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U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting June 18, 2026

FDA Review of Efficacy, Immunogenicity, and Safety of mFlusiva (mRNA-1010)

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Outline

- Introduction
- Overview of Clinical Studies
- Efficacy Data
- Immunogenicity Data
- Safety Data
- Risk Mitigation: Pharmacovigilance Plan and PMR Study
- Summary and Voting Questions for VRBPAC

mFlusiva (mRNA-1010)

Vaccine composition	Three mRNAs (12.5 µg each, for a total of 37.5 µg of RNA) encoding the hemagglutinin (HA) glycoproteins of influenza A/H1N1, A/H3N2 and B/Victoria-lineage, encapsulated in lipid nanoparticles.
Dosing regimen	A single dose administered as 0.375 mL intramuscularly
Applicant's proposed indication	Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B represented in the vaccine.
Applicant's proposed approval pathway	Traditional Approval: Adults 50 through 64 years of age Accelerated Approval: Adults ≥65 years of age

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Overview of Phase 3 Clinical Studies

Study Number	Study Sites	Dates	Study Design	# Receiving mRNA-1010 (formulation)	# Receiving Comparator (formulation)
mRNA-1010-P304	Belgium, Bulgaria, Canada, Estonia, Finland, Georgia, Germany, South Korea, Taiwan, UK, U.S.	September 2024 to August 2025	Phase 3 safety, efficacy, and immunogenicity in ≥50 yoa	20,350 (TIV)	20,353 (SD QIV/TIV)
mRNA-1010-P303	U.S.	Part A*: April 2023 to November 2023 Part B*: November 2023 to June 2024	Phase 3 immunogenicity, reactogenicity, and safety A*: ≥18 yoa B*: 18 to <65 yoa	A*: 1220 (QIV) B*: 1492 (QIV)	A*: 1180 (SD, QIV) B*: 1488 (SD, QIV)
		Part C: November 2023 to June 2024	C: ≥65 yoa	C: 1502 (QIV)	C: 1490 (HD, QIV)
mRNA-1010-P301*	Argentina, Australia, Colombia, Panama, Philippines	June 2022 to September 2023	Phase 3 immunogenicity, reactogenicity, and safety in ≥18 yoa	3035 (original^, QIV)	3048 (SD, QIV)
mRNA-1010-P302*	Bulgaria, Canada, Denmark, Estonia, Germany, Poland, Spain, Taiwan, UK, U.S.	September 2022 to January 2024	Phase 3 safety, reactogenicity, and efficacy in ≥50 yoa	11,210 (original^, QIV)	11,200 (SD, QIV)

- QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine; SD: standard dose; HD: high dose; yoa: years of age
- *P301, P302, and P303 Parts A and B contribute to the Integrated Summary of Safety only
- ^original refers to an earlier formulation of mRNA-1010 with influenza B antigens manufactured differently than those in the formulation intended for licensure

