



**Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

From: Margarita Maria Gomez Lorenzo, MD
Medical Officer, Pharmacovigilance Branch 2 (PB2)
Division of Pharmacovigilance (DPV), Office of Biostatistics
and Pharmacovigilance (OBPV), CBER, FDA

To: Santosh Nanda, DVM, PhD
Chair of the Review Committee
Chemistry Manufacturing and Control Branch 3, Division of
Vaccines and Related Product Applications
Office of Vaccines Research and Review, CBER

Through: Christopher Jason, MD
Branch Chief, PB2 DPV, OBPV, CBER, FDA

Narayan Nair, MD
Director, DPV OBPV, CBER, FDA

Subject: Review of core Risk Management Plan

Product: Respiratory Syncytial Virus (RSV) mRNA (encoding the
RSV F glycoprotein stabilized in the prefusion conformation)
Vaccine in Lipid Nanoparticles (SM-102, PEG2000-DMG,
DSPC, and Cholesterol), mRNA-1345

Sponsor: Moderna TX, Inc.

**Application
Type /Number:** BLA 125796/0

Proposed indication: Active immunization for the prevention of Lower Respiratory
Tract Disease caused by RSV in persons 60 years of age
and older.

Submission Date: September 11, 2023
(Rolling Submission 2 of 2 for BLA mRNA-1345)

Action Due Date: May 10, 2024

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the Pharmacovigilance Plan (included in the Sponsor's proposed Core Risk Management Plan (RMP) for mRNA-1345, submitted under BLA 125796) and to identify potential safety issues that may require additional post-authorization pharmacovigilance activities such as active surveillance studies, Post-Marketing Requirements (PMRs), and/or Post-Marketing Commitments (PMCs) or Risk Evaluation and Mitigation Strategy (REMS), should this product be approved.

Please refer to [Appendix A](#) for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of Acute Respiratory Disease in elderly and adults with chronic lung and heart disease (Falsey AR, 2005). A 4-year prospective cohort study indicated that RSV infection developed annually in 3% to 7% of healthy elderly subjects and in 4% to 10% of high-risk adults, translating to an estimated 177,000 hospital admissions, 14,000 deaths, and hospitalization costs exceeding \$1 billion each year in the US (Falsey AR, 2005). Respiratory syncytial virus also is the leading viral cause of serious Lower Respiratory Tract Disease (LRTD) in infants and young children with more than 30 million cases of LRTD occurring annually among children < 5 years old (Nair H, 2010). In the US, RSV is the etiology of approximately 35% of hospitalizations for acute respiratory infections in children less than 5 years of age, resulting in approximately 58,000 hospitalizations in this age group each year (Rha B, 2020).

RSV is an enveloped, nonsegmented, negative-sense RNA virus that belongs to the Pneumoviridae family. The F glycoprotein is highly conserved among RSV isolates from both A and B subgroups, with amino acid sequence identities of 90% or higher (McLellan JS, 2013). The prefusion conformation of F (pre-F) has highly neutralization-sensitive antigenic sites that do not exist on the rearranged postfusion conformation of the protein (post-F) and is a target of the natural immune response to RSV (Graham BS, 2019, McLellan JS, 2013). RSV prefusion F protein (RSVpreF) vaccines have been recently approved (Arexvy, Abrysvo).

The ModernaTX, Inc. mRNA-1345 vaccine is comprised of a single mRNA sequence encoding the RSV F glycoprotein stabilized in the prefusion conformation. Nonclinical studies in a variety of animal models demonstrate that mRNA-1345 induces a dose-dependent RSV neutralizing antibody response, elicits an RSV-specific T cell response, and affords protection from RSV challenge.

The Sponsor plans to develop mRNA-1345 vaccine first for the indication of prevention of RSV-associated LRTD in adults > 60 years of age.

3 PRODUCT INFORMATION

3.1 Product description

mRNA-1345 is a custom lipid nanoparticle (LNP)–encapsulated messenger RNA (mRNA) – based vaccine for the prevention of respiratory syncytial virus (RSV)–

associated LRTD. mRNA-1345 consists of a single mRNA drug substance encoding the RSV fusion (F) protein formulated in an LNP dispersion composed of 4 lipids: heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6(undecyloxy)hexyl)amino) octanoate (SM-102); 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol (PEG2000 DMG); 1,2 distearoyl-snglycero-3-phosphocholine (DSPC); and cholesterol. This is the same SM-102-containing LNP matrix that is present in other respiratory mRNA vaccines manufactured by the Sponsor, including the Sponsor's coronavirus disease 2019 (COVID-19) vaccine (SPIKEVAX™, mRNA-1273).

