the rates of SAEs and deaths regardless of relationship to study vaccination were similar between vaccine groups. The numbers of SAEs, deaths, and AESIs related to study vaccination per investigator assessment were 6 (<0.1%), 1 (<0.1%), and 2 (<0.1%) in the mRNA-1010 group and 1 (<0.1%), 0, and 1 (<0.1%) in the Fluarix SD group. No related SAEs, deaths, or AESIs were reported in the Fluzone HD group.

Throughout the study, similar rates of SAEs, deaths, and AESIs were reported between vaccine groups. The numbers of SAEs, deaths, and AESIs related to study vaccination per investigator assessment were 9 (<0.1%), 1 (<0.1%), and 5 (<0.1%) in the mRNA-1010 group and 2 (<0.1%), 0, and 2 (<0.1%) in the Fluarix SD group. One (<0.1%) Fluzone HD recipient experienced a related SAE.

Table 36. Overall Summary of Unsolicited Adverse Events After Injection (ISS Set)

Event	mRNA-1010 N=35,965 n (%)	Fluarix SD N=34,461 n (%)	Fluzone HD N=1,490 n (%)
Unsolicited AEs up to 28 Days after Injection, Regardless of Relationship to Study Vaccination	--	--	--
Serious	180 (0.5)	156 (0.5)	7 (0.5)
Fatal	13 (<0.1)	14 (<0.1)	0
AESI per Investigator Assessment	7 (<0.1)	4 (<0.1)	0
Unsolicited AEs up to 28 Days after Injection, Related to Study Vaccination	--	--	--
Serious	6 (<0.1)	1 (<0.1)	0
Fatal	1 (<0.1)	0	0
AESI per Investigator Assessment	2 (<0.1)	1 (<0.1)	0
Unsolicited AEs Throughout the Study, Regardless of Relationship to Study Vaccination	--	--	--
Serious	1,129 (3.1)	989 (2.9)	38 (2.6)
Fatal	102 (0.3)	96 (0.3)	1 (<0.1)
AESI per Investigator Assessment	36 (0.1)	36 (0.1)	1 (<0.1)
Unsolicited AEs Throughout the Study, Related to Study Vaccination	--	--	--
Serious	9 (<0.1)	2 (<0.1)	1 (<0.1)
Fatal	1 (<0.1)	0	0
AESI per Investigator Assessment	5 (<0.1)	2 (<0.1)	0

The active comparators consist of Fluarix TIV SD (U.S. and Canada sites in Study P304), Fluarix QIV SD (Studies P301, P302, and P303 Parts A and B, non-U.S./Canada sites in Study P304), and Fluzone QIV HD (Study P303 Part C). The investigational product, mRNA-1010, consists of mRNA-1010 TIV administered in Study P304, and mRNA-1010 QIV administered in Studies P301, P302, and P303.

The summarized adverse event is for any event not present before but occurring after injection or any event already present before then worsening after injection.

Any solicited local or systemic adverse reactions that met the definition of an SAE were considered as AE.

Source: ISS Table 14.3.1.1, submitted to STN 125869/0.16.

Tables 37 and 38 summarize the rates of SAEs, deaths, and AESIs in each age group. The pattern of differences in the rates of SAEs, deaths, and AESIs between vaccine groups in each age group was generally similar to that observed in the overall population.

Table 37. Summary of Unsolicited Adverse Events (ISS Set; 50 to 64 Years)

Event	mRNA-1010 N=18,398 n (%)	Fluarix SD N=18,396 n (%)	Fluzone HD N=1 ^a % (n/N1)
Unsolicited AEs up to 28 Days after Injection, Regardless of Relationship to Study Vaccination	--	--	
Serious	70 (0.4%)	76 (0.4%)	0
Fatal	3 (<0.1%)	6 (<0.1%)	0
AESI per Investigator Assessment	4 (<0.1%)	2 (<0.1%)	0
Unsolicited AEs up to 28 Days after Injection, Related to Study Vaccination	--	--	--
Serious	2 (<0.1%)	0	0
Fatal	0	0	0
AESI per Investigator Assessment	1 (<0.1%)	1 (<0.1%)	0
Unsolicited AEs Throughout the Study, Regardless of Relationship to Study Vaccination	--	--	--
Serious	484 (2.6%)	424 (2.3%)	0
Fatal	33 (0.2%)	34 (0.2%)	0
AESI per Investigator Assessment	17 (<0.1%)	17 (<0.1%)	0
Unsolicited AEs Throughout the Study, Related to Study Vaccination	--	--	--
Serious	5 (<0.1%)	0	0
Fatal	0	0	0
AESI per Investigator Assessment	4 (<0.1%)	1 (<0.1%)	0

The active comparators consist of Fluarix TIV SD (U.S. and Canada sites in Study P304), Fluarix QIV SD (Studies P301, P302, and P303 Parts A and B, non-U.S./Canada sites in Study P304), and Fluzone QIV HD (Study P303 Part C). The investigational product, mRNA-1010, consists of mRNA-1010 TIV administered in Study P304, and mRNA-1010 QIV administered in Studies P301, P302, and P303.

The summarized adverse event is for any event not present before but occurring after injection or any event already present before then worsening after injection.

Any solicited local or systemic adverse reactions that met the definition of an SAE were considered as AE.

^a In Study P303 Part C, 1 participant, 64 years of age, received Fluzone HD during the study, and this was captured as a protocol deviation.

Source: ISS, Table 14.3.1.4, submitted to STN 125869/0.16.

