Summary Basis for Regulatory Action

Date:	August 5, 2026
From:	(b) (6), OVRR/(b) (6)
BLA STN:	125869/0
Applicant:	ModernaTX, Inc.
Submission Receipt Date:	December 5, 2025
Priority Review (Yes/No)	Yes (Priority Review Voucher Redeemed)
PDUFA***Action Due Date:**	August 5, 2026
Proper Name:	Influenza Vaccine, mRNA
Proprietary Name:	MFLUSIVA
Indication:	MFLUSIVA is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine. MFLUSIVA is approved for use in persons 50 years of age and older.

* PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and (b) (6) • Facilities review (b) (6) • QC, Test Methods, Product Quality (b) (6)	(b) (6) (b) (6) (b) (6)
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (b) (6) • (b) (6)	(b) (6)
Statistical • Clinical data (b) (6) • Nonclinical data	(b) (6)
Non-clinical/Pharmacology/Toxicology • Toxicology/Developmental toxicology (Product Office) • Animal pharmacology	(b) (6) (b) (6)
Clinical Pharmacology	(b) (6)
Labeling • Promotional (b) (6)	(b) (6)
Other Review (not captured in above categories): • PNR (b) (6) • Data Standards • DHT • PMR/PMC Coordinator • Regulatory Project Management	(b) (6)
Advisory Committee Summary	(b) (6)

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1. Introduction

MFLUSIVA (Influenza Vaccine, mRNA; mRNA-1010) is a sterile, preservative-free, trivalent mRNA-based seasonal influenza vaccine developed and sponsored by ModernaTX, Inc. (b) (4)). The drug product is manufactured as a single-dose, ready-to-use suspension for intramuscular administration, supplied in a prefilled, 1 mL cyclic olefin copolymer syringe. Each dose delivers 12.5 µg of hemagglutinin (HA)-encoding mRNA per influenza strain (37.5 µg total mRNA), formulated within three monovalent lipid nanoparticles (LNPs) composed of SM-102, cholesterol, DSPC, and PEG2000-DMG. MFLUSIVA is indicated for active immunization

for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine, in persons 50 years of age and older.

This Summary Basis of Regulatory Action (SBRA) pertains to Biologics License Application (BLA) STN 125869/0, submitted by ModernaTX, Inc. on December 5, 2025. The applicant redeemed a priority review voucher (PRV BLA 125685) along with their BLA submission, which entitled them to receive a priority review of the submission with a PDUFA action due date of August 5, 2026. The application has been reviewed under a dual regulatory pathway: Traditional Approval for adults 50 through 64 years of age, based on clinical efficacy data demonstrating substantial evidence of effectiveness compared with a U.S.-licensed standard-dose (SD) influenza vaccine, and Accelerated Approval for adults 65 years of age and older, based on surrogate endpoints (hemagglutination inhibition (HAI) antibody titers) reasonably likely to predict clinical benefit, as measured against a CDC-preferentially recommended high-dose (HD) influenza vaccine comparator

Traditional Approval in adults 50 through 64 years of age is based on Study mRNA-1010-P304 (NCT06602024), a Phase 3, randomized, observer-blind, active-controlled efficacy trial which enrolled 40,805 adults ≥50 years of age across 11 countries. MFLUSIVA demonstrated statistically significant superiority over the SD comparator in preventing RT-PCR–confirmed, protocol-defined influenza-like illness, with an overall relative vaccine efficacy (rVE) of 26.6% (95% CI: 16.7, 35.4) and consistent point estimates across both age strata (adults 50 through 64 years of age and adults ≥65 years of age) and as well as both influenza subtypes A and type B, although the confidence interval around the rVE for influenza B/Victoria was wide due to the small number of cases accrued. The basis for Accelerated Approval in adults ≥65 years of age derives from Study mRNA-1010-P303 Part C, a Phase 3 immunogenicity trial in which mRNA-1010 (QIV) (Moderna mRNA quadrivalent influenza vaccine)[1] demonstrated statistically significant superiority over Fluzone High-Dose Quadrivalent (a CDC-preferentially recommended vaccine for older adults) across all four vaccine-matched strains as measured by GMT ratio and seroconversion rate at Day 29.

In Study P304 and P303 Part C, reactogenicity of MFLUSIVA and mRNA-1010 (QIV) respectively, was elevated relative to comparators but was predominantly mild to moderate in severity and transient in duration. No vaccine-related serious safety signals were identified. Safety was evaluated in an Integrated Summary of Safety (ISS) across four clinical trials including more than 35,000 mRNA-1010[2] recipients aged 50 years and older.

The Vaccine and Related Biological Products Advisory Committee (VRBPAC) unanimously voted on June 18, 2026, that the benefits of MFLUSIVA outweigh its risks for both age groups.

Several issues warranting further discussion in this document include: the regulatory and scientific basis for the bifurcated approval pathway, including an initial Refusal to File

[1] An unlicensed Moderna mRNA quadrivalent influenza vaccine manufactured using the same process as MFLUSIVA and differs only in the addition of the RNA encoding the B/Yamagata antigen.

[2] The ISS includes recipients of multiple formulations of mRNA-1010, including MFLUSIVA, mRNA-1010 (QIV), and an earlier formulation of mRNA-1010 with influenza B antigens manufactured differently than those in the formulation intended for licensure.

and subsequent revised regulatory approach; the use of cell-propagated viruses in HAI immunogenicity assays and associated positive bias relative to egg-derived comparators; residual uncertainty regarding strain-specific effectiveness against influenza B/Victoria; an observed numerical imbalance in deaths of unspecified cause in the ISS; and postmarketing requirements, including a mandatory confirmatory efficacy study in adults ≥65 years of age (Study mRNA-1010-P910), deferred pediatric studies under PREA, postmarketing commitment study with active surveillance for death (both unspecified and all cause), myocarditis, pericarditis, and Guillain Barre syndrome (GBS), a postmarketing commitment study to evaluate microneutralization titers as a correlate of risk, and a postmarketing commitment study to further evaluate immune responses using both egg- and cell-derived assays in parallel during the 2026–2027 and 2027–2028 influenza seasons, the latter coinciding with the confirmatory postmarketing requirement study (Study mRNA-1010-P910).

2. Background

Influenza is responsible for 3 to 5 million cases of severe illness and up to 650,000 deaths annually worldwide[1], with U.S. estimates of up to 710,000 hospitalizations and 52,000 deaths per season[2]. The burden falls disproportionately on older adults and those with underlying comorbidities: adults ≥65 years of age account for 70–85% of influenza-related deaths and 50–70% of influenza-related hospitalizations in the United States, while adults 50 through 64 years of age experience hospitalization and mortality rates substantially exceeding those in younger adults[3]. The risk gradient by age is further amplified by the high prevalence of chronic conditions, including cardiovascular, pulmonary, metabolic, renal, and immunocompromising conditions[3], which affect an estimated 78.4% of U.S. adults 35 through 64 years of age and 93% of those ≥65 years of age[4]; notably, the co-morbidity burden accumulates most rapidly between 45 and 65 years of age[5]. These epidemiological patterns establish a strong public health rationale for an efficacious influenza vaccine specifically indicated for adults ≥50 years of age.

Influenza A and B viruses, both members of the *Orthomyxoviridae* family, are responsible for annual seasonal epidemics. Influenza A viruses are classified into subtypes based on their two principal surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), while influenza B viruses circulate as distinct lineages. Continuous antigenic drift (minor but cumulative variation in HA and NA sequences) generates novel circulating strains each season and necessitates periodic strain-composition updates to seasonal influenza vaccines[7]; influenza A/H3N2 is particularly prone to antigenic drift and to egg-adaptive mutations that can alter HA conformation and reduce vaccine immunogenicity[8]. Currently licensed egg-based vaccines, which account for the majority of seasonal influenza vaccine supply[9], are susceptible to such adaptive mutations during manufacture, contributing to variable effectiveness that is generally estimated at up to 60% under conditions of optimal antigenic match and considerably lower during strain mismatch seasons[10]. These manufacturing constraints, combined with the biological imperative for rapid strain reformulation, underscore the unmet need for manufacturing technologies capable of scalable, egg-independent production.

The Applicant submitted Investigational New Drug (IND) 27460 on May 27, 2021, to develop an mRNA-based seasonal influenza vaccine, titled “Influenza Virus (HA; mRNA-1010; A/H1N1 Strain; A/H3N2 Strain; B/Victoria and B/Yamagata lineages) in Lipid

Nanoparticles (SM-102; PEG2000-DMG; 1,2-distearoyl-sn-glycero-3 phosphocholine (DSPC); Cholesterol)".

At a **pre-BLA meeting on August 22, 2025**, CBER requested that, in their BLA submission, the Applicant include a comprehensive benefit-risk assessment for MFLUSIVA in adults 50 through 64 years of age and ≥65 years of age, including justification for the relative vaccine efficacy (rVE) results given Study P304's use of a non-preferentially recommended comparator (Fluarix) in older adults. CBER also required final safety data with at least 6 months of follow-up, safety summaries of all SAEs, AESIs, and deaths from Phase 3 studies P301–P304 individually and integrated, to support a thorough benefit-risk assessment and evaluation of rare adverse events.

STN 125869/0 was submitted on December 5, 2025.

On February 3, 2026, CBER issued a **Refusal to File Letter (RTF)** to the Applicant for STN 125869/0. On February 10, 2026, the Applicant requested a post-RTF, **Type A meeting**. On February 17, 2026, the Applicant submitted a meeting package that included a **proposal for a revised regulatory approach** that reflects the benefit–risk considerations across the two age strata within the proposed indication for MFLUSIVA (adults ≥50 years of age):

- **Traditional Approval** for adults 50 through 64 years of age, based on the totality of demonstrated clinical efficacy and supportive safety data; and
- **Accelerated Approval** for adults ≥65 years of age. Influenza is recognized as a serious disease in adults in this age group. The Applicant justified that MFLUSIVA provides a meaningful benefit over existing therapies on the basis that its manufacturing technology allows for a more rapid ability to update the vaccine in response to emerging influenza virus strains and because their mRNA manufacturing platform will not be subject to egg-adaptive mutations which may alter antigenicity and possibly reduce effectiveness. The Applicant proposed demonstrating VE of MFLUSIVA based on surrogate endpoints (HAI antibody titers) as measured against a CDC-preferentially recommended high-dose comparator. As a postmarketing requirement (PMR) to support an Accelerated Approval licensure pathway, the Applicant proposed a pragmatic, randomized comparative clinical efficacy study for adults ≥65 years of age, with the primary endpoint being rVE against a CDC-preferentially recommended high-dose comparator.

On February 17, 2026, the Applicant presented their proposal for the revised regulatory approach to STN 125869/0 at their Type A meeting teleconference. **CBER subsequently issued a Filing Notification Letter with Deficiencies Identified,** which outlined concerns regarding the following:

1. Study P304's use of Fluarix as the comparator vaccine for participants ≥65 years of age, rather than a vaccine preferentially recommended by the Advisory Committee on Immunization Practices (ACIP) for use in older adults (e.g., Fluzone HD, Flublok, Fluad).
2. The potential insufficiency of comparing the immunogenicity of MFLUSIVA to an ACIP-preferentially recommended vaccine for adults ≥65 years to demonstrate substantial evidence of effectiveness for traditional approval, given the absence of a validated surrogate endpoint accepted by CBER as evidence of clinical benefit.