Route of Administration: Intramuscular injection

Dose Form: Single dose of 50 µg (solution for injection)

3.2 Proposed indication

Active immunization for the prevention of LRTD caused by RSV in persons 60 years of age and older.

4 PERTINENT REGULATORY HISTORY

Please refer to Table 1 for regulatory milestones and dates.

Table 1. Regulatory Milestones and Dates for mRNA-1345

Date	Milestone
July 20, 2020	The mRNA-1345 original submission IND 23342 was filed
July 30, 2021	Fast-track designation granted
September 2021	Pre-Phase 2/3 Type C consultation, the FDA confirmed the acceptability of the clinical data to support the initiation of a Phase 2/3 safety, immunogenicity, and efficacy trial of mRNA-1345 vaccine in adults ≥60 years of age (original protocol underwent amendments on September 28, 2022 and November 18, 2022)
November 29, 2023	The Advertising and Promotional Labeling Branch (APLB) completed the review of the proposed proprietary name, MRESVIA and recommended that the proposed proprietary name, MRESVIA, be found acceptable.
November 30, 2022	Primary efficacy was confirmed at the <i>Primary Analysis of Efficacy</i> in the Phase 2/3 Study P301 (based on November 30 2022, data cutoff date).
March 2023	The Sponsor aimed to gain concurrence and insight from the Agency (Type B pre-BLA meeting) about the adequacy of the clinical datasets to support the vaccine indication. The FDA originally issued the pre-BLA WRO (Clinical & Nonclinical) on March 21, 2023 and provided subsequent clarifications on May 2, 2023 as follows: <ul style="list-style-type: none"> Initial BLA submission will include data on at least six months of safety follow-up on N=35,541 participants in study mRNA-

	<p>1345-P301 in addition to at least 4 months of safety follow-up on N=1,021 participants of whom N=911 are > 80 years of age.</p> <ul style="list-style-type: none"> • Two months after filing, the Sponsor will submit an 'Addendum Report' with safety events not previously reported at the time of filing for participants who have subsequently completed 6 months of safety follow-up. • The sBLA planned for Q1 2024 will include a revised full clinical study report (CSR) with updated efficacy data through the second RSV season (additional cases of LRTD and acute respiratory disease and data on hospitalizations), cumulative safety data on 100% of participants on all safety endpoints with at least 6 months follow-up, and available immunogenicity data. The sBLA will include additional secondary analyses with pooled data from relevant populations in studies mRNA-1345-P101 (P101), mRNA-1345-P301 (P301), and mRNA-1345-P30 (P302) • A core Risk Management Plan (RMP) instead of a Pharmacovigilance Plan (PVP) is acceptable. The synopses for the post-approval safety studies are to be attached as appendices of the core RMP.
January 25 2023	Breakthrough Therapy Designation for the prevention of RSV-associated LRTD, initially in adults > 60 years of age was granted
March 9, 2023	<p>Upon review of the iPSP the FDA provides agreement with the Sponsor's plan to:</p> <ul style="list-style-type: none"> • Request a partial waiver of the pediatric assessment for the pediatric population from birth to less than 2 months of age. • Request a deferral of submission of the pediatric assessment for the pediatric population from 2 months to less than 5 years and the pediatric population including adolescents from 5 years to less than 18 years of age with certain disease conditions (severe asthma, chronic lung disease, cystic fibrosis, congenital heart disease, or neuromuscular disorders).
May 17, 2023	<p>Rolling BLA submission plan agreed between FDA and Sponsor (refer to <u>Appendix B</u> for rolling submission plan):</p> <ul style="list-style-type: none"> • June 29, 2023: Submission of the first of the two portions of the BLA for mRNA-1345 • September 11, 2023: Submission of the second of the two portions of the BLA for mRNA-1345
July 21, 2023	Breakthrough Therapy Designation for the prevention of lower respiratory tract illness (LRTI) and severe LRTI caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals was <u>denied</u> .