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Study P304 Design

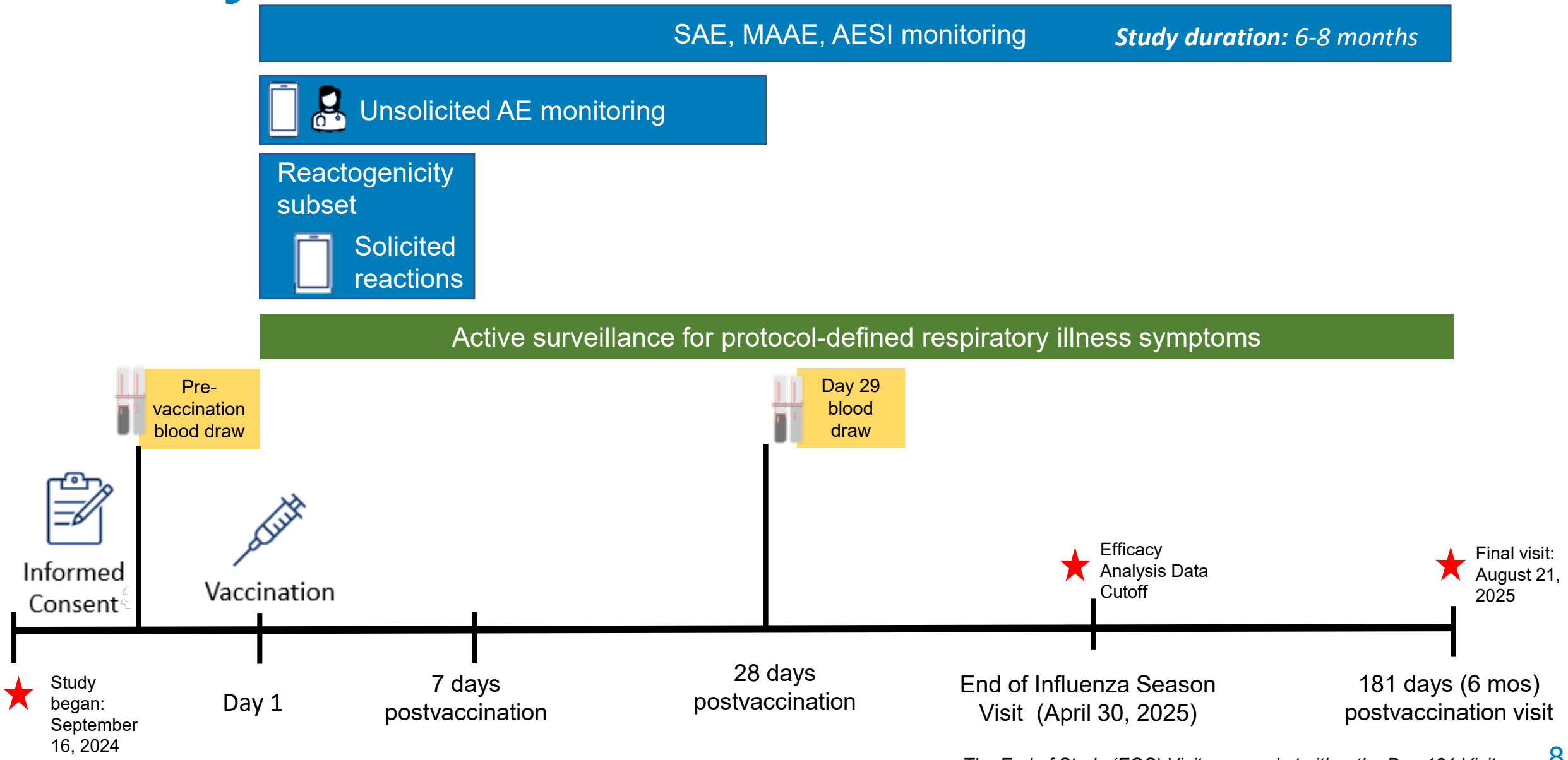
Phase 3 Relative Efficacy, Immunogenicity & Safety Study

- 40,805 participants ≥50 years of age (yoa) randomized 1:1 to mRNA-1010 (TIV) or standard dose (SD) comparator (Fluarix TIV or QIV)
- Stratified by age (50 to <65 yoa, ≥65 yoa) & previous influenza season vaccination
- Conducted during 2024-2025 NH influenza season at 301 sites in 11 countries (North America, Europe, East Asia)

- **Primary rVE analysis:** Pre-specified interim analysis at end of season (April 30, 2025) with 968 cases (exceeded target of 836; no second season) used full one-sided alpha of 2.5%.
- **Primary endpoint:** First episode of RT-PCR–confirmed protocol-defined ILI with onset ≥14 days postvaccination through end of influenza season, caused by any influenza A or B strain
- **Statistical success criteria:** Sequential testing for Applicant-defined prespecified noninferiority (NI; LL of 95% CI of rVE > −10%), superiority (LL > 0%), and super-superiority (LL > 9.1%)

Protocol defined influenza like illness (ILI): at least one systemic symptom (temperature >37.2°C (>99.0°F), chills, feverish, tiredness, headaches, or myalgia) AND at least 1 respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing)

Study P304 Timeline



SAE: serious adverse event; MAAE: medically attended adverse event; AESI: adverse event of special interest

The End of Study (EOS) Visit occurred at either the Day 181 Visit or the End of Influenza Season Visit, whichever was later.