On June 18, 2026, data from this BLA was discussed at a VRBPAC meeting. The committee unanimously voted that the benefits of MFLUSIVA outweighed its risks for the prevention of influenza disease in adults 50 through 64 years of age and adults 65 years of age and older.

A summary of the regulatory events leading to approval of this BLA is outlined in **Table 1**.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. IND 27460 submission	27-May-2021
2. Pre-BLA meeting	22-Aug-2025
3. BLA 125869/0 submission	5-Dec-2025
4. BLA filed	17-Feb-2026
5. Mid-Cycle communication	6-April-2026
6. Late-Cycle meeting	5-June-2026
7. VRBPAC Meeting	18-June-2026
8. Action Due Date*	5-Aug-2026

***** a priority review voucher was redeemed with this BLA submission which shortened the review clock from 12 months to 8 months.

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Description of Final Product

The MFLUSIVA (mRNA-1010) Drug Product (DP) is an mRNA-lipid complex suspension that contains monovalent lipid nanoparticles (LNPs). The mRNA in each monovalent LNP encodes the hemagglutinin (HA) glycoprotein of the seasonal influenza virus strain. Each LNP consists of the following four lipids: SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate), cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), and PEG2000-DMG (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000). The DP is supplied as a sterile single dose, ready-to-use suspension for intramuscular (IM) administration in a 1-mL prefilled syringe (PFS). Each PFS delivers 12.5 µg of each seasonal influenza HA surface glycoprotein encoding mRNA (37.5 µg of total mRNA) and 759 µg of total lipids as a suspension in preservative-free buffer containing (b) (4) mM Tris, and (b) (4) g/L sucrose at (b) (4).

Manufacturing Overview

The MFLUSIVA manufacturing process involves (b) (4) drug substance (DS) components, messenger RNA (mRNA) (b) (4) which are (b) (4) to produce LNPs. Three monovalent LNPs are then (b) (4) to formulate the DP.

mRNA Manufacturing: The mRNA DS is (b) (4)

(b) (4)

Drug Product: The DP comprises three monovalent LNPs (one per influenza strain) formulated as a sterile, single-dose ready-to-use suspension in a prefilled, cyclic olefin copolymer syringe containing 12.5 µg of each HA-encoding mRNA and 759 µg total lipids.

Process controls, critical parameters, and in-process testing are implemented at each manufacturing stage to ensure robust, consistent production of high-quality vaccine.

Drug Substance (DS)

(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

Drug Product (DP)

The MFLUSIVA DP is an mRNA-lipid complex dispersion that contains three monovalent LNPs; the mRNA in each monovalent LNP encodes for the proteins as listed in **Table 2** below. The LNP consists of four lipids that act as protectants and carriers of the mRNA. The four lipids are SM-102, cholesterol, DSPC, and PEG2000-DMG. The buffer components and composition of the DP are also listed in **Table 2** below. The DP is supplied as a sterile single dose, ready-to-use liquid for intramuscular (IM) administration in a 1-mL prefilled syringe (PFS). The DP manufacturing process and controls are designed on the basis of a 37.5-µg dose at (b) (4) mg/mL. Each PFS delivers 12.5 µg of each seasonal influenza hemagglutinin surface glycoprotein (HA) encoding mRNA and 759 µg of total lipids as a white to off-white dispersion in preservative-free buffer containing (b) (4) mM Tris, and (b) (4) g/L sucrose at (b) (4)

Use of LNP-100 vs LNP-102 Manufacturing Processes

While the commercial DP manufacturing process to be licensed is formulated with LNP inputs formulated by the LNP-102 process, the clinical trials were conducted with DP formulated with LNP-100-derrived LNP inputs. The LNP-102 manufacturing process incorporates (b) (4) step to (b) (4) . Comparability of DP formulated with LNP-102 and LNP-100 inputs was demonstrated using a combination of release and extended characterization testing against pre-defined acceptance criteria, stability monitoring, and nonclinical immunogenicity. DP formulated with LNP-102 inputs will be evaluated in Phase 4 clinical studies to generate additional safety and effectiveness data.

Table 2. MFLUSIVA DP Composition

Component	Function	Unit Formula (mg/mL)	Unit Formula (µg/dose)[a]
Total mRNA	Contains mRNA encoding glycoprotein hemagglutinin (HA) of the seasonal influenza virus strains	(b) (4)	**37.5**
mRNA for Influenza A/H1N1	Encodes HA of Influenza A/H1N1	0.033	12.5
mRNA for Influenza A/H3N2	Encodes HA of Influenza A/H3N2	0.033	12.5
mRNA for Influenza B/Victoria	Encodes HA of Influenza B/Victoria	0.033	12.5
Total Lipids	Individual lipids make up the lipid components of the LNP	**2**	**759**
SM-102	Component of the LNP	(b) (4)	
Cholesterol	Component of the LNP		
DSPC	Component of the LNP		
PEG2000-DMG	Component of the LNP		
Tris	Buffer components in Tris buffer	(b) (4)	**189**
Tris-HCl	Buffer components in Tris buffer		**934**
Sucrose	Cryoprotection		**32.6mg**
Water for injection	Diluent	**q.s. to volume**	**q.s. to volume**

mRNA = messenger ribonucleic acid; LNP = lipid nanoparticle; SM-102 = heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG = 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000; q.s = quantum sufficit; [a] The calculation is performed with (b) (4) mL dose volume.

Manufacturing Process Development – MFLUSIVA DP

Process Versions A and B supplied early-phase clinical studies using an integrated comprehensive manufacturing process, while Versions D–F supplied later clinical studies (mRNA-1010-P301/P302, P303 Parts B&C, P304) using a conventional aseptic process aligned with the intended commercial process. Specifically, Process Version A-2 supplied mRNA-1010-P303 Part A, and Versions E/F supplied mRNA-1010-P303 Parts B&C and mRNA-1010-P304. The DP process comprises the same unit operations regardless of mRNA sequence, with multiple mRNA sequences used across studies to match circulating seasonal influenza variants.

Key manufacturing changes across process versions are as follows:

<u>DP Containing LNP derived from the LNP-100 Process</u>

- **Version A** (mRNA-1010-P101-Ph1/2, P303 Part A): Integrated sequential batch process; (b) (4) .
- **Version B** (mRNA-1010-P101-Ph2): Conventional aseptic process; introduced (b) (4)
- **Versions D-F** (mRNA-1010-P301/P302, P303 Parts B&C, P304): Conventional aseptic process; (b) (4) .

<u>DP Containing LNP derived from the LNP-102 Process</u>

- **Commercial process** (b) (4)

Comparability Assessment – MFLUSIVA DP

A comparability assessment was conducted to confirm that MFLUSIVA DP quality attributes are comparable across clinical studies through PPQ. Comparability was evaluated using release and extended characterization testing against pre-defined acceptance criteria, and stability monitoring. To support commercial manufacturing consistency, (b) (4) -agnostic quality attributes were assessed using tightened comparability limits derived from SPIKEVAX (mRNA-1273) DP comparability criteria, which are based on n = (b) (4) lots spanning multiple scales, sites, and development stages.

(b) (4) was assessed by (b) (4) with (b) (4) Stability comparability between LNP-100 and LNP-102 lots stored at 23–27°C was evaluated by equivalency testing of degradation rates for four quantitative Critical Quality Attributes (CQAs): mRNA Purity, (b) (4), and Total Lipid Impurities. Equivalence was concluded when two-sided (b) (4) CIs on the difference in mean slopes fell within predefined ±EAC bounds.

Release, extended characterization, and stability results collectively demonstrate that the LNP-102 commercial process produces DP comparable to clinical study material, and that LNP-102 lots exhibit quality and stability profiles comparable to or superior to LNP-100 lots. Degradation rates for (b) (4) and Total Lipid Impurities were equivalent between groups; for mRNA Purity and (b) (4), statistically significant differences were observed, but DP formulated with LNP-102 input demonstrated improved accelerated stability performance. Refer to the CMC Review memo for a discussion of the observed increase in (b) (4) in DP formulated with LNP-102 inputs relative to LNP-100 inputs.

In a nonclinical mouse immunogenicity study comparing DP lots formulated with LNP-100 input versus LNP-102 input, MFLUSIVA induced robust HA binding antibodies against all three encoded influenza strains regardless of LNP process. Overall results indicated immunogenicity equivalence between DP lots manufactured with LNP-102 and LNP-100 processes for all three influenza strains (NH24/25 season) at the 1-µg and 2-µg dose levels at both Day 21 and Day 36 timepoints.

MFLUSIVA DP Stability Summary and Conclusion

The DP stability program for MFLUSIVA was conducted in accordance with (b) (4), with statistical modeling aligned to (b) (4). The proposed shelf life is 12 months at 2°C-8°C, inclusive of up to 12 hours at 8°C-25°C.

The shelf-life assessment is primarily supported by stability data from representative (b) (4) DP lots (b) (4), including (b) (4) Primary Stability Batches (PSBs) and (b) (4) development lots. Direct MFLUSIVA LNP-102 stability data comprising (b) (4) development lots and (b) (4) with data up to 9 months at 4°C were also submitted and evaluated.

(b) (4)

Stability-indicating CQAs include mRNA Purity, (b) (4) and Total Lipid Impurities, all of which exhibit degradation trends over time under refrigerated and accelerated conditions. (b) (4), and (b) (4) are stable across all conditions. Total RNA Content, Lipid Content, and (b) (4) are not stability-indicating and were not included in the statistical shelf-life model.

(b) (4) photostability testing demonstrated that light exposure caused meaningful reductions in mRNA purity and increases in total lipid impurities in the absence of secondary packaging, necessitating a "Protect from Light" label statement. (b) (4) studies across (b) (4) showed only minor increases in (b) (4), both well within acceptance criteria, indicating no meaningful impact on product quality.

End-of-shelf-life (EoSL) was established using regression modeling incorporating degradation rates, slope uncertainty, and assay variability. The minimum clinically supported Effective Delivered Dose (EDD) of (b) (4) per strain at EoSL was established based on results from clinical trials showing comparable immunogenicity to pivotal clinical trials. In response to IR#25 and IR#76, the Applicant (b) (4) the RNA Ratio release specification (b) (4), the (b) (4) release specification ((b) (4), and the RNA Purity stability specification (b) (4) to provide additional quality assurance. CBER accepted the Applicant's justification for excluding (b) (4) and Lipid Content from the EoSL worst-case calculation. In response to IR#35, the Applicant demonstrated comparable degradation profiles between MFLUSIVA and (b) (4) DPs across all three influenza strains under both long-term and accelerated conditions, supporting the use of (b) (4) data in the original shelf-life justification.

The available MFLUSIVA LNP-102 stability data, combined with the demonstrated comparability to (b) (4), support the proposed 12-month shelf life at 2°C-8°C with up to 12 hours at 8°C-25°C. An end-to-end confirmatory stability study is ongoing. The Applicant commits to annual stability placement of at least one labeled DP lot, with continued trend monitoring.

b. Testing Specifications

The analytical methods and/or qualifications reviewed for MFLUSIVA drug substances and drug product were found to be adequate for their intended use.

Release and Stability Specifications

Release and stability specifications for the DP are detailed in **Table 3**. These have been established in accordance with (b) (4), incorporating critical quality attributes defined under (b) (4) and are supported by clinical experience, nonclinical immunogenicity data, manufacturing process capability, and prior knowledge from platform mRNA vaccine programs. Specifications for mRNA purity (release: (b) (4); stability: (b) (4), and lipid content and impurity limits are appropriately justified. The end-of-shelf-life mRNA purity specification is supported by clinical data demonstrating consistent immunogenicity across a range of effective delivered dose (EDD) values.

