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mRNA-1010
INFLUENZA VACCINE FOR ADULTS ≥50 YEARS OLD

SPONSOR BRIEFING DOCUMENT

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

MEETING DATE: JUNE 18, 2026

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List of Abbreviations

Acronym	Definition
Ab	antibody
AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
BLA	Biologics Licensed Application
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	Confidence interval
CVV	candidate vaccine virus
EOS	End of study
ER	Emergency room
FDA	Food and Drug Administration
GMFR	geometric mean fold-rise
GMR	geometric mean titer ratio
GMT	geometric mean titer
HA	hemagglutination
HAI	hemagglutination inhibition
HD	High dose
ILI	Influenza-like illness
ISS	Integrated summary of safety
LB	Lower bound
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MN	microneutralization assay
NA	neuraminidase
PP	Per-protocol
PPIS	Per-Protocol Immunogenicity Set/Subset
PT	Preferred term
QIV	quadrivalent influenza vaccine
RT-PCR	reverse transcription polymerase chain reaction
RWE	Real-world evidence
rVE	Relative vaccine efficacy
SAE	Serious adverse event
SD	Standard dose
SMQ	standardized MedDRA query
SRC	seroconversion rate
SOC	system organ class

Acronym	Definition
TEAE	Treatment Emergent Adverse Event
TIV	trivalent influenza vaccine
US	United States
WHO	World Health Organization

1 INTRODUCTION

ModernaTX, Inc. (Moderna) is seeking approval of mRNA-1010, a lipid nanoparticle (LNP)-encapsulated, mRNA-based influenza vaccine for active immunization for the prevention of influenza disease in individuals 50 years of age and older. The mRNA-1010 clinical development program encompasses 5 completed studies, including the pivotal Phase 3 safety and efficacy study (304), which enrolled 40,703 adults ≥50 years of age, and the Phase 3 safety and immunogenicity study (303 Part C), which enrolled 2,992 adults ≥65 years. The safety profile is further supported by the analysis of an integrated safety summary of more than 71,000 participants ≥50 years from 4 Phase 3 studies.

The Biologics Licensed Application (BLA) was submitted based on positive Phase 3 results demonstrating that mRNA-1010 provides superior relative vaccine efficacy (rVE) against influenza illness, enhanced immunogenicity, and an acceptable safety profile versus standard-dose (SD) comparator vaccine. Additionally, mRNA-1010 demonstrated superior immunogenicity and a similar safety profile to high-dose (HD) comparator vaccine. The efficacy, immunogenicity, and safety profile of mRNA-1010 is supplemented by the mRNA platform that avoids virus propagation in chicken eggs or cell-based cultures and, as such, avoids adaptive mutations which can reduce vaccine antigenicity. Further, a shorter manufacturing time can allow later influenza strain selection, which can avoid strain mismatches. Taken together, these data support a positive benefit-risk profile for active immunization with mRNA-1010 to prevent influenza disease in individuals ≥50 years.

Following discussions between Moderna and the Food and Drug Administration (FDA), two BLA approval pathways are submitted:

- Traditional approval for adults 50 to 64 years of age, and
- Accelerated approval for adults 65 years and older (fully described in Section 5).

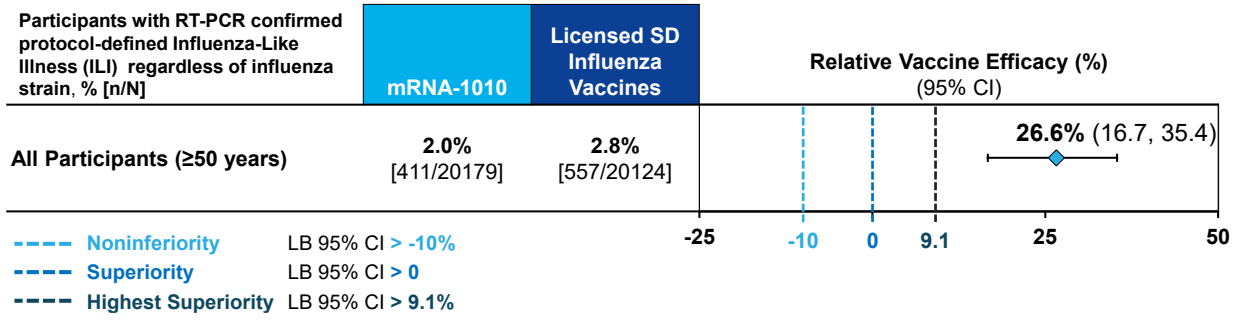
This Briefing Document summarizes the overall clinical data package supporting the indication on adults ≥50 years (Section 2 and Appendix Section 13.2), followed by efficacy and immunogenicity data supporting the indication in adults 50 to 64 years and those 65 years and older. Reactogenicity and safety data are summarized in Section 9.

2 SUMMARY OF OVERALL CLINICAL DATA FOR INDIVIDUALS 50 YEARS AND OLDER

The mRNA-1010 pivotal efficacy study (Study 304) successfully met all protocol-prespecified efficacy criteria for the prevention of influenza-like illness (ILI). The primary efficacy endpoint was to assess the reduction of reverse transcription polymerase chain reaction (RT-PCR)-confirmed, protocol-defined ILI caused by any influenza A or B strain relative to SD comparator in adults 50 years and older. Study 304 began vaccinations in September 2024 and performed comprehensive surveillance for ILI until the end of the 2024/2025 influenza season (30 Apr 2025). More than 40,000 adults ≥50 years of age were included in the efficacy analysis.

The primary analysis of RT-PCR-confirmed protocol-defined ILI cases provided a robust determination of the efficacy endpoint: the relative efficacy of mRNA-1010 versus SD comparator was 26.6% (95% confidence interval [CI]: 16.7, 35.4), meeting all prespecified efficacy success criteria, including the highest level (lower bound [LB] 95% CI >9.1%, 1-sided p-value=0.0005; Figure 1). The superior efficacy of a single dose of mRNA-1010 relative to SD comparator was evident early after vaccination and was maintained to the end of the influenza season.

Figure 1: mRNA-1010 Demonstrates Superior Efficacy Relative to Licensed SD Comparator



CI: confidence interval; LB: lower bound; RT-PCR: reverse transcription polymerase chain reaction; SD: standard dose
Source: Leroux-Roels et al 2026

A high total number (968) of confirmed ILI cases were accrued over the 2024/2025 season, representing all 3 influenza strains (538 influenza A/H1N1, 360 influenza A/H3N2, and 60 influenza B cases). Accordingly, a supplemental analysis of rVE by strain was performed in the overall ≥50-year-old population: A/H1N1 rVE=29.6% [95% CI: 16.4, 40.7]; A/H3N2 rVE=22.2% [95% CI: 4.3, 36.9]; B rVE=29.1% [95% CI: -18.5, 57.5], Figure 18, Appendix 13.2). Previously licensed influenza vaccines

in the enhanced category including Fluzone HD and Flublok showed a similar pattern in VE relative to SD comparator in efficacy studies: both met rVE success criteria for the overall endpoint (any influenza A or B), with more uncertainty for rVE by individual strain. For mRNA-1010, the relatively small number of B/Victoria cases resulted in a wide 95% CI, although the B/Victoria point estimate was consistent with the overall rVE point estimate. Similar uncertainty in the determination of rVE against ILI caused by influenza B (i.e., wide 95% CI) was also evident for Fluzone HD [rVE 27.4%, 95% CI: −13.1 to 53.8, based on 89 Influenza B cases] and for Flublok [rVE 4%, 95% CI: −72 to 46, based on 47 influenza B cases]) (DiazGranados et al 2014; Dunkle et al 2017). The accrual of fewer influenza B cases across registrational influenza vaccine studies reflects the lower burden of disease caused by influenza B in older adults. The uncertainty in B strain rVE is thus evident across influenza vaccines and did not prevent full approval of Fluzone HD or Flublok as enhanced vaccines.

Efficacy of mRNA-1010 relative to SD comparator was maintained when alternate ILI case definitions were assessed. Using case definitions tested in other studies of enhanced vaccines that required the occurrence of temperature ≥37.2ºC accompanied by cough and/or sore throat (modified Centers for Disease Control and Prevention [CDC] ILI case definition), rVE remained consistent (23.5%; 95% CI: 9.0, 35.8).

In the Study 304 population, 56.9% of participants were considered at high risk for severe ILI, and 25% of participants ≥65 years were considered of vulnerable or frail status. rVE was assessed across population subgroups including those at high risk and of frail status, and results were consistent with those of the overall Study 304 rVE.

As part of an exploratory analysis of healthcare encounters associated with confirmed ILI, results showed fewer occurrences in the mRNA-1010 group than in the SD comparator group (Table 1). The rVE for participants seeking a higher level of care (hospitalization, emergency room [ER] visit, or urgent care visit) was 47.9% (95% CI: 12.8, 68.9; 22 mRNA-1010 vs 42 SD comparator participants). Even for categories with numbers too small to calculate rVE, case splits were favorable for mRNA-1010 (hospitalization: 4 mRNA-1010 vs 8 SD comparator; ER visits: 6 mRNA-1010 vs 12 SD comparator).

Table 1: mRNA-1010 Reduces ILI-associated Healthcare Outcomes Relative to Licensed SD Comparator in Adults ≥ 50 Years (Per Protocol Set)

	mRNA-1010 N=20179	Comparator N=20124	rVE (95% CI)
Healthcare encounter	80 (0.4)	120 (0.6)	33.7 (12.0, 50.0)
Seek higher level of care	22 (0.1)	42 (0.2)	47.9 (12.8, 68.9)
Hospitalization	4 (<0.1)	8 (<0.1)	n.c.
ER	6 (<0.1)	12 (<0.1)[nc]	n.c.
Urgent care clinical visit	13 (<0.1)	24 (0.1)	46.1 (-5.8, 72.6)
Outpatient clinical visit	59 (0.3)	81 (0.4)	27.6 (-1.3, 48.2)

CI: confidence interval; ER: emergency room; ILI: influenza-like illness; nc: not calculated; rVE: relative vaccine efficacy

n.c.: rVE not calculated due to too few cases.

In the Study 304 population, 56.9% of participants were considered at high risk for severe ILI, and 26.5% of participants ≥65 years were considered of vulnerable or frail status. rVE was assessed across population subgroups including those at high risk and of frail status, and results were consistent with those of the overall Study 304 rVE.

The immunogenicity of mRNA-1010 was measured using the hemagglutinin inhibition assay (HAI), a conventional measure of influenza vaccine immunogenicity. Antibody (Ab) responses were also measured using a microneutralization assay (MN), although these were exploratory objectives supplementing results of the HAI assay. Ab levels measured in the pivotal clinical efficacy study (304) showed that mRNA-1010 consistently induced higher levels of HAI Ab relative to SD comparator for all 3 influenza strains: the point estimates for Day 29 GMR (mRNA-1010/SD comparator) were all >1.5 (95% CI LBs were >1.4) and seroconversion rate (SCR) differences were all positive (95% CI LBs were >15%). Superior clinical efficacy was supported by higher HAI Ab levels in the pivotal efficacy study. Further, in a head-to-head comparison of HAI Ab levels in adults 65 years and older (Phase 3 303C study), mRNA-1010 responses met prespecified superiority criteria relative to HD comparator. In both 304 and 303C studies, results of MN assays were consistent with those based on HAI assays. Thus, like other licensed SD and HD influenza vaccines, superior clinical efficacy of mRNA-1010 is aligned with mRNA-1010-induced Ab levels that are higher than those of SD and superior to those of HD comparators.

Reactogenicity in Study 304 (adults ≥50 years with SD comparator) and Study 303C (adults ≥65 years with HD comparator) was higher for mRNA-1010 than for comparator, but most solicited local and systemic adverse reactions (ARs) were Grade 1 or 2 in severity and transient. Grade 3 solicited local and systemic ARs were more frequent in the mRNA-1010 group than comparator groups, but these too were transient (median

duration of 1 day in the mRNA-1010 group) and generally resolved without medical attention. Analysis of individual safety data from Studies 304 and 303C identified no safety concerns with mRNA-1010. Unsolicited adverse events (AEs) reported in the 28 days post-injection were balanced between study groups in both studies.

Analysis of pooled Phase 3 (Study 301, 302, 303, and 304) integrated summary of safety (ISS) data from more than 70,000 adults ≥50 years of age were similarly reassuring: the overall incidence of deaths, other serious AEs (SAEs), and AEs of special interest (AESIs) for the study duration was similar between the mRNA-1010 and SD/HD comparator groups.

Data from Studies 304 and 303C together with safety data from the entire clinical program, including the ISS, show that mRNA-1010 is anticipated to provide meaningful clinical benefit in the prevention of ILI in adults 50 years and older. mRNA-1010 demonstrated superior protection against clinical ILI relative to SD comparator, at a level exceeding the highest prespecified success criterion (rVE 26.6%; 95% CI: 16.7, 35.4) and fully aligned with levels of VE relative to SD comparator obtained for approved enhanced vaccines (i.e., Fluzone HD and Flublok). The superior mRNA-1010 rVE from the pivotal efficacy study corresponds with induced HAI Ab levels that are consistently higher than comparator Ab levels, as HAI induced by mRNA-1010 are superior to those elicited by Fluzone HD (Study 303C). Further, the pattern of mRNA-1010-induced immunogenicity is consistent when measured using the HAI Ab assay or the functional MN Ab assay. In total, direct clinical efficacy taken together with superior HAI and MN Ab levels predict mRNA-1010 efficacy at a level comparable to that afforded by enhanced vaccines. Additionally, the mRNA platform provides manufacturing advantages over licensed influenza vaccines likely to provide additional benefits relative to existing vaccines, including more precise strain matching without the risk of inadvertent egg-adaptive mutations and faster manufacturing timelines that enable strain selection closer to the start of influenza season. Given the natural seasonal variability and antigenic drift of influenza virus, better vaccine antigenic fidelity is a key distinguishing potential advantage of mRNA-1010 compared to currently available influenza vaccines.

3 INFLUENZA BACKGROUND

Summary

- Influenza is a highly transmissible respiratory disease that continues to cause substantial morbidity and mortality in the United States (US).
- Adults ≥50 years old remain disproportionately affected compared to younger adults; adults ≥65 years old account for 70% to 85% of influenza-related deaths and 50% to 70% of hospitalizations.
- Although vaccination remains the most effective preventive measure against influenza, the effectiveness of licensed vaccines is constrained by manufacturing limitations and frequent strain mismatches caused by antigenic changes.
- Most seasonal influenza vaccines are manufactured using egg-based processes, which are subject to strain-dependent variability in antigen yield. In some seasons there are challenges generating high-yield candidate vaccine viruses (CVVs) without introducing egg-adaptive mutations that can impact vaccine immunogenicity.
- Influenza continues to drive substantial hospitalizations and deaths among US adults ≥50 years, and currently licensed vaccine technologies do not consistently deliver the level of protection or manufacturing flexibility needed to address this ongoing public health burden.

3.1 Clinical/Pathophysiology of Condition

Influenza is a highly contagious respiratory virus that contributes significantly to global morbidity and mortality. Human influenza viruses are segmented, negative-sense, single-stranded RNA viruses belonging to the Orthomyxoviridae family (Bouvier and Palese 2008). Human-to-human transmission occurs predominantly via respiratory droplets from coughing, sneezing or indirectly via respiratory secretions on hands, tissues, or other surfaces (ECDC 2022). Viral transmission is enhanced in colder and drier conditions (Lowen et al 2007) and seasonal epidemics of influenza occur in winter months in temperate regions (WHO 2025).

*3.1.1 **Influenza Burden of Disease***

The World Health Organization (WHO) estimates that seasonal influenza viruses cause approximately 1 billion illnesses, 3 to 5 million severe illnesses, and up to 650,000 deaths globally each year (WHO 2025). In the US between 2010 and 2024, influenza has resulted in up to 41 million illnesses, up to 710,000 hospitalizations, and up to 52,000 deaths annually (CDC 2024a). The 2024/2025 US influenza season was

classified as high severity by the US CDC (CDC 2025a) and was characterized by high transmission, with in-season estimates of 51 million infections, 710,000 hospitalizations, and 45,000 deaths (CDC 2025b).

Influenza type A and B viruses are responsible for seasonal influenza epidemics in humans each year (CDC 2023a). Influenza A and B viruses have 2 surface glycoproteins, HA and neuraminidase (NA). Influenza A viruses are classified into subtypes according to the combination of HA and NA glycoproteins expressed on the viral surface (e.g., A/2009H1N1 pdm09, A/H3N2), while influenza B viruses are classified into 2 lineages: B/Victoria and B/Yamagata (CDC 2023a). Since the initiation of mRNA-1010 studies, the WHO has updated its seasonal influenza vaccine recommendation to exclude B/Yamagata because this lineage is no longer circulating (WHO 2023; WHO 2024).

Year-to-year variability exists in the circulation and predominance of influenza A and B strains globally. Though the peak circulation timing of each strain varies by year, in temperate zones, influenza B on average peaks approximately 4 weeks later than influenza A (Muscatello 2019). Different subtypes vary by season and by region, such that a subtype may attain high prevalence in one season or geographic area while remaining sporadic or undetected in others (Zanobini et al 2022; Zheng et al 2023). In the 2024-2025 influenza season, influenza A/H1N1pdm09 and influenza A/H3N2 circulated at nearly equal levels, with influenza B circulating at a lower percentage of the total (~10%) (CDC 2025c). Influenza B disease is largely concentrated in children and adolescents and generally represents a smaller share of the influenza burden in adults ≥65 years than influenza A. In the 2024-2025 season, influenza B represented 0.8% of total influenza cases in adults ≥65 years (CDC 2026a).

Substantial antigenic drift occurs among influenza A subtypes and influenza B lineages, resulting in changes in circulating strains over time (Chen et al 2020; CDC 2022a). Accordingly, all influenza vaccine strains are assessed on an annual basis to determine whether updates to seasonal influenza strain recommendations are warranted. Influenza A/H3N2 is most frequently updated because it is more prone to antigenic drift and egg adaptations than the other vaccine components (Bedford et al 2014; Rajaram et al 2020).

*3.1.2 **Clinical Spectrum of Disease***

Disease resulting from influenza virus infection primarily presents with respiratory symptoms such as cough, nasal congestion, pharyngitis, sinusitis, or otitis media, and systemic symptoms that may include fever, chills, vomiting, or diarrhea; symptoms may range from mild to severe (CDC 2022b). Infection with influenza virus may lead to serious or life-threatening complications (including pneumonia, bacterial superinfection, respiratory failure, and exacerbations of chronic obstructive pulmonary disease) and

can lead to increased risk of myocardial infarction, heart failure and stroke (Kwong et al 2018; Sin et al 2022; Nguyen et al. 2025; Jain et al. 2015; Lei et al. 2025). Influenza infection is also associated with neurological, muscular, and renal complications (Rosero et al 2025; Sellers et al 2017).

The age distribution of affected individuals varies annually based on the dominant strains and the level of population immunity, but in general adults ≥50 years are at greater risk of developing severe influenza complications. Globally, the highest influenza mortality rate from lower respiratory tract infections occurred among adults >70 years (16.4 deaths per 100,000) (GBD 2017 Influenza Collaborators 2019). In the US, adults ≥65 years accounted for 70% to 85% of influenza-related deaths and 50% to 70% of influenza-related hospitalizations in recent years (CDC 2024b). During the 2024/2025 season, US hospitalization and mortality rates among adults ≥65 years were 666.3 and 51.9 per 100,000, respectively, which represents an over 8-fold increase in hospitalizations and over 25-fold increase in deaths compared to adults 18-49 years (CDC 2026b). A significant burden of influenza also exists in adults 50 to 64 years, who account for a large proportion of the workforce. During the 2024/2025 season in the US, the rates of hospitalization and mortality were 223.3 and 15.3 per 100,000 among adults 50 to 64 years, compared to 79.0 and 2.0 per 100,000 among those 18 to 49 years (CDC 2026b).

In addition to age-related risk, the presence of chronic conditions increases the risk of severe influenza outcomes, including hospitalization and death (CDC 2024c). The CDC FluSurv-NET survey showed that approximately 95% of adults hospitalized with influenza in the 2024/2025 season reported having a chronic medical condition (FluSurv-NET 2025). Among US adults, chronic conditions are common among all ages but become more prevalent with increasing age: in 2018 at least 1 chronic comorbidity was estimated in 27.5% of adults 18 to 44 years, 63.4% of adults 45 to 64 years, and 87.6% of adults ≥65 years (Boersma et al 2020). According to the WHO, the prevalence of multiple comorbidities increases most rapidly between the ages of 50 and 60 years in high-income countries (WHO 2015). Thus, many individuals 50 to 64 years have an increased risk of severe influenza complications.

3.2 Currently Available Influenza Vaccines

Vaccination is the most effective means of reducing the burden of influenza disease. The vast majority of seasonal influenza vaccines are manufactured using egg-based processes; the remaining supply is provided from cell-based processes or recombinant technology (Taaffe et al 2025). Challenges facing current seasonal influenza vaccines include limitations in effectiveness, reliable egg supply, variability in viral growth and antigen yield, and challenges generating high-yield CVVs without introducing egg-adaptive mutations. Effectiveness of current vaccines rarely exceeds 60% in the

prevention of ILI and may be reduced when circulating influenza virus is poorly matched to strains selected for vaccine inclusion (CDC 2024d). Between 2011-2025, influenza vaccine effectiveness ranged from 8-65% in adults ages 50-64 years and 12-50% in adults 65 years and older, with lowest effectiveness in years with the lowest percentage of match between influenza vaccine strain and circulating influenza viruses (CDC 2026c; Russell et al 2024; Merced-Morales et al 2022; CDC 2023b; CDC2024e; CDC 2025c). To address such limitations in effectiveness, particularly in older, more vulnerable populations, recombinant vaccines and egg-grown vaccines with higher antigen content (HD) or adjuvanted formulations have been developed.

Licensure studies for an egg-grown HD vaccine and a recombinant vaccine showed higher clinical efficacy in the prevention of ILI relative to SD vaccines. The egg-grown HD vaccine demonstrated superior efficacy relative to SD vaccine based on an rVE of 24.2% (95% CI: 9.7, 36.5; the superiority criterion required LB 95% CI >9.1%) (DiazGranados et al 2014). Similarly, the recombinant vaccine showed superior efficacy relative to SD egg-grown vaccine based on an rVE of 30% (95% CI: 10, 47; the superiority criterion required LB 95% CI >9%) (Dunkle et al 2017). This superior efficacy of enhanced vaccines in the prevention of ILI relative to SD vaccines translated to reduced rates of influenza-associated hospitalizations and deaths among adults 65 years and older. The adjuvanted influenza vaccine was licensed under accelerated approval based on its elicited immune response, contingent upon verification of clinical benefit in a post-authorization effectiveness trial (FLUAD 2025). Reduction in rates of hospitalization and deaths in older adults resulted in recent preferential recommendation for enhanced influenza vaccines in adults ≥65 years in some global regions, including the US.