October 24, 2023	FDA receives 2-Month Safety Addendum Report for Study mRNA-1345-P301 (data cutoff date of June 24, 2023) under BLA 125796.0.7, received October 24, 2023.
March 04, 2024	Action due date was revised to August 10, 2024 based on the review of data included in Amendment 36 , which was considered as a Major Amendment by CBER.

5 DESCRIPTION OF THE SAFETY DATABASE

5.1 Introduction

The clinical development of the mRNA-1345 RSV vaccine to support use in the adult population consists of 3 clinical trials being conducted in the US and globally: a Phase 1, randomized, observer-blind, placebo-controlled, dose escalation study (P101), a Phase 2/3, randomized, observer-blind, placebo-controlled case driven pivotal efficacy trial (P301) and a Phase 3, randomized, observer-blind study (P302).

The safety and immunogenicity data from the mRNA-1345-P101 older adults (Cohorts 7 to 11) provided the basis of dose selection in P301. The Phase 1 Study P101 and the Phase 2/3 Study P301 provide the core clinical data of the BLA, although the efficacy and safety profile of mRNA-1345 is primarily established based on Study P301.

The two primary endpoints of Study P301 met the pre-specified statistical success criteria at the interim analysis (based on November 30, 2022 data cutoff). The Sponsor considers the interim analysis where early efficacy is demonstrated as the Primary Analysis of the primary efficacy endpoints and uses it as the foundation of the BLA submission.

Of note, assessments of relatedness in this memorandum reflect investigator's opinion unless noted otherwise.

5.2 SAFETY ANALYSIS OF STUDY mRNA-1345-P301 (P301)

Study P301 is an ongoing Phase 2/3 randomized, observer-blind, placebo controlled, case-driven, pivotal efficacy trial to evaluate the safety, tolerability, and efficacy of mRNA-1345 vaccine as compared with placebo in adults ≥ 60 years of age.

The study has the following endpoints:

- Primary safety endpoints:
 - Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) up to 7 days post-injection
 - Unsolicited adverse events (AEs) up to 28 days post-injection
 - Medically-attended adverse events (MAAEs), adverse events of special interest (AESIs), serious adverse events (SAEs), and AEs leading to withdrawal up to 24 months post-injection

In Study P301 each participant received a single dose of study injection (50 μ g mRNA-1345) or placebo in a 1:1 ratio as a 0.5-mL intramuscular (IM) injection on Day 1.

Participants were assessed for safety, efficacy, and immunogenicity endpoints up to 24

months after the study injection and had 8 scheduled visits [Screening, Day 1, Day 15 (for Phase 2), Day 29, Day 181, Day 365, Day 546, and Day 730] and safety contacts [Day 8, Day 15 (for Phase 3), Day 60, and then monthly].

Participants were adults ≥ 60 years of age who are primarily responsible for self-care and activities of daily living. The study excluded specifically subjects with history of myocarditis, pericarditis, or myopericarditis within 2 months prior to screening, subjects with poorly controlled hypertension and subjects who experienced Guillain-Barre within 6 weeks of influenza vaccination among other conditions (refer to P301 Protocol Amendment 2, dated November 16, 2022 for study entry criteria, IND # 023342 Sequence No. 0058)

The study was conducted in 2 phases (Phase 2 and Phase 3) under the oversight of an independent DSMB. In both phases, assignment was stratified by age (60 to 74 years versus ≥ 75 years) and risk factors for LRTD (present versus absent). The study transition from the Phase 2 to the Phase 3 segment allowed for safety and efficacy endpoints in both segments to be analyzed in combination.

✓ Phase 2 segment:

The purpose of the Phase 2 segment of the study was to assess the tolerability and safety of the mRNA-1345 vaccine dosage of 50 μg (selected based on safety and immunogenicity data from the Phase 1 study [mRNA-1345-P101]).

The first study participant was enrolled on November 17, 2021 and enrollment ended on February 16, 2022, with 2,000 participants enrolled. A DSMB reviewed the Day 29 safety data from the first 400 participants who received the study vaccine while further enrollment in the Phase 2 segment remained ongoing (up to 2,000 subjects). The DSMB review supported advancement to full Phase 3 enrollment.

✓ Phase 3 segment:

The Phase 3 segment aimed to enroll approximately 35,000 subjects (Study P301 was planned as a case-driven study, with the final sample size of the Phase 3 segment depending on real-time local surveillance of RSV circulation external to the study).