Table 3. MFLUSIVA DP Testing Specifications

Analytical Method	Release Sampling Point	Release Acceptance Criteria	Stability Acceptance Criteria
Appearance by Visual Inspection	(b) (4)	White to off-white dispersion. May contain visible, white or translucent product-related particulates	White to off-white dispersion. May contain visible, white or translucent product-related particulates
Identity by (b) (4) (b) (4)		(b) (4)	(b) (4)
Total RNA Content by (b) (4) (b) (4)			
mRNA Purity by (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)			
Lipid Identity by (b) (4) SM-102 Cholesterol DSPC PEG2000-DMG			
Lipid Content by (b) (4) SM-102 Cholesterol DSPC PEG2000-DMG			
Lipid Impurities by (b) (4)			

Abbreviations: (b) (4)

(b) (4) analytical methods covering identity (by (b) (4) , mRNA purity and product-related impurities (b) (4) , total RNA content (b) (4) lipid identity/content/impurities (b) (4) have been validated or verified in accordance with (b) (4) at all relevant testing sites, including Moderna (b) (4) -agnostic platform methods were validated using representative mRNA-1273 materials and confirmed applicable to

MFLUSIVA through product-specific verification activities. (b) (4) -specific methods, including identity, mRNA purity for DP, (b) (4) , have been fully validated or supplementally validated with MFLUSIVA materials, including both the LNP-100 and LNP-102 manufacturing processes. The LNP-102 process change, incorporating (b) (4) , was confirmed to have no adverse impact on method performance. Successful method transfers have been demonstrated at all testing sites, with all acceptance criteria met.

(b) (4) methods for bioburden, sterility, bacterial endotoxin, (b) (4) , (b) (4) , and deliverable volume have been qualified in compliance with (b) (4) , with method suitability confirmed through bacteriostatic/fungistatic studies demonstrating the absence of product inhibition across all tested matrices and sites. One pending commitment regarding supplemental quantitative validation of (b) (4) at the (b) (4) site is expected by September 1, 2026, and does not preclude an overall determination of adequacy. The (b) (4)) has been incorporated in the DP release specifications and as a report-only stability parameter, with trending and agency notification commitments in place.

Taken together, the analytical methods and their associated validations, transfers, and qualifications are considered adequate to support consistent lot release and stability monitoring of MFLUSIVA throughout its proposed shelf life, and the overall analytical control strategy is acceptable to support biological product approval.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Influenza Vaccine, mRNA are listed in the table below. The activities performed and inspectional histories are noted in **Table 4**.

Table 4. Manufacturing Facilities for MFLUSIVA (Influenza Vaccine, mRNA; mRNA-1010)

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification /Results
(b) (4) *Manufacture of* (b) (4)	(b) (4)	(b) (4)	Waiver	(b) (6) (b) (4) NAI
ModernaTX, Inc. (b) (4) *DS intermediates and DS manufacturing*	(b) (4)	(b) (4)	Waiver	(b) (6) (b) (4) NAI

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification /Results
(b) (4) *DP manufacturing*	(b) (4)	(b) (4)	Waiver	(b) (6) (b) (4) VAI
(b) (4) *DP primary labeling, packaging, and release testing*	(b) (4)	(b) (4)	Waiver	MRA(b)(3);(b)(4) Assessed by (b) (6): VAI (b) (6) (b) (4) VAI
(b) (4) *DP* (b) (4)	(b) (4)	(b) (4) 0	Waiver	(b) (6) (b) (4) NAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waiver	(b) (6) (b) (4) NAI
(b) (4) *DP batch release and DP release testing*	(b) (4)	(b) (4)	Waiver	(b) (6) (b) (4) NAI

Acronym key: (b) (4) DP: drug product; DS: drug substance; DUNS: data universal numbering system; FEI: FDA establishment identifier; (b) (4) ; MRA: mutual recognition agreement; NAI: no action indicated; (b) (4) VAI: voluntary action indicated

(b) (6) performed a surveillance inspection of (b) (4) . No Form FDA 483 was issued, and the inspection was classified as NAI.

(b) (6) performed a surveillance inspection of ModernaTX, Inc. in (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

(b) (6) performed a surveillance inspection of (b) (4) . A Form FDA 483 Inspectional Observations was issued at the conclusion of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

The (b)(3);(b)(4) performed a GMP inspection of (b) (4) . In accordance with the MRA between the FDA and European regulators, (b) (6) assessed the inspection report and determined the inspection was

classified as VAI. (b) (6) performed a pre-approval inspection of (b) (4) . A Form FDA 483 Inspectional Observations was issued at the conclusion of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

(b) (6) performed a surveillance inspection of (b) (4) . No Form FDA 483 was issued, and the inspection was classified as NAI.

(b) (6) performed a surveillance inspection of (b) (4) . No Form FDA 483 was issued, and the inspection was classified as NAI.

(b) (6) performed a surveillance inspection of Moderna (b) (4) . No Form FDA 483 was issued, and the inspection was classified as NAI.

e. Container/Closure System

The prefilled syringe (PFS) container closure system consists of a 1-mL long cyclic olefin copolymer syringe barrel with a halobutyl rubber tip cap in a rigid plastic cover manufactured by (b) (4) , 1-mL long halobutyl rubber plunger with fluoropolymer coating on the product contact surface manufactured by (b) (4) , and a polypropylene plunger rod manufactured by (b) (4) performed the container closure integrity testing at the (b) (4) , employing a (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. CBER concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted a comprehensive nonclinical package for MFLUSIVA that included one developmental and reproductive toxicity (DART) study, one non-GLP repeat-dose toxicity study, and one GLP repeat-dose toxicity study using earlier formulations of mRNA-1010 manufactured similarly to MFLUSIVA (see **Table 5**). The submission also contained seven additional repeat-dose toxicity studies of other mRNA vaccines formulated with (b) (4) lipid nanoparticle (LNP), six genotoxicity studies of the LNP component, seven nonclinical pharmacology studies, and six pharmacokinetic (PK) studies. A summary of these studies is outlined in **Table 5**.

Table 5. Summary of Nonclinical Pharmacology and Pharmacokinetic Studies

Study Type	Test Article and Dose (µg)	Species, Strain	Method of Administration; Immunization Schedule	GLP	Report Number
Evaluation of in vivo immunogenicity and protective efficacy of mRNA-1010 in mice	mRNA-1010-SH21 (10 µg) FLUAD (6 µg)	(b) (4) mice	IM; Prime only (Day 0) Intranasal challenge with 10^4 TCID50 H3N2 A/Hong Kong/1/1968 or 10^5 TCID50 of H1N1pdm09 A/Netherlands/602/2009 virus on Day 21	No	2810880
Evaluation of in vivo immunogenicity and protective efficacy of mRNA-1010 in ferrets	mRNA-1010-SH21(100 µg) FLUAD (60 µg)	*Mustela putorius furo* ferrets	IM; Prime/Boost (3-week interval) Intranasal (0.3 mL, 10^5 TCID50) and intrathecal (3.0 mL, 10^5 TCID50) challenge with H1N1pdm09 A/Victoria/2570/2019 virus on Day 42	No	2810881
Evaluation of the impact of (b) (4) on the immunogenicity of mRNA-1010 in mice	mRNA-1010 NH21/22 or mRNA-1010 NH21/22 (b) (4) (0.5, 1, 2, or 4 µg)	(b) (4) mice	IM; Prime only	No	MOD-4731
Evaluation of in vivo immunogenicity of different versions of mRNA-1010 in (b) (4) mice	mRNA-1010 mRNA-1010.6 mRNA-1010.4 (2 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-5814-1010
Evaluation of in vivo immunogenicity (antibody and T cell responses) of a trivalent mRNA vaccine against influenza virus	mRNA-1010 TIV (1.5 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7512-1010-TIV
Evaluation of in vivo immunogenicity of a trivalent mRNA vaccine against influenza virus comparing 2 LNP manufacturing processes	mRNA-1010 TIV LNP-100, mRNA-1010 TIV LNP-102 (0.5, 1, or 2 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7488-1010-TIV
Evaluation of in vivo immunogenicity of mRNA-1010 encoding for hemagglutinin of seasonal influenza viruses[i]	mRNA-1010 (0.045, 0.19, or 0.75 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7776-1010

Study Type	Test Article and Dose (µg)	Species, Strain	Method of Administration; Immunization Schedule	GLP	Report Number
Single-dose biodistribution study of (b) (4) mRNA in SM-102/PEG2000-DMG	(b) (4) mRNA in SM-102/ PEG2000-DMG-containing LNPs: 100 µg/dose	(b) (4) rats	Single IM dose	No	2308-582 Amendment 1
Single- or repeat-dose biodistribution study of mRNA-1273	mRNA-1273: 78 µg/dose[a]	(b) (4) rats	Single- or repeat IM dose on Days 1 and 28	No	20456513 Amendment 1
Identification and profiling of metabolites of SM-102 in rat, monkey, and human hepatocytes	NT-FIX mRNA in SM-102-containing LNPs: 10 µM SM-102	Cryopreserved hepatocytes from (b) (4) rats, (b) (4) monkey, and human	Incubation of SM-102-containing LNPs with rat, monkey, and human hepatocytes	No	NCS-BA-2022-010
Metabolite profile and identification of SM-102 in rat plasma, urine, and bile following IV infusion of SM-102-containing LNPs to male (b) (4) rats	(b) (4) mRNA in SM-102-containing LNPs: 0.7 mg/kg/dose	(b) (4) rats	Single 10- minute IV infusion	No	QV-0236- DA-RE-RPT- 01
PEG2000-DMG in vitro metabolite profiling and identification	PEG2000-DMG: 122.5 µM	Rat, monkey, and human serum	Incubation of PEG2000-DMG with rat, monkey, and human serum	No	NCS-BMA- 2023-06

Abbreviations: Admin = administration, DP = drug product, FLUAD = adjuvanted influenza vaccine, GLP =Good Laboratory Practice, H1N1 = influenza A virus, H3N2 = influenza A virus subtype H3N2, HA = hemagglutinin, (b) (4), IM = intramuscular, IV = intravenous, LNP = lipid nanoparticle, mRNA = messenger RNA, NCS = non-coding sequences, NH = Northern Hemisphere (b) (4), PEG2000-DMG = 1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene glycol-2000. PK = pharmacokinetic, RNA = ribonucleic acid, SH = Southern Hemisphere, SM-102 = heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-((undecyloxy)hexyl)amino)octanoate), TCID50 = median tissue culture infectious dose, TIV = trivalent vaccine, (b) (4), WHO = World Health Organization

Pharmacology Studies

In a ferret efficacy study (Report 2810881), female ferrets received mRNA-1010 (100 µg) or FLUAD (15 or 60 µg) on a prime/boost schedule (Days 0/21) and were challenged intranasally and intratracheally with H1N1pdm09 A/Victoria/2570/2019 on Day 42. mRNA-1010 induced HAI and high neutralization titers comparable to FLUAD. Vaccinated ferrets demonstrated reduced viral loads across tissues with complete lung protection; MRNA-1010 showed lower viral levels in the nose, throat, and nasal turbinate compared to FLUAD.

(b) (4) of each mRNA component did not impact immunogenicity, as confirmed by robust IgG anti-HA titers across dose levels (0.5–4 µg) in (b) (4) mice (b) (4) (Report MOD-4731).