Although the egg-grown HD vaccines have improved efficacy, enhanced vaccines nonetheless face challenges inherent to manufacturing processes and to the time required from strain selection to vaccine production that can result in potential mismatch between vaccine and circulating influenza strains (Bartley et al 2021; Gouma et al 2020; Russell et al 2024). Egg-based vaccine production relies on an assured supply of embryonated chicken eggs which can be vulnerable to supply challenges. Further, sequence mutations often occur to adapt to growth in eggs or cell culture systems, and these adaptation-mutations can lead to antigenic changes in produced vaccines compared to circulating influenza virus. Vaccines that can deliver high efficacy using reliable and rapid manufacturing processes are warranted.

3.3 Unmet Medical Need

Despite the availability of seasonal influenza vaccines, influenza continues to cause substantial morbidity and mortality annually. Vaccine effectiveness is variable across seasons but rarely exceeds 60% and is influenced by egg-adaptive changes and

antigenic mismatch between vaccine and circulating strains. Egg-based manufacture, which accounts for the overwhelming majority of influenza vaccine supply, including enhanced influenza vaccines, is dependent on egg availability and efficient viral propagation and often introduces egg-adaptive antigenic changes that can affect vaccine immunogenicity. Consequently, advancing influenza vaccine platforms that do not rely on egg-based manufacture has been emphasized as a public health priority. Current manufacturing processes require strain selection ~7 months in advance of the influenza season, which in some years results in a mismatch between vaccine composition and circulating strains. Later strain selection enabled by rapid production timelines and lack of reliance on egg-based production can reduce mismatch.

Reduced effectiveness is observed in certain populations, including older adults and individuals with underlying medical conditions. Although enhanced vaccines (e.g. high-dose, adjuvanted, and recombinant formulations) have demonstrated improved relative efficacy and/or effectiveness compared with standard-dose vaccines, influenza-associated hospitalizations and deaths persist, particularly among high-risk groups.

These factors indicate that limitations remain with current influenza prevention strategies and support the need for improved vaccines that provide more consistent protection with greater antigenic match and that can be manufactured with greater flexibility and timeliness.

4 MRNA-1010 OVERVIEW

Summary

- mRNA-1010 is an LNP-encapsulated trivalent influenza mRNA-based vaccine encoding the full-length, membrane-bound influenza HA glycoproteins of the 3 seasonal influenza strains recommended by the WHO.
- The mRNA-based vaccine platform enables efficient manufacturing scale-up of safe and effective vaccines without reliance on processes and substrates that are specific to each pathogen.
- By avoiding replication in eggs or complex cell culture systems, the mRNA-1010 vaccine enables greater manufacturing flexibility and high fidelity of vaccine antigen to disease-causing virus.

4.1 Proposed Indication and Posology

The proposed indication for the mRNA-1010 vaccine is active immunization for the prevention of disease caused by influenza virus subtypes A and type B represented in the vaccine, in persons 50 years of age and older.

The approval for persons 65 years of age and older is proposed under accelerated approval pathway based on clinical efficacy and immune response. Full approval for this age group may be contingent upon confirmation of clinical benefit in a post-marketing confirmatory trial.

mRNA-1010 is intended for intramuscular administration as a single dose of 37.5 µg (12.5 µg per strain).

4.2 mRNA-1010 Description and Mechanism of Action

mRNA-1010 is an LNP-encapsulated trivalent influenza mRNA-based vaccine encoding the full-length, membrane-bound influenza HA glycoproteins of the 3 seasonal influenza strains recommended by the WHO for cell- or recombinant-based vaccines (A/H1N1, A/H3N2, and B/Victoria-lineage). Each strain is present in an equal RNA mass ratio (1:1:1), with a total RNA content of 37.5 µg per dose (12.5 µg RNA per strain). The RNA encodes native A/H1N1 and A/H3N2 strain HA antigens. For the B/Victoria-lineage strain, the RNA encoding the HA antigen includes point mutations in non-antigenic sites to optimize antigenic expression.

Moderna's mRNA-based vaccine platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express encoded antigens. The delivered mRNA does not enter the cellular nucleus, does not interact with the genome, is nonreplicating, is expressed transiently, and does not persist in the body. To

protect mRNA from rapid degradation in plasma and serum by ribonucleases and to aid in mRNA uptake by cells, mRNA is delivered through encapsulation within a proprietary LNP (Goody et al 2026; Sohn et al 2026).

After delivery into cells, the mRNA serves as a template for the synthesis of the intended proteins. The HA proteins encoded by mRNA-1010 are translated and then expressed on the cell surface. The membrane-bound HA glycoproteins of the encoded influenza strains are recognized by immune cells as a foreign antigen, eliciting immune responses, which contribute to protection against influenza.

Importantly, the precision and standardization of the mRNA-based vaccine platform enable efficient manufacturing scale-up of safe and effective vaccines without reliance on processes and substrates that are specific to each pathogen. Additionally, the mRNA-based platform provides the capability to rapidly update the targeted viral strains in response to changes in circulating viruses (and associated regulatory authority and advisory organization recommendations for vaccines) and reliably manufacture the updated vaccines at commercial scale. Furthermore, by avoiding replication in eggs or complex cell culture systems, the mRNA-1010 vaccine avoids the need to obtain and optimize CVVs for antigen yield and fidelity to the vaccine antigen.

5 REGULATORY HISTORY

Summary

- Moderna engaged in iterative and constructive consultations with the FDA throughout clinical development regarding the Phase 3 study design and submission strategy.
- Following the successful completion of the Phase 3 efficacy trial in which mRNA-1010 met all agreed upon prespecified primary endpoints, the BLA seeking approval in adults ≥50 years of age was submitted in December 2025.
- The FDA accepted the BLA for filing via two approval pathways: traditional approval for adults 50–64 years of age and accelerated approval for adults ≥65 years of age.

5.1 Regulatory Milestones

In February 2024, Moderna engaged with FDA regarding the Phase 3 efficacy study design, including use of a licensed standard-dose influenza vaccine comparator. FDA provided additional feedback during the August 2025 pre-BLA interaction, including recommendations related to the comparator strategy and ISS. Moderna incorporated this feedback into the BLA submission.

The mRNA-1010 BLA was submitted on December 5, 2025. Thereafter, FDA and Moderna engaged in discussions regarding the most appropriate regulatory framework for evaluating the evidence package across the proposed age groups. These interactions focused on differences in the standard of care between adults 50–64 years of age and adults 65 years of age and older, including the preferential use of enhanced influenza vaccines in older adults.

Based on these interactions and the totality of available evidence, Moderna proposed a differentiated regulatory approach consisting of traditional approval for adults 50–64 years of age and accelerated approval for adults 65 years of age and older.

This framework incorporated direct efficacy data from Study P304, comparative immunogenicity data versus high-dose influenza vaccine, analyses supporting HAI antibody responses as a surrogate endpoint reasonably likely to predict clinical benefit, and a planned post-marketing confirmatory study. FDA accepted the BLA for filing on 17 February 2026, under the approval pathways described below.

5.2 Approval Pathways

Moderna is seeking licensure of mRNA-1010 through a differentiated regulatory approach that reflects the totality of evidence and the benefit-risk profile across age groups.

- **Traditional Approval (Adults 50–64 Years of Age):**
  For adults 50 through 64 years of age, Moderna seeks traditional approval based on direct demonstration of clinical efficacy and safety from the pivotal Phase 3 study (mRNA-1010-P304). In this randomized, active-controlled trial, mRNA-1010 met prespecified success criteria and demonstrated statistically significant relative vaccine efficacy compared with a licensed standard-dose influenza vaccine.
- **Accelerated Approval (Adults ≥65 Years of Age):**
  For adults 65 years of age and older, Moderna seeks approval under the Accelerated Approval pathway (21 CFR § 601.40 and § 601.41), recognizing the high burden of influenza and unmet need in this population. This approach is supported by data including clinical endpoint efficacy results from the ≥65-year subgroup of the Phase 3 study (mRNA-1010-304), paralleled by consistently higher or superior levels of HAI Ab among recipients of mRNA-1010 relative to SD and HD comparators (Studies 304 and 303 C).

  Specifically, mRNA-1010 meets the criteria for accelerated approval in adults ≥65 years of age based upon the following:

  - **Criterion 1 Serious Disease**: Addresses an unmet need in serious condition: Recent studies show that adults 65 years and older account for 50-70% of influenza-associated hospitalizations and 70-85% of influenza-associated deaths in the US (CDC 2024b). Thus, while currently approved enhanced vaccines provide benefit, there remains an important unmet need in this population.
  - **Criterion 2 Meaningful Advantage over Available Therapy:** The mRNA-1010 vaccine provides better potential vaccine antigenic fidelity against a virus known for high seasonal variability, which is a unique potential advantage of mRNA-1010 compared to currently available vaccines. The combination of clinical endpoint efficacy, higher or superior immunogenicity, and improved production flexibility and scalability constitutes a meaningful advantage over current licensed influenza vaccines.
  - **Criterion 3 Surrogate Marker Reasonably Likely to Predict Clinical Benefit:** Among adults 65 years and older, mRNA-1010 demonstrated higher HAI Ab responses relative to SD vaccine (Study 304) and superior

HAI Ab responses relative to HD Fluzone (Study 303 C). HAI Ab levels are routinely used in evaluation of licensed vaccines and have supported both accelerated approvals and immunobridging approaches. The higher Ab levels induced by mRNA-1010 are aligned with superior clinical endpoint efficacy against ILI relative to SD vaccine in adults 65 years and older (Study 304). Taken together, superior efficacy and robust HAI Ab levels predict that mRNA-1010 will provide meaningful clinical benefit to adults 65 years and older.

- **Criterion 4 Post-Marketing Confirmatory Study:** A post-marketing study will be conducted to confirm the clinical benefit of mRNA-1010 in adults ≥65 years of age. The study will compare vaccine effectiveness of mRNA-1010 with a licensed enhanced influenza vaccine in real-world settings (see Section 10).

This proposed regulatory approach is designed to enable timely access to mRNA-1010 while ensuring that evidence supporting safety and effectiveness is appropriate for each population.

6 OVERVIEW OF mRNA-1010 CLINICAL DEVELOPMENT PROGRAM

Summary

- The mRNA-1010 clinical development program was initiated with Study 101, which informed dose selection for subsequent Phase 3 studies.
- A total of four Phase 3 studies were conducted; the primary efficacy, immunogenicity, and safety data supporting the BLA come from Phase 3 Studies 304 and 303C.
- Study 304 evaluated the safety, efficacy, and immunogenicity of mRNA-1010 vs SD comparator in adults ≥50 years of age.
    - The primary efficacy endpoint was rVE of mRNA-1010 versus licensed SD comparator to prevent the first episode of RT-PCR-confirmed ILI caused by any influenza A or B strain.
- Study 303C evaluated the immunogenicity, reactogenicity, and safety of mRNA-1010 vs a HD comparator in adults ≥65 years of age.
    - The primary immunogenicity endpoint was the Day 29 geometric mean titer (GMT) and proportion of participants reaching seroconversion.
- An ISS from >70,000 participants (across all mRNA-1010 Phase 3 studies including studies 301, 302 and 303 Parts A and B) contributed to a comprehensive evaluation of the safety of mRNA-1010.

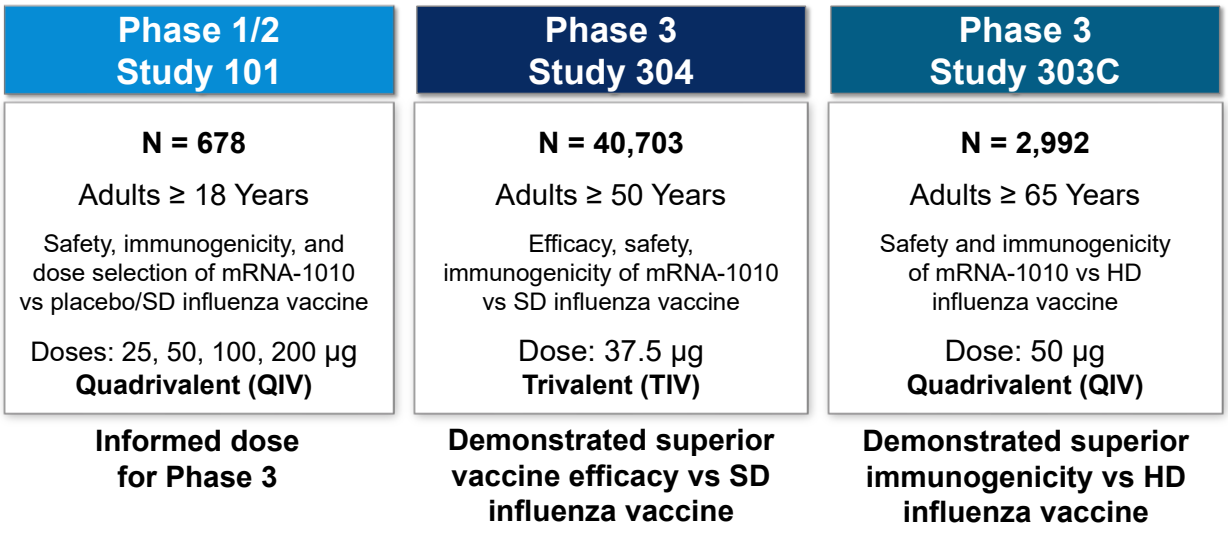
6.1 Studies Supporting Development of mRNA-1010

The mRNA-1010 clinical development program includes 5 completed studies. Critical data supporting the approval of mRNA-1010 for the prevention of ILI derive from the Phase 1/2 Study 101 (informing dose selection); Phase 3 Study 304 (demonstrating superior rVE against the primary endpoint, immunogenicity and safety); and Phase 3 Study 303C (immunogenicity and safety) (Figure 2). Other Phase 3 studies (Studies 301 and 302; conducted with an earlier version of mRNA-1010, and 303 Parts A and B, conducted in participants across a younger age range) provide additional safety data included in the analyses of the ISS.

The primary efficacy, immunogenicity, and safety data supporting the BLA come from Studies 304 and 303C:

- Study 304: Pivotal Phase 3 that evaluated the rVE, immunogenicity and safety of mRNA-1010 trivalent influenza vaccine (TIV) 37.5 µg relative to licensed SD comparator in 40,703 participants ≥50 years.
    - rVE evaluation was based on surveillance throughout the 2024/2025 influenza season (ending 30 Apr 2025).
    - Safety evaluation based on at least 6 months of safety follow-up for all participants.
- Study 303C: Phase 3 study that evaluated Immunogenicity, reactogenicity and safety of mRNA-1010 quadrivalent influenza vaccine (QIV) 50 µg relative to a licensed HD comparator in participants ≥65 years in the US.

Figure 2: Key Studies Supporting mRNA-1010



HD: high dose; SD: standard dose

To further characterize the mRNA-1010 safety profile in the intended population, supportive safety data are provided from the pooled analysis (ISS) of data for SAEs, deaths, and AESIs among 71,916 participants ≥50 years from all 4 Phase 3 studies (Studies 301, 302, 303, and 304):

- ISS 50-64 years: 18,398 participants received mRNA-1010 (TIV or QIV), 18,396 participants received active SD comparator (TIV or QIV; 1 participant in this age group was administered HD comparator [QIV]).

- ISS ≥65 years: 17,567 participants received mRNA-1010 (TIV or QIV), 16,065 received active SD comparator (TIV or QIV), and 1,489 received HD comparator (QIV).

6.1.1 Study mRNA-1010-101

The mRNA-1010 clinical development program was initiated with Study 101, which informed dose selection for subsequent Phase 3 studies. Study 101 was a Phase 1/2, randomized, stratified, observer-blind (participant- and assessor-blind), dose-ranging safety, reactogenicity, and immunogenicity study. The study evaluated dosages including 25, 50, 100, and 200 µg of a QIV formulation. Study 101 was conducted in the US between 28 Jun 2021 and 27 Sep 2022. A dosage of 50 ug (12.5 ug/strain; QIV) was selected based on overall assessment including HAI Ab levels.

Study results are summarized in Appendix Section 13.1.

6.1.2 Study mRNA-1010-304

6.1.2.1 Design Overview

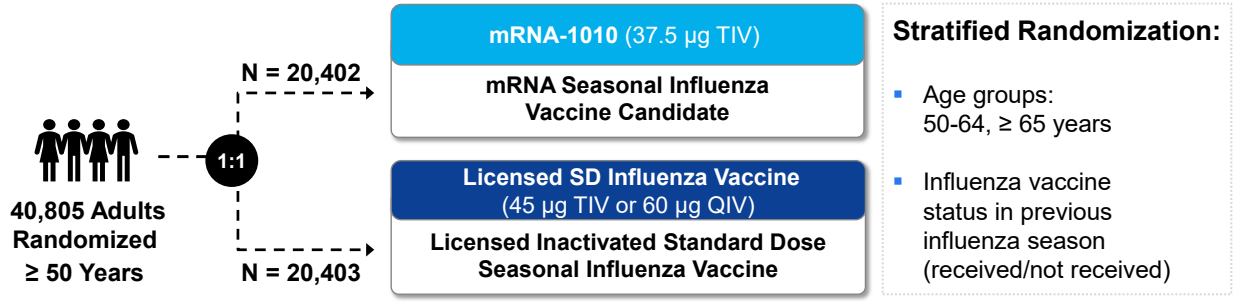
Study 304 was a Phase 3, randomized, observer-blind (participant- and assessor-blind), active-controlled study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 vs SD comparator in adults ≥50 years of age. The study was conducted in 11 countries across 301 study sites in the northern hemisphere from 16 Sep 2024 to 21 Aug 2025.

Participants were randomized in a 1:1 ratio to receive a single injection of either mRNA-1010 (37.5 µg; 12.5 µg/strain) or SD comparator (Figure 3). Randomization was stratified by age (50 – 64 or ≥65 years) and influenza vaccine status (received or not received).

The use of a licensed SD influenza vaccine comparator in the pivotal efficacy study was discussed with FDA. Although FDA recommended consideration of an enhanced comparator, use of an enhanced influenza vaccine was not required. This approach is consistent with the historical development paradigm for enhanced influenza vaccines, which were established relative to SD influenza vaccines.

Because the study was conducted globally across regions with differing standards of care, a licensed SD comparator was selected. Where enhanced vaccines were preferentially recommended for older adults, these recommendations were explicitly described in the informed consent. The study was reviewed and endorsed by the applicable local regulators, institutional review boards, and ethics committees.

Figure 3: Study 304 Design



QIV: quadrivalent influenza vaccine; SD: standard dose; TIV: trivalent influenza vaccine

The study included up to 3 in-person visits (Screening, Day 1 [Baseline], and Day 29) and up to 4 telephone contacts (Day 8, Month 3 [Day 91], Month 6 [Day 181], and the End of the Influenza Season Visit). Additionally, in-person unscheduled visits were conducted for participants who met prespecified criteria for protocol-defined respiratory illness. All participants were prompted to complete the symptom eDiary twice weekly from Day 1 (Baseline) to the end of the influenza season to capture the presence or absence of respiratory symptoms. Protocol-defined ILI cases included in the efficacy analysis required confirmatory nasopharyngeal swabs testing positive for influenza by RT-PCR. The planned target accrual of 836 was exceeded following the end of the 2024/2025 season and the primary analysis of vaccine efficacy was performed at that time (VE of mRNA-1010 relative to SD comparator).

The primary rVE endpoint was the first episode of RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strain. Cases for primary rVE analysis were counted starting 14 days after study injection and through the end of the influenza season.

The immunogenicity endpoints (secondary) measured HAI Ab GMT, SCR, and GMFR (relative to Baseline) at Day 29 (MN Ab levels were also measured as exploratory endpoints).

Reactogenicity was assessed based on solicited ARs collected for 7 days and all AE were collected for 28 days after study injection. Safety follow-up (SAE, medically attended adverse event (MAAE), AE leading to discontinuation, AESI, and deaths) continued up to 6 months after study injection (and throughout the study for SAEs assessed as related to study injection per Investigator).

Efficacy, immunogenicity, and safety (solicited ARs and unsolicited AEs) results were assessed by protocol-described subgroups, including age subgroups (50-64 years; ≥65 years; ≥75 years).

Endpoints and analysis sets are further described in Section 6.2.

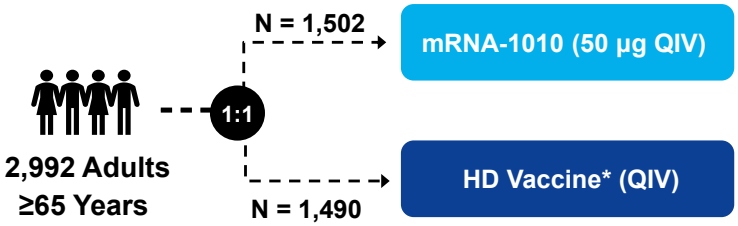
6.1.3 Study mRNA-1010-303C

6.1.3.1 Design Overview

Study 303C was a Phase 3, randomized, observer-blind (participant- and assessor-blind), active-controlled study that evaluated the immunogenicity, reactogenicity, and safety of mRNA-1010 vs a HD comparator in adults 65 years and older. The study was conducted in the US from 13 Nov 2023 to 24 Jun 2024.

Participants were randomized 1:1 to receive a single injection of mRNA-1010 (QIV 50 µg; 12.5 µg/strain) or HD comparator (Fluzone HD) (Figure 4). Randomization was stratified by the previous influenza season vaccination status (received or not received). The HD comparator was used in accordance with CDC recommendations for adults ≥65 years.

Figure 4: Study 303C Design



- **Non-inferiority and superiority assessed**
- **Follow up through 6 months (median 171 days)**

*HD Vaccine - Fluzone HD, a licensed high-dose influenza vaccine containing 4x the antigen of a Standard-Dose influenza vaccine
QIV = Quadrivalent influenza vaccine

In-person visits were scheduled for Screening and Days 1 (Baseline), 29 (Month 1), and 181 (Month 6 [subset of participants]). Participants provided blood samples for assessment of immunogenicity parameters on Days 1, 29, and end of study (EOS)/

Day 181. Solicited ARs and safety events were collected as described above for Study 304.