Study P304 Participant Demographics

- Demographic and baseline characteristics were balanced across the mRNA-1010 (TIV) and SD comparator groups.
- Median age: 64 years (range 50 through 97);
  - 52% of participants were 50 to <65 years of age.
  - 48% were ≥ 65 years of age.
  - 12% were ≥75 years of age.
- 70% were from North America study sites.
- 47% of participants received influenza vaccine in previous season.
- 57% of participants had at least one high-risk condition at baseline, most common being BMI ≥ 30 kg/m^2.
- Of the participants ≥ 65 years of age, the majority were considered fit (73%) and not vulnerable or frail based on the Edmonton Frail Scale.

P304: Analysis of Primary Relative Vaccine Efficacy Endpoint (Hypothesis Tested)

rVE for mRNA-1010 (TIV) vs. SD Comparator Against RT-PCR–Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strains in Participants ≥ 50 Years of Age (PP Set)

mRNA-1010 (TIV) N=20,179 Cases n (%)	SD Comparator N=20,124 Cases n (%)	rVE (%) (95% CI)	Prespecified Success Criteria
411 (2.0)	557 (2.8)	26.6 (16.7, 35.4)	✓ NI (LL >−10%) ✓ Superiority (LL >0%) ✓ Super-Superiority (LL >9.1%)

- Median efficacy follow-up: 181 days (~6 months)

Relative Vaccine Efficacy (rVE): Measures how much mRNA-1010 reduces the risk of the specified outcome when compared against a U.S.-licensed SD influenza vaccine. It does **not** evaluate absolute efficacy (which would require a comparison to a placebo).
rVE represents the **additional benefit** of mRNA-1010 beyond what the SD comparator provides.

P304: rVE Against RT-PCR-Confirmed Protocol-Defined ILI Caused by Any Influenza A or B Strain by Age Subgroup (Descriptive, Prespecified)

Age Group	mRNA-1010 (TIV) Cases, n/N (%)	SD Comparator Cases, n/N (%)	Descriptive rVE (%) (95% CI)	Interpretation
50 to <65 years of age	229/10,542 (2.2)	307/10,501 (2.9)	26.1 (12.3, 37.7)	CI excludes zero; suggests superiority
≥65 years of age	182/9637 (1.9)	250/9623 (2.6)	27.4 (12.1, 40.0)	CI excludes zero; suggests superiority
65 to <75 years of age	138/7307 (1.9)	191/7289 (2.6)	28.0 (10.4, 42.2)	CI excludes zero; suggests superiority
≥75 years of age	44/2230 (1.9)	59/2334 (2.5)	25.3 (-10.4, 49.5)	CI crosses zero; wide CI due to small N; directionally consistent

- N=number of participants in the age subgroup

P304: rVE Against RT-PCR-Confirmed Protocol-Defined ILI by Influenza Strain Type (Descriptive, Prespecified)

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

- Influenza A strains predominated, accounting for 94.0% of all influenza cases and driving the overall rVE estimate.

P304: rVE Against RT-PCR-Confirmed Protocol-Defined ILI With Antigenic Match (Descriptive, Prespecified)

rVE Endpoint	mRNA-1010 (TIV) N=20,178 Cases, n (%)	SD Comparator N=20,122 Cases, n (%)	Descriptive rVE (%) (95% CI)
Any influenza A or B	261 (1.3)	364 (1.8)	28.7 (16.4, 39.2)
Influenza A	246 (1.2)	345 (1.7)	29.1 (16.5, 39.8)
Influenza A/H1N1	181 (0.9)	252 (1.3)	28.5 (13.5, 41.0)
Influenza A/H3N2	65 (0.3)	93 (0.5)	30.5 (4.6, 49.4)
Influenza B/Victoria	15 (<0.1)	19 (<0.1)	21.6 (-54.3, 60.2)

- Antigenic match between circulating and vaccine strains varied: for A/H1N1 (~98%), for B/Victoria (~94%), for A/H3N2 (~52–56%).
- For A/H3N2:
  - rVE against all strains: 22.2% (95% CI: 4.3, 36.9).
  - rVE against antigenically matched strains: 30.5% (95% CI: 4.6, 49.4).

P304: rVE Against RT-PCR-Confirmed Modified CDC-Defined ILI, Overall (Hypothesis Tested) and by Age Subgroup (Descriptive, Prespecified)

Variable	mRNA-1010 (TIV) N=20,179 Cases, n (%)	SD Comparator N=20,124 Cases, n (%)	rVE (%) (95% CI)	Prespecified Success Criteria
≥50 years of age	223 (1.1)	290 (1.4)	23.5 (9.0, 35.8)	✓ NI & Superiority X Super-Superiority
50 to < 65 years of age	129 (1.2)	162 (1.5)	21.1 (0.5, 37.4)	N/A
≥65 years of age	94 (1.0)	128 (1.3)	26.7 (4.4, 43.9)	N/A

- Modified CDC-defined ILI requires a temperature above 37.2°C and cough and/or sore throat.