An unlicensed Moderna mRNA quadrivalent influenza vaccine manufactured using the same process as MRNA-1010 incorporating revised influenza B HA coding sequences (2 point substitutions) and updated UTRs induced IgG and HAI antibody titers against all four antigens comparable to the original vaccine (Report MOD-5814-1010). The B HA

substitutions produced a modest increase in binding antibody to B/Austria HA after Dose 1 but did not affect B/Phuket HA responses. All formulations induced CD4+ Th1 and CD8+ T-cell responses.

A manufacturing process comparison of LNP-100 versus LNP-102 in MRNA-1010 (Report MOD-7488-1010-TIV) demonstrated immunogenicity equivalence at the 1- and 2-µg dose levels across all three influenza strains at Days 21 and 36, with slightly higher variability at 0.5 µg favoring LNP-102.

Across all pharmacology studies, MFLUSIVA consistently induced robust IgG binding and HAI antibodies, as well as CD4+ Th1 and CD8+ T cell responses against encoded influenza HA antigens.

Pharmacokinetic (PK) studies
Nonclinical PK evaluations included *in vivo* distribution, persistence, and clearance of mRNAs, SM-102 lipid, and/or expressed proteins using other representative mRNA-LNP DPs formulated in the same 4 lipids as MFLUSIVA.

Biodistribution studies
The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics and route of administration (as opposed the mRNA cargo). Consequently, mRNAs are expected to distribute similarly when encapsulated by LNPs of the same composition and administered via the same route of administration. A summary of the distribution studies and the obtained results is presented below.

To support the development of MFLUSIVA, 3 biodistribution studies were conducted using mRNA-LNP DPs comprised of the same 4 lipids and generally similar lipid:mRNA ratios as MFLUSIVA. The biodistribution and kinetics of SM-102 lipid, mRNA, and/or expressed protein(s) following a single IM administration were evaluated using (b) (4) mRNA encapsulated in SM-102/PEG2000-DMG-containing LNPs and (b) (4)). In the study with mRNA-1273, the biodistribution and kinetics of SM-102 lipid, mRNA, and/or expressed protein(s) following a single IM administration. Results from the biodistribution studies showed general similarities in exposure tissue rank order and kinetics across mRNA-LNP DPs (highest concentrations of mRNA and SM-102 were observed at the injection site, spleen, and lymph nodes). Tissue distribution of mRNA and SM-102 lipid is similar following 1 or 2 administrations of mRNA-1273. While expressed (b) (4) protein in tissues was largely not quantifiable, expressed SARS-CoV-2 protein was generally higher in tissues than in serum, where lymph nodes, injection site, spleen, and/or liver had highest exposures. Exposures of expressed SARS-CoV-2 protein in brain, heart, and lung were generally undetectable. In a single-dose biodistribution study conducted using (b) (4) in male rats, all 6 mRNA constructs contained within (b) (4) were detected in plasma and tissues, with the highest concentrations observed at the injection site, lymph nodes, and spleen. Only a small fraction of the administered dose reached distant tissues, and mRNA concentrations in most tissues became undetectable within 1 to 3 days, except at the injection site, lymph nodes, and spleen. A summary of the nonclinical toxicology studies is outlined in **Table 6**.

Table 6. List of Nonclinical Toxicology Studies

Study Type	Species/ Strain	Test Article	Admin. Route	Duration of Dosing	Doses	GLP	Testing Facility	Report Number
Combined developmental and perinatal/ postnatal reproductive toxicity study	Rat, (b) (4)	mRNA-1010	IM	4 doses over 6 weeks (every 2 weeks)	0 and 100 µg/dose	Yes	(b) (4)	20323624 Amendment 1
3-week repeat-dose immunogenicit y and toxicity study in rats	Rat, (b) (4)	mRNA-1010	IM	2 doses over 3 weeks (every 3 weeks)	0, 30, 60, and 100 µg/dose	No	(b) (4)	20287009 Amendment 2
3-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	mRNA-1010.6	IM	2 doses over 3 weeks (every 3 weeks)	0, 5, 10, and 18 µg/dose	Yes	(b) (4)	20457846 Amendment 1
4-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	(b) (4)	IM	3 doses over 4 weeks (every 2 weeks)	(b) (4)	Yes	(b) (4)	5002033
6-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	(b) (4)	IM	4 doses over 6 weeks (every 2 weeks)	(b) (4)	Yes	(b) (4)	5002034 Amendment 1
4-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	(b) (4)	IM	3 doses over 4 weeks (every 2 weeks)	(b) (4)	Yes	(b) (4)	5002045
6-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	(b) (4)	IM	4 doses over 6 weeks (every 2 weeks)	(b) (4)	Yes	(b) (4)	5002158 Amendment 1
4-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	(b) (4)	IM	3 doses over 4 weeks (every 2 weeks)	(b) (4)	Yes	(b) (4)	5002231
4-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	(b) (4)	IM	3 doses over 4 weeks (every 2 weeks)	(b) (4)	Yes	(b) (4)	5002400
4-week repeat-dose toxicity study in rats with a 2-week recovery	Rat, (b) (4)	(b) (4)	IM	3 doses over 4 weeks (every 2 weeks)	(b) (4)	Yes	(b) (4)	5002033
(b) (4)	Rat, (b) (4)	(b) (4)	IV bolus	Single dose evaluated at 24 h and 48 h postdose	(b) (4)	Yes	(b) (4)	9800399

Study Type	Species/ Strain	Test Article	Admin. Route	Duration of Dosing	Doses	GLP	Testing Facility	Report Number
(b) (4)	Rat, (b) (4)	(b) (4) mRNA	IV bolus	Single dose evaluated at 2 h, 6 h, 24 h, and 48 h postdose	0, 0.32/3.3, 1.07/10.9, 3.21/32.7 mg/kg RNA/SM-102, respectively	No	(b) (4)	AF87FU.1250 12NGLPICH. BTL Amendment 1
PEG2000-DMG bacterial reverse mutation test in (b) (4)	(b) (4)	PEG2000-DMG (b) (4)	*In vitro*	67 h and 57 min of incubation with or without (b) (4)	0, 1.58, 5.0, 15.8, 50, 158, 500, 1581, 5000 µg/(b) (4)	Yes	(b) (4)	9601035
PEG2000-DMG (b) (4) s test in human peripheral blood lymphocytes	Human peripheral blood lymphocytes	PEG2000-DMG (b) (4))	*In vitro*	4 h of incubation with or without (b) (4) and 24 h of incubation without (b) (4)	0, 3.25, 5.68, 9.95, 17.4, 30.5, 53.3, 93.3, 163, 286, 500 µg/mL	Yes	(b) (4)	9601036
SM-102 bacterial reverse mutation test in (b) (4)	(b) (4)	SM-102	*In vitro*	67 h and 29 min of incubation with or without (b) (4)	0, 1.58, 5, 15.8, 50, 158, 500, 1581, 5000 µg/(b) (4)	Yes	(b) (4)	9601567
SM-102 (b) (4) test in human peripheral blood lymphocytes	Human peripheral blood lymphocytes	SM-102	*In vitro*	4 h of incubation with or without (b) (4) and 24 h of incubation without (b) (4)	0, 3.25, 5.68, 9.95, 17.4, 30.5, 53.3, 93.3, 163, 286, 500 µg/mL	Yes	(b) (4)	9601568

Abbreviations: Admin = administration; (b) (4); DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; DTPA = diethylenetriaminepentaacetic acid; eCTD = electronic common technical document; F = female; (b) (4); GLP = Good Laboratory Practice; h = hour(s); H1N1 = influenza A virus; H3N2 = influenza A virus subtype H3N2; HA = hemagglutinin; (b) (4); IM = intramuscular; IV = intravenous; (b) (4); M = male; min = minute(s); mRNA = messenger RNA; NaCl = sodium chloride; (b) (4); PEG2000-DMG = 1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene glycol-2000; (b) (4) SM 102 = heptadecan-9-yl 8-((2-hydroxyethyl)(6- oxo-6-((undecyloxy) hexyl) amino) octanoate); SoA = Summary of Analysis; Tris = tris(hydroxymethyl)aminomethane; WHO = World Health Organization; (b) (4).

GLP Combined Perinatal/Postnatal Developmental & Reproductive Toxicity Study

Administration of mRNA-1010 twice during the premating period (28 and 14 days prior to mating) and twice during the gestation period (GDs 1 and 13) to female rats was well tolerated. It did not result in any effects on estrus cycling, mating and maternal systemic toxicity, pregnancy, and fertility index. There was no test article-related effect on fetal weight, visceral and skeletal malformations and variations or postnatal development reported in the study. Antibody titers were reported in all females receiving the vaccine,

indicating an active delivery of the test article to the animals. The titers were also reported in the fetuses and pups from the dams receiving the test article, indicating transfer of immunogenicity in utero. Further, antibody titers were reported in maternal milk on LD 13 and LD 21. GLP study deviations or amendments: Minor protocol amendments were recorded in the draft report. None of them influenced the quality, integrity, or interpretation of the results.

General Toxicity Studies

The Applicant submitted one non-GLP and one GLP repeat-dose toxicity study evaluating the candidate vaccine MFLUSIVA along with seven additional repeat dose toxicity studies evaluating other mRNA vaccines using the same LNP formulation. The non-GLP study (Report 20287009 Amendment 2) conducted with MFLUSIVA demonstrated transient, dose-dependent edema and erythema at the injection site, along with elevated neutrophil and eosinophil counts, decreased lymphocytes, and shifts in albumin/globulin ratios reflecting inflammation, with robust HA IgG antibody responses confirmed across all dose groups; no necropsy data were collected. The GLP repeat-dose toxicity study conducted with MFLUSIVA (Report 20457846 Amendment 1) confirmed dose-responsive increases in WBC, neutrophils (up to 5.73×), eosinophils (up to 3.92×), and fibrinogen (up to 3.03×), with clinical chemistry changes (decreased albumin, increased globulin, increased cholesterol at higher doses) indicative of an acute-phase response; microscopic target organs included the injection site (mixed cell inflammation), iliac and inguinal lymph nodes (increased lymphocyte cellularity), sciatic nerve (perineural mixed cell inflammation representing extension of local inflammation), spleen (decreased PALS cellularity, increased extramedullary hematopoiesis), sternum bone marrow (increased myeloid hematopoiesis), and adrenal gland (cortical vacuolation in males); the NOAEL was established at 18 µg, and all findings were fully or partially reversed after the 2-week recovery period.

Across all nine general toxicity studies conducted in (b) (4) rats via intramuscular (IM) injection, the overarching toxicological profile of mRNA-LNP vaccines (mRNA-1010, (b) (4) was consistent and most observations were the expected local and systemic inflammatory/immune responses. The consistent target organs of toxicity were the injection site (local reactogenicity with inflammation, edema, and pain), draining lymph nodes (reactive lymphadenopathy), sciatic nerve (perineural inflammation due to anatomic proximity), spleen and bone marrow (reactive hematopoietic changes), liver (hepatocellular vacuolation and Kupffer cell hypertrophy, particularly notable with (b) (4), warranting clinical liver function monitoring), and adrenal glands (cortical vacuolation/hypertrophy). Systemic inflammatory responses, including marked leukocytosis, elevated fibrinogen, and elevated inflammatory cytokines (IP-10, MCP-1, MIP-1α), represent potential clinical safety signals, particularly fever, injection-site pain, and systemic reactogenicity. The reversibility of most findings within the 2-week recovery period is reassuring, though hepatic vacuolation (b) (4) and injection-site changes (b) (4) in particular) were only partially reversible. No mortality, no adverse effects on body weight (with minor exceptions), no genotoxicity by IM route, and no reproductive toxicity were observed, supporting an acceptable nonclinical safety profile for clinical use.