Please refer to Appendix C2 for additional study details for study mRNA-1345-P301

After primary efficacy was confirmed at the *Primary Analysis of Efficacy* (based on the November 30, 2022, data cutoff date), a subsequent analysis, designated the *Additional Analysis*, was conducted with 36,557 randomized participants and performed when $>90\%$ of participants had completed at least 6 months of study follow-up (April 30, 2023, data cutoff date). The *Additional Analysis* demonstrated efficacy of mRNA-1345 (50 μg) in preventing RSV-LRTD (with ≥ 2 symptoms and with ≥ 3 symptoms) in adults ≥ 60 years of age, meeting the primary efficacy objective as follows:

- ✓ The VE of mRNA-1345 against RSV-LRTD with ≥ 2 symptoms was 83.7%
- ✓ The VE of mRNA-1345 against RSV-LRTD with ≥ 3 symptoms was 82.4%

5.2.1 Safety data as of April 30 2023 data cutoff (n= 36,557 participants followed ≥ 6

months, **Safety Data Set**)

At the time of the 30 Apr 2023 data cutoff, a total of 36,557 participants were randomized to receive study injection: 18,304 participants in the mRNA-1345 group and 18,253 participants in the placebo group.

The median duration of follow-up was 257 days (range: 1 to 530 days) and, per protocol, subjects will continue in the study for follow-up 24 months after receiving Investigational Product (IP). Deaths, SAEs, Medically Attended Adverse events (MAAEs), Adverse Events of Special Interest (AESIs), and Adverse events (AEs) leading to discontinuation were collected throughout the study.

Of the 36,429 subjects in the safety data set (received IP injection), 18,245 received mRNA-1345 and 18,184 received placebo. Please refer to Table 2 below for a summary of participant disposition.

Table 2. Participant disposition in the randomization set (data cutoff date of April 30, 2023)

	Placebo (N=18,253) n (%)	mRNA-1345 50 µg (N=18,304) n (%)	Total (N=36,557) n (%)
Number of Participants			
Received IP Injection	18,184 (99.6)	18,245 (99.7)	36,429 (99.6)
Completed the Study [1]	0	0	0
Discontinued from Study	954 (5.2)	904 (4.9)	1858 (5.1)
Primary Reason for Discontinuation			
Adverse Event	11 (<0.1)	8 (<0.1)	19 (<0.1)
Death	82 (0.4) *	81 (0.4) *	163 (0.4)
Lost to Follow-Up	314 (1.7)	326 (1.8)	640 (1.8)
Non-Compliance with Study Drug	3 (<0.1)	1 (<0.1)	4 (<0.1)
Physician Decision	52 (0.3)	34 (0.2)	86 (0.2)
Protocol Violation	9 (<0.1)	9 (<0.1)	18 (<0.1)
Withdrawal of Consent by Participant	438 (2.4)	405 (2.2)	843 (2.3)
Other	45 (0.2)	40 (0.2)	85 (0.2)

IP=Investigational Product; SAR=Solicited Adverse Reaction.

Percentages are based on the number of randomized participants. Numbers are based on planned treatment group.

[1] Participants are considered to have completed the study if they complete the final visit at Day 730, i.e., 24 months after the date of injection of investigational product.

(*) Four additional deaths -3 in the mRNA-1345 and one in the placebo group- are not included in this table because at the time of data cutoff, no end-of-study CRF was present for these 4 participants. But are included in the fatal TEAE table (Table 5)

The most common ($\geq 0.5\%$) reasons for study discontinuation in both groups were withdrawal of consent by participant (405 (2.2%) in the mRNA-1345 group and 438 (2.4%) in the placebo group) and lost to follow-up (326 (1.8%) in the mRNA-1345 group and 314 (1.7%) in the placebo group). As noted in Table 2, the frequencies of reasons for discontinuation were balanced between study groups.

5.2.1.1 Solicited Adverse Reactions

Solicited Adverse Reactions (ARs) were captured via eDiary for 7 days (including Day #1, injection day). Solicited local ARs were reported for 10,591 (58.3%) participants in the mRNA-1345 group and 2,939 (16.2%) participants in the placebo group. The most reported solicited systemic ARs ($\geq 20\%$ of participants in the mRNA-1345 group) was injection site pain, present in 55.9% and 13.8% of participants in the mRNA-1345 and placebo groups, respectively. Grade 3 solicited local ARs were reported for 3.1% and 1.7% of participants in the mRNA-1345 and placebo groups, respectively. No Grade 4 solicited local ARs were reported.