P304: rVE to Prevent Health Outcomes Associated with RT-PCR-Confirmed Protocol-Defined ILI (Descriptive, Prespecified)

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

- In adults ≥65 years of age, rVE for health care encounters seeking higher level of care associated with protocol-defined ILI was 65.1% (95% CI: 17.4, 85.2), with case split of 7 (mRNA-1010) vs. 20 (SD comparator).

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Study P303 Part C Design

Phase 3 Safety and Immunogenicity Study

- 3,003 participants ≥65 years of age, randomized 1:1 to mRNA-1010 (QIV) or Fluzone HD (QIV), stratified by previous season influenza vaccination
- Conducted during NH 2023-2024 influenza season at 96 sites in the U.S.

Primary immunogenicity analysis: HAI antibody responses at Day 29 postvaccination

- **Primary endpoints:** HAI geometric mean titer (GMT) and seroconversion rate (SCR) at Day 29 for all four vaccine-matched influenza strains
- **Statistical success criteria:** (Tested sequentially; superiority evaluated after NI demonstrated for all eight coprimary endpoints)
  - NI: For GMT ratio, LL of 95% CI >0.667 for each strain; for SCR difference, LL of 95% CI >−10% for each strain
  - Superiority: For GMT ratio, LL of 97.5% CI >1.0 for each strain; for SCR difference, LL of 97.5% CI >0% for each strain

P303 Part C Participant Demographics

- Demographic and baseline characteristics were balanced across the mRNA-1010 (QIV) and Fluzone HD (QIV) groups.
- Median age: 70 years of age (range: 64–93 years).
  - 78% were 65 to <75 years of age.
  - 22% were ≥75 years of age.
- 53% received previous season influenza vaccination.
- 39% of participants had at least one high-risk factor*, most commonly diabetes mellitus.

*defined post-hoc

P303 Part C : Primary Endpoint (GMTs)

GMTs as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29

Endpoint	mRNA-1010 (QIV) N=1425 GMT (95% CI)	Fluzone HD (QIV) N=1409 GMT (95% CI)	GMT Ratio (mRNA-1010 [QIV] / Fluzone HD [QIV]) (95% CI)- NI (97.5% CI)- Superiority
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)

- NI and superiority met for all four strains based on GMT ratio.

P303 Part C: Primary Endpoint (SCR)

SCRs as Measured by HAI for Vaccine-Matched Influenza Strains at Day 29

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

- NI and superiority met for all four strains based on SCR difference.
- SCR 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.

P303 Part C: Day 181 GMTs (Descriptive)

GMTs as Measured by HAI for Vaccine-Matched Influenza Strains at EOS/Day 181

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

P303 Part C: Day 181 SCR (Descriptive)

SCR as Measured by HAI for Vaccine-Matched Influenza Strains at EOS/Day 181

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

SCR 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.

Post Hoc Descriptive Analysis of mRNA-1010 TIV vs QIV

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

Influenza Type	Model-Based GMT (95% CI) mRNA-1010 (TIV) Study P304 (N=586)	Model-Based GMT (95% CI) mRNA-1010 (QIV) Study P303 Part C (N=1425)	Model-based GMT Ratio (TIV/QIV) (95% CI)	Interpretation
Influenza A/H1N1	159.36 (148.08, 171.50)	161.13 (153.80, 168.81)	0.989 (0.906, 1.080)	✓NI suggested GMT ratio≈1.0; no meaningful difference
Influenza A/H3N2	158.13 (146.26, 170.95)	138.85 (132.12, 145.92)	1.139 (1.037, 1.250)	✓ NI suggested GMT ratio & LL>1.0 (TIV induced higher response)
Influenza B/Victoria	289.93 (272.69, 308.25)	234.78 (225.85, 244.07)	1.235 (1.148,1.328)	✓ NI suggested GMT ratio & LL>1.0 (TIV induced higher response)