***In vivo* and *In vitro* Genotoxicity Studies**

Taken together, the totality of evidence from all six genotoxicology studies (2 (b) (4) assays and four (b) (4) assays evaluating the LNP excipients SM-102, PEG2K-DMG, and (b) (4) supports an overall negative genotoxicity profile for the MFLUSIVA vaccine platform.

5. Clinical Pharmacology

The Applicant's mRNA-based proprietary vaccine platform using SM-102-containing LNPs is based on the principle and observation that cells can take up mRNA, translate it, and then express viral antigen(s) on the cell surface.

6. Clinical/Statistical

a. Clinical Program

Clinical Diagnostic Assays Used to Support Clinical Endpoints

Molecular Diagnostic Assay of Respiratory Pathogens

The PCR-based molecular diagnostic assay, (b) (4), was used for the qualitative detection of influenza nucleic acid to determine infection status for the phase 3 study, mRNA-1010-P304. The (b) (4) is a (b) (4)

The assay (b) (4) was developed and validated by (b) (4) and used in Study P304. The performance characteristics are provided and are acceptable. See the CMC Review Memo for additional information on molecular diagnostic assays used by The Applicant for other clinical studies submitted under STN 125869/0.

Immunological Assays for Antibody Quantification

Quantification of anti-HA Abs by HAI Assay

The anti-HA antibody HAI assay, designed for the quantification of functional anti-HA antibodies in human serum samples, was used to assess primary endpoints in both pivotal Phase 3 studies mRNA-1010-P303C and mRNA-1010-P304. (b) (4)

(b) (4)

The proprietary serological method “CSP 039-01 Quantification of anti-HA Antibodies by Hemagglutination Inhibition (HAI) Assay” was initially developed and qualified by (b) (4) and was applied in Study P101. The proprietary serological methods “(TSOP.119.01032-FDX) HAI Test for Titrating Influenza Virus A and B Specific Antibodies-(b) (4) ” was validated by (b) (4) for both influenza A and B strains used in Studies P301, P302, and P303 (Part A and B). The following parameters were evaluated: inter-assay precision, intra-assay precision, (b) (4) linearity, relative accuracy, limits of quantitation (LLOQ and ULOQ), specificity, matrix interference, and robustness (b) (4) The predefined acceptance criteria are acceptable. All parameters evaluated met the acceptance criteria showing that the assay is adequate for its intended use. Validation parameter results are provided and are acceptable.

HAI assays used in studies mRNA-1010-P303 and mRNA-1010-P304 employed (b) (4) . To address this, CBER has requested a postmarketing commitment (PMC) to evaluate immune responses in a sample subset using egg-derived virus or both egg-derived and cell-derived virus HAI assays in parallel.

(b) (4)-Based MN Assay for Quantification of Anti-Influenza Virus Antibodies

The (b) (4)-based MN assay detects and quantifies influenza-specific neutralizing antibodies in clinical serum samples. (b) (4)

(b) (4)

The validation parameter results were provided and are acceptable.

Antigenic Typing and Other Assays Used to Support Clinical Endpoints

Antigenic typing was performed using an HAI-based assay, in which (b) (4)

These validation parameter results are provided and are acceptable.

Please refer to the CMC Review Memo for additional information on assessment of T-cell activation for an exploratory endpoint in Study mRNA-1010-P304 as well as an additional molecular diagnostic assay used in clinical studies P101, P301, P302 and P303 Part A.

Surrogate Marker Reasonably Likely to Predict Clinical Benefit

The Applicant's CoR analysis supported a statistically meaningful association between HAI titers and RT-PCR-confirmed influenza illness caused by A/H1N1 and A/H3N2. For B/Victoria, however, the CoR analysis was inconclusive due to low case accrual, and non-statistically significant correlation (See Clinical Review Memo). Additionally, the strain-specific rVE point estimate, while directionally consistent, had a wide confidence interval that crossed zero. Notwithstanding these limitations, the review team concluded that HAI remained a surrogate endpoint reasonably likely to predict clinical benefit for prevention of influenza disease caused by influenza type B represented in the vaccine, supported by the directional consistency of the rVE estimate, the biological plausibility of

HAI-mediated protection, and methodological constraints inherent to strain-specific analyses.

The Applicant is required to conduct a Phase 4 confirmatory PMR study in adults 65 years of age and older, incorporating strain-specific rVE as an objective to verify and further describe clinical benefit.

Overview of Clinical Studies

The clinical development program for MFLUSIVA comprises five studies, as outlined in **Table 7**. Early-phase dose-selection was conducted in Study P101 (Phase 1/2), which, along with Studies P301 and P302, evaluated a pre-modified formulation containing earlier-generation influenza B antigens. Studies P301 and P302 contribute safety data to the ISS only; Studies P301 and P302 are not discussed in further detail in this review, as they employed the pre-modified formulation and failed to meet their primary objectives. Studies P303 Parts A and B evaluated modified quadrivalent formulations (mRNA-1010.6 and mRNA-1010.4, respectively) in adults ≥18 years of age and also contribute to the ISS only.

The pivotal Phase 3 program consists of two studies. Study P304 provides primary relative vaccine efficacy and safety data for MFLUSIVA in adults ≥50 years of age and serves as the primary evidentiary basis for demonstrating effectiveness for Traditional Approval in adults 50 through 64 years of age. Study P303 Part C provides immunogenicity and safety data for Moderna mRNA quadrivalent influenza vaccine compared with Fluzone HD (QIV) in adults ≥65 years of age and serves as the primary evidentiary basis for inferring effectiveness for Accelerated Approval in that population.

Table 7. Clinical Studies Submitted in Support of Efficacy and Safety Determinations of MFLUSIVA

Study Number (Country); Study Dates	Study Design	Total mRNA-1010 Recipients Total Comparator Recipients	Formulation and Dose Levels of mRNA-1010 Evaluated
mRNA-1010-P304 (Belgium, Bulgaria, Canada, Estonia, Finland, Georgia, Germany, South Korea, Taiwan, UK, U.S.) September 16, 2024 to August 21, 2025	Phase 3, randomized, stratified, observer blinded (participant and assessor-blind), active-controlled, safety, efficacy, and immunogenicity study in adults ≥50 years of age.	mRNA-1010 (TIV): N=20,350 SD comparator (TIV or QIV): N=20,353	mRNA-1010.4 (TIV) 37.5 µg
mRNA-1010-P303 (U.S.) Part A*: April 17, 2023 to November 28, 2023 Part B*: November 13, 2023 to June 20, 2024 Part C: November 13, 2023 to June 24, 2024	Phase 3, randomized, stratified, observer blind, active-controlled, immunogenicity, reactogenicity, and safety study. Part A*: adults ≥18 years Part B*: adults 18 to <65 years Part C: adults ≥65 years	Part A*: mRNA-1010 (QIV): N=1220 SD comparator (QIV): N=1180 Part B*: mRNA-1010 (QIV): N=1492 SD comparator (QIV): N=1488 Part C: mRNA-1010 (QIV): N=1502 Fluzone HD (QIV): N=1490	Part A*: mRNA-1010.6# (QIV) 50 µg Part B*: mRNA-1010.4 (QIV) 50 µg Part C: mRNA-1010.4 (QIV) 50 µg

Study Number (Country); Study Dates	Study Design	Total mRNA-1010 Recipients Total Comparator Recipients	Formulation and Dose Levels of mRNA-1010 Evaluated
mRNA-1010-P101* (U.S.) June 28, 2021 to September 27, 2022	Phase 1/2, randomized, stratified, observer blind, dose-ranging safety, reactogenicity, and immunogenicity study in healthy adults ≥18 years of age.	mRNA-1010 (original, QIV): N=736 Afluria (QIV): N=104 Placebo: N=45	mRNA-1010 (original, QIV) 6.25 µg 12.5 µg 25 µg 50 µg 100 µg 200 µg
mRNA-1010-P301* (Argentina, Australia, Colombia, Panama, and Philippines) June 6, 2022 to September 4, 2023	Phase 3, randomized, stratified, observer blind, active-controlled, immunogenicity, reactogenicity, and safety study in adults ≥18 years of age.	mRNA-1010 (original, QIV): N=3035 SD comparator (QIV): N=3048	mRNA-1010 (original, QIV) 50 µg
mRNA-1010-P302* (Bulgaria, Canada, Denmark, Estonia, Germany, Poland, Spain, Taiwan, UK, U.S.) September 14, 2022 to January 5, 2024	Phase 3, randomized, observer-blind, active-controlled, safety, reactogenicity, and efficacy, study in adults ≥50 years of age.	mRNA-1010 (original, QIV): N=11,210 SD comparator (QIV): N=11,200	mRNA-1010 (original, QIV) 50 µg

Source: Adapted from STN 125869/0, Clinical Overview.
Abbreviations: HD, high dose; QIV, quadrivalent influenza vaccine; SD, standard dose; TIV, trivalent influenza vaccine; UK, United Kingdom; U.S., United States
* P301, P302, and P303 Parts A and B contribute to the Integrated Summary of Safety only and will not be discussed individually in this memo.
^original refers to an earlier formulation of mRNA-1010 with influenza B antigens manufactured differently than those in the formulation intended for licensure
mRNA-1010.4 and mRNA1010.6 are identical, with the only difference being the scale of manufacturing. They both include modified influenza B antigen(s) encoding 2 stabilizing point mutations in non-surface exposed regions that do not impact antigenic epitopes.

Study mRNA-1010-P304 (NCT06602024)

Study mRNA-1010-P304 (P304) was a Phase 3, randomized, observer-blind, active-controlled study evaluating the safety, efficacy, and immunogenicity of trivalent MFLUSIVA versus a licensed standard-dose trivalent or quadrivalent inactivated influenza vaccine (SD comparator [TIV/QIV]) for prevention of influenza A or B in adults ≥50 years of age. The study was conducted at 301 sites across 11 countries in North America, Europe, and East Asia. A total of 40,805 participants were randomized 1:1 to a single intramuscular dose of either MFLUSIVA or SD comparator. The trivalent SD comparator was used in North America; the quadrivalent formulation was used in Europe and East Asia where the trivalent was unavailable. Strains encoded in MFLUSIVA were aligned with CBER recommendations for the 2024–2025 Northern Hemisphere influenza vaccine (cell- or recombinant-based). Randomization was stratified by age (50 to <65 years or ≥65 years of age) and prior-season influenza vaccination status. The study was conducted from September 16, 2024, to August 21, 2025. Primary efficacy and immunogenicity analyses used a data cutoff of April 30, 2025 (database lock June 3, 2025); supportive end-of-study analyses used a cutoff of August 21, 2025 (database lock September 16, 2025).

Study mRNA-1010-P304 Objectives

Primary efficacy objective:
The primary efficacy objective was to evaluate the relative vaccine efficacy (rVE) of MFLUSIVA versus the SD comparator against RT-PCR–confirmed protocol-defined influenza-like illness (ILI) (see Clinical Review Memo for case definitions) caused by any influenza A or B strain. The clinical endpoint evaluated was the first episode of RT-PCR–confirmed protocol-defined ILI with onset at least 14 days after study intervention through the end of the influenza season, caused by any influenza A or B strain. Noninferiority (NI) was demonstrated if the lower limit (LL) of the two-sided 95% confidence interval (CI) of rVE of MFLUSIVA relative to the SD comparator was greater than −10%. Once NI was demonstrated, the same endpoint was tested sequentially for superiority (LL of two-sided 95% CI of rVE >0%) and then "super-superiority" (LL of two-sided 95% CI of rVE >9.1%). Definitions and thresholds of superiority and "super-superiority" were defined by the Applicant.