Safety and reactogenicity were assessed based on unsolicited AEs and solicited ARs, as described in Section 6.2.

6.2 Study Endpoints and Analysis Sets

6.2.1 Efficacy Endpoints

6.2.1.1 Study 304 Primary Efficacy Endpoint

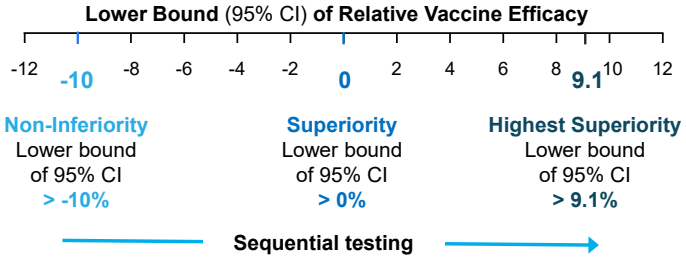
In Study 304, the primary rVE endpoint was the first episode of RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strain that begins at least 14 days after study injection and through the end of the influenza season. Specifically, rVE required a positive nasopharyngeal swab test for influenza by RT-PCR and both of the following present ±7 days of the nasopharyngeal swab collection date:

- ≥1 systemic symptom (oral temperature >37.2°C [>99.0°F]), chills, feverish, tiredness, headaches, or myalgia) AND
- ≥1 respiratory illness symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing).

The rVE of mRNA-1010 vs SD comparator was defined as the percent reduction in the hazard of the primary endpoint (mRNA-1010 vs SD comparator) and was estimated as 100 × (1-hazard ratio)% using the stratified Cox proportional hazard model.

The primary objective was met if the noninferiority of mRNA-1010 vs SD comparator was demonstrated (p-value for rejecting rVE ≤-10% or hazard ratio ≥1.1 was less than the 1-sided 2.5% significance level). Subsequent testing was conducted in a sequential manner for the superiority and highest superiority objectives (Figure 5). A hierarchical testing strategy was applied for multiplicity adjustments over the primary and secondary efficacy endpoints.

Figure 5: Sequential Testing of rVE Endpoint



CI: confidence interval

6.2.1.2 Study 304 Secondary and Exploratory Efficacy Endpoints

The secondary efficacy endpoints included the first episode of RT-PCR-confirmed modified CDC-defined ILI that began at least 14 days after study injection through the end of the influenza season caused by any influenza A or B strains. This definition required a temperature >37.2°C (>99.0°F) together with cough and/or sore throat. Although older individuals (≥65 years) with ILI are less likely to manifest fever than younger individuals, this endpoint was evaluated in a previous study of a licensed enhanced influenza vaccine in this older population (DiazGranados et al 2014).

Exploratory endpoints were prespecified for case definitions including CDC-defined ILI (unmodified; requiring body temperature ≥37.8°C [≥100°F] accompanied by cough and/or sore throat), WHO-defined ILI (acute respiratory infection with body temperature ≥38.0°C [≥100.4°F] and cough with onset within the last 10 days), and influenza infection regardless of presence of clinical symptoms. Additionally, an exploratory endpoint of medically-attended influenza was evaluated in participants who sought medical attention for a case of RT-PCR-confirmed protocol-defined ILI.

6.2.2 Immunogenicity Endpoints

In both Study 304 and Study 303C, HAI titers were measured at Baseline and Day 29 (testing for MN Ab was also performed as exploratory endpoints). HAI Ab assays are strain-specific and reflect the vaccine-included influenza strains. The following influenza strains were tested:

- Study 304: A H1N1/Wisconsin/67/2022, A H3N2/Massachusetts/18/2022, and B/Connecticut/01/2021 (B-Victoria lineage) (WHO-recommended Northern Hemisphere 2024/2025 strains)
- Study 303C: A H1N1/Wisconsin/67/2022, A H3N2 A/Darwin/6/2021, B/Connecticut/01/2021 (B-Victoria lineage) and B/Phuket/3073/2013 (B/Yamagata-lineage) (WHO-recommended Northern Hemisphere 2023/2024 strains)

HAI Ab endpoints were reported as GMT, SCRs, and the proportion of participants with HAI titers ≥1:40). The GMR and its corresponding 95% CI was estimated from the least squares mean difference estimate and 95% CI obtained from the model on the log-transformed scale using back-transformation. The corresponding 2-sided 95% CI of GMR was provided to assess the difference in immune response between study intervention groups on Day 29. SCR was defined as the proportion of participants with either a Baseline HAI titer <1:10 and a post-Baseline titer ≥1:40 or a Baseline HAI titer ≥1:10 and a minimum 4-fold-rise in postbaseline HAI Ab titer.

For each study, strain-specific Ab results from each study group (i.e., mRNA-1010 vs SD comparator for 304 and mRNA-1010 vs HD comparator for 303C) were compared.

6.2.3 Safety Endpoints

Reactogenicity assessments (solicited ARs) were based on data collected up to Day 7 after injection and included evaluation of incidence, severity, and duration of the following solicited ARs:

- Local ARs: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), axillary (underarm) swelling or tenderness ipsilateral to the side of the injection.
- Systemic ARs: fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills.

Safety assessments other than reactogenicity were performed in all participants who received any dose of study injection and included all unsolicited AEs collected up to 28 days after injection and AEs leading to discontinuation, SAEs, AESIs, and MAAEs collected through at least the Day 181/EOS visit (some studies had longer follow-up). For the four Phase 3 studies, Investigators were instructed to report unsolicited AEs within the following categories as AESIs:

- thrombocytopenia
- new onset of or worsening of Guillain-Barré syndrome, acute disseminated encephalomyelitis, idiopathic peripheral facial nerve palsy (Bell's palsy), or seizures
- anaphylaxis associated with study injection
- myocarditis, pericarditis, or myopericarditis. Any suspected cases of myocarditis, pericarditis, or myopericarditis were reviewed by the independent blinded Cardiac Event Adjudication Committee (CEAC) to determine if they met CDC case definitions for "probable" or "confirmed" events (Gargano et al 2021).

In addition, safety data from participants ≥50 years of age from all Phase 3 mRNA-1010 studies were pooled to provide a comprehensive analysis of safety across all studies, complementing the analysis of safety from the pivotal 304 study and 303C. The ISS includes SAEs, AESIs, and deaths from each of the 4 Phase 3 studies (301, 302, 303, and 304).

6.2.4 Analysis Sets

Key analysis sets from Studies 304 and 303C included:

- Randomization Set: all participants who were randomized, regardless of the participants' treatment status in the study. Participants were analyzed according to the study intervention group to which they were randomized.

- Per Protocol Set (PP Set): all participants who received any study injection, excluding those with important protocol deviations that could impact efficacy assessments. The PP Set was only in Study 304 and used as the primary analysis set for efficacy endpoints .
- Per-Protocol Immunogenicity Set/Subset (PPIS): participants who received the planned TIV dose, had Baseline and Day 29 HAI Ab assessments with no protocol deviations impacting immunogenicity assessment. The PPIS was used for all analyses of immunogenicity in Studies 304 and 303C unless specified otherwise. In Study 304, the PPIS was derived from a stratified random subset of 2400 participants from North America where TIV SD comparator was used, stratified by age and prior year influenza vaccine status (balanced across strata). Participants with RT-PCR-confirmed ILI between Baseline and Day 29 were removed from the PPIS. All Study 303 C participants meeting PPIS criteria were included in the analysis.
- Safety Set: All randomized participants who received any study injection; this population was used for analyses of safety data other than solicited ARs.
- Solicited Safety Set/Subset: All participants in the Safety Set who contributed any solicited AR data; this population was used for the analysis of solicited ARs.
    - In Study 304, solicited ARs were collected from a subset of approximately 6000 participants assigned by the interactive response technology.
- ISS Set: a pooled safety set from the 4 Phase 3 studies (P301, P302, P303, and P304) to evaluate the safety of mRNA-1010 (QIV or TIV) vs SD/HD comparators (Fluarix SD TIV or QIV; Fluzone HD QIV). The ISS Set consists of all randomized participants ≥50 years of age who received any study injection in Studies P301, P302, P303, or P304. The ISS Set was used for all pooled analyses, and participants were analyzed according to the actual study injection they received.

6.3 Enrolled Participants

6.3.1 Study 304 Study Population (≥50 Years)

6.3.1.1 Disposition

A total of 40,805 participants were randomized: 20,402 participants to mRNA-1010 and 20,403 participants to SD comparator (Table 2). More than 95% of participants completed the study. The most common reasons for study discontinuation were lost to follow-up and withdrawal of consent.

Analysis sets for the overall study population and age subgroups are presented in Table 3.

Table 2: Study 304 Participant Disposition (Randomization Set)

	mRNA-1010 37.5 µg (N=20,402) n (%)	Active SD Comparator (N=20,403) n (%)
Received injection	20349 (99.7)	20354 (99.8)
Completed the study[a]	19568 (95.9)	19622 (96.2)
Discontinued from the study	834 (4.1)	781 (3.8)
Reason for discontinuation of study		
Lost to follow-up	435 (2.1)	420 (2.1)
Withdrawal of consent	261 (1.3)	255 (1.2)
Death	40 (0.2)	34 (0.2)
Physician decision	42 (0.2)	25 (0.1)
Randomized by mistake	17 (<0.1)	16 (<0.1)
Adverse event	3 (<0.1)	2 (<0.1)
Protocol deviation	2 (<0.1)	1 (<0.1)
SAR/reactogenicity event	0	0
Other	34 (0.2)	28 (0.1)

SAR: serious adverse reaction; SD: standard dose.
Numbers are based on planned vaccination group and percentages are based on the number of participants in the Randomization 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.

Table 3: Study 304 Analysis Sets

	≥50 Years		50–64 Years		≥65 Years	
	mRNA-1010 37.5 µg	Active SD Comparator	mRNA-1010 37.5 µg	Active SD Comparator	mRNA-1010 37.5 µg	Active SD Comparator
Randomization Set	20402	20403	10645	10641	9757	9762
Per-Protocol Set, n (%)[a]	20178 (98.9)	20122 (98.6)	10542 (99.0)	10501 (98.7)	9637 (98.8)	9623 (98.6)
Per-Protocol Immunogenicity Subset, n (%)[a,b]	1167 (5.7)	1175 (5.8)	581 (5.5)	592 (5.6)	586 (6.0)	583 (6.0)
Safety Set, n (%)[a]	20350 (99.7)	20353 (99.8)	10624 (99.8)	10615 (99.8)	9726 (99.7)	9738 (99.8)
Solicited Safety Subset, n (%)[a, b]	3015 (14.8)	2997 (14.7)	1510 (14.2)	1502 (14.1)	1505 (15.4)	1495 (15.3)

SD: standard dose

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

b. The Per-Protocol Immunogenicity Subset was based on a target of 2400 participants, and the Solicited Safety Subset was based on a target of approximately 6000 participants.

6.3.1.2 Demographics and Baseline Characteristics

Baseline demographics and characteristics were balanced between the mRNA-1010 and SD comparator groups.

In the total Safety Set of 40,303 participants, the median age was 64.0 years (range: 50 to 97 years); 52.2% of participants were 50-64 years and 47.8% of participants were ≥65 years, including 11.6% of participants who were ≥75 years. Most (82.7%) participants were White and identified as not Hispanic or Latino (88.2%); 56.8% were female (Table 4).

Table 4: Study 304 Demographics (Safety Set)

	≥50 Years		50–64 Years		≥65 Years	
	mRNA-1010 37.5 µg (N=20350)	Active SD Comparator (N=20353)	mRNA-1010 37.5 µg (N=10624)	Active SD Comparator (N=10615)	mRNA-1010 37.5 µg (N=9726)	Active SD Comparator (N=9738)
Age (years)						
Median (min, max)	64.0 (50, 97)	64.0 (50, 96)	58.0 (50, 64)	58.0 (50, 64)	70.0 (65, 97)	70.0 (65, 96)
Sex, n (%)						
Male	8834 (43.4)	8720 (42.8)	4,447 (41.9)	4,487 (42.3)	4,387 (45.1)	4,233 (43.5)
Female	11516 (56.6)	11633 (57.2)	6177 (58.1)	6128 (57.7)	5339 (54.9)	5505 (56.5)
Race, n (%)						
White	16814 (82.6)	16811 (82.6)	8,423 (79.3)	8,419 (79.3)	8,391 (86.3)	8,392 (86.2)
Black or African American	2687 (13.2)	2698 (13.3)	1,655 (15.6)	1,626 (15.3)	1,032 (10.6)	1,072 (11.0)
Asian	496 (2.4)	483 (2.4)	326 (3.1)	332 (3.1)	170 (1.8)	151 (1.6)
American Indian or Alaska Native	72 (0.4)	86 (0.4)	38 (0.4)	49 (0.5)	34 (0.3)	37 (0.4)
Native Hawaiian or Other Pacific Islander	20 (<0.1)	19 (<0.1)	38 (0.4)	49 (0.5)	3 (<0.1)	6 (<0.1)
Multiple	109 (0.5)	104 (0.5)	64 (0.6)	72 (0.7)	45 (0.5)	32 (0.3)
Other	51 (0.3)	55 (0.3)	38 (0.4)	39 (0.4)	13 (0.1)	16 (0.2)
Ethnicity, n (%)						
Not Hispanic or Latino	17908 (88.0)	17985 (88.4)	9260 (87.2)	9257 (87.2)	13 (0.1)	16 (0.2)
Hispanic or Latino	2147 (10.6)	2067 (10.2)	1,222 (11.5)	1,211 (11.4)	925 (9.5)	856 (8.8)
Region, n (%)[a]						
North America	14333 (70.4)	14340 (70.5)	7,034 (66.2)	7,022 (66.2)	7299 (75.1)	7319 (75.2)
Europe	5843 (28.7)	5833 (28.7)	3458 (32.5)	3460 (32.6)	2385 (24.5)	2373 (24.4)
East Asia	174 (0.9)	180 (0.9)	132 (1.2)	133 (1.3)	42 (0.4)	47 (0.5)

SD: standard dose

a. North America includes United States and Canada; Europe includes Belgium, Bulgaria, Estonia, Finland, Georgia, Germany and United Kingdom; East Asia includes South Korea and Taiwan.

6.3.2 Study 303C Study Populations (≥65 Years)

6.3.2.1 Disposition

A total of 3003 participants were included in the randomized set: 1507 participants in the mRNA-1010 group and 1496 participants in the HD comparator group (Table 5). More than 97% of participants completed the study. The most common reasons for study discontinuation were lost to follow-up and withdrawal of consent.

Analysis sets are presented in Table 6.

Table 5: Study 303C Disposition of Participants (Randomization Set)

	mRNA-1010 50 µg (N=1507) n (%)	Active HD Comparator (N=1496) n (%)
Received injection	1504 (99.8)	1492 (99.7)
Completed the study[a]	1484 (98.5)	1456 (97.3)
Discontinued from the study	23 (1.5)	40 (2.7)
Reason for discontinuation of study		
Lost to follow-up	10 (0.7)	25 (1.7)
Withdrawal by participant	9 (0.6)	10 (0.7)
Death	3 (0.2)	1 (<0.1)
Physician decision	1 (<0.1)	1 (<0.1)
Noncompliance with study procedure	0	1 (<0.1)
Other	0	2 (0.1)

HD: high dose

a. Participants are considered completed the study if they completed the final visit on Day 181 (Month 6).

Table 6: Study 303C Analysis Sets

	mRNA-1010 50 µg	Active HD Comparator
Randomization Set	1507	1496
Per-protocol Immunogenicity Set[a], n (%)	1425 (94.6)	1409 (94.2)
Safety Set[a,b]	1502 (99.7)	1490 (99.6)
Solicited Safety Set[a,b], n (%)	1502 (99.7)	1490 (99.6)

HD: high dose; SD: standard dose
Participants who received more than 1 study injection (mRNA-1010 and/or active comparator) were considered duplications and were only included in the Randomization Set.
1 participant randomized to Active HD Comparator received SD comparator and was only included in the Randomization Set.
a. b. Safety Set and Solicited Safety Set were based on the actual study vaccine received.

6.3.2.2 Demographics and Baseline Characteristics

Baseline demographics and characteristics were balanced across study intervention groups (Table 7).

In Study 303C Safety Set, 57.8% of participants were female, 77.9% were aged 65-74 years, and 22.1% were aged ≥75 years. The majority of participants identified as White (82.7%), followed by Black or African American (15.3%).

Table 7: Study 303C Baseline Demographics and Characteristics (Safety Set)

	mRNA-1010 50 μg (N=1502)	Active HD Comparator (N=1490)
Age (years)		
Mean (standard deviation)	71.1 (4.92)	71.0 (4.95)
Median (min, max)	70.0 (65, 93)	70.0 (64, 93)
Age Group, n (%)		
65-74 years	1176 (78.3)	1154 (77.4)
≥75 years	326 (21.7)	335 (22.5)
Sex, n (%)		
Female	878 (58.5)	852 (57.2)
Male	624 (41.5)	638 (42.8)
Race, n (%)		
White	1255 (83.6)	1220 (81.9)
Black or African American	224 (14.9)	235 (15.8)
Asian	10 (0.7)	10 (0.7)
American Indian or Alaska Native	4 (0.3)	9 (0.6)
Native Hawaiian or Other Pacific Islander	2 (0.1)	0
Multiple	2 (0.1)	6 (0.4)
Other	1 (<0.1)	4 (0.3)
Ethnicity, n (%)		
Not Hispanic or Latino	1037 (69.0)	1021 (68.5)
Hispanic or Latino	450 (30.0)	454 (30.5)

HD: high dose

7 EFFICACY AND IMMUNOGENICITY IN ADULTS 50–64 YEARS

Summary

- In Study 304, mRNA-1010 demonstrated superior efficacy vs SD comparator in adults 50–64 year of age (rVE: 26.1% [95% CI: 12.3, 37.7]). rVE point estimates by individual strain were consistent with the overall rVE; like other licensed enhanced vaccines, greater uncertainty was observed for B/Victoria, reflecting the smaller case numbers typical of the epidemiology in older adults.
- The efficacy advantage for mRNA-1010 was observed early and maintained over a full influenza season.
- mRNA-1010 induced higher HAI Ab levels for each influenza strain, aligning with the superior VE induced by mRNA-1010 relative to SD comparator against clinical ILI.

7.1 Epidemiology Introduction

Adults 50-64 years of age represent a substantial and often underrecognized portion of the influenza disease burden. In the US, adults 50-64 years consistently account for a considerable proportion of influenza-related hospitalizations each season, with hospitalization rates substantially higher than those observed in younger adults. During the 2024/2025 season, the hospitalization rate among adults 50-64 years reached 223.3 per 100,000, nearly three times higher than that observed in adults 18-49 years (CDC 2026b).

The burden of influenza in adults 50-64 years is influenced by an increasing prevalence of underlying medical conditions, which rises sharply beginning in midlife and are a key driver of severe influenza outcomes. The higher comorbidity rate in this population contributes to the increase in risk of complications, including hospitalization and death, compared with younger adult populations.

In addition to clinical burden, influenza in adults 50-64 years has important societal implications. Individuals in this age group represent a large proportion of the workforce, and influenza-related illness contributes to absenteeism, reduced productivity, and indirect economic costs. Together, these factors underscore the public health importance of improving influenza prevention strategies in adults 50-64 years of age.

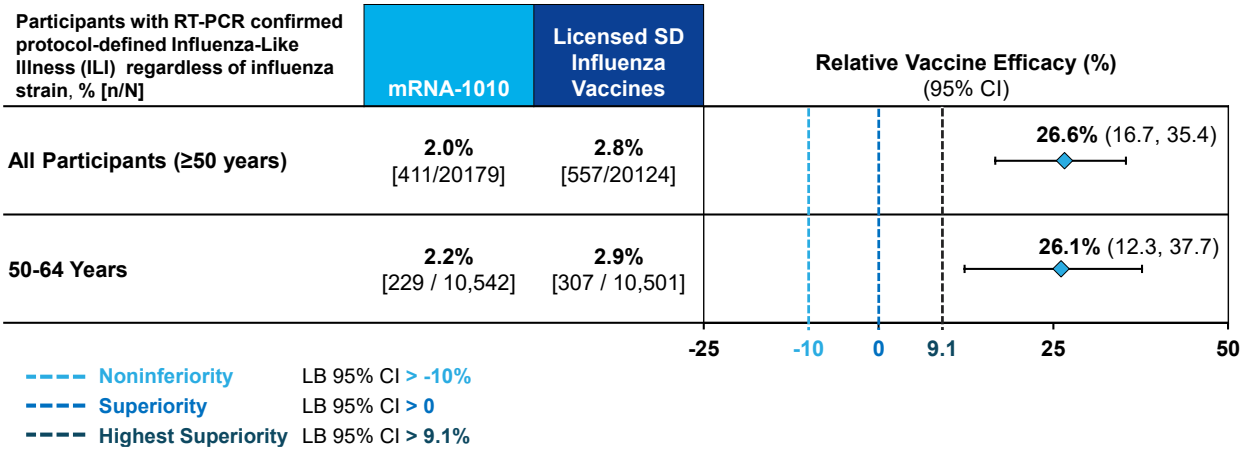
7.2 Efficacy and Immunogenicity (50–64 years)

7.2.1 Relative Vaccine Efficacy

The primary analysis of efficacy for adults 50–64 years was performed in the subgroup of 21,043 participants in the PP Set. A total of 536 PCR-confirmed ILI cases were accrued and analysis of these yielded an rVE of 26.1% (95% CI: 12.3, 37.7; mRNA-1010 relative to SD comparator).

Although success criteria were not designated for this supportive analysis, the point estimate and LB of the 95% CI (12.3) illustrate that efficacy in the 50-64 year age group is consistent with that in the overall population, which met the highest level of success specified for the primary analysis: LB of the 95% CI >9.1% (Figure 6).