ANCOVA=Analysis of Covariance; PCA= Principal Component Analysis

- Demographic and baseline characteristics included in the analysis: age, race, sex, ethnicity, baseline BMI group, previous influenza vaccine status, baseline high-risk status

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Sources of Safety Data

- Two primary sources of safety data
  - Study P304 (50 yoa and older)
  - Study P303 Part C (65 yoa and older)
- Integrated Safety Summary (ISS)
  - Pooled safety data from participants 50 yoa and older from all four Phase 3 studies (P301, P302, P303, and P304)
  - 71,916 participants (35,965 mRNA-1010 recipients and 35,951 SD/HD comparator recipients)
  - Median follow-up of 198 days in both groups
  - Includes studies of both TIV and QIV formulations of mRNA-1010 and the SD/HD comparator

Safety Profile of mRNA-1010 versus Comparator

Safety Domain	mRNA-1010	Comparator	FDA Assessment
Study P304	TIV	SD TIV/QIV	
Solicited Local Reactions (7 days)	67.5%	32.1%	More frequent; Grade 3: 1.7%; median duration 2 days
Solicited Systemic Reactions (7 days)	58.0%	32.4%	More frequent; Grade 3: 5.5%; median duration 2 days
Unsolicited AEs (28 days)	5.9%	5.7%	Balanced
Integrated Safety Summary	TIV/QIV	SD/HD TIV/QIV	
Serious Adverse Events (median follow-up 198 days)	3.1%	2.9%	Balanced; <0.1% assessed as related
Deaths	0.3%	0.3%	Balanced; none assessed as related
AESIs (median follow-up 198 days)	0.1%	0.1%	Balanced
Myocarditis/Pericarditis	10 cases	7 cases	No signal; no cases in 42-day risk window
Guillain-Barré Syndrome	1 case (Day 134)	0 cases	Outside 42-day risk window; not related
Bell's Palsy	1 case	4 cases	No signal; 1 case in each group in 42-day risk window

Study P304 Solicited Local Adverse Reactions (≥50 years of age)

Solicited Adverse Reaction Category, Grade	mRNA-1010 (TIV) N=3015 %	SD Comparator (TIV + QIV) N=2997 %
Any local adverse reaction	--	--
Any	67.5	32.1
Grade 3	1.7	0.1
Pain	--	--
Any	65.8	29.8
Grade 3	0.9	<0.1
Erythema	--	--
Any ≥25 mm	3.9	1.3
Grade 3	0.3	<0.1
Swelling	--	--
Any ≥25 mm	5.7	1.5
Grade 3	0.3	0.1
Axillary swelling or tenderness	--	--
Any	17.2	6.1
Grade 3	0.3	<0.1

Grade 3 injection site pain, axillary swelling or tenderness: prevent daily activity
Grade 3 injection site erythema, swelling: ≥100 mm

Study P304 Solicited Systemic Adverse Reactions (≥50 years of age)

Solicited Adverse Reaction Category, Grade	mRNA-1010 (TIV) N=3015 %	SD Comparator (TIV + QIV) N=2997 %
Any systemic adverse reaction	--	--
Any	58.0	32.4
Grade 3	5.5	0.9
Fever	--	--
Any	5.8	0.9
Grade 3	0.6	0.1
Headache	--	--
Any	37.8	18.0
Grade 3	2.0	0.3
Fatigue	--	--
Any	45.1	20.3
Grade 3	3.2	0.4
Myalgia	--	--
Any	35.4	11.6
Grade 3	2.5	0.2
Arthralgia	--	--
Any	27.8	10.6
Grade 3	1.9	0.2
Nausea/vomiting	--	--
Any	8.6	3.4
Grade 3	0.2	<0.1
Chills	--	--
Any	22.8	4.3
Grade 3	2.1	0.1
Use of antipyretic or pain medication	28.5	9.1

- Headache, fatigue, myalgia, arthralgia, and chills: Grade 3= prevent daily activity
- Fever: Grade 3= 39.0-40.0° C or 102.1-104.0° F
- Nausea/vomiting: Grade 3=prevent daily activity or requires outpatient intravenous hydration.