Secondary Objectives:
The secondary efficacy objectives were to 1) evaluate rVE of MFLUSIVA versus the SD comparator against RT-PCR–confirmed modified Centers for Disease Control and Prevention (CDC)-defined ILI (see Table 44 in Appendix B of the clinical review memo for case definitions) caused by any influenza A or B strain and 2) To evaluate rVE of MFLUSIVA versus the SD comparator against RT-PCR–confirmed protocol-defined ILI or modified CDC-defined ILI caused by influenza A or B strains with antigenic match to the vaccine strains.

Secondary immunogenicity objectives were to 1) evaluate the humoral immunogenicity of MFLUSIVA relative to the SD comparator against vaccine-matched influenza A and B strains in a prespecified subset of approximately 2,400 participants and 2) evaluate HAI titers as a correlate of risk (CoR) and correlate of protection (CoP) against RT-PCR–confirmed protocol-defined ILI for MFLUSIVA and the SD comparator.

mRNA-1010-P304 Study Results

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

The primary efficacy objective was to demonstrate that MFLUSIVA is noninferior to the SD comparator in preventing the first episode of protocol-defined ILI. As shown in **Table 8**, MFLUSIVA demonstrated an rVE of 26.6% (95% CI: 16.7, 35.4) in all participants ≥50 years of age, meeting the prespecified NI criterion (LL of 95% CI of rVE >−10%). The case split was 411 cases (2.0%) in the MFLUSIVA group and 557 cases (2.8%) in the SD comparator group. Sequential testing for superiority (LL of 95% CI >0%) and "super-superiority" (LL of 95% CI >9.1%) were then conducted and both were also demonstrated.

Table 8. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for MFLUSIVA Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strains in Participants 50 Years of Age and Older (PP Set), Study P304

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

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

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

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

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

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

Table 9 presents a supportive analysis of rVE against RT-PCR–confirmed protocol-defined ILI by influenza strain. Point estimates for rVE were consistent across all strains. For B/Victoria, the rVE point estimate was consistent with the overall estimate, but the 95% CI was wide with a LL below zero (LL of 95% CI: −18.5), likely due to the small number of influenza B cases. The rVE analysis was primarily driven by results against influenza A strains, which accounted for 94.0% of influenza cases across both groups.

Table 9. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for MFLUSIVA **Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Influenza Strain Type in Participants 50 Years of Age and Older (PP Set), Study P304**

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

Source: Adapted from STN 125869/0, mRNA-1010 P304 Clinical Study Report, Tables 14.2.1.1.1.1 and 14.2.1.1.3.1. Data cutoff: April 30, 2025.

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

[a] Percentages are based on the number of participants in the analysis set. The case is the first RT-PCR–confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of influenza season caused by any influenza A or B strains, regardless of vaccine match. Participants can have more than one influenza strain infection simultaneously.

[b] rVE was defined as 100×(1−hazard ratio [MFLUSIVA versus the Active Comparator]). The rVE and the CI are based on a stratified Cox proportional hazards model with the study vaccination group as a fixed effect, adjusting by the randomized stratification factors: age group (≥50 to <65 years or ≥65 years) and the status of influenza vaccine in the previous influenza season (received or not received). Efron´s method is used to handle ties. If there were <20 events total in the two vaccination groups combined, rVE was not provided.

Descriptive analyses of rVE by age subgroup are shown in **Table 10**. The rVE point estimate for each age subgroup was consistent with the overall study population; in adults ≥75 years of age, the 95% CI was wide and crossed zero, likely due to the small sample size.

Table 10. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) for MFLUSIVA Versus SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strains by Age Group (PP Set), Study P304

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

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

See the Clinical Review Memo for discussion of additional supportive subgroup analyses of the primary efficacy endpoint and analysis of the secondary/exploratory objectives for Study P304.

Study mRNA-1010-P303 Part C (NCT05827978)

Study mRNA-1010-P303 (P303) was a Phase 3, multicenter, randomized, stratified, observer-blind, active-controlled study evaluating the immunogenicity, reactogenicity, and safety of Moderna mRNA quadrivalent influenza vaccine.

The clinical experience with Moderna mRNA quadrivalent influenza vaccine is relevant to MFLUSIVA. The Moderna mRNA quadrivalent influenza vaccine (containing 50 micrograms [mcg] of total RNA, with equal amounts [12.5 mcg] of each of the four RNAs encoding the hemagglutinin [HA] glycoproteins of A/Wisconsin/67/2022 pdm09-like virus [H1N1], A/Darwin/6/2021-like virus [H3N2], B/Austria/1359417/2021-like virus [B/Victoria], and B/Phuket/3073/2013-like virus [B/Yamagata]) is manufactured using the same process as MFLUSIVA and differs only in the addition of the RNA encoding the B/Yamagata antigen.

Part C of Study P303 (P303C) compared immunogenicity and safety of Moderna mRNA quadrivalent influenza vaccine to Fluzone High Dose Quadrivalent (Fluzone HD [QIV]) in adults 65 years of age and older. Fluzone HD (QIV) is one of three influenza vaccines

preferentially recommended by the CDC for this age group. The study was initiated on November 13, 2023, and completed on June 24, 2024. The final database lock date was July 22, 2024.

Study mRNA-1010-P303 Part C Objectives

Primary Immunogenicity Objective

The primary immunogenicity objective of Study P303C was to evaluate the humoral immunogenicity of Moderna mRNA quadrivalent influenza vaccine for noninferiority relative to Fluzone HD (QIV) against four vaccine-matched influenza A and B strains at Day 29 in adults ≥65 years of age, as measured by HAI. There were eight coprimary endpoints based on Geometric mean titer (GMT) ratio and Seroconversion Rate (SCR) difference for the four vaccine-matched strains (assessed at Day 29). Each endpoint was evaluated for noninferiority of Moderna mRNA quadrivalent influenza vaccine versus Fluzone HD (QIV) at a two-sided alpha level of 0.05. Study success required all eight coprimary endpoints to meet the noninferiority criteria. There were eight coprimary endpoints based on GMT ratio and SCR difference for the four vaccine-matched strains. Study success required all eight coprimary endpoints to meet the noninferiority criteria.

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

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

Superiority testing was conducted upon successful demonstration of noninferiority for all eight coprimary endpoints. Superiority at Day 29 was demonstrated if, for each of the four influenza strains:

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

Primary Safety Objective

The primary safety objective of Study P303C was to evaluate the safety and reactogenicity of Moderna mRNA quadrivalent influenza vaccine, including: frequency and severity of solicited local and systemic adverse reactions (ARs) through Day 7; frequency and severity of unsolicited adverse events (AEs) through Day 28; and serious adverse events (SAEs), medically attended adverse events (MAAEs), adverse events of special interest (AESIs), and AEs leading to study discontinuation through Day 181/end of study (EOS).

mRNA-1010-P303 Part C Study Results

Analyses of Primary Objective

Analyses of the primary immunogenicity endpoints, as measured by HAI for vaccine-matched influenza strains at Day 29 postvaccination, are shown in **Table 11** (GMTs and GMT ratios) and **Table 12** (SCRs and SCR differences). Baseline GMTs were similar

across groups. Day 29 GMTs and SCRs were higher in the Moderna mRNA quadrivalent influenza vaccine group than in the Fluzone HD (QIV) group for all four influenza strains.

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

Table 11. Analyses of Primary Immunogenicity Endpoint of GMTs as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29 Postvaccination, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

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

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

Table 12. Analyses of Primary Immunogenicity Endpoint of SCRs as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29 Postvaccination, Participants 65 Years of Age and Older, PPIS, Study P303 Part C

Endpoint	Moderna mRNA quadrivalent influenza vaccine N=1425 SCR%[a] (95% CI)	Fluzone HD (QIV) N=1409 SCR%[a] (95% CI)	Difference in SCR (Moderna mRNA quadrivalent influenza vaccine Fluzone HD [QIV]) (95% CI)[b] (97.5%CI)[c]
Influenza A/H1N1	49.7 (47.1, 52.3)	36.3 (33.8, 38.8)	13.4 (9.8, 17) (9.3, 17.5)
Influenza A/H3N2	56.4 (53.8, 59)	47.8 (45.2, 50.5)	8.6 (4.9, 12.2) (4.4, 12.8)

Endpoint	Moderna mRNA quadrivalent influenza vaccine N=1425 SCR%[a] (95% CI)	Fluzone HD (QIV) N=1409 SCR%[a] (95% CI)	Difference in SCR (Moderna mRNA quadrivalent influenza vaccine Fluzone HD [QIV]) (95% CI)[b] (97.5%CI)[c]
Influenza B/Victoria	29.8 (27.5, 32.3)	20.2 (18.1, 22.4)	9.7 (6.5, 12.8) (6, 13.3)
Influenza B/Yamagata	26.0 (23.8, 28.4)	20.2 (18.1, 22.4)	5.9 (2.8, 8.9) (2.3, 9.4)

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

Post Hoc Analysis of Moderna mRNA quadrivalent influenza vaccine and MFLUSIVA

To justify the use of immunogenicity data from the Moderna mRNA quadrivalent influenza vaccine evaluated in Study P303 Part C to support licensure of MFLUSIVA in adults 65 years of age and older, the Applicant conducted a post hoc analysis comparing Day 29 HAI GMTs between the PPISs of Study P304 and Study P303 Part C, restricted to participants ≥65 years of age, shown in **Table 13**, using an ANCOVA model that accounted for differences in baseline demographic factors between the two groups, including age, race, sex, ethnicity, baseline BMI group, previous influenza vaccine status, and baseline high-risk status. Although the analysis was not hypothesis tested, noninferiority of the Day 29 HAI GMT ratio (MFLUSIVA / Moderna mRNA quadrivalent influenza vaccine) would have been met for all three shared strains using a threshold of the LL of the 95% CI >0.667.

Table 13. Day 29 HAI for Vaccine-Matched Strains Comparing MFLUSIVA (Study iP304) and Moderna mRNA quadrivalent influenza vaccine (Study P303 Part C) in Adults ≥65 Years of Age, Model 1: ANCOVA With 6 PCA Factors

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

Source: Adapted from STN 125869/0, Amendment 32, Response to IR Database lock/data extraction dates: July 22, 2024 (P303 Part C) and June 3, 2025 (P304).
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GMT, geometric mean titer; PCA, principal components analysis; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine
The ANCOVA model includes vaccine (Moderna mRNA quadrivalent influenza vaccine in P303C or MFLUSIVA in P304) as a fixed factor, log-transformed baseline HAI titer as a fixed covariate, adjusted for the selected top principal components from the PCA of the demographic and baseline characteristics. Model 1 incorporates 6 PCA factors which explained 82% of the total variance

b. (b) (6) – Clinical/Statistical/Pharmacovigilance

Three (b) (6) inspections were issued for two domestic and one foreign clinical study investigators that participated in the conduct of clinical study mRNA-1010-P304. The inspections are complete but two of the Establishment Inspection Reports are pending review and final classification of the inspection. The (b) (6) review will be updated as soon as all inspections have been reviewed and the inspections final classified.

c. Pediatrics

Because this application contains a new active ingredient, it is subject to the requirements of the Pediatric Research Equity Act (PREA). The Applicant requested a partial waiver for infants from birth to less than 6 months of age on the grounds that studies are impossible or highly impractical, and a deferral of studies for infants and children 6 months to less than 18 years of age pending the completion of additional safety and efficacy data in adults.