Figure 6: Study 304 Relative Vaccine Efficacy (PP Set 50–64 years)



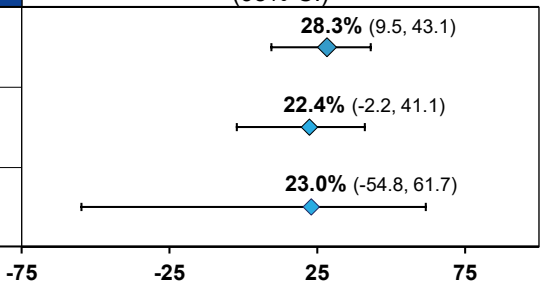
CI: confidence interval; LB: lower bound; PP: Per-Protocol; RT-PCR: reverse transcription polymerase chain reaction; SD: standard dose

7.2.1.1 Results by Strain

PCR-confirmed ILI cases were accrued from each of the three vaccine-matched strains (293 H1N1, 205 H3N2, and 32 B/Victoria). Results in participants 50–64 years were generally aligned with those of the overall study population. Wider 95% CIs are evident for rVE against B/Victoria, reflecting the relatively small number of B/Victoria cases accrued. Nonetheless, the consistent rVE point estimates across strains is reassuring (Figure 7).

Figure 7: Study 304 Relative Vaccine Efficacy by Strain (PP Set 50–64 Years)

50–64-Year-Old Participants with ILI[1] by influenza strain, % [n]	mRNA-1010 (N = 10,542)	Licensed SD Influenza Vaccines (N = 10,501)
Influenza A H1N1	**1.2%** [123]	**1.6%** [170]
Influenza A H3N2	**0.9%** [90]	**1.1%** [115]
Influenza B Victoria	**0.1%** [14]	**0.2%** [18]



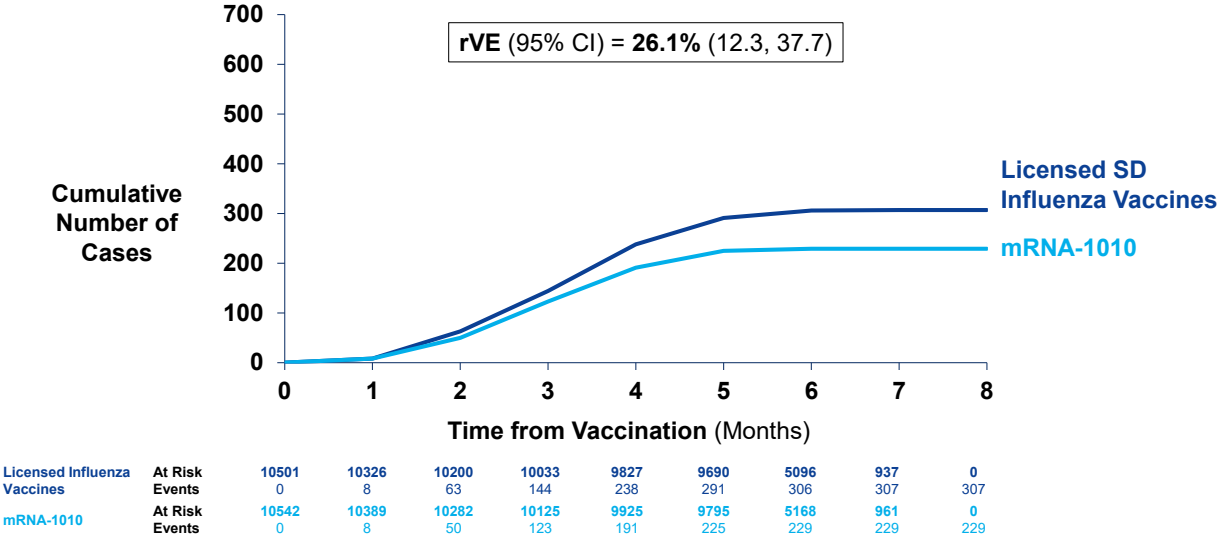
CI: confidence interval; ILI: influenza-like illness; PP: per-protocol; RT-PCR: reverse transcription polymerase chain reaction; SD: standard dose
1. Based on RT-PCR-confirmed protocol-defined ILI

Efficacy of mRNA-1010 relative to SD comparator was maintained when alternate ILI case definitions were assessed. Using case definitions tested in other studies of enhanced vaccines that required the occurrence of temperature ≥37.2ºC (modified CDC ILI case definition, DiazGranados et al 2014), rVE remained consistent (21.1%; 95% CI: 0.5, 37.4).

7.2.1.2 Analysis of Cumulative Incidence of Primary Endpoint over Time

Analysis of the cumulative incidence (Kaplan-Meier analysis) of efficacy endpoints over time showed that the efficacy advantage for mRNA-1010 was observed early and maintained over a full influenza season (Figure 8). Results in the 50–64-year age group thus align with those of the overall 304 study group.

Figure 8: Study 304 Cumulative Number of RT-PCR-confirmed Protocol-Defined ILI Cases (PP Set 50–64 years)



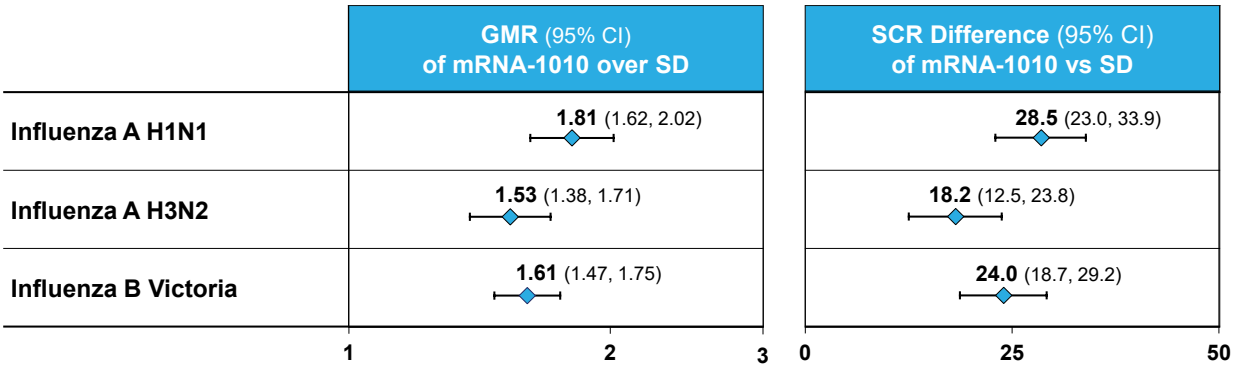
CI: confidence interval; ILI: influenza-like illness; PP: per-protocol; RT-PCR: reverse transcription polymerase chain reaction; rVE: relative vaccine efficacy; SD: standard dose
Based on RT-PCR-confirmed protocol-defined ILI

7.2.2 Immunogenicity

Vaccine-induced HAI Ab responses were measured per strain, and vaccine-induced responses were compared between study groups.

In participants 50–64 years, mRNA-1010 induced higher HAI Ab levels for each influenza strain, aligning with the superior VE induced by mRNA-1010 relative to SD comparator against clinical ILI. For each influenza strain, the point estimates for Day 29 GMR (mRNA-1010/SD comparator) were all >1.5 (95% CI LBs were >1.3) and SCR differences ([mRNA-1010 SCR] – [SD comparator SCR]) were all positive (95% CI LBs were >12%) (Figure 9).

Figure 9: Study 304 HAI Ab GMR and SCR Differences at Day 29 (PPIS 50–64 Years)



ANCOVA: analysis of covariance; CI: confidence interval; GMR: geometric mean titer ratio; HAI Ab: hemagglutination inhibition antibody; PPIS: Per-Protocol Immunogenicity Set; SD: standard dose; SRC: seroconversion rate

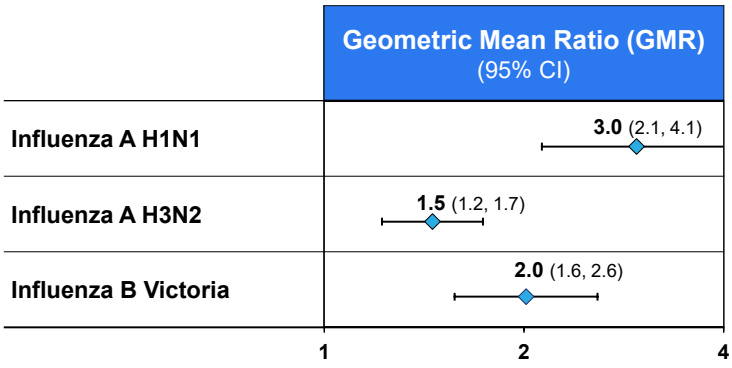
Number of participants in PPIS: 581 in mRNA-1010 group and 592 in active comparator group.

The log-transformed antibody levels are analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed Baseline HAI titers as a fixed covariate, adjusting for the randomization stratification factor(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine). The model-based GMR, and its corresponding 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Rate of seroconversion is defined as the proportion of participants with either a Baseline HAI titer <1:10 and a postbaseline titer ≥1:40 or a Baseline HAI titer ≥1:10 and a minimum 4-fold-rise in postbaseline HAI antibody titer; 95% CI is calculated using the Miettinen-Nurminen (score) method.

mRNA-1010-induced Ab measured by HAI assay are aligned with those measured by MN assay. Neutralizing Ab levels showed same pattern of responses to those of the HAI assay, with higher MN Ab levels for each influenza strain relative to SD comparator. For each influenza strain, the point estimates for Day 29 GMR (mRNA-1010/SD comparator) were all >1.5 (95% CI LBs were >1.2) (Figure 10).

Figure 10: Study 304 MN Ab GMR at Day 29 (PPIS, Participants with MN Ab Values 50–64 Years)



Ab: antibody; ANCOVA: analysis of covariance; CI: confidence interval; MN: microneutralization assay; PPIS: Per-protocol Immunogenicity Set

Number of participants in PPIS with MN values at Baseline and Day 29: 123 in mRNA-1010 and 128 in active comparator.

The log-transformed antibody levels are analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed Baseline MN titers as a fixed covariate, adjusting for the randomization stratification factor(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine). The model-based GMR, and its corresponding 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

7.3 HAI Ab Levels and Protection

Consistent with the established relationship between HAI Ab responses and licensed influenza vaccine protection from ILI, superior rVE in Study 304 was accompanied by higher post-vaccination HAI Ab levels across influenza strains. Formal correlates-of-protection analyses demonstrated an association between higher Day 29 HAI antibody titers and reduced risk of ILI for influenza A/H1N1 and influenza A/H3N2 that reached statistical significance, supporting the relevance of HAI responses as a marker reasonably likely to predict clinical benefit (Table 16, Appendix 13.2). For influenza B, a statistically significant association was not observed for either mRNA-1010 or the licensed SD comparator, suggesting this was not specific to mRNA-1010. Interpretation was limited in part by the relatively small number of influenza B cases and a marked geographic concentration of cases, with most arising from a single country (Bulgaria). Analyses excluding this geography showed a positive relationship between HAI Ab levels and protection against B strains in both vaccine groups, although statistical significance was not achieved because of the small number of cases (Table 17,

Appendix 13.2). Taken together, the efficacy and immunogenicity data support a consistent relationship between HAI Ab responses and protection, with the strongest statistical evidence observed for the influenza A strains. Importantly, mRNA-1010 rVE against influenza B was directionally consistent with overall rVE and consistent with rVE observed for licensed enhanced vaccines. Overall, evidence remains consistent with a protective effect despite the limitations of the influenza B correlates analyses. Additional analyses are ongoing.

7.4 Conclusions: Efficacy and Immunogenicity, in Adults 50–64 Years

Data supporting the efficacy and immunogenicity of mRNA-1010 in adults 50–64 years are summarized from 21,239 participants in Study 304. Pivotal clinical efficacy data (Study 304) show that mRNA-1010 efficacy met superiority criteria (LB 95% CI >9.1%) relative to SD comparator for the primary endpoint (PCR-confirmed ILI caused by any A or B influenza strain). Results show consistent rVE point estimates across individual influenza strains with more uncertainty for the B/Victoria, reflecting the smaller accrual of influenza B cases typical of older populations and other enhanced vaccine trials. Protection induced by mRNA-1010 is maintained through the full influenza season. mRNA-1010 induced HAI Ab responses were higher than those of the comparator, paralleling the superiority in clinical efficacy. The mRNA-1010 vaccine provides better potential vaccine antigenic fidelity against a virus known for high seasonal variability and antigenic drift. As such, mRNA-1010 offers unique potential advantages compared to vaccines currently licensed for individuals 50 to 64 years of age.

8 EFFICACY AND IMMUNOGENICITY IN ADULTS ≥65 YEARS

Summary

- Adults ≥65 years of age account for most influenza-related hospitalizations and deaths in the US and globally.
- In Study 304, mRNA-1010 demonstrated superior efficacy vs SD comparator in adults 65 years and older (rVE: 27.4% [95% CI: 12.1, 40.0]). rVE point estimates by individual strain were consistent with the overall rVE; like other licensed enhanced vaccines, greater uncertainty was observed for B/Victoria, reflecting the smaller case number typical of the epidemiology in older adults.
- The efficacy advantage for mRNA-1010 was observed early and maintained over a full influenza season.
- The superior rVE demonstrated by mRNA-1010 in Study 304 is paralleled by levels of HAI Ab that are higher than those of the SD comparator in Study 304 and superior to those of a licensed HD comparator (Fluzone HD) in Study 303C.
- The relationship between immunogenicity and efficacy observed in Study 304 provides confidence that the efficacy of mRNA-1010 will be similar compared to HD vaccines.

8.1 Epidemiology Introduction

Adults ≥65 years of age bear the highest burden of severe influenza disease, accounting for most influenza-related hospitalizations and deaths in the US and globally. In recent years, adults ≥65 years have represented approximately 50-70% of influenza-associated hospitalizations and 70-85% of influenza-associated deaths in the US (CDC 2024b). During the 2024/2025 season, hospitalization and mortality rates in adults ≥65 years reached 666.3 and 51.9 per 100,000, respectively, markedly exceeding those observed in younger age groups (CDC 2026b).

The increased susceptibility to severe outcomes in older adults likely relates to factors including immunosenescence and chronic comorbid conditions common to older adults. Among individuals 65 years and older, enhanced influenza vaccines (e.g., high-dose, adjuvanted, and recombinant formulations) have improved protection compared with standard-dose vaccines. Nonetheless, a substantial residual disease burden remains. As a result, adults ≥65 years remain a priority population for improved influenza vaccines and prevention strategies aimed at reducing severe disease outcomes.

8.2 Conclusions: Efficacy and Immunogenicity in Adults ≥65 Years

Data summarized in this report support approval of mRNA-1010 in adults 65 years and older. Results show that mRNA-1010 met efficacy criteria for superiority relative to SD comparator (Study 304; rVE LB 95% CI >9.1%) for the primary endpoint (PCR-confirmed ILI caused by any A or B strain). Results show consistent rVE point estimates across individual influenza strains, with more uncertainty for the B/Victoria, reflecting the smaller accrual of influenza B cases typical of older populations and other enhanced vaccine trials. Protection induced by mRNA-1010 is maintained through the full influenza season. Superior efficacy of mRNA-1010 was paralleled by higher Ab responses relative to SD comparator in Study 304 and by superior responses to those induced by Fluzone HD in Study 303C. Taken together, results establish that mRNA-1010 elicits protection in older adults of similar magnitude to that of enhanced vaccines. The mRNA-1010 vaccine provides greater manufacturing flexibility and high antigenic fidelity against a virus known for high seasonal variability and antigenic drift. As such, mRNA-1010 offers unique potential advantages compared to vaccines currently licensed for adults 65 years and older.

8.3 Efficacy and Immunogenicity (≥65 years)

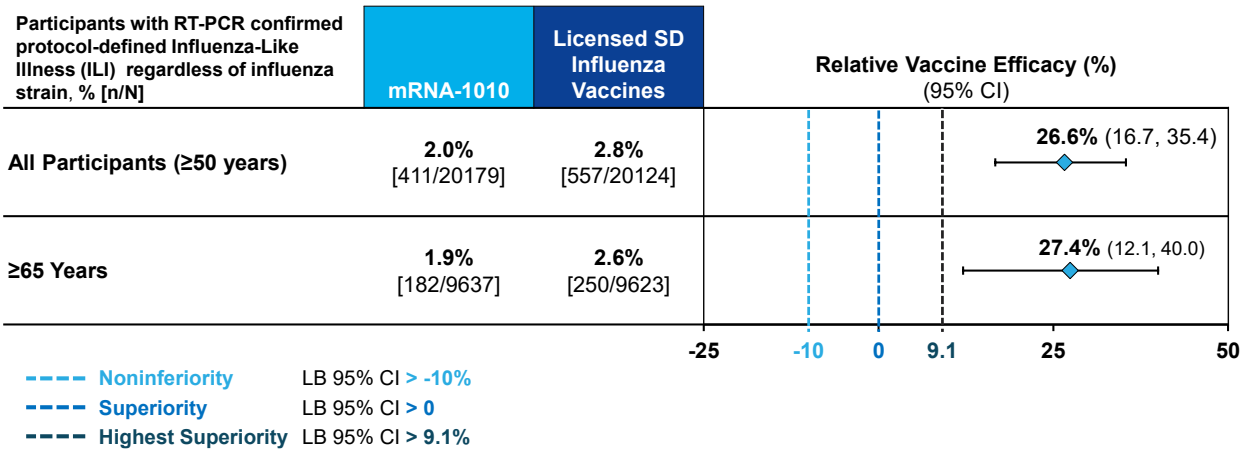
8.3.1 Relative Vaccine Efficacy

The primary analysis of efficacy for adults ≥65 years was performed in the subgroup of 19,260 participants in the PP Set. A total of 432 PCR-confirmed ILI cases were accrued, and analysis of these yielded an rVE of 27.4% (95% CI: 12.1, 40.0; mRNA-1010 relative to SD comparator). Although success criteria were not designated for this supportive analysis, the point estimate and LB of the 95% CI (12.1) illustrate that efficacy in the ≥65 year age group is consistent with that in the overall 304 study population (which met the highest level of success specified for the primary analysis: LB of the 95% CI >9.1%; Figure 11).

The level of rVE demonstrated by mRNA-1010 in the Phase 3 Study 304 is comparable to levels of rVE against SD comparator that led to approval of enhanced influenza vaccines for adults ≥65 years (i.e., Fluzone HD vs Fluzone; Flublok vs Fluarix). The comparable level of rVE predicts that mRNA-1010 will deliver similar protection against ILI in older adults to that of other enhanced vaccines.

Efficacy of mRNA-1010 relative to SD comparator was maintained when alternate ILI case definitions were assessed. Using case definitions tested in other studies of enhanced vaccines that required the occurrence of temperature ≥37.2^{o}C (modified CDC ILI case definition), rVE remained consistent (26.7%; 95% CI: 4.4, 43.9).

Figure 11: Study 304 Relative Vaccine Efficacy Influenza-Like Illness Events (PP Set ≥65 Years)

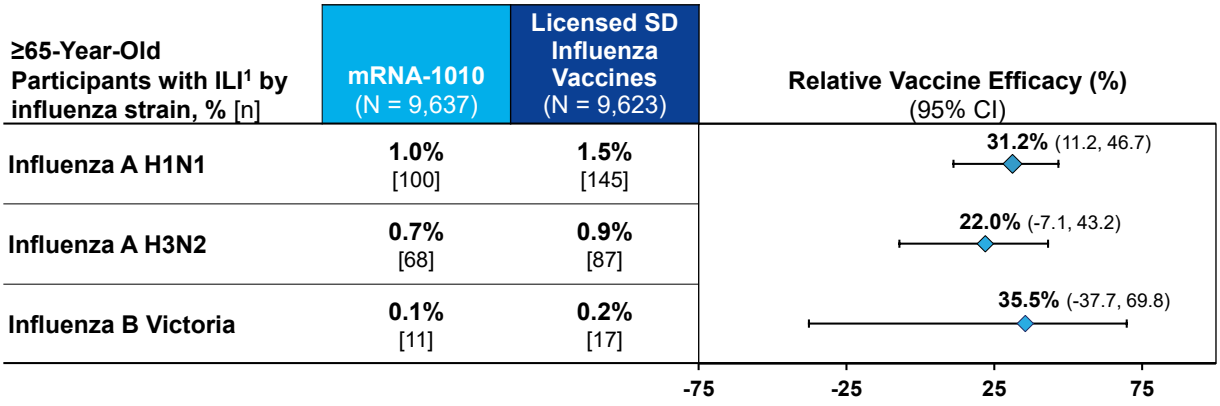


CI: confidence interval; LB: lower bound; PP per=protocol; RT-PCR: reverse transcription polymerase chain reaction; SD: standard dose

8.3.1.1 Results by Strain

PCR-confirmed ILI cases were accrued in this age subgroup from each of the three vaccine-matched strains (245 A/H1N1, 155 A/H3N2 and 28 B/Victoria). Results in participants ≥65 years were generally aligned with those of the overall study population. Wider 95% CIs are evident for rVE against B/Victoria, reflecting the relatively small number of B/Victoria cases accrued. Nonetheless, the consistent rVE point estimates across strains is reassuring (Figure 12).

Figure 12: Study 304 Relative Vaccine Efficacy by Influenza Strain (PP Set ≥65 Years)

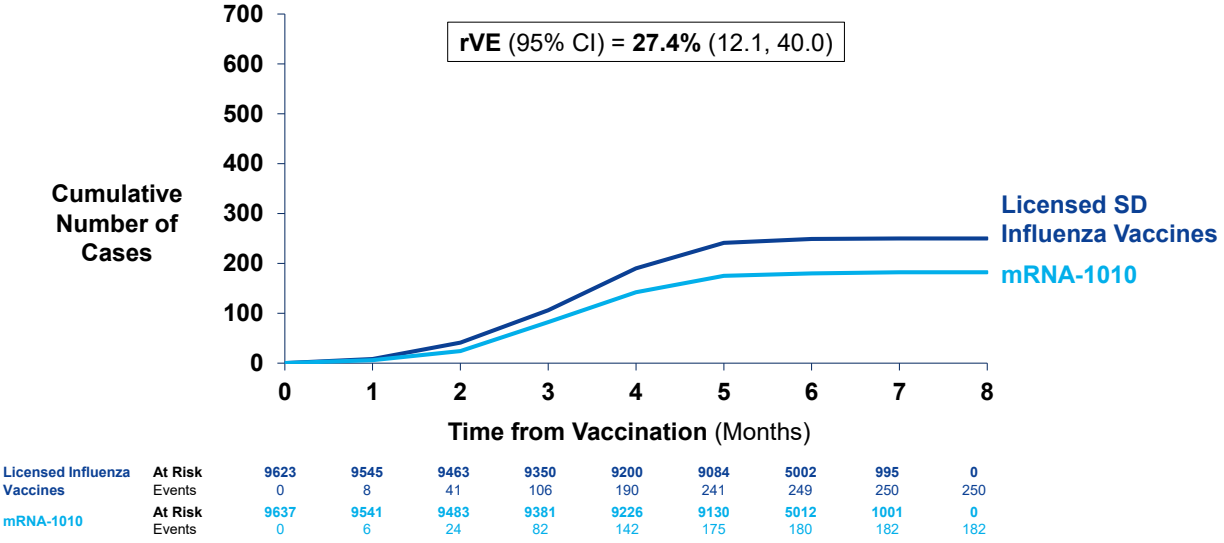


CI: confidence interval; ILI: influenza-like illness; PP: per-protocol; RT-PCR: reverse transcription polymerase chain reaction; SD: standard dose
1. Based on RT-PCR-confirmed protocol-defined ILI

8.3.1.2 Analysis of Cumulative Incidence of Primary Endpoint over Time

Analysis of the cumulative incidence (Kaplan-Meier analysis) of efficacy endpoints over time showed that the efficacy advantage for mRNA-1010 was observed early and maintained over a full influenza season (Figure 13). Results in the ≥65-year age group thus align with those of the overall 304 study group.