Table 38. Summary of Unsolicited Adverse Events (ISS Set; ≥65 Years)

Event	mRNA-1010 N=17,567 n (%)	Fluarix SD N=16,065 n (%)	Fluzone HD N=1,489 % (n/N1)
Unsolicited AEs up to 28 Days after Injection, Regardless of Relationship to Study Vaccination	--	--	--
Serious	110 (0.6%)	80 (0.5%)	7 (0.5%)

Event	mRNA-1010 N=17,567 n (%)	Fluarix SD N=16,065 n (%)	Fluzone HD N=1,489 % (n/N1)
Fatal	10 (<0.1%)	8 (<0.1%)	0
AESI per Investigator Assessment	3 (<0.1%)	2 (<0.1%)	0
Unsolicited AEs up to 28 Days after Injection, Related to Study Vaccination	--	--	--
Serious	4 (<0.1%)	1 (<0.1%)	0
Fatal	1 (<0.1%)	0	0
AESI per Investigator Assessment	1 (<0.1%)	0	0
Unsolicited AEs Throughout the Study, Regardless of Relationship to Study Vaccination	--	--	--
Serious	645 (3.7%)	565 (3.5%)	38 (2.6%)
Fatal	69 (0.4%)	62 (0.4%)	1 (<0.1%)
AESI per Investigator Assessment	19 (0.1%)	19 (0.1%)	1 (<0.1%)
Unsolicited AEs Throughout the Study, Related to Study Vaccination	--	--	--
Serious	4 (<0.1%)	2 (<0.1%)	1 (<0.1%)
Fatal	1 (<0.1%)	0	0
AESI per Investigator Assessment	1 (<0.1%)	1 (<0.1%)	0

The active comparators consist of Fluarix TIV SD (U.S. and Canada sites in Study P304), Fluarix QIV SD (Studies P301, P302, and P303 Parts A and B, non-U.S./Canada sites in Study P304), and Fluzone QIV HD (Study P303 Part C). The investigational product, mRNA-1010, consists of mRNA-1010 TIV administered in Study P304, and mRNA-1010 QIV administered in Studies P301, P302, and P303.

The summarized adverse event is for any event not present before but occurring after injection or any event already present before then worsening after injection.

Any solicited local or systemic adverse reactions that met the definition of an SAE were considered as AE.

Source: ISS, Table 14.3.1.4, submitted to STN 125869/0.16.

8.5 Additional Safety Evaluations

No additional safety evaluations are considered in this review.

8.6 Safety Conclusions

I defer to the clinical reviewer on the overall safety conclusions from the ISS.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues identified.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The efficacy objectives of P304 were met. The study accumulated 968 cases in the 2024-2025 influenza season resulting in an rVE of 26.6% (95% CI: 16.7%, 35.4%), which met the pre-specified noninferiority (LB of 95% CI > -10%), superiority (LB of 95% CI > 0%), and super-superiority (LB of 95% CI > 9.1%) criteria. The rVE point estimates were

consistent across influenza A and B and across age groups (50-64 years: 26.1% [95% CI: 12.3%, 37.7%]; ≥ 65 years: 27.4% [95% CI: 12.1%, 40%]).

The applicant conducted a correlation of risk (CoR) analysis to evaluate the relationship between strain-specific influenza disease risk and Day 29 HAI titer. Data showed statistically significant negative correlation between Day 29 titer and protocol-defined ILI for A/H1N1 and A/H3N2. No meaningful association between Day 29 titer and disease risk was observed for B/Victoria. Data also suggested that the relationship between the Day 29 titer and disease risk may differ across vaccine groups for A/H1N1. These conclusions were consistent across age groups (50-64 years and ≥ 65 years).

In P303 Part C, the primary and secondary immunogenicity objectives of demonstrating noninferiority and superiority in terms of the Day 29 HAI GMT and SCR were met for all four strains. The GMR comparing mRNA-1010 to HD comparator for A/H1N1, A/H3N2, B/Victoria, and B/Yamagata were, respectively, 1.34 (97.5% CI: 1.24, 1.45), 1.21 (97.5% CI: 1.12, 1.32), 1.25 (97.5% CI: 1.18, 1.33), and 1.14 (97.5% CI: 1.08, 1.21). SCR differences were, respectively, 13.42% (97.5% CI: 9.27%, 17.52%), 8.59% (97.5% CI: 4.38, 12.76), 9.67% (97.5% CI: 6.04%, 13.29%), and 5.88% (97.5% CI: 2.33%, 9.42%).

In both studies and age groups, rates of solicited local and systemic adverse reactions were higher in the mRNA-1010 group compared with the SD or HD comparator. In both age groups, the most frequently reported local reaction after study vaccination was pain at the injection site, and the most frequently reported systemic adverse reaction was fatigue. Among mRNA-1010 recipients, the median onset and median duration of local and systemic adverse reactions were two days.

In both studies, there were no notable differences in rates of unsolicited AEs, SAEs, deaths, MAAEs, and AESIs between mRNA-1010 and SD or HD comparator recipients within 28 days of study vaccination. There were no deaths assessed as related to study vaccination per investigator throughout either study. Similar observations were made in the ISS comprising Studies P301, P302, P303 (all parts), and P304. In the ISS, there was one death due to natural causes in the mRNA-1010 group in Study P303 Part A assessed as related to the study vaccination by the investigator.

10.2 Conclusions and Recommendations

Overall, the data support the efficacy of mRNA-1010 against influenza disease caused by any influenza strain present in the vaccine and by A/H1N1 and A/H3N2 in adults 50-64 years of age. However, due to the smaller number of cases accrued for B/Victoria and the lack of meaningful association between B/Victoria-specific Day 29 HAI titer and disease risk, the efficacy of mRNA-1010 against B/Victoria remains uncertain in this age group. Similarly, the immunogenicity data, together with the CoR analysis results, support the effectiveness of mRNA-1010 against A/H1N1 and A/H3N2 among adults ≥ 65 years of age; however, effectiveness against B/Victoria remains uncertain.