The Applicant's pediatric study plan was presented to the (b) (6) on May 12, 2026. (b) (6) agreed with both requests: the partial waiver for infants birth to less than 6 months of age was granted because conducting a clinical efficacy study in this age group would be operationally impossible or highly impractical, and the deferral for infants and children 6 months to less than 18 years of age was granted pending completion of adult safety and efficacy data. (b) (6) also agreed to the following proposed postmarketing requirement (PMR) language and timelines:

- Study #1: A Phase 1/2 randomized, observer-blind, active-controlled, age de-escalation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1010 TIV in infants, children, and adolescents 6 months to <18 years of age.
    - Final Protocol Submission: May 31, 2027
    - Study Completion: July 31, 2029
    - Final Report Submission: December 31, 2029

- Study #2: A Phase 3 randomized, observer-blind, active-controlled study to evaluate the safety and effectiveness of mRNA-1010 TIV in healthy participants 9 to <18 years of age
    - Final Protocol Submission: May 31, 2028
    - Study Completion: July 31, 2029
    - Final Report Submission: December 31, 2029

- Study #3: A Phase 3 observer-blind, active-controlled study to evaluate the safety and effectiveness of mRNA-1010 TIV vaccine in children 3 to <9 years
    - Final Protocol Submission: May 31, 2029
    - Study Completion: July 31, 2030
    - Final Report Submission: December 31, 2030

- Study #4: A Phase 3 randomized, observer-blind, inactive-controlled study to evaluate safety, efficacy, and immunogenicity of mRNA-1010 TIV vaccine in healthy children aged 6 to <36 months

- Final Protocol Submission: May 31, 2029
- Study Completion: July 31, 2031
- Final Report Submission: December 31, 2031

d. Other Special Populations

Efficacy and safety have not been established in immunocompromised individuals, very frail older adults, pregnant or lactating women, or individuals younger than 18 years of age. Caution is warranted in individuals with a prior history of Guillain-Barré syndrome (GBS) within 6 weeks of any influenza vaccination. Data on concomitant administration with routinely co-administered vaccines (e.g., coronavirus disease 2019 [COVID-19], respiratory syncytial virus [RSV], pneumococcal vaccines) are also unavailable.

7. Safety and Pharmacovigilance

Clinical Safety

The safety of MFLUSIVA was evaluated in an ISS encompassing 35,965 vaccine recipients 50 years of age and older across four Phase 3 studies (Studies P301, P302, P303, and P304). The two primary studies, Study P304 (N=20,350 MFLUSIVA recipients; median follow-up 184 days) and Study P303 Part C (N=1,502 Moderna mRNA quadrivalent influenza vaccine recipients; median follow-up 171 days), contributed the principal safety data supporting licensure.

Reactogenicity

Solicited local and systemic adverse reactions (ARs) within 7 days of vaccination were reported more frequently among mRNA-1010[4] recipients than comparator recipients across both primary studies. In Study P304, any solicited AR was reported in 75.7% of MFLUSIVA recipients versus 46.7% of standard-dose (SD) comparator recipients. The most common reactions were injection site pain, fatigue, headache, myalgia, arthralgia, and chills. Solicited ARs were predominantly Grade 1-2 in severity, with a median onset and resolution of 2 days. Grade 3 solicited ARs occurred in 1.7% (local) and 5.5% (systemic) of MFLUSIVA recipients versus 0.1% and 0.9% in the SD comparator group. Similar reactogenicity patterns were observed in Study P303 Part C relative to the high-dose comparator. Reactogenicity was modestly attenuated in participants 65 years of age and older compared with those 50 through 64 years of age, a pattern consistent with age-related immune senescence.

Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)

Across both primary studies, SAE rates were balanced between treatment groups: 2.2% versus 1.9% in Study P304, and 2.7% versus 2.6% in Study P303 Part C. A single SAE (syncope on Day 2 in a 62-year-old MFLUSIVA recipient in Study P304) was assessed as likely related to vaccination by the review team. No SAEs were assessed as related to Moderna mRNA quadrivalent influenza vaccine in Study P303 Part C.

In the ISS, rates of SAEs and AESIs were balanced between study groups. No cases of myocarditis or pericarditis were reported within 42 days postvaccination in the mRNA-

[4] The ISS includes recipients of multiple formulations of mRNA-1010, including MFLUSIVA, mRNA-1010 (QIV), and an earlier formulation of mRNA-1010 with influenza B antigens manufactured differently than those in the formulation intended for licensure.

1010 group. Beyond the 42-day risk window and through the completion of all four Phase 3 studies, 10 (<0.1%) cases of myocarditis, pericarditis, or myopericarditis were reported in the mRNA-1010 group compared with 7 (<0.1%) cases in the SD/HD comparator group. Cardiac Event Adjudication Committee (CEAC)-confirmed cases were balanced across groups (4 in each group). Based on review of event narratives, latency of onset postvaccination, and presence of plausible alternative etiologies, none of these events were assessed as related to mRNA-1010 by the review team.

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

Pharmacovigilance

The CBER (b) (6) reviewer evaluated the supporting clinical trial safety data of MFLUSIVA to assess the adequacy of the Applicant's proposed Pharmacovigilance Plan. The reviewer concluded that the proposed activities in the Pharmacovigilance Plan were acceptable, including conduct of routine postmarketing pharmacovigilance surveillance activities per 21 CFR 600.80, comprising submissions of periodic safety reports (Periodic Adverse Experience Reports) to monitor for and assess any emerging risks associated with the vaccine.

The Applicant also plans to provide aggregate safety assessments (based on interval and cumulative data) of the following AESIs in their periodic safety reports for the first 3 years post-approval:

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

- Myocarditis, pericarditis, and myopericarditis

The Applicant has additionally proposed a PMC study using the same study population as that of the PMR confirmatory study to expand active surveillance for deaths (unspecified and all-cause), myocarditis/pericarditis/myopericarditis, and GBS to the indicated population aged 50 years and older as a postmarketing commitment (PMC).The Applicant provided the study synopsis of the PMC study (Post-Authorization Active Surveillance Safety Study Using Secondary Healthcare Data to Monitor Real-World Safety of MFLUSIVA (mRNA-1010) Vaccine for the Prevention of Influenza Disease in the United States, fv1.0, July 24, 2026) and the Safety Working group agreed to the conduct of the PMC at the July 31, 2026, meeting.

Please see the Addendum to the Pharmacovigilance Review Memo dated August 5, 2026, for further details.

8. Labeling

The proposed proprietary name, MFLUSIVA, was reviewed by the (b) (6) on February 23, 2026, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on March 5, 2026.

Through July 11, 2026, (b) (6) iteratively reviewed the draft PI, the patient package insert and the package and container labels with the MFLUSIVA Review Team. (b) (6) provided additional comments pertaining to the revised prescribing information submitted on June 11, 2026, patient package insert submitted on December 5, 2025, and package and container labels submitted on April 24, 2026, and May 12, 2026. (b) (6) labeling review memo was finalized from a promotional and comprehension perspective.

The Review Committee negotiated revisions to the PI, PPI, and package/container labels with ModernaTX Inc. Eight versions of the PI (in the original application and amendments 9, 18, 73, 96, 108, 113 and 116), four versions of carton labels/ three versions of the container labels (submitted in the original application and amendments 18, 38 and 50), and 3 versions of the PPI (in the original application and amendments 18 and 110) were submitted to STN 125752 by ModernaTX Inc. during labeling negotiations. The PI submitted on August 3, 2026 (amendment 116), the carton labels submitted on May 12, 2026 (amendment 50), container labels submitted on April 4, 2026 (amendment 38) and the PPI submitted on July 30, 2026 (amendment 110) were considered final for approval.

9. Advisory Committee Meeting

The Vaccine and Related Biological Products Advisory Committee convened on June 18, 2026, to discuss and vote on whether the available efficacy and safety data support a favorable benefit-risk profile of MFLUSIVA for use in the prevention of influenza in individuals 50 years of age and older. A bifurcated regulatory pathway presented that encompassed (1) Traditional Approval requested for use in adults 50 through 64 years of age, based on safety, immunogenicity, and clinical efficacy data, and (2) Accelerated Approval requested for use in adults ≥65 years of age, based on safety, comparative immunogenicity data, as well as supportive evidence (e.g., rVE against a SD

comparator), and a postmarketing Phase 4 randomized confirmatory study requirement. Nine out of the nine committee members voted yes to both voting questions posed:

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

The committee expressed general concerns regarding recent increases in vaccine hesitancy and poor vaccine uptake for the influenza vaccine in some populations. They signaled a need to effectively communicate the potential benefits of this vaccine while also being transparent about the increased reactogenicity seen with this and other mRNA-based vaccines. The committee also acknowledged the discussion of an observed imbalance in deaths of an unspecified cause in CBER's review of the Applicant's Integrated Summary of Safety (ISS). Although CBER's review determined this imbalance is unlikely to represent a safety signal for MFLUSIVA, the committee recommended using the proposed Phase 4 PMR study to gather additional mortality data. However, the Applicant asserted that active surveillance for death would infeasible in the PMR study design. Therefore, the Applicant proposed a separate Postmarketing Commitment Study to conduct active surveillance for death (unspecified cause and all-cause), myocarditis and pericarditis, and GBS.

10. Other Relevant Regulatory Issues

Priority Review Voucher (PRV)
A priority review voucher (PRV BLA 125685) was redeemed by the Applicant for this submission, which shortened the review timeline from 12 months to 8 months

Filing Action – Traditional Approval Regulatory Pathway (for Use in Adults 50 years of age and older)

The Applicant's initial request submitted in their December 5, 2026, application was for CBER to consider approval of MFLUSIVA under a Traditional Approval regulatory pathway with an indication for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine in persons 50 years of age and older.

Office of Vaccines Research and Review Office of the Director (OVRR OD) Filing Recommendation

In a January 24, 2026, memorandum addressed to the Center for Biologics Evaluation and Research Office of the Center Director (CBER OCD), OVRR OD recommended filing BLA 125869 without major deficiencies. This memorandum detailed the findings of the review committee and the conclusion that the application meets minimum filing standards under SOPP 8404 and contains adequate scientific data for substantive review, including complete clinical data from a well-designed, adequately powered study demonstrating statistical superiority to an FDA-licensed comparator. OVRR OD acknowledged CBER OCD's concerns regarding the use of Fluarix as a comparator in participants greater than 65 years of age, where CDC preferentially recommends high-dose or adjuvanted vaccines. However, OVRR OD concluded that this comparator selection constitutes a review issue rather than a fundamental deficiency that prevents meaningful scientific evaluation.

CBER OCD Non-Concurrence Memorandum and Refusal to File

On February 2, 2026, the CBER Center Director issued a Refuse to File (RTF) determination for BLA 125869. The RTF was based on the determination that the Applicant's pivotal randomized trial used a control arm (standard-dose influenza vaccine) that did not reflect the U.S. standard of care at the time of study design and conduct, given that CBER had previously notified the Applicant in writing to use an ACIP-preferentially recommended vaccine for adults ≥65 years of age (Fluzone HD, Flublok, or Fluad). In a February 2, 2026, CBER OCD Non-concurrence Memorandum, CBER OCD concluded that the application did not contain an adequate and well-controlled study as required for filing and that arguments in favor of filing were considered but did not alter this determination. An RTF letter was issued to the Applicant on February 3, 2026.