Figure 13: Study 304 Cumulative Number of Influenza Cases (PP Set ≥65 years)



CI: confidence interval; ILI: influenza-like illness; PP: per-protocol; RT-PCR: reverse transcription polymerase chain reaction; rVE: relative vaccine efficacy; SD: standard dose
Based on RT-PCR-confirmed protocol-defined ILI

8.3.1.3 rVE Against ILI-associated Healthcare Encounters

Adults ≥65 years are at increased risk of more severe outcomes from ILI – including hospitalization – than adults <65 years of age. As part of an exploratory analysis of healthcare encounters associated with RT-PCR-confirmed protocol-defined ILI, results showed fewer occurrences in the mRNA-1010 than for SD comparator group in participants ≥65 years (Table 8). The rVE for participants seeking a higher level of care (hospitalization, ER visit, or urgent care visit) was 65.1% (95% CI: 17.4, 85.2; 7 mRNA-1010 vs 20 SD comparator participants). Even for categories with numbers too small to calculate rVE, case splits were favorable for mRNA-1010 (hospitalization: 1 in mRNA-1010 vs 4 in SD comparator; ER visits: 1 in mRNA-1010 vs 5 in SD comparator).

Table 8: mRNA-1010 Reduces ILI-associated Healthcare Outcomes Relative to Licensed SD Comparator in Adults ≥ 65 (Per-Protocol Set)

	mRNA-1010 N=9637	Comparator N=9623	rVE (95% CI)
Healthcare encounter	37 (0.4)	56 (0.6)	34.1 (0.1, 56.5)
Seek higher level of care	7 (0.10)	20 (0.2)	65.1 (17.4, 85.2)
Hospitalization	1 (<0.1)	4 (<0.1)	n.c.
ER	1 (<0.1)	5 (<0.1)	n.c.
Urgent care clinical visit	5 (<0.1)	12 (0.1)	n.c.
Outpatient clinical visit	30 (0.3)	38 (0.4)	21.2 (-27.1, 51.2)

CI: confidence interval; ER: emergency room; ILI: influenza-like illness; nc: not calculated; rVE: relative vaccine efficacy

n.c.: rVE not calculated due to too few cases.

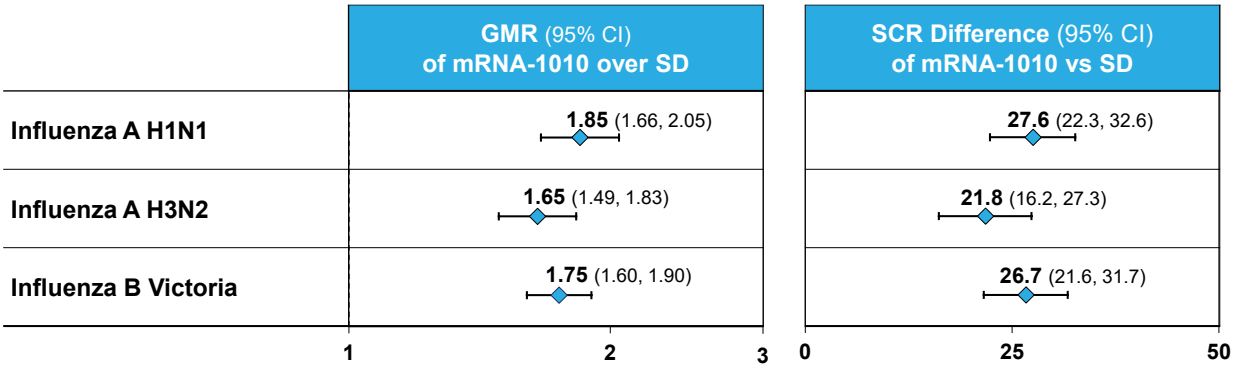
8.3.2 Immunogenicity

The immunogenicity of mRNA-1010 in adults 65 years and older was evaluated in two separate Phase 3 studies: Study 304 assessed the level of HAI Ab induced by mRNA-1010 relative to SD comparator in adults ≥65 years in the pivotal study (1,169 participants); Study 303C tested mRNA-1010-induced responses for noninferiority relative to HD comparator in adults ≥65 years (2,834 participants). HAI Ab levels were measured for all vaccine-matched strains at Baseline and Day 29 in both studies.

8.3.2.1 Study 304 (mRNA-1010 vs SD comparator)

In adults ≥65 years in Study 304, analyses of GMR (mRNA-1010 Day 29 GMT/SD comparator Day 29 GMT) showed that mRNA-1010 induced higher HAI Ab levels than did the SD comparator (all point estimates ≥1.6 [95% CI LBs were ≥1.5]) (Figure 14). Similarly, SCR differences ([mRNA-1010 SCR] – [SD comparator]) were all positive (95% CI LBs were >16%). Accordingly, the higher induced HAI Ab responses were congruent with the superior clinical efficacy of mRNA-1010 relative to SD comparator in Study 304 participants ≥65 years.

Figure 14: Study 304 HAI Ab GMR and SCR at Day 29 (PPIS ≥65 Years)



ANCOVA: analysis of covariance; CI: confidence interval; GMR: geometric mean titer ratio; HAI Ab: hemagglutination inhibition antibody; PPIS: Per-Protocol Immunogenicity Set; SRC: seroconversion rate

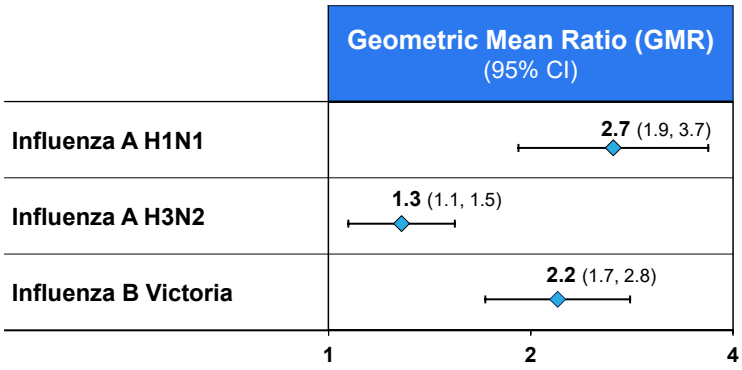
Number of participants in PPIS: 586 in mRNA-1010 group and 583 in active comparator group.

The log-transformed antibody levels are analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed Baseline HAI titers as a fixed covariate, adjusting for the randomization stratification factor(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine). The model-based GMR, and its corresponding 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Rate of seroconversion is defined as the proportion of participants with either a Baseline HAI titer <1:10 and a postbaseline titer ≥1:40 or a Baseline HAI titer ≥1:10 and a minimum 4-fold-rise in postbaseline HAI antibody titer; 95% CI is calculated using the Miettinen-Nurminen (score) method.

mRNA-1010-induced Ab measured by HAI assay are aligned with those measured by MN assay. Neutralizing Ab levels showed same pattern of responses to those of the HAI assay, with higher MN Ab levels for each influenza strain relative to SD comparator. For each influenza strain, the point estimates for Day 29 GMR (mRNA-1010/SD comparator) were all >1.3 (95% CI LBs were >1.0) (Figure 15).

Figure 15: Study 304 MN Ab GMR at Day 29 (PPIS Participants with MN Ab Values ≥65 Years)



ANCOVA: analysis of covariance; CI: confidence interval; GMR: geometric mean titer ratio; MN Ab: microneutralization antibody; PPIS: Per-Protocol Immunogenicity Set

Number of participants in PPIS with MN values at Baseline and Day 29: 124 in mRNA-1010 and 125 in active comparator.

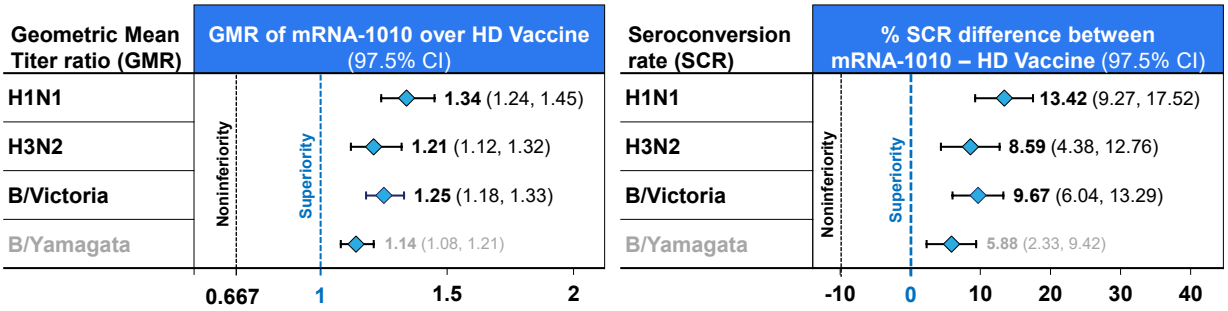
The log-transformed antibody levels are analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed Baseline MN titers as a fixed covariate, adjusting for the randomization stratification factor(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine). The model-based GMR, and its corresponding 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

8.3.2.2 Study 303C (mRNA-1010 vs HD comparator)

Immunogenicity results from Study 303C build further on those of the pivotal 304 efficacy study. In Study 303C, mRNA-1010-induced HAI Ab levels that were superior to HD comparator based on prespecified success criteria across all vaccine-matched strains (i.e., Day 29 GMR 97.5% CI LB >1.0 and SCR difference 97.5% CI LB >0% for all 8 co-primary endpoints; Figure 16).

An analysis of the correlation between induced HAI and occurrence of ILI confirms that mRNA-1010 induces HAI Ab and that increased Ab levels correspond with reduction in ILI. This pattern echoes that of conventional influenza vaccine (i.e. SD comparator), and as such supports the use of HAI to help infer effectiveness of mRNA-1010 (as with conventional vaccines). The induction of superior HAI Ab levels relative to HD comparator (Study 303C), together with direct clinical efficacy of mRNA-1010 in adults ≥65 years (Study 304), infer the effectiveness of mRNA-1010 in older adults.

Figure 16: Study 303C GMR and SCR at Day 29 (PPIS ≥65 Years)



ANCOVA: analysis of covariance; CI: confidence interval; GMR: geometric mean titer ratio; HAI: hemagglutination inhibition; HD: high dose; PPIS: Per-Protocol Immunogenicity Set; SRC: seroconversion rate

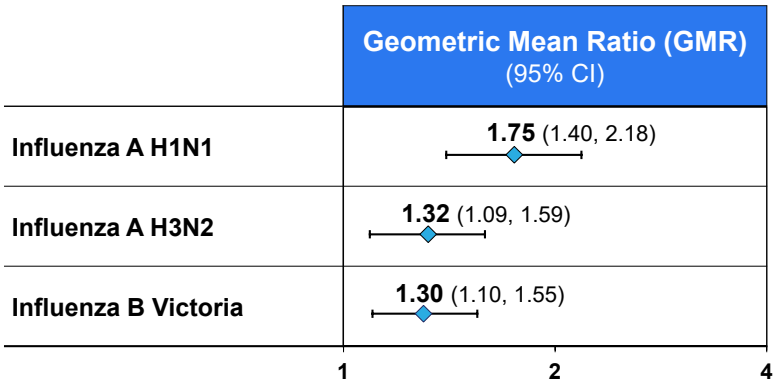
Number of participants in PPIS: 1425 in mRNA-1010 group and 1409 in active comparator group.

The log-transformed antibody levels are analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed Baseline HAI titers as a fixed covariate, adjusting for the randomization stratification factor(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine). The model-based GMR, and its corresponding 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

Rate of seroconversion is defined as the proportion of participants with either a Baseline HAI titer <1:10 and a postbaseline titer ≥1:40 or a Baseline HAI titer ≥1:10 and a minimum 4-fold-rise in postbaseline HAI antibody titer; 95% CI is calculated using the Miettinen-Nurminen (score) method.

The parallel between Ab levels measured by HAI assay or by MN assay was evident as well in comparison to HD comparator. Neutralizing Ab levels were superior to HD comparator for each influenza strain, with the point estimates for Day 29 GMR (mRNA-1010/HD comparator) all >1.3 (95% CI LBs were >1.09) (Figure 17).

Figure 17: Study 303C MN Ab GMR at Day 29 (PPIS, Participants with MN Ab Values ≥65 Years)



Ab: antibody; ANCOVA: analysis of covariance; CI: confidence interval; MN: microneutralization assay; PPIS: Per-protocol Immunogenicity Set

Number of participants in PPIS with MN values at Baseline and Day 29: 250 in mRNA-1010 and 250 in active comparator.

The log-transformed antibody levels are analyzed using an ANCOVA model with vaccination group as the fixed variable, log-transformed Baseline MN titers as a fixed covariate, adjusting for the randomization stratification factor(s): age group (≥50 to <65 years and ≥65 years) and flu vaccine status in the previous influenza season (received seasonal flu vaccine, did not receive seasonal flu vaccine). The model-based GMR, and its corresponding 95% CI are obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

9 OVERVIEW OF SAFETY IN ADULTS ≥50 YEARS

Summary

- Safety was evaluated in:
  - Pivotal Study 304, which evaluated mRNA-1010 TIV (37.5 µg) vs SD comparator in 40,703 adults ≥50 years
  - Study 303C, which evaluated mRNA-1010 QIV (50 µg) vs HD comparator in 2,992 adults ≥65 years
  - Integrated safety data from participants ≥50 years in the 4 completed Phase 3 studies, in which 71,916 adults received mRNA-1010 TIV or QIV (12.5 µg per strain) or SD/HD comparator (TIV or QIV) and had at least 6 months of safety follow-up.
- Rates of reported solicited local and systemic ARs were higher in the mRNA-1010 group than in SD or HD comparator groups, but most solicited ARs were Grade 1 or 2 in severity, transient, and resolved without medical attention. Injection site pain was the most common solicited local AR, and fatigue was the most common solicited systemic AR.
- No safety concerns were identified based on review of unsolicited AEs from individual Phase 3 studies nor based on review of an integrated summary safety analysis of deaths, SAEs, and AESIs, from a dataset of 35,965 mRNA-1010-recipients ≥50 years (17,567 of whom were ≥65 years).
- Unsolicited AEs within 28 days and during the entire study period were reported in similar proportions of participants in each treatment group. Incidence of fatal SAEs and other SAEs was generally balanced between the pooled study intervention groups.

The safety and reactogenicity profile of a single injection of mRNA-1010 (12.5 µg per strain) is clinically acceptable in adults ≥50 years.

9.1 Safety Database

The safety profile for mRNA-1010 is primarily based on the following data sources:

- Reactogenicity data from Study 304 in adults ≥ 50 years of age forms the basis for reactogenicity evaluation. Data are supplemented with results from Study 303C which evaluated mRNA-1010 relative to HD comparator in adults ≥ 65 years of age.

- Unsolicited AEs from Study 304 and Study 303C.
- A pooled analysis (ISS) of data for SAEs, deaths, and AESIs among 71,916 participants ≥50 years from all 4 Phase 3 studies.

9.2 Reactogenicity

In Study 304 and in Study 303C, most solicited local and systemic ARs were Grade 1 or Grade 2 in severity, transient, and reported by a greater proportion of participants in the mRNA-1010 group compared with the comparator group (Table 9 and Table 10). The most frequently reported solicited local AR was injection site pain and the most frequently reported solicited systemic AR was fatigue in the mRNA-1010 group and in the SD and HD comparator groups. Grade 3 solicited local and systemic ARs were more frequent in the mRNA-1010 group than in the SD or HD comparator groups, but the overall incidence was low, these were transient and did not require medical attention. No Grade 4 solicited ARs were reported in Study 304. For any solicited local or any solicited systemic AR, the median onset day was Day 2 in the mRNA-1010 group and Day 1 or Day 2 in the SD and HD groups. The median duration for any solicited local or any solicited systemic AR was 2 days in the mRNA-1010 and HD groups and 1 or 2 days in the SD group. Rates of any Grade 3 or 4 solicited local or systemic ARs were higher after enhanced influenza vaccine (i.e., for HD comparator in Study 303C) than SD vaccine comparator in 304. Like other vaccines delivering superior VE relative to that provided by SD vaccines, mRNA-1010 also results in higher levels of transient Grade 3 reactogenicity. In summary, although mRNA-1010 is associated with higher rates of transient reactogenicity than comparator influenza vaccines, the absolute incidence of Grade 3 reactions remained low (0.3%–1.5% for local reactions and 0.2%–3.2% for systemic reactions), reactions generally were short-lived with median durations of approximately 1 day and did not require medical attention. In analyses of solicited local and systemic ARs by age subgroups (50-64 and ≥65 years) from Study 304, in both the mRNA-1010 and SD comparator groups, reporting of solicited ARs was numerically lower in the older age groups than in younger age groups.

Table 9: Study 304 and Study 303C Summary of Participants with Solicited Local ARs within 7 Days After Injection by Maximum Toxicity Grade (Solicited Safety Subset/Set)

	Study 304 (≥50 Years)		Study 303C (≥65 Years)	
	mRNA-1010 37.5 µg (N=3015) n (%)	Active (SD) Comparator (N=2997) n (%)	mRNA-1010 50 µg (N=1502) n (%)	Active (HD) Comparator (N=1490) n (%)
Solicited local ARs – N1	3015	2997	1502	1490
Any[a]	2034 (67.5)	961 (32.1)	993 (66.1)	580 (38.9)
95% CI[b]	65.8, 69.1	30.4, 33.8	63.7, 68.5	36.4, 41.5
Grade 3	51 (1.7)	4 (0.1)	36 (2.4)	12 (0.8)
Grade 4	0	0	0	0
Pain – N1	3015	2997	1502	1490
Any[a]	1985 (65.8)	894 (29.8)	971 (64.6)	547 (36.7)
Grade 3	27 (0.9)	1 (<0.1)	23 (1.5)	6 (0.4)
Grade 4	0	0	0	0
Erythema (redness) – N1	3015	2997	1502	1489
Any[a]	117 (3.9)	38 (1.3)	42 (2.8)	20 (1.3)
Grade 3	10 (0.3)	2 (<0.1)	6 (0.4)	3 (0.2)
Grade 4	0	0	0	0
Swelling/induration (hardness) – N1	3015	2997	1502	1489
Any[a]	172 (5.7)	45 (1.5)	67 (4.5)	25 (1.7)
Grade 3	9 (0.3)	4 (0.1)	6 (0.4)	2 (0.1)
Grade 4	0	0	0	0
Axillary swelling or tenderness – N1	3015	2997	1502	1489
Any[a]	520 (17.2)	184 (6.1)	252 (16.8)	128 (8.6)
Grade 3	10 (0.3)	1 (<0.1)	8 (0.5)	6 (0.4)
Grade 4	0	0	0	0

AR: adverse reaction; CI: confidence intervals; HD: high dose; SD: standard dose. N = number of exposed participants who reported the event on any day within 7 days of study injection.
A Any = Grade 1 or higher.
B 95% CI was calculated using the Clopper-Pearson method.
Numbers are based on actual group and percentages are based on the number of exposed participants who submitted any data for the event (N1).

Table 10: Study 304 and Study 303C Summary of Participants with Solicited Systemic ARs Within 7 Days After Injection by Maximum Toxicity Grade (Solicited Safety Subset/Set)

	Study 304 (≥50 Years)		Study 303C (≥65 Years)	
	mRNA-1010 37.5 µg (N=3015) n (%)	Active (SD) Comparator (N=2997) n (%)	mRNA-1010 50 µg (N=1502) n (%)	Active (HD) Comparator (N=1490) n (%)
Solicited systemic ARs – N1	3015	2997	1502	1489
Any[a]	1750 (58.0)	970 (32.4)	920 (61.3)	490 (32.9)
95% CI[b]	56.3, 59.8	30.7, 34.1	58.7, 63.7	30.5, 35.4
Grade 3	167 (5.5)	27 (0.9)	101 (6.7)	25 (1.7)
Grade 4	0	0	2 (0.1)	0
Fever – N1	3001	2992	1502	1488
Any[a]	174 (5.8)	26 (0.9)	127 (8.5)	21 (1.4)
Grade 3	17 (0.6)	3 (0.1)	9 (0.6)	1 (<0.1)
Grade 4	0	0	2 (0.1)	0
Headache – N1	3015	2997	1502	1489
Any[a]	1140 (37.8)	538 (18.0)	592 (39.4)	258 (17.3)
Grade 3	59 (2.0)	10 (0.3)	35 (2.3)	10 (0.7)
Grade 4	0	0	0	0
Fatigue – N1	3015	2997	1502	1489
Any[a]	1360 (45.1)	609 (20.3)	669 (44.5)	293 (19.7)
Grade 3	97 (3.2)	13 (0.4)	52 (3.5)	12 (0.8)
Grade 4	0	0	0	0
Myalgia – N1	3015	2997	1502	1489
Any[a]	1067 (35.4)	348 (11.6)	626 (41.7)	239 (16.1)
Grade 3	76 (2.5)	7 (0.2)	48 (3.2)	11 (0.7)
Grade 4	0	0	0	0
Arthralgia – N1	3015	2997	1502	1489
Any[a]	839 (27.8)	317 (10.6)	529 (35.2)	210 (14.1)
Grade 3	57 (1.9)	6 (0.2)	35 (2.3)	11 (0.7)
Grade 4	0	0	0	0
Nausea/ vomiting – N1	3015	2997	1502	1489
Any[a]	259 (8.6)	102 (3.4)	192 (12.8)	63 (4.2)

Grade 3	5 (0.2)	2 (<0.1)	4 (0.3)	3 (0.2)
Grade 4	0	0	0	0
Chills – N1	3015	2997	1502	1489
Any[a]	688 (22.8)	129 (4.3)	443 (29.5)	115 (7.7)
Grade 3	62 (2.1)	4 (0.1)	18 (1.2)	5 (0.3)
Grade 4	0	0	0	0

AR: adverse reaction; CI: confidence intervals; HD: high dose; SD: standard dose. N = number of exposed participants who reported the event on any day within 7 days of study injection.
a. Any = Grade 1 or higher.
b. 95% CI was calculated using the Clopper-Pearson method.
Numbers are based on actual group and percentages are based on the number of exposed participants who submitted any data for the event (N1).