Study P303 Part C Solicited Local Adverse Reactions (≥65 years of age)

Solicited Adverse Reaction Category, Grade	mRNA-1010 (QIV) N=1502 %	Fluzone HD (QIV) N=1490 %
Any solicited local adverse reaction	--	--
Any	66.1	38.9
Grade 3	2.4	0.8
Injection site pain	--	--
Any	64.6	36.7
Grade 3	1.5	0.4
Erythema (redness)	--	--
Any	2.8	1.3
Grade 3	0.4	0.2
Swelling (hardness)	--	--
Any	4.5	1.7
Grade 3	0.4	0.1
Axillary swelling or tenderness	--	--
Any	16.8	8.6
Grade 3	0.5	0.4

Grade 3 injection site pain, axillary swelling or tenderness: prevent daily activity
Grade 3 injection site erythema, swelling: ≥100 mm

Study P303 C Solicited Systemic Adverse Reactions (≥65 years of age)

Solicited Adverse Reaction Category, Grade	mRNA-1010 (QIV) N=1502 %	Fluzone HD (QIV) N=1490 %
Solicited systemic ARs	--	--
Any	61.3	32.9
Grade 3	6.7	1.7
Grade 4	0.1	0
Fever	--	--
Any	8.5	1.4
Grade 3	0.6	<0.1
Grade 4	0.1	0
Headache	--	--
Any	39.4	17.3
Grade 3	2.3	0.7
Fatigue	--	--
Any	44.5	19.7
Grade 3	3.5	0.8

Solicited Adverse Reaction Category, Grade	mRNA-1010 (QIV) N=1502 %	Fluzone HD (QIV) N=1490 %
Myalgia	--	--
Any	41.7	16.1
Grade 3	3.2	0.7
Arthralgia	--	--
Any	35.2	14.1
Grade 3	2.3	0.7
Nausea/vomiting	--	--
Any	12.8	4.2
Grade 3	0.3	0.2
Chills	--	--
Any	29.5	7.7
Grade 3	1.2	0.3

- Headache, fatigue, myalgia, arthralgia, and chills: Grade 3= prevent daily activity
- Fever: Grade 3= 39.0-40.0° C or 102.1-104.0° F; Grade 4= ≥40.0° C or >104.0° F.
- Nausea/vomiting: Grade 3=prevent daily activity or requires outpatient intravenous hydration

Serious Adverse Events/Deaths (Pooled Analysis)

- Through a median follow-up of 198 days, SAEs were reported in 3.1% of mRNA-1010 recipients and 2.9% of SD/HD comparator recipients
  - SAEs also reported at similar rates across groups within 28 days postvaccination (0.5% in each group)
- By MedDRA Preferred Term (PT), 3 SAEs were numerically higher in the mRNA-1010 group AND had risk differences (RD) that excluded zero: death (unspecified) (23 vs. 9), anemia (9 vs. 2), and UTI (25 vs. 12)
- Deaths due to any cause were reported at similar rates across groups (0.3% in each group) through a median follow-up of 198 days
  - Within 28 days postvaccination, deaths due to any cause were few and comparable across groups (13 in the mRNA-1010 group vs. 14 in the SD/HD comparator group; <0.1% in both)

SAEs – Deaths: Unspecified Cause (Pooled Analysis)

- Imbalance in events of death (unspecified): 23 (mRNA-1010) vs. 9 (comparator)
  - Expanded analysis, including sudden death (4 vs 2) and sudden cardiac death (2 vs 1): 29 vs 12
- Median time to onset of 131 days in the mRNA-1010 group, with no temporal clustering
- Death within 28 days of vaccination was balanced: 3 vs. 2
- Almost all participants had cardiovascular/metabolic risk factors
- Balanced rates of PTs frequently associated with sudden death: myocardial infarction (7 vs. 7), cardiac arrest (6 vs. 6), cerebrovascular accident (4 vs. 5), and sepsis-related death (5 vs. 6)
- No deaths were assessed as vaccine-related by the Investigator, with one exception:
  - 76-year-old female with prior myocardial infarction and coronary artery bypass graft (CABG), atrial fibrillation, and type 2 diabetes mellitus, with death on Day 2 after receipt of mRNA-1010; assessed as related by Investigator for temporality
  - FDA assessment: Participant's significant cardiac history represents more plausible alternative etiology
- Overall FDA assessment: The numerical imbalance in death (unspecified) is unlikely to represent a vaccine safety signal for mRNA-1010

SAEs –Anemia and UTIs (Pooled Analysis)