Filing Action – Dual Regulatory Pathway

On February 10, 2026, the Applicant requested a post-RTF Type A meeting and on February 17, 2026, the Applicant submitted a meeting briefing package that included a proposal for a revised regulatory approach that reflects the benefit–risk considerations across the two age strata within the proposed indication for MFLUSIVA (adults ≥50 years of age):

- Traditional approval for adults 50 through 64 years of age, based on the totality of demonstrated clinical efficacy and supportive safety data; and
- Accelerated Approval for adults ≥ 65 years of age. The Applicant proposed demonstrating VE of MFLUSIVA based on a surrogate immunogenicity endpoint (HAI antibody titers) as measured against a CDC-preferentially recommended high-dose comparator. As a postmarketing requirement (PMR) to support an Accelerated Approval licensure pathway, the Applicant proposed a pragmatic, randomized comparative clinical efficacy study for adults ≥65 years of age, with the primary endpoint being rVE against a CDC-preferentially recommended high-dose comparator.

On February 17, 2026, the Applicant presented their proposal for the revised regulatory approach to STN 125869/0 as part of the Type A meeting teleconference. CBER subsequently issued a **Filing Notification Letter with Deficiencies Identified**, which outlined CBER's concerns regarding:

1. Pivotal efficacy Study mRNA-1010-P304's use of Fluarix as the comparator vaccine for participants ≥65 years of age, rather than a vaccine preferentially recommended by ACIP for use in older adults (e.g., Fluzone HD, Flublok, Fluad).
2. The potential insufficiency of comparing the immunogenicity of MFLUSIVA to an ACIP-preferentially recommended vaccine for adults ≥65 years to demonstrate substantial evidence of effectiveness for traditional approval, given the absence of a validated surrogate endpoint accepted by CBER as evidence of clinical benefit.

Basis of Accelerated Approval

The Accelerated Approval pathway for MFLUSIVA in adults ≥65 years of age (21 CFR § 601.41) is based primarily on immunogenicity data from Study mRNA-1010-P303 Part C, a Phase 3 trial in which HAI titers were compared against a CDC-preferentially recommended high-dose influenza vaccine (the established standard of care in this age

group). It should be noted that the standard-dose comparator used in Study mRNA-1010-P304 is not CDC-preferentially recommended for adults ≥65 and the relative vaccine effectiveness data from that study were insufficient to serve as the primary basis for approval, though they provided critical supportive evidence of clinical benefit. Accelerated Approval criteria were met based on the following:

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

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

3. Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit: The Applicant proposes Day 29 HAI titers as surrogate endpoints. While HAI titers have historically served as surrogate endpoints in influenza vaccine development, prior supporting evidence was derived from studies of inactivated, egg-adapted vaccines. Given that the mRNA manufacturing technology may elicit a distinct immune response profile, the Applicant conducted a pre-specified correlate of risk (CoR) analysis in Study P304 evaluating the association between Day 29 HAI titers and RT-PCR-confirmed, protocol-defined ILI (see Section 6.1.11.9). The CoR analysis demonstrated a statistically significant association between HAI titers and ILI caused by influenza A/H1N1 and A/H3N2. Results were inconclusive for B/Victoria due to low case accrual and a non-statistically significant magnitude of correlation, leaving residual uncertainty regarding protection against this strain. Notwithstanding this uncertainty, HAI titers, along with the totality of available clinical data, support the clinical benefit of this vaccine based on: (1) the biological plausibility of HAI as a mechanism of protection against influenza, reinforced by the observed correlation between HAI and rVE for both influenza A strains in the Study P304 CoR analysis for MFLUSIVA; (2) superior immunogenicity of Moderna mRNA quadrivalent influenza vaccine relative to Fluzone HD (QIV) in Study P303 Part C, with potential improved effectiveness against influenza A strains alone carrying substantial public health significance for this high-risk population; (3) a directionally consistent B/Victoria-specific rVE point estimate of 29.1% from Study P304, with the wide 95% confidence interval (-18.5, 57.5) attributable to low case accrual rather than absence of effect; (4) an overall rVE of 27.4% (95% CI: 12.1, 40.0) in adults ≥65 years of age (Study P304), comparable in magnitude to rVE estimates observed in CDC-preferentially recommended influenza vaccines in this age group (i.e., Fluzone HD and Flublok) when compared with SD vaccines; and (5) the Applicant's agreement to further characterize B/Victoria effectiveness through the postmarketing requirement (PMR) study.

4. Postmarketing Requirement Confirmatory Study: The Applicant will conduct a pragmatic, randomized study to evaluate relative vaccine effectiveness of mRNA-1010 versus HD influenza vaccine in U.S. adults ≥65 years of age to verify and describe clinical benefit (see Section 11c - Recommendation for Postmarketing Activities below).

Influenza Vaccine Strain Composition and Annual Strain Updates

Influenza viruses undergo continuous antigenic evolution, necessitating annual updates to vaccine strain composition to maintain alignment with circulating strains. Each year, the World Health Organization (WHO) evaluates global influenza surveillance data and issues recommendations for the strains to be included in vaccines for the upcoming Northern and Southern Hemisphere influenza seasons. In the United States, licensed influenza vaccines are updated accordingly, considering VRBPAC discussion and recommendations, with manufacturers submitting CMC data to CBER to support each seasonal strain change. For mRNA-based influenza vaccines such as MFLUSIVA, strain updates are implemented by substituting the mRNA DS encoding the hemagglutinin (HA) glycoprotein of each recommended influenza strain, while the lipid nanoparticle delivery platform and drug product manufacturing process remain unchanged. Each strain update requires process verification, analytical comparability assessment, and nonclinical immunogenicity data to confirm that the updated composition produces consistent product quality and elicits appropriate immune responses prior to approval for the new season.

The initial CMC information that the Applicant submitted for BLA STN 125869 on December 5, 2025, corresponded with the trivalent formulation of cell- or recombinant-based influenza vaccines for the U.S. 2024-2025 influenza season, comprising (b) (4) (A/Wisconsin/67/2022, A/H1N1), (b) (4) (A/Massachusetts/18/2022, A/H3N2), and (b) (4) (B/Austria/1359417/2021, B/Victoria lineage). Subsequent amendments (STN 125869/0.18, 59, 88, and 93) were submitted between March and July 2026 to support the 2026-2027 Formula update, incorporating (b) (4) (A/Missouri/11/2025, A/H1N1), (b) (4) (A/Michigan/105/2025, A/H3N2), and (b) (4) (B/Pennsylvania/19/2025, B/Victoria lineage). CMC data for the updated strains, including process verification, comparability assessments, and batch analyses, were reviewed and found acceptable. The formulation of MFLUSIVA being considered for approval under STN 125869/0 corresponds to the 2026-2027 formula (b) (4) .

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in this original BLA submission, the Review Committee recommends approval of MFLUSIVA for the labeled indication and usage.

b. Benefit/Risk Assessment

Influenza imposes a substantial public health burden, with disproportionate morbidity and mortality in adults 50 years of age and older. The totality of clinical evidence supports a favorable benefit-risk profile for MFLUSIVA across this population. In adults 50 through 64 years of age, MFLUSIVA demonstrated robust relative vaccine efficacy against RT-PCR-confirmed influenza-like illness compared with a licensed standard-dose comparator, meeting all three pre-specified success criteria (sequentially tested) - for noninferiority, two-sided 95% CI lower limit >-10%; and for more stringent pre-specified success criteria, >0% and >9.1%. In adults 65 years of age and older, MFLUSIVA

elicited superior hemagglutination inhibition immune responses relative to a CDC-preferentially recommended high-dose comparator (a surrogate endpoint reasonably likely to predict clinical benefit) with supportive relative efficacy data in this age group. The reactogenicity profile, while elevated compared with active comparators, was predominantly mild to moderate in severity and transient, with no vaccine-related serious safety signals identified across an integrated safety population of more than 35,000 MFLUSIVA recipients. Residual uncertainties, including strain-specific effectiveness against influenza B/Victoria and effectiveness in frail or immunocompromised individuals and unspecified death imbalance, will be addressed through a postmarketing confirmatory efficacy study and ongoing pharmacovigilance. The Vaccine and Related Biological Products Advisory Committee unanimously agreed that benefits outweigh risks for both age groups. These findings collectively support Traditional Approval in persons 50 through 64 years of age and Accelerated Approval in persons 65 years of age and older.

c. Recommendation for Postmarketing Activities

Modera has committed to conduct the following postmarketing activities, which are specified in the approval letter.

POSTMARKETING REQUIREMENT FOR ACCELERATED APPROVAL SUBJECT TO REPORTING UNDER 506(c) of the FDCA

The required study is listed below.

1. A Pragmatic, Randomized Study to Evaluate Relative Vaccine Effectiveness of mRNA-1010 Versus High-Dose Influenza Vaccine in U.S. Adults ≥65 Years of Age (Study mRNA-1010-P910).

   Final Protocol Submission: May 22, 2026 (Submitted)

   Study Initiation: August 31, 2026

   Interim Study Report 1 Submission: December 31, 2027

   Interim Study Report 2 Submission: December 31, 2028

   Interim Study Report 3 Submission: December 31, 2029

   Study Completion: July 31, 2029

   Final Report Submission: May 31, 2030

POSTMARKETING REQUIREMENTS SUBJECT TO REPORTING UNDER the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

The required studies are listed below.

2. Study #1: Deferred pediatric study under PREA to evaluate the safety, reactogenicity, and immunogenicity of MFLUSIVA in infants, children, and adolescents 6 months through <18 years of age.

   Final Protocol Submission: May 31, 2027

   Study Completion Date: July 31, 2029

Final Report Submission: December 31, 2029

3. Study #2: Deferred pediatric study under PREA to evaluate the safety and effectiveness of MFLUSIVA in healthy children, and adolescents 9 years through <18 years of age.

   Final Protocol Submission: May 31, 2028

   Study Completion Date: July 31, 2029

   Final Report Submission: December 31, 2029

4. Study #3: Deferred pediatric study under PREA to evaluate the safety and effectiveness of MFLUSIVA in children 3 years through <9 years of age.

   Final Protocol Submission: May 31, 2029

   Study Completion Date: July 31, 2030

   Final Report Submission: December 31, 2030

5. Study #4: Deferred pediatric study under PREA to evaluate safety, efficacy, and immunogenicity of MFLUSIVA in healthy infants and children 6 months through <36 months of age.

   Final Protocol Submission: May 31, 2029

   Study Completion Date: July 31, 2031

   Final Report Submission: December 31, 2031

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

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

   Final Protocol submission: December 31, 2026

   Study Completion Date: December 31, 2030

   Final Report Submission: December 31, 2031

7. You commit to conduct and submit results of Study mRNA-1010-P304, an Exploratory Microneutralization Antibody Correlate of Risk Analysis for Influenza B/Victoria Lineage.

   Final Report Submission: December 31, 2026

8. A Phase 4, Randomized Study to Assess the Immunogenicity of an Updated mRNA Seasonal Influenza Vaccine Composition to evaluate the humoral

immunogenicity of mRNA-1010 relative to that of a licensed high-dose comparator in adults ≥65 years of age assessed with assays using both egg- and cell-based viruses.

Final Protocol Submission: September 14, 2026

Study Initiation: October 15, 2026

End of Season 1 Report: April 15, 2027

Study Completion: November 30, 2027

Final Report Submission: December 31, 2028

12. References

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