9.2.1 Study 304

9.2.1.1 Solicited Local Adverse Reactions

In Study 304, solicited local ARs were reported more frequently in the mRNA-1010 group compared with the SD comparator group (Table 9). Injection site pain was the most frequently reported solicited local AR. Most solicited local ARs were Grade 1 or Grade 2 in severity and transient in duration. Grade 3 solicited local ARs were more frequently reported in the mRNA-1010 group than in the SD comparator groups, but these too were transient and did not lead participants to seek medical attention. No Grade 4 solicited local ARs were reported in Study 304. The median onset day of any solicited local AR was Day 2 in both treatment groups. The median duration of any solicited local ARs was 2 days in the mRNA-1010 group and 1 day in the SD comparator group. The median duration of Grade 3 solicited local ARs was 1 day in the mRNA-1010 group and 1.5 days in the SD comparator group.

9.2.1.2 Solicited Systemic Adverse Reactions

In Study 304, most solicited systemic ARs were Grade 1 or Grade 2 in severity, transient, and reported more frequently in the mRNA-1010 group compared with the SD comparator group (Table 10). The most frequently reported solicited systemic AR was fatigue followed by headache and myalgia. Grade 3 solicited systemic ARs were more frequently reported in the mRNA-1010 group than in the SD comparator groups, but these too were transient and generally did not lead participants to seek medical attention. No Grade 4 solicited systemic ARs were reported in Study 304. The median onset for any solicited systemic ARs was Day 2 in both study intervention groups. The median duration of any solicited systemic ARs was 2 days in both study groups. The median duration of Grade 3 solicited systemic ARs was 1 day in both groups.

9.2.1.3 Solicited Adverse Reactions by Age Subgroup

Overall, the reactogenicity profile was generally similar across age groups. In both the mRNA-1010 and SD comparator groups, reporting of solicited ARs was numerically lower in the older age groups than in younger age groups (see Appendix Table 18 and Table 19).

9.2.2 Study 303 Part C

9.2.2.1 Solicited Local Adverse Reactions

In Study 303C, solicited local ARs were reported more frequently in the mRNA-1010 group than the HD comparator group (Table 9). As in Study 304, injection site pain was the most frequently reported solicited local AR. Most solicited local ARs were Grade 1 or Grade 2 in severity and transient in duration. Grade 3 solicited local ARs were more frequently reported in the mRNA-1010 group than in the HD comparator groups, but these were transient with a median duration of 1 day. No Grade 4 solicited local ARs were reported in Study 303C. The median onset for any solicited local ARs was Day 2 in the mRNA-1010 group and Day 1 in the HD comparator group. The median duration of any solicited local AR was 2 days in both study groups.

9.2.2.2 Solicited Systemic Adverse Reactions

In Study 303C, most solicited systemic ARs were Grade 1 or Grade 2 in severity, transient, and reported more frequently in the mRNA-1010 group compared with the HD comparator group (Table 10). The most frequently reported solicited systemic AR was fatigue followed by myalgia and headache. Grade 3 solicited systemic ARs were more frequently reported in the mRNA-1010 group than in the HD comparator groups, but these were transient with a median duration of 1 day. Two participants in the mRNA-1010 group had Grade 4 solicited systemic ARs of fever that lasted for 1 day and did not cause the participants to seek medical attention. No other Grade 4 solicited systemic ARs were reported in Study 303C. The median onset for any solicited systemic ARs was Day 2 in both study intervention groups. The median duration of any solicited systemic ARs was 2 days in both groups.

9.3 Unsolicited Adverse Events

9.3.1 Study 304

9.3.1.1 Unsolicited Adverse Events Up to 28 days after Injection

Overall, and across each of the unsolicited AE categories, the proportion of participants with unsolicited AEs up to 28 days after injection was generally balanced between the study groups (Table 11). AEs assessed as related to study injection by the Investigator

were reported in 98/20,350 (0.5%) of mRNA-1010-recipients and 49/20,353 (0.2%) of SD comparator recipients. The difference in the frequency of related AEs between study groups was primarily driven by nonserious AEs suggestive of reactogenicity, which are identical to or similar to solicited AR terms and that occurred more frequently within 7 days after injection in the mRNA-1010 group than in the SD comparator group. By referred term (PT), the most frequently reported unsolicited AEs assessed by the Investigator as related to study injection in the mRNA-1010 group and the SD comparator group included malaise (10 vs 3), dizziness (9 vs 3), blood pressure increased (6 vs 4), hypertension (4 vs 7), and urticaria (1 vs 6) (all <0.1%).

Table 11: Study 304 Overall Summary of Unsolicited AEs Up to 28 Days After Injection (Safety Set)

	mRNA-1010 37.5 µg (N=20,350) n (%)	Active Comparator (N=20,353) n (%)
Participants with unsolicited AEs up to 28 days after injection, regardless of relationship to study vaccination		
All	1204 (5.9)	1167 (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)
Participants with unsolicited AEs up to 28 days after injection, related to study vaccination		
All	98 (0.5)	49 (0.2)
Serious	2 (<0.1)	1 (<0.1)
Fatal	0	0
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)

AE: adverse event; AESI: adverse event of special interest; SAE: serious adverse event. Any solicited local or systemic adverse reactions that meets the definition of an SAE are considered as AE. Numbers are based on actual vaccination group and percentages are based on the number of participants in the Safety Set.

Overall, rates of unsolicited AEs by system organ class (SOC) were comparable between the study intervention groups. In both study intervention groups, the most frequently reported unsolicited AEs up to 28 days after injection by SOC were infections and infestations (1.4% in each group), musculoskeletal and connective tissue disorders (0.8% vs 0.7%), injury, poisoning and procedural complications (0.7% in each group), and gastrointestinal disorders (0.6% in each group); unsolicited AEs occurred in ≤0.5% of participants in each study intervention group across all other SOCs. The most frequently reported unsolicited AEs by PT in both study intervention groups included hypertension (0.3% in each group), COVID-19 (0.3% in each group), urinary tract

infection (0.2% vs 0.3%), and diarrhoea (0.2% in each group); all other unsolicited AEs by PT occurred in <0.2% of participants in each study intervention group.

9.3.1.2 Unsolicited Adverse Events Throughout the Study

Throughout the study, the proportions of participants with unsolicited AEs overall and across AE categories were generally similar between the groups as shown in Table 12.

Table 12: Study 304 Overall Summary of Unsolicited AEs Throughout the Study (Safety Set)

	mRNA-1010 37.5 µg (N=20,350) n (%)	Active Comparator (N=20,353) n (%)
Participants with unsolicited AEs throughout the study, regardless of relationship to study vaccination		
Serious	455 (2.2)	392 (1.9)
Fatal	40 (0.2)	34 (0.2)
Medically attended	2509 (12.3)	2439 (12.0)
Leading to study discontinuation	3 (<0.1)	1 (<0.1)
AESI per Investigator assessment	17 (<0.1)	15 (<0.1)
Participants with unsolicited AEs throughout the study, 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)

AE: adverse event; AESI: adverse event of special interest; SAE: serious adverse event. Any solicited local or systemic adverse reactions that meets the definition of an SAE are considered as AE. Numbers are based on actual vaccination group and percentages are based on the number of participants in the Safety Set.

9.3.1.3 Deaths

No patterns in SAEs with fatal outcomes were evident across SOCs and PTs, time to onset, or other event characteristics that would suggest a safety concern for mRNA-1010. None of the fatal events were assessed as related to study injection by the Investigator. The events were generally attributable to underlying medical history, intrinsic factors, concomitant medications, and clinical context.

Up to 28 days after study injection, SAEs with a fatal outcome were reported for <0.1% of participants in each group (7/20,350 in the mRNA-1010 group vs 9/20,353 in the SD

comparator group) and none of these were assessed by the Investigator as related to study injection.

Throughout the study, SAEs with a fatal outcome were reported for 0.2% of participants in each group (40/20,350 in the mRNA-1010 group vs 34/20,353 in the SD comparator group) and none of these were assessed by the Investigator as related to study injection. PTs reported for >1 participant in either group were death (12 vs 4 participants), cardiac arrest (3 each), myocardial infarction (2 vs 3), septic shock (3 vs 1), cardio-respiratory arrest (2 vs 1), road traffic accident (2 vs 1), injury (2 vs 0), cerebrovascular accident (1 vs 2), sepsis (0 vs 2), and cardiac failure (0 vs 2) (all <0.1%).

The overall incidence of fatal SAEs was balanced between groups. An additional review of fatal SAEs coded to the PT of death (without further specification or unknown etiology) was conducted as these events were reported in 12 participants in the mRNA-1010 group and 4 participants in the SD comparator group. A detailed review was performed for these events with PT of death. Investigators were instructed to report a specific term that resulted in death and clinical sites were queried following any deviation from this instruction, but often no further information could be obtained by the site; no autopsies were performed, family members did not wish to release additional information, and/or causes of death remained unknown. Based on medical review of the individual cases in both groups, events with the PT of death occurred in participants with comorbidities including cardiovascular disease (e.g., hypertension) and metabolic disorders (e.g., diabetes mellitus), and the nature of the reported conditions was consistent with background mortality in an older, comorbid population. Among the 12 participants in the mRNA-1010 group with an event with the PT of death, the age range was 53 to 72 years and the timing of death ranged from 24 to 194 days after study injection. Among the 4 participants in the SD comparator group, the age range was 52 to 83 years and the timing of death ranged from 9 to 172 days after study injection. Within 28 days after injection, the incidence of events with the PT of death were similar across treatment groups and were reported for 1 participant in the mRNA-1010 group (a 67-year-old male participant with medical history including hypertension died on Day 24 after study injection) and 2 participants in the SD comparator group (a 52-year-old female participant with medical history including hypertension, hypercholesterolemia, and type 2 diabetes mellitus died on Day 9 after study injection; and an 83-year-old female participant with medical history including hypertension died on Day 27 after study injection). No temporal or clinical patterns suggesting a causal relationship with mRNA-1010 were identified for events with the PT of death. Overall, given the balanced incidence of all fatal events up to 28 days and throughout the study, lack of temporal clustering, underlying risk factors, and available clinical details, no safety concerns were identified upon a comprehensive review of all fatal events.

9.3.1.4 Serious Adverse Events

SAEs were distributed heterogeneously across SOCs and PTs, and throughout the study, few SAEs were assessed by the Investigator as related to study injection (4/20,350 participants in the mRNA-1010 group and 2/20,353 participants in the SD comparator group [<0.1% of participants in each group]). Individual case review identified confounding factors including underlying conditions and/or concomitant medications and no safety concern was identified for mRNA 1010.

Up to 28 days after injection, SAEs were reported for 0.5% of participants in each group (92/20,350 in the mRNA-1010 group vs 92/20,353 in the SD comparator group). Regardless of causality, SAEs were most frequently reported in the SOC for infections and infestations (21 [0.1%] participants in the mRNA-1010 group vs 18 [<0.1%] participants in the SD comparator group) and the most frequent SAE by PT was road traffic accident (4 vs 3 [both <0.1%]). Up to 28 days after injection, SAEs assessed by the Investigator as related to study injection were reported for 2 participants in the mRNA-1010 group (syncope on Day 2 in a 62 year-old female with likely dehydration evaluated by EMTs; hypotension on Day 2 in a 67 year-old male with history of hypertension with reportedly “negative” testing) and 1 participant in the SD comparator group (laryngeal dyspnoea on Day 6 in a 67 year-old male with history of angioedema).

Throughout the study, SAEs were reported for 2.2% of participants (455/20,350) in the mRNA-1010 group and 1.9% of participants (392/20,353) participants in the SD comparator group. Regardless of causality, SAEs were most frequently reported in the SOC of infections and infestations (90 participants [0.4%] in the mRNA-1010 group vs 76 participants [0.4%] in the SD comparator group). SAEs assessed by the Investigator as related to study injection were reported for a total of 4 participants in the mRNA-1010 group and a total of 2 participants in the SD comparator group. In the mRNA-1010 group, SAEs assessed as related by the Investigator included 2 additional participants beyond Day 28 with 3 SAEs: one 54 year-old female participant with multiple cardiac risk factors including uncontrolled type 2 diabetes had onset on Day 95 of congestive cardiomyopathy and myopericarditis (adjudicated as not a charter-defined event by the CEAC); and one 64 year-old male participant had myocarditis (adjudicated as myopericarditis) with onset on Day 183 with prior respiratory symptoms. In the SD comparator, SAEs assessed as related by the Investigator included 1 additional participant beyond Day 28 with an SAE of pericarditis (adjudicated as acute pericarditis by the CEAC) with onset on Day 60.

9.3.1.5 Adverse Events of Special Interest

Reporting of AESIs was similar between study groups up to 28 days after injection (Table 11) and throughout the study (Table 12). Throughout the study, AESIs that were assessed by the Investigator as related to study injection were reported for 3/20,350

participants in the mRNA-1010 group and 2/20,353 participants in the SD comparator group (both <0.1%). No safety concern was identified for mRNA-1010 based on analysis of per protocol AESIs, as follows:

- No anaphylactic reactions were reported in the mRNA-1010 group.
- No safety concerns were identified for Bell's palsy or seizure. One serious AESI of facial paresis was reported in the mRNA-1010 group with onset on Day 21; the event occurred in the setting of a concurrent nonserious AE of herpes zoster and was assessed by the Investigator as not related to study injection. In the SD comparator group, there was 1 nonserious AESI of Bell's reported with onset on Day 18 assessed as related to study injection by the Investigator and one additional participant with 1 nonserious AESI of Bell's palsy with onset on Day 53 in the context of a preceding event of upper respiratory illness assessed as not related by the Investigator.
- No safety concerns with mRNA-1010 were identified for Guillain-Barré syndrome or acute disseminated encephalomyelitis. One serious AESI of demyelinating polyneuropathy that was assessed by the Investigator as not related to study injection was reported in the mRNA-1010 group. Event onset was on Day 134, which is outside the typical 42-day risk window for Guillain-Barré syndrome.
- No safety concerns with mRNA-1010 were identified for thrombocytopenia.
- No CEAC-confirmed events of acute myocarditis, acute pericarditis, or myopericarditis were reported in either group within the 42-day risk window. Throughout the study, the incidence of CEAC-confirmed events was balanced between the groups (1 case of myopericarditis in the mRNA-1010 group [Day 183] and 1 case of acute pericarditis in the SD comparator group [Day 60]).

9.3.1.6 Analysis of Unsolicited Adverse Events by Standardized MedDRA Queries

No relevant differences were observed between study injection groups in the reporting of AEs by narrow scope SMQ up to 28 days after injection and throughout the study. No events in the standardized MedDRA query (SMQ) for anaphylactic reaction were reported in the mRNA-1010 group. Analyses of AEs reported in the SMQs for arthritis, cardiac arrhythmias, convulsions, demyelination, Guillain-Barré syndrome, hematopoietic cytopenias, hypersensitivity, immune-mediated/autoimmune disorders, noninfectious myocarditis/pericarditis, and peripheral neuropathy did not identify a safety concern for mRNA-1010. Reporting of events in the hypersensitivity SMQ was similar between the study intervention groups, including for events assessed by the Investigator as related to study injection (12 participants in the mRNA-1010 group and 13 participants in the SD comparator group) and included PTs commonly seen in the general population (e.g., contact dermatitis, eczema, and allergic rhinitis). No clinically

meaningful differences between study injection groups were observed in the reporting of AEs by SMQ or PT.

9.3.1.7 Unsolicited Adverse Events by Subgroups

No clinically relevant differences between or within study injection groups were observed in analyses of AEs by subgroups based on age, race, and sex.

9.3.2 Study 303 Part C

Study 303C evaluated the safety of the mRNA-1010 vaccine in participants ≥65 years who received either mRNA-1010 (N=1502) or HD comparator (N=1490), with median follow-up of 171 days across both study intervention groups. Overall, the proportion of participants with unsolicited AEs was similar between the mRNA-1010 and HD comparator groups up to 28 days after injection and through the end of the study. An overview of analyses of unsolicited AEs from Study 303C are summarized below:

- Unsolicited AEs up to 28 days after injection were reported in 155/1502 (10.3%) participants in the mRNA-1010 group and 137/1490 (9.2%) participants in the HD comparator group. By SOC, unsolicited AEs up to 28 days after injection were most frequently (≥1%) reported in infections and infestations (4.5% vs 4.4%), musculoskeletal and connective tissue disorders (1.1% vs 1.2%), and injury, poisoning and procedural complications (1.2% vs 0.7%). By PT, the most frequently (≥0.5%) reported unsolicited AEs were consistent with common infections or associated signs/symptoms and included upper respiratory tract infection (1.4% vs 1.1%) and COVID-19 (0.9% in each group).
- Throughout the study, fatal SAEs occurred in 3 (0.2%) participants and 1 (<0.1%) participant in the mRNA-1010 and HD comparator groups, respectively. In the mRNA-1010 group, these included participants 65 to 93 years of age with fatal SAEs of acute myocardial infarction reported in 2 participants (Day 26 and Day 49 [died on Day 57]), who had risk factors including smoking, hypertension, diabetes, and hyperlipidemia, and 1 participant with the fatal SAE of death (verbatim: clinical death – natural causes, elderly; Day 68). In the HD comparator group, a 65-year-old female experienced a fatal SAE of acute myocardial infarction on Day 96. No patterns were evident based on PTs, time to onset, or other event details that would suggest a safety concern for mRNA-1010. None of the deaths were assessed as related to study injection by the Investigator.
- Throughout the study, SAEs were reported in 41 (2.7%) participants and 38 (2.6%) participants in the mRNA-1010 and HD comparator groups, respectively. By PT, the most frequently (≥0.1%) reported SAEs were pneumonia (0.2% vs <0.1%), urinary tract infection (0.1% vs <0.1%), transient ischemic attack (0.1% vs 0), acute myocardial infarction (0.1% vs <0.1%), pulmonary embolism (0.1%

vs <0.1%), nephrolithiasis (0 vs 0.1%), hip fracture (<0.1% vs 0.1%), fall (0 vs 0.1%), and subdural hematoma (0 vs 0.1%). All SAEs were assessed as not related to study injection by the Investigator, except for the following SAE in the HD comparator group: pulmonary embolism (Day 76) was reported for a participant with a history of hypertension, chronic kidney disease, generalized osteoarthritis, and Alzheimer's dementia and was resolving as of EOS.

- Throughout the study, AESIs were reported in 2 (0.1%) participants in the mRNA-1010 group and 1 (<0.1%) participant in the HD comparator group . Evaluation of AESIs did not suggest a safety concern for mRNA-1010.

  − No AESIs of thrombocytopenia were reported during the study for either study intervention group.

  − AESIs of new onset or worsening of specific neurological disorders were reported in 1 (<0.1%) participant in each study intervention group throughout the study; no AESIs of Guillain-Barré syndrome or acute disseminated encephalomyelitis reported. There were no AESIs of seizure reported in either study intervention group within 28 days of injection. Throughout the study, none of the protocol-defined AESIs were assessed as related to study injection by the Investigator.

  − No AESIs of anaphylaxis were reported during the study for either study intervention group. There was 1 AESI of swelling face (not a protocol-defined AESI) assessed as related to study injection by the Investigator which was a participant in the mRNA-1010 group with a history of asthma, cat fur/dander allergy, and dust allergy who experienced the nonserious AE of swelling face (Day 2).

  − No AESIs of myocarditis/pericarditis were reported during the study for either study intervention group.

9.3.3 Integrated Summary of Safety (ISS)

The ISS presents pooled data for deaths, SAEs, and AESIs, for all participants ≥ 50 years who received any version of mRNA-1010 QIV or TIV (12.5 µg per strain) or active comparator (Fluarix SD [QIV or TIV] or Fluzone HD QIV; referred to as SD/HD comparator) in any of the mRNA-1010 Phase 3 studies (301, 302, 303 and 304). All these studies are completed and final safety analyses were integrated. Study 301 and Study 302 had 1 year of safety follow-up and Study 303 and Study 304 had 6 months of safety follow-up. The median duration of follow-up for participants in the mRNA-1010 and SD/HD comparator group in the ISS Set was 198.0 days for both study intervention groups. Analysis of ISS data demonstrates no safety concern with mRNA-1010 in the ≥50 years population from the combined Phase 3 studies.

9.3.3.1 Participant Population

In the ISS Set (participants ≥50 years), 35,965 participants received mRNA-1010 and 35,951 participants received SD/HD comparator and the median follow-up was 198 days in both pooled study intervention groups. Demographic characteristics were similar between the mRNA-1010 and SD/HD comparator groups: the median age was 64.0 years in both groups; approximately half of participants in both groups were ≥65 years (Table 13); 56.5% and 56.9% were female, 79.4% and 79.0% were White, and 44.2% and 44.0% had received an influenza vaccine in the prior season.

Table 13: Number of Participants in the ISS Set by Age Subgroups

	mRNA-1010 (N = 35,965)	Fluarix SD (N = 34,461)	Fluzone HD (N = 1,490)	Fluarix SD or Fluzone HD (N = 35,951)
Age Group, n (%)				
≥50 to <65years	18,398 (51.2)	18,396 (53.4)	1 (<0.1)	18,397 (51.2)
≥65 years	17,567 (48.8)	16,065 (46.6)	1,489 (>99.9)	17,554 (48.8)
≥75 years	4,098 (11.4)	3,779 (11.0)	335 (22.5)	4,114 (11.4)

HD: high dose; ISS: integrated summary of safety; SD: standard dose

9.3.3.2 ISS Overview of Unsolicited Adverse Events

The incidence of SAEs, deaths and AESIs was similar across treatment groups up to 28 days after injection and throughout the studies (Table 14).