- Anemia
  - 9 (mRNA-1010) vs. 2 (SD/HD comparator); expanded analysis, including anemia of chronic disease, blood loss anemia, hypochromic anemia, iron deficiency anemia, and normocytic anemia: 14 vs 8
  - Median time to onset was 134 days in the mRNA-1010 group, with no temporal clustering
  - MAAEs of anemia in Study P304 occurred at comparable rates between groups
  - Majority of the participants had underlying risk factors
  - No events were assessed as vaccine-related by the Investigator
- UTIs
  - 25 (mRNA-1010) vs. 12 (SD/HD comparator); expanded analysis, including UTI bacterial, Escherichia UTI, cystitis, kidney infection, pyelonephritis, pyelonephritis acute, and urosepsis: 38 vs 22
  - Median time to onset was 135 days in the mRNA-1010 group, with no temporal clustering
  - MAAEs of UTI in Study P304 occurred at comparable rates between groups
  - Majority of the participants had underlying risk factors
  - No events were assessed as vaccine-related by the Investigator
- **FDA assessment**: imbalances observed unlikely to reflect a causal association with mRNA-1010

Adverse Events of Special Interest (Pooled Analysis)

- Through a median follow-up of 198 days, AESIs were reported in 0.1% of participants in both the mRNA-1010 and SD/HD comparator groups
- There were no cardiac AESIs (myocarditis, pericarditis, myopericarditis) reported in the 42-day risk window.
- There were no cases of Guillain-Barré Syndrome reported in the 42-day risk window
- There was one case of Bell's palsy reported in each group within the 42-day risk window

Outline

- Introduction
- Overview of Clinical Studies
- Efficacy Data
- Immunogenicity Data
- Safety Data
- Risk Mitigation: Pharmacovigilance Plan and PMR Study
- Summary and Voting Questions for VRBPAC

Applicant's Proposed Pharmacovigilance Plan

- Based on the totality of safety data, there are no important identified/potential risks or missing information requiring additional pharmacovigilance beyond routine surveillance
- The Applicant will conduct routine postmarketing pharmacovigilance surveillance activities, including the submission of periodic safety reports to monitor for and assess any emerging risks associated with the vaccine
- Although no safety concerns were identified for protocol-defined AESIs, the Applicant will provide aggregate safety assessments of the following AESIs in their periodic safety reports for the first 3 years post-approval:
  - Thrombocytopenia
  - Guillain-Barré syndrome, acute disseminated encephalomyelitis, Bell's palsy, seizures
  - Anaphylaxis
  - Myocarditis, pericarditis, myopericarditis
- The details of the pharmacovigilance plan remain subject to discussion between FDA and the Applicant

Postmarketing Requirement (PMR) Study

- If mFlusiva is approved for use in individuals ≥65 years of age under the Accelerated Approval pathway, the Applicant will be required to conduct a study to verify and describe the clinical benefit of mFlusiva in this age group
- The Applicant has proposed to conduct a Phase 4, cluster-randomized, active-controlled, pragmatic study to evaluate the relative vaccine effectiveness of mFlusiva compared with an agreed upon CDC-preferentially recommended vaccine in U.S. adults 65 years of age and older
  - **Design:** Vaccine clinics will be cluster-randomized, alternating weekly between mRNA-1010 and comparator vaccine throughout the influenza season
  - **Enrollment:** ~800,000 (400,000 per season) adults 65 yoa and older in a 1:1 allocation (2 full seasons, 2027–2028 and 2028–2029)
- The study design and endpoints are currently under review and are the subject of ongoing discussions between FDA and the Applicant

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Summary

- mRNA-1010 demonstrated superior rVE vs. SD comparator in adults ≥50 yoa and superior immunogenicity vs. a CDC-preferentially recommended comparator in adults ≥65 yoa
- The reactogenicity profile, while elevated relative to the comparators, was predominantly mild to moderate, resolving within 2 days
- Overall rates of SAEs, deaths, and AESIs were balanced between mRNA-1010 and comparator groups
- Data limitations include: single-season follow-up; no data in immunocompromised and limited data in very frail older adults; no concomitant vaccine data
- Ongoing safety surveillance planned through postmarketing pharmacovigilance
- Verification of clinical benefit in adults ≥65 yoa through a cluster-randomized Phase 4 confirmatory study

Voting Questions for VRBPAC

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

   Please vote "Yes", "No", or "Abstain"

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

   Please vote "Yes", "No", or "Abstain"