Table 14: ISS Overall Summary of Unsolicited Adverse Events (ISS Set)

	mRNA-1010 (N = 35,965)	Fluarix SD (N = 34,461)	Fluzone HD (N = 1,490)	Fluarix SD or Fluzone HD (N = 35,951)
Participants with unsolicited AEs up to 28 days after Injection, regardless of relationship to study vaccination				
Serious	180 (0.5)	156 (0.5)	7 (0.5)	163 (0.5)
Fatal	13 (<0.1)	14 (<0.1)	0	14 (<0.1)
AE of Special Interest	7 (<0.1)	4 (<0.1)	0	4 (<0.1)
Participants with unsolicited AEs throughout the study, regardless of relationship to study vaccination				
Serious	1129 (3.1)	989 (2.9)	38 (2.6)	1027 (2.9)
Fatal	102 (0.3)	96 (0.3)	1 (<0.1)	97 (<0.1)
AE of Special Interest	36 (0.1)	36 (0.1)	1 (<0.1)	37 (0.1)

AE: adverse event; HD: high dose; ISS: integrated summary of safety; SD: standard dose

9.3.3.3 ISS Deaths

The frequency of fatal SAEs with onset up to 28 days after injection was balanced between the mRNA-1010 and SD/HD comparator groups. Up to 28 days after injection, fatal SAEs were reported for <0.1% of participants in each pooled study intervention group. One death in the mRNA-1010 group was assessed as related to study injection by the Investigator due to temporality (occurrence on Day 2); however, this participant was a 76-year-old female with significant cardiovascular risk factors and concomitant medication use associated with fatal arrhythmias.

Throughout the studies, the overall incidence of fatal SAEs was balanced between study intervention groups and were reported for 0.3% of participants in each pooled study intervention group. Other than the death on Day 2, no other fatal SAEs were assessed by the Investigator as related to study injection. The most common SOC for fatal SAEs was cardiac disorders (reported for 24 participants in the mRNA-1010 group vs 30 participants in the SD/HD comparator group; both <0.1%). The median (range) time of death from injection was 143.5 days (2 to 357 days) in the mRNA-1010 group and 118.5 days (3 to 368 days) in the SD/HD comparator group. Among the total number of deaths reported in the mRNA-1010 (N=102) and the SD/HD comparator (N=97) groups, approximately two-thirds (N=70 and N=60, respectively) occurred more than 90 days after injection. Comprehensive review of all fatal events (with and without specific PTs) in each pooled study intervention group, considering the timing of events, participant age, sex, underlying medical history, concomitant medications, and available clinical details, revealed no pattern or clustering of deaths to suggest a safety concern for mRNA-1010.

9.3.3.4 ISS Serious Adverse Events

Up to 28 days after injection, the frequency and distribution of SAEs were balanced between the mRNA-1010 and SD/HD comparator groups. Up to 28 days after injection, SAEs were reported for 0.5% of participants in each pooled study intervention group and were most commonly in the SOC for infections and infestations (45 participants in the mRNA-1010 group vs 34 participants in the SD/HD comparator group; both ≤0.1%). The most frequent SAEs by PT were pneumonia (8 vs 5), acute myocardial infarction (4 vs 6), osteoarthritis (2 vs 5), and acute kidney injury (2 vs 5); all other SAEs occurred in ≤4 participants in either study intervention group.

Throughout the studies, SAEs were reported for 3.1% of participants in the mRNA-1010 group and 2.9% of participants in the SD/HD comparator group and were most commonly in the SOC for infections and infestations (0.7% in the mRNA-1010 group vs 0.6% in the SD/HD comparator group). By PT, the most frequently (≥30 participants in either group) reported SAEs were pneumonia (36 vs 32), COPD (35 vs 24),

cerebrovascular accident (32 vs 29), and atrial fibrillation (30 vs 21) (all <0.1%). SAEs were distributed across SOCs and PTs without any pattern.

Throughout the studies, SAEs that were assessed by the Investigator as related to study injection were reported for <0.1% of participants in each pooled study intervention group (9/35,965 participants in the mRNA-1010 group and 3/35,951 participants in the SD/HD comparator group). SAEs assessed as related by the Investigator in Study 304 are presented in detail in Section 9.3.1.4 above. Other SAEs assessed as related by the Investigator in the mRNA-1010 group included the following events:

- Study 301: acute coronary syndrome in 1 participant on Day 3 in a 53 year-old male with multiple cardiovascular risk factors
- Study 302: angioedema (Day 5) in a 78-year-old female with a history of idiopathic angioedema and pulmonary embolism (Day 9) in an 86 year-old female with multiple cardiovascular risk factors, including severely limited mobility
- Study 303 (Part A): deep vein thrombosis and pulmonary embolism (1 participant with 2 events total and multiple cardiovascular risk factors including smoking; Day 128 and Day 132, respectively) and death (Day 2 as previously noted in Section 9.3.3.3)

In the SD/HD comparator group, the SAEs assessed by the Investigator as related to study injection were laryngeal dyspnoea (Study 304; 1 participant, Day 6), pericarditis (Study 304; 1 participant, Day 60), and pulmonary embolism (Study 303C; 1 participant Day 76, see Section 9.3.2).

Individual case details included confounding factors such as medical history conditions and concomitant medications that were more likely to be causal than study injection.

9.3.3.5 ISS Adverse Events of Special Interest

Up to 28 days after injection, AESIs were reported for <0.1% of participants in each pooled study intervention group (7/35,965 participants in the mRNA-1010 group and 4/35,951 participants in the SD/HD comparator group). This included 1 participant in each pooled group who had an AESI of Bell's palsy that was assessed by the Investigator as related to study injection (details are provided below). In addition, an event of swelling face (not a protocol-defined AESI) on Day 2 was reported as an AESI assessed by the Investigator as related to study injection for a participant in the mRNA-1010 group in Study 303C.

Throughout the studies, AESIs were reported for 0.1% of participants in each pooled study intervention group (36/35,965 participants in the mRNA-1010 group and 37/35,951 participants in the SD/HD comparator group).

Medical review of AESIs based on the ISS Set for participants ≥50 years did not identify any safety concerns for mRNA-1010, Findings for each of the protocol-defined AESI concepts are summarized as follows:

- **Thrombocytopenia**: Medical review of AESIs in this category did not suggest a safety concern for mRNA-1010. Incidence in the blood and lymphatic disorders SOC was similar between the pooled study intervention groups up to 28 days after injection (1 [<0.1%] participant in the mRNA-1010 group vs 0 participants in the SD/HD comparator group) and throughout the studies (12 [<0.1%] vs 12 [<0.1%]). One participant in the mRNA-1010 group had an event of thrombocytopenia on Day 84 that was assessed by the Investigator as related to study injection; however, multiple confounding factors were present.
- **New onset or worsening of specified neurological diseases**: Medical review of AESIs in this category did not suggest a safety concern for mRNA-1010. Incidence in the nervous system disorders SOC was similar between the pooled study intervention groups up to 28 days after injection (5 [<0.1%] vs 3 [<0.1%] participants) and throughout the studies (12 [<0.1%] vs 18 [<0.1%] participants). Overall, 2 participants in the mRNA-1010 group and 4 participants in the SD/HD comparator group had AESIs of Bell's palsy and facial paresis. Of these, the incidence within the relevant 42-day risk window was similar. One participant in each of the pooled study intervention groups had an event of Bell's palsy assessed by the Investigator as related to study injection: in the mRNA-1010 group, the event occurred on Day 16 in a participant with medical history including obesity and who was diagnosed with hypertension and type 2 diabetes mellitus in the same medical encounter (Study 303B); in the SD/HD comparator group, the event of Bell's palsy occurred on Day 18 in a participant with no reported risk factors consistent with the Brighton Collaboration case definition (Rath et al 2017) (Study 304). One additional participant in the mRNA-1010 group (Study 304) had an unrelated serious AESI of facial paresis (Day 21) in the setting of a concurrent nonserious AE of herpes zoster. Thus, no safety concerns were identified for Bell's palsy. No AESIs of seizure were assessed by the Investigator as related to study injection. No AESIs of acute disseminated encephalomyelitis were reported. One serious AESI of demyelinating polyneuropathy that was assessed by the Investigator as not related to study injection occurred in the mRNA-1010 group on Day 134, outside the 42-day risk window for Guillain-Barré syndrome (Study 304).
- **Anaphylaxis**: No AESIs of anaphylaxis were reported in either of the pooled study intervention groups throughout the study.
- **Myocarditis/pericarditis**: Medical review of AESIs did not suggest a safety concern for mRNA-1010. No AESIs of myocarditis, pericarditis, or myopericarditis

were reported in either pooled study intervention group up to 28 days after injection. Throughout the studies, AESIs in the cardiac disorders SOC were reported for 10 (<0.1%) participants in the mRNA-1010 group and 6 (<0.1%) participants in the SD/HD comparator group; an additional AESI of viral pericarditis (SOC: infections and infestations) was reported for 1 participant in the SD/HD comparator group. None of the reported AESIs in the category of myocarditis/pericarditis occurred within the 42-day risk window. CEAC-confirmed events in the ISS Set among participants ≥50 years were balanced between the pooled study intervention groups: 4 cases were reported in the mRNA-1010 group (1 case of myopericarditis and 3 cases of acute pericarditis) and 4 cases were reported in the SD/HD comparator group (all 4 acute pericarditis).The events were assessed by the Investigator as related to study injection for 1 participant in each group, both of whom were in Study 304 as described in Section 9.3.1.4.

9.3.3.6 ISS Subgroup Analyses by Age

The frequency of SAEs, fatal events and AESIs was similar between vaccine groups through 28 days after injection and up to Day 181 in both the 50 to 64 year-old subgroup and the ≥ 65-year-old subgroup as shown in Table 15. There was no pattern in the type or incidence of unsolicited AEs or clinically relevant differences across age subgroups suggestive of a potential safety concern for mRNA-1010.

Table 15: Overall Summary of Unsolicited Adverse Events by Age Group (ISS Set)

	50 – 64 Years		≥65 Years	
	mRNA-1010 (N = 18,398) n (%)	Licensed SD/HD Comparator (N = 18,397) n (%)	mRNA-1010 (N = 17,567) n (%)	Licensed SD/HD Comparator (N = 17,554) n (%)
Unsolicited AEs Through 28 Days after Injection				
Serious	70 (0.4)	76 (0.4)	110 (0.6)	87 (0.5)
Fatal	3 (<0.1)	6 (<0.1)	10 (<0.1)	8 (<0.1)
AE of Special Interest	4 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)
Unsolicited AEs Through Day 181 (End of Study)				
Serious	484 (2.6)	424 (2.3)	645 (3.7)	603 (3.4)
Fatal	33 (0.2)	34 (0.2)	69 (0.4)	63 (0.4)
AE of Special Interest	17 (<0.1)	17 (<0.1)	19 (0.1)	20 (0.1)

AE: adverse event; HD: high dose; ISS: integrated summary of safety; SD: standard dose

9.3.4 Safety Conclusions

The mRNA-1010 vaccine has been administered to 20,350 participants ≥50 years of age, with median follow-up of 184 days in the completed pivotal, Phase 3 study (Study 304). In total, mRNA-1010 products have been administered to 39,537 participants ≥18 years across the clinical development program, including 35,965 participants ≥50 years across the Phase 3 studies of whom 17,567 participants were ≥65 years.

The mRNA-1010 vaccine administered as a single dose demonstrated tolerable reactogenicity based on solicited ARs and an acceptable safety profile based on unsolicited AEs across the clinical development program.

10 CONFIRMATORY STUDY FOR ADULTS 65 YEARS AND OLDER

10.1 Study Design

Moderna is committed to evaluating influenza vaccine performance in real-world settings and has generated effectiveness evidence for previously approved enhanced influenza vaccines (Ku et al 2024; Rayens et al 2024). Building on this experience, Moderna plans to generate high-quality post-licensure real-world effectiveness data to further characterize the performance of mRNA-1010. As a Post-Marketing Requirement, Moderna intends to demonstrate that mRNA-1010 provides meaningful clinical benefit to adults ≥65 years of age, consistent with enhanced vaccines recommended for this age group. To fulfill this requirement and support full approval of mRNA-1010 in the US, Moderna will conduct a real-world evidence (RWE) study comparing vaccine effectiveness of mRNA-1010 with that of an enhanced influenza vaccine in adults ≥65 years.

Following consultation with the FDA, Moderna developed a pragmatic, randomized study to evaluate the rVE of mRNA-1010 compared with an enhanced influenza vaccine in adults ≥65 years of age within an integrated healthcare system in the US. The primary objective of the proposed study is to estimate the rVE of mRNA-1010 compared with an enhanced influenza vaccine in preventing PCR-confirmed medically attended influenza. Secondary objectives will estimate the rVE of mRNA-1010 compared with an enhanced influenza vaccine in preventing moderate-to-severe influenza and will assess primary and secondary objectives by PCR-confirmed influenza type A and/or B (separately). To accomplish these objectives, Moderna expects to enroll hundreds of thousands of adults into this rVE study.

The full protocol was submitted to FDA and is currently under Agency review. In parallel, Moderna is advancing study start-up activities, including operational planning and site readiness activities, to support timely implementation of the study following protocol alignment with FDA. Additional details and features of the study are currently under discussion with the Agency.

Results of this proposed RWE study, together with mRNA-1010's demonstrated superior immunogenicity relative to high-dose vaccine (Study 303C) and the efficacy estimates within the range of approved enhanced vaccines in adults ≥65 years of age (Study 304), will be used to confirm meaningful clinical benefit in this population.

11 BENEFITS AND RISKS CONCLUSIONS

11.1 Therapeutic Context

Influenza virus is a primary cause of respiratory tract infection and is associated with severe outcomes in adults ≥50 years. Vaccines are essential for the prevention of influenza disease, but the effectiveness of currently licensed vaccines is variable. Influenza vaccines with enhanced activity (through delivery of higher antigen content, inclusion of adjuvants, or recombinant manufacturing) have been developed, particularly for more vulnerable older adults (≥65 years). This category of vaccine has shown reduction in rates of influenza virus-associated hospitalization and deaths in adults ≥65 years. Inherent aspects of current influenza vaccine production however, including for some enhanced vaccines, hinder optimal vaccine effectiveness.

The mRNA manufacturing platform enables rapid design and synthesis of strain-specific influenza virus vaccines. Unlike traditional egg-based production, synthetic mRNA vaccine manufacturing does not depend on embryonated chicken egg supply or viral reassortment processes. Egg-based manufacturing requires a reliable supply of eggs, which may be vulnerable to disruption, particularly during outbreaks affecting poultry. Additionally, vaccine manufactured in eggs often acquire adaptive mutations that can enhance growth in eggs but may alter antigenic properties compared to circulating influenza viruses. The greater manufacturing speed and flexibility of mRNA therefore represent an important advance for both seasonal influenza prevention and pandemic influenza preparedness.

Overall, the combination of clinical endpoint efficacy, higher or superior immunogenicity, and improved production flexibility and scalability constitutes a meaningful advantage over current licensed influenza vaccines.

11.2 Benefit-Risk Analysis Evaluation in Adults 50–64 Years of Age

In the US, licensed SD influenza vaccines are recommended for the prevention of influenza in adults 50–64 years of age. Evidence supporting a positive benefit-risk profile of mRNA-1010 in this age group is based on data from 21,239 adults in the pivotal efficacy trial, Study 304, and 36,794 adults in a safety analysis of pooled Phase 3 data (ISS).

A single dose of mRNA-1010 (TIV; 37.5 µg) resulted in an rVE of 26.1% (95% CI: 12.3, 37.7; Study 304) relative to SD comparator against the primary efficacy endpoint (PCR-confirmed ILI caused by any type A or B influenza virus). This rVE in adults 50-64 years is consistent with the level of superior efficacy reached in the overall 304 study population (and exceeding the prespecified statistical primary rVE success criterion for superiority [rVE 95% CI LB >9.1%]).

The clinical efficacy of mRNA-1010 relative to SD comparator was evident early after vaccination and was maintained to the end of the influenza season and rVE point estimates were consistent across influenza strains.

The superior clinical efficacy of mRNA-1010 relative to SD comparator in Study 304 was paralleled by higher immune responses (HAI Ab) for all vaccine strains: GMR point estimates were all >1.5 (95% CI LBs were >1.3) and SCR differences were all positive (95% CI LBs were >12%).

mRNA-1010 has an acceptable safety profile in adults 50-64 years. Higher rates of reactogenicity were reported in the mRNA-1010 than the SD comparator group, but most solicited local and systemic ARs were Grade 1 or 2 in severity and transient in duration. Grade 3 solicited local and systemic ARs were also more frequent in the mRNA-1010 group than comparator group, but these too were transient and generally resolved without medical attention.

Analysis of individual safety data from study 304 identified no safety concerns with mRNA-1010 in adults 50-64 years. Unsolicited AEs reported in the 28 days post-injection and throughout the study were balanced between study groups. Analysis of pooled Phase 3 safety data in the large ISS database were similarly reassuring: the overall incidence of deaths, other SAEs, and AESIs throughout these studies was balanced between mRNA-1010 and SD comparator groups. In adults 50-64, there were no events of myocarditis/pericarditis within the relevant risk window and no mRNA-1010-related deaths reported across all studies.

Results of mRNA-1010 efficacy, immunogenicity, and comprehensive safety assessment provide substantial evidence supporting traditional approval of mRNA-1010 for the prevention of influenza disease in adults 50–64 years of age. mRNA-1010 may better match circulating seasonal influenza variants by avoiding egg-based manufacturing (and egg-adaptive mutations). Shorter potential production timeline from strain selection to vaccine availability for mRNA-1010 may further enhance the likelihood of vaccine match and clinical benefit.

11.3 Benefit-Risk Analysis Evaluation in Adults 65 Years and Older

Compared to younger adults, individuals 65 years and older are at increased risk of severe outcomes associated with influenza disease, including pneumonia, hospitalization and death. Enhanced influenza vaccines (including HD formulations) reduce such outcomes in older adults, which led to preferential recommendation in the United States in this age group. Enhanced vaccines nonetheless face challenges inherent to manufacturing processes (including egg-adaptive mutations) and to the time required from strain selection to vaccine availability that can result in potential mismatch between vaccine and circulating influenza strains. mRNA-1010 efficacy, immunogenicity

and safety data summarized in this report, together with the known fidelity of the mRNA-1010 manufacturing process, support the accelerated approval of mRNA-1010 influenza vaccine for use in adults 65 years and older.

Evidence supporting accelerated approval of mRNA-1010 in adults 65 years and older is based on data from 19,464 adults in the pivotal efficacy Study 304 and 35,121 older adults in a safety analysis of pooled Phase 3 data (ISS).

A single dose of mRNA-1010 (TIV; 37.5 µg) results in an rVE of 27.4% (95% CI: 12.1, 40.0; Study 304) relative to SD comparator against the primary efficacy endpoint (PCR-confirmed ILI caused by any type A or B strain). This rVE is consistent with rVE for the overall 304 study population, and results in adults 65 years and older exceeded the prespecified statistical primary rVE success criterion for superiority [rVE 95% CI LB >9.1%]. Further, this level of superior efficacy relative to SD comparator is aligned with that of previously approved enhanced influenza vaccines. An exploratory efficacy analysis showed that mRNA-1010 reduced ILI-associated healthcare encounters (hospitalization, ER visit, or urgent care visit) relative to SD comparator (rVE of 62.9% [95% CI: 11.6, 88.4]). Like currently licensed enhanced vaccines, it is anticipated that the superior rVE of mRNA-1010 will translate to meaningful clinical benefit following use in older adults.

The clinical efficacy of mRNA-1010 relative to SD comparator in participants 65 years and older was evident early after injection and was maintained to the end of the influenza season, and rVE point estimates were consistent across influenza strains.

The superior clinical efficacy of mRNA-1010 relative to SD comparator in Study 304 was paralleled by higher immune responses (HAI Ab) for all vaccine-included influenza strains: GMR point estimates were all >1.6 (95% CI LBs were >1.5) and SCR differences were all positive (95% CI LBs were >16%). In a head-to-head comparison of the immunogenicity of mRNA-1010 and HD comparator (Study 303C), mRNA-1010 successfully met prespecified superiority criteria. (i.e. Day 29 GMR 97.5% CI LB >1.0 and SCR difference 97.5% CI LB >0% for all 8 co-primary endpoints).

The safety profile of mRNA-1010 in adults 65 years and older was acceptable. Solicited AR were more frequently reported in mRNA-1010 than comparator groups (Studies 304 and 303C), but most solicited AR were Grade 1 or 2 in severity and transient in duration. Grade 3 solicited ARs were also more frequently reported in the mRNA-1010 than comparator groups, but these too were transient and generally resolved without medical attention. With increasing age, a trend is observed toward a lower frequency of local and systemic solicited ARs for the mRNA-1010 group and toward a lower frequency of local solicited ARs for the SD comparator group.

Comprehensive analysis of individual safety data from Studies 304 and 303 identified no safety concerns with mRNA-1010. Unsolicited AEs reported in the 28 days post-

injection and throughout the studies were balanced between study groups. Analysis of pooled Phase 3 safety data in the large ISS database was similarly reassuring. The overall incidence of deaths, SAEs, and AESIs throughout these studies was similar between the mRNA-1010 and SD/HD comparator groups. No CEAC-confirmed cases of myocarditis/pericarditis (within the relevant 42 day risk window) were reported across all studies in the mRNA-1010 group. The one death assessed as related by the Investigator in a mRNA-1010 recipient occurred in a participant over 75 years old with multiple cardiovascular risk factors.

Results of mRNA-1010 efficacy, immunogenicity and comprehensive safety assessment support accelerated approval of mRNA-1010 for the prevention of influenza disease in adults 65 years and older. mRNA-1010 may better match circulating seasonal influenza variants by avoiding egg-based manufacturing (and egg-adaptive mutations). Shorter potential production timeline from strain selection to vaccine availability for mRNA-1010 may further enhance the likelihood of vaccine match and clinical benefit. A planned real-world effectiveness study is anticipated to confirm data summarized in this report and demonstrate that mRNA-1010 provides meaningful clinical benefit consistent with approved enhanced vaccines.

11.4 Conclusions

Data summarized here establish that in adults 50-64 years and those 65 years and older, mRNA-1010 has an acceptable safety profile, induces superior rVE against influenza disease and induces Ab responses higher than SD comparator and superior to HD comparator (in adults ≥65 years). mRNA-1010 manufacturing avoids reliance on embryonated chicken eggs, maintains sequence match with circulating virus, and shortens the time from strain selection to vaccine availability. Together, data support that mRNA-1010 will be a valuable addition to the category of enhanced influenza vaccines and help reduce the annual burden of influenza disease in adults 50 years and older.

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13 APPENDICES

13.1 Study 101

13.1.1 Design

Study 101 was a Phase 1/2, randomized, observer-blind, dose-ranging first-in-human study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1010 vaccine in adult participants ≥18 years of age. The study consisted of 3 parts: Phase 1/2 (placebo-controlled), Phase 2 NH (active-controlled), and Phase 2 Extension (active-controlled).

In the Phase 1/2 part, 180 participants were randomly assigned in a 1:1:1:1 ratio to receive either 50 µg, 100 µg, or 200 µg of mRNA-1010 or placebo, with 45 participants randomly assigned to each vaccination group. In the Phase 2 NH part, 503 participants were randomly assigned in a 3:3:3:1 ratio to receive either 25 µg, 50 µg, or 100 µg of mRNA-1010 or the active comparator, Afluria Quadrivalent 60 µg. In the Phase 2 Extension part, 202 participants were randomly assigned in a 1:1:1:1 ratio to receive either 6.25 µg, 12.5 µg, or 25 µg of mRNA-1010 or the active comparator.

13.1.2 Results

The primary immunogenicity objective was to evaluate the humoral immunogenicity of 3 dose levels (50 µg, 100 µg, and 200 µg) of mRNA-1010 vaccine administered as a single dose against vaccine-matched Influenza A and B strains at Day 29.

Key immunogenicity results were as follows:

- At Day 29, GMFRs were approximately 7.5- to 11-fold for H1N1, 6- to 7-fold for H3N2, 2-fold for Victoria-lineage, and 3- to 4-fold for Yamagata-lineage in the mRNA-1010 groups; no meaningful change in GMFRs was observed in the placebo group.
- The GMTs elicited at the 50 µg dose level were comparable with the titers elicited at higher dose levels. Seroconversion on Day 29 was noted for >65% of participants for the Influenza A strains.
- Seroconversion was lower for the Influenza B strains; it was 14.0% to 25.0% for Victoria-lineage and 41.9% to 51.2% for Yamagata-lineage.
- For the Influenza A strains, the GMTs were higher in the ≥18 to <50 years group compared with the ≥50 years group.
- The GMFRs for H1N1 increased approximately 9.5- to 13-fold in the ≥18 to <50 years group compared with approximately 5.5- to 9-fold in the ≥50 years group.

The GMFRs for H3N2 increased approximately 6- to 8-fold in the ≥18 to <50 years group compared with approximately 6.5- to 7-fold in the ≥50 years group.

At the Day 181/EoS timepoint, anti-HA antibody GMTs for all vaccine strains dropped below Day 29 levels. However, they stayed above baseline levels for H1N1 and H3N2 and reached near baseline levels for Victoria-lineage and Yamagata-lineage. The proportion of participants meeting criteria for seroconversion in the mRNA-1010 groups ranged from 33.3% to 43.6% for H1N1, from 43.9% to 50.0% for H3N2, from 5.7% to 14.6% for Victoria-lineage, and from 2.8% to 12.2% for Yamagata-lineage.

Intramuscular administration of mRNA-1010 at doses ranging from 6.25 µg to 200 µg was generally well-tolerated; however, the reactogenicity profile was higher in frequency and severity compared with the active comparator:

- The incidence of local and systemic solicited ARs was higher in participants receiving mRNA-1010 compared with those receiving the active comparator or placebo; however, most of the solicited ARs were Grade 1 or Grade 2 in severity.
- Within the ≥50 µg mRNA-1010 groups, the incidence of solicited ARs and use of medications to treat pain and fever was generally lower in older adults than in younger adults, although the day of onset and duration of solicited ARs was comparable.

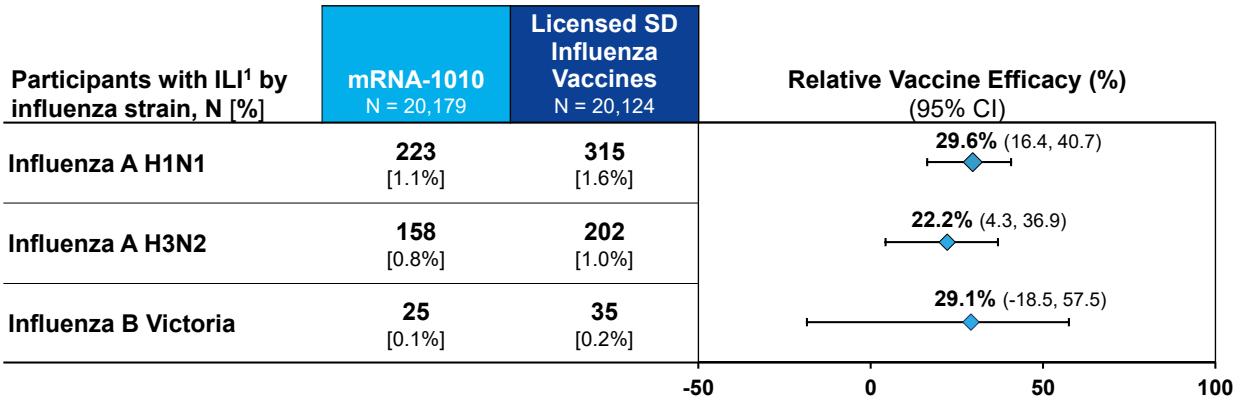
The overall safety profile was consistent with that seen with the use of other mRNA vaccines with a low incidence of unsolicited treatment-emergent AEs (TEAEs), severe TEAEs, and serious TEAEs. No AESIs or vaccination-related serious TEAEs were reported during this study.

Based on the results of this study, 50 µg (12.5 µg / strain) was selected for future studies based on a balance of immunogenicity and reactogenicity compared to the standard dose comparator.

13.2 Study 304 Results in Adults ≥ 50 Years

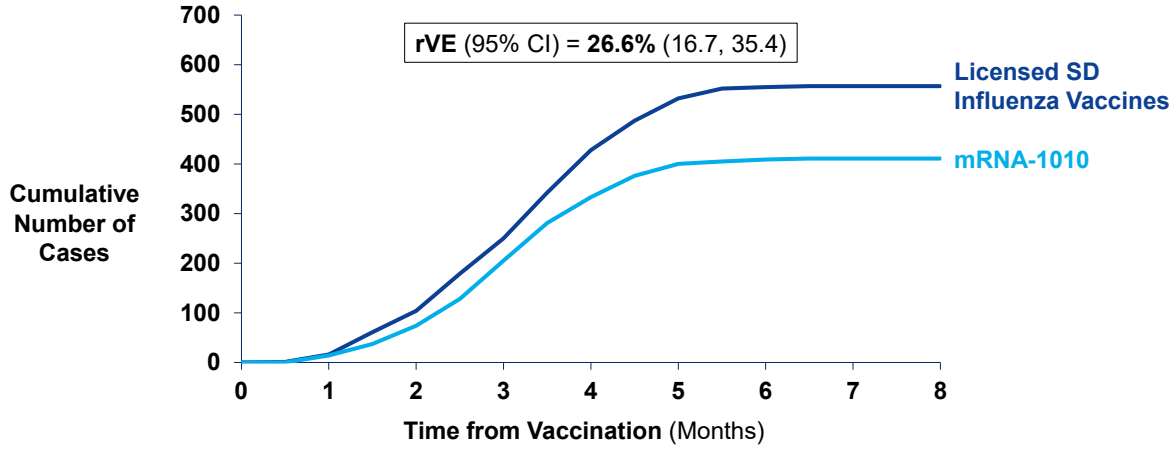
Figure 18: Study 304 ILI Events by Strain- Per-Protocol Set

Participants with ILI[1] by influenza strain, N [%]	mRNA-1010 N = 20,179	Licensed SD Influenza Vaccines N = 20,124	Relative Vaccine Efficacy (%) (95% CI)
Influenza A H1N1	223 [1.1%]	315 [1.6%]	**29.6%** (16.4, 40.7)
Influenza A H3N2	158 [0.8%]	202 [1.0%]	**22.2%** (4.3, 36.9)
Influenza B Victoria	25 [0.1%]	35 [0.2%]	**29.1%** (-18.5, 57.5)



CI: confidence interval; ILI: influenza-like illness; RT-PCR: reverse transcription polymerase chain reaction SD: standard dose
1. Based on RT-PCR-confirmed protocol-defined IL

Figure 19: Study 304 Cumulative Incidence Rates of Influenza Cases Per-Protocol Set

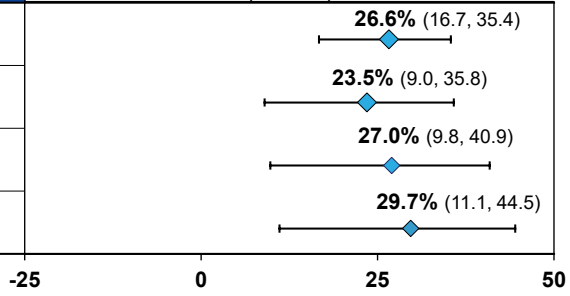


Licensed Influenza Vaccines	At Risk	20124	19871	19663	19383	19027	18774	10098	1932	0
	Events	0	16	104	250	428	532	555	557	557
mRNA-1010	At Risk	20179	19930	19765	19506	19151	18925	10180	1962	0
	Events	0	14	74	205	333	400	409	411	411

CI: confidence interval; ILI: influenza-like illness; RT-PCR: reverse transcription polymerase chain reaction; rVE: relative vaccine efficacy; SD: standard dose
*Per Protocol-defined ILI - all cases required RT-PCR confirmation within 7 days of illness onset

Figure 20: Study 304 by Influenza-like Illness Definition Per-Protocol Set

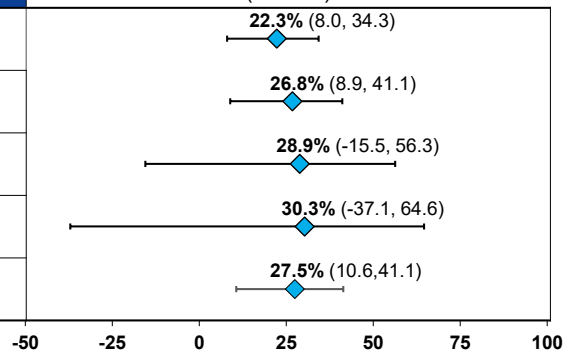
Participants With ILI by Definition, N [%]	mRNA-1010 N = 20,179	Licensed SD Influenza Vaccines N = 20,124	Relative Vaccine Efficacy (%) (95% CI)
Protocol-defined ILI	411 [2.0%]	557 [2.8%]	26.6% (16.7, 35.4)
Modified CDC-defined ILI	223 [1.1%]	290 [1.4%]	23.5% (9.0, 35.8)
CDC-defined ILI	149 [0.7%]	203 [1.0%]	27.0% (9.8, 40.9)
WHO-defined ILI	118 [0.6%]	167 [0.8%]	29.7% (11.1, 44.5)



CI: confidence interval; ILI: influenza-like illness; RT-PCR: reverse transcription polymerase chain reaction; rVE: relative vaccine efficacy; SD: standard dose
All cases of ILI required RT-PCR confirmation within 7 days of illness onset.
Huang G, et al 2025

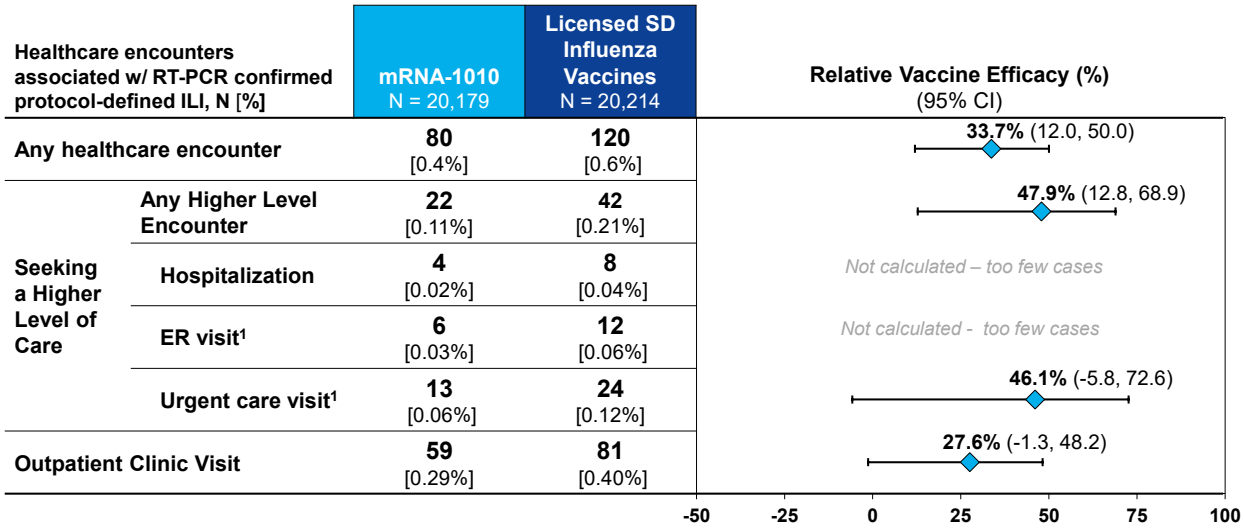
Figure 21: Study 304 High Risk and Frailty Subgroups Per-Protocol Set

Participants with ILI by Category, % [n/N]		mRNA-1010	Licensed SD Influenza Vaccines	Relative Vaccine Efficacy, (%) (95% CI)
High Risk Conditions	with ≥ 1 high-risk condition[a]	2.1% [241/11,465]	2.7% [309/11,457]	22.3% (8.0, 34.3)
Frailty Status[b] ≥ 65 years	Fit (0-3)	2.0% [140/7,079]	2.7% [190/7,059]	26.8% (8.9, 41.1)
	Vulnerable (4-5)	1.6% [28/1,737]	2.3% [39/1,708]	28.9% (-15.5, 56.3)
	Frail (≥ 6)	1.7% [14/806]	2.5% [21/837]	30.3% (-37.1, 64.6)
BMI	≥ 30 kg/m²	1.9% [153/7,958]	2.6% [211/7,892]	27.5% (10.6,41.1)



CI: confidence interval; BME: body mass index; ILI: influenza-like illness; SD: standard dose
a. High-risk conditions: BMI ≥30 kg/m², diabetes, pulmonary disorders, cardiac disorders, nervous systems disorders, etc.
b. Frailty based on Edmonton Frail Scale; score only available for participants ≥65 years

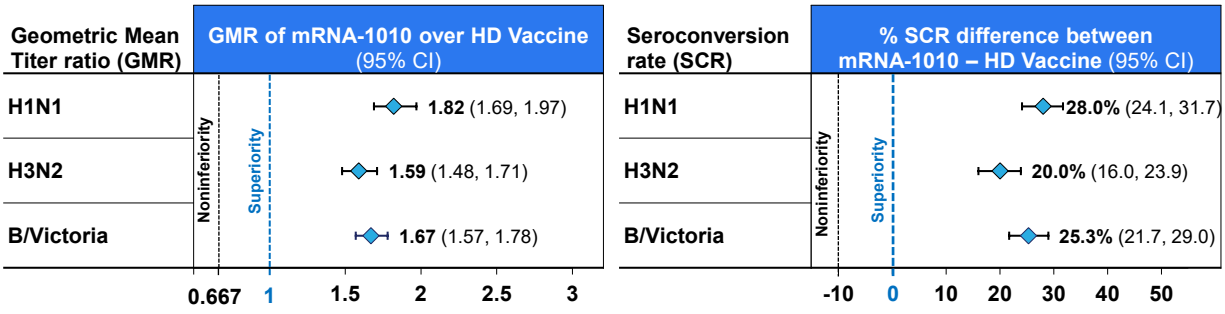
Figure 22: Study 304 Medically Attended Illness in Participants ≥50 Years



CI: confidence interval; ILI: influenza-like illness; RT-PCR: reverse transcription polymerase chain reaction; SD: standard dose

1. Malkin E et al. IDWeek, 2025

Figure 23: Study 304 - GMR and SCR at Day 29 Per-Protocol Immunogenicity Subset



GMR: ratio of mean titer of mRNA-1010 over mean titer for SD vaccine; SD: standard-dose licensed influenza vaccine;
mRNA-1010, n = 1167; licensed SD vaccine, n = 1175.
GMR, and corresponding 95% CI obtained by transforming least square mean estimate and CI back to original scale for presentation
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Table 16: Comparison of HAI Ab GMT (Day 29) for ILI Cases Versus Non-cases for mRNA-1010 and for the Active Comparator (by Influenza Strain)

Immunologic Marker	Treatment Group	Cases GMT (95% CI)		Non-Cases GMT (95% CI)		Ratio of GMT (Cases/Non-Cases) (95% CI)
		n	Day 29 HAI	n	Day 29 HAI	
Influenza A/H1N1 HAI Titer	mRNA-1010	208	57 (50, 65)	1696	150 (141, 159)	0.4 (0.3, 0.4)
	Active Comparator	296	44 (40, 48)	1744	82 (78, 87)	0.5 (0.5, 0.6)
Influenza A/H3N2 HAI Titer	mRNA-1010	150	89 (76, 106)	1754	149 (140, 157)	0.6 (0.5, 0.7)
	Active Comparator	187	60 (52, 70)	1853	93 (88, 99)	0.6 (0.5, 0.8)
Influenza B/Victoria HAI Titer	mRNA-1010	25	249 (170, 366)	1879	254 (242, 266)	1.0 (0.7, 1.4)
	Active Comparator	34	183 (133, 251)	2006	158 (151, 166)	1.2 (0.8, 1.6)

CI: confidence interval; GMT: geometric mean titer ratio; HAI ab hemagglutination inhibition antibody; ILI: influenza-like illness

Table 17: Day 29 B/Victoria HAI GMT by the Corresponding Strain-Specific ILI Case Status in Each Vaccine Group in Overall, Bulgaria, and Non-Bulgaria Regions (Study 304, Per Protocol Correlate of Analysis Set)

Region	Treatment group or GMT ratio	Cases GMT (95% CI)		Non-cases GMT (95% CI)		GMT ratio (cases/non-cases) (95% CI)
		n	Day 29	*n*	Day 29	Day 29
Overall	mRNA-1010	25	249 (170, 366)	1879	254 (242, 266)	0.98 (0.67, 1.45)
	Active comparator	34	183 (133, 251)	2006	158 (151, 166)	1.15 (0.84, 1.59)
	GMT ratio (mRNA-1010/active comparator) (95% CI)	1.36 (0.83, 2.24)		1.60 (1.50, 1.71)		
Non-Bulgaria	mRNA-1010	5	160 (79, 326)	1754	252 (240, 264)	0.64 (0.31, 1.30)
	Active comparator	8	108 (68, 173)	1867	153 (146, 160)	0.71 (0.44, 1.14)
	GMT ratio (mRNA-1010/active comparator) (95% CI)	1.48 (0.63, 3.46)		1.65 (1.54, 1.76)		
Bulgaria	mRNA-1010	20	279 (180, 432)	125	279 (220, 354)	1.00 (0.61, 1.65)
	Active comparator	26	215 (148, 312)	139	245 (190, 314)	0.88 (0.56, 1.38)
	GMT ratio (mRNA-1010/active comparator) (95% CI)	1.30 (0.73, 2.30)		1.14 (0.81, 1.61)		

CI: confidence interval; GMT: geometric mean titer ratio; ILI: influenza-like illness; HAI ab hemagglutination inhibition antibody

n is the number of participants in each subgroup who had Day 29 B/Victoria HAI titer data.

13.3 Study 304 Safety Results by Age Subgroup

Table 18: Study 304 Solicited Local ARs by Age Group

	Study 304 50-64 year		Study 304 ≥65 year	
	mRNA-1010 37.5 µg (N=1,510) n (%)	Active SD Comparator (N=1,502) n (%)	mRNA-1010 37.5 µg (N=1,505) n (%)	Active (SD) Comparator (N=1,495) n (%)
Any solicited local adverse reactions	1057 (70.0)	545 (36.3)	977 (64.9)	416 (27.8)
95% CI	67.6, 72.3	33.8, 38.8	62.4, 67.3	25.6, 30.2
Grade 3	28 (1.9)	2 (0.1)	23 (1.5)	2 (0.1)
Grade 4	0	0	0	0
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
Grade 4	0	0	0	0
Erythema (redness)				
Any	66 (4.4)	19 (1.3)	51 (3.4)	19 (1.3)
Grade 3	4 (0.3)	1 (<0.1)	6 (0.4)	76 (5.0)
Grade 4	0	0	0	0
Swelling/induration (hardness)				
Any	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)
Grade 4	0	0	0	0
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
Grade 4	0	0	0	0

AR: adverse reaction; CI: confidence interval; SD: standard dose

Table 19: Study 304 Solicited Systemic Adverse Reactions by Age Group

	Study 304 50 – 64 Years		Study 304 ≥65 Years	
	mRNA-1010 37.5 µg (N=1,510) n (%)	SD Comparator (N=1,502) n (%)	mRNA-1010 37.5 ug (N=1,505) n (%)	Active SD Comparator (N=1,495) n (%)
Any Solicited systemic ARs	927 (61.4)	506 (33.7)	823 (54.7)	464 (31.0)
95% CI	58.9, 63.9	31.3, 36.1	52.1, 57.2	28.7, 33.5
Grade 3	98 (6.5)	16 (1.1)	69 (4.6)	11 (0.7)
Grade 4	0	0	0	0
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)
Grade 4	0	0	0	0
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)
Grade 4	0	0	0	0
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)
Grade 4	0	0	0	0
Myalgia				
Any	613 (40.6)	196 (13.0)	454 (30.2)	152 (10.2)
Grade 3	44 (2.9)	4 (0.3)	32 (2.1)	3 (0.2)
Grade 4	0	0	0	0
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)
Grade 4	0	0	0	0
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)
Grade 4	0	0	0	0

	Study 304 50 – 64 Years		Study 304 ≥65 Years	
	mRNA-1010 37.5 µg (N=1,510) n (%)	SD Comparator (N=1,502) n (%)	mRNA-1010 37.5 ug (N=1,505) n (%)	Active SD Comparator (N=1,495) n (%)
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)
Grade 4	0	0	0	0

AR: adverse reaction; CI: confidence interval; SD: standard dose