Solicited systemic ARs were reported for 8,613 (47.4%) participants in the mRNA-1345 and 5,959 (32.9%) participants in the placebo group. The most reported solicited systemic ARs ($\geq 20\%$ of participants in the mRNA-1345 group) were fatigue (30.8% in the mRNA-1345 group versus 20.0% in the placebo group), headache (26.7% versus 18.8%), myalgia (25.6% versus 14.4%), and arthralgia (21.7% versus 14.0%). Grade 3 solicited systemic ARs were reported for 3.8% and 2.7% of participants in the mRNA-1345 and placebo groups, respectively. The only solicited systemic AR reported in any participant at Grade 4 was fever (oral temperature $>40.0^{\circ}\text{C}/>104.0^{\circ}\text{F}$), reported in 0.2% of participants in each group.

Solicited ARs with onset within 60 minutes after injection were reported in 6% and 6.5% of participants in the mRNA-1345 and placebo groups, respectively. The median onset of solicited local and systemic ARs was 2 days after injection in both groups. The median duration for any solicited AR was also 2 days in each group. In the mRNA-1345 group, solicited local ARs were reported for 61.2% of participants 60 to 69 years of age, 55.4% of participants 70 to 79 years of age, and 46.3% of participants ≥ 80 years of age. Solicited systemic ARs were reported for 48.8% of participants 60 to 69 years of age, 46.4% of participants 70 to 79 years of age, and 40.1% of participants ≥ 80 years of age. In the placebo group, no consistent trends for solicited AR incidence were observed based on age group.

Solicited ARs were reported for 70.3% of participants 60 to 69 years of age, 67.7% of participants 70 to 79 years of age, and 57.9% of participants ≥ 80 years of age. In the mRNA-1345 group, reporting of solicited ARs was 73% among female participants and 63.5% among male participants.

Reviewer comment

Solicited local and systemic ARs were reported at higher rates in the mRNA-1345 group than in the placebo group. Most solicited local and systemic ARs were Grade 1 in severity, occurred within 1 to 2 days after injection, and resolved within 1 to 2 days after

onset. The most reported solicited local AR was injection site pain. The most reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. Fever was the only solicited AR to be reported at Grade 4, and reporting was balanced between the groups. In the mRNA-1345 group, the incidence of solicited ARs decreased with increasing age and reporting of solicited ARs was higher among female participants than among male participants.

5.2.1.2 Unsolicited Adverse Events

Unsolicited AEs were collected during the 28-day follow-up period after injection.

Within 7 days after injection, 1,743 (9.6%) participants reported unsolicited AEs in the mRNA-1345 group versus 1,439 (7.9%) in the placebo group. The most reported SOC was General disorders and administration site conditions (3.8% in the mRNA-1345 group versus 2.7% in the placebo group), including the PTs of fatigue (2.6% versus 2.1%) and injection site pain (0.7% versus 0.3%).

There were 27 (0.1%) participants with SAEs in the mRNA-1345 group versus 70 (0.4%) in the placebo group. There were no fatal events in the mRNA-1345 group and one fatal event in the placebo group.

There were 70 (0.4%) participants with severe/ \geq Grade 3 AEs in the mRNA-1345 group versus 70 (0.4%) in the placebo group.

The most commonly reported SOCs ($\geq 1\%$ of participants in the mRNA-1345 group) with the first 2 PTs in each were as follows:

- General disorders and administration site conditions (3.8% in the mRNA-1345 group versus 2.7% in the placebo group), including fatigue (2.6% versus 2.1%) and injection site pain (0.7% versus 0.3%).
- Musculoskeletal and connective tissue disorders (2.9% versus 2.6%), including arthralgia (2.1% versus 1.9%) and myalgia (1.6% versus 1.4%).
- Infections and infestations (1.6% versus 1.5%), including COVID-19 (0.4% in each group) and upper respiratory tract infection (0.2% in each group).
- Nervous system disorders (1.5% versus 1.2%), including headache (1.3% versus 1.1%) and dizziness ($<0.1\%$ in each group).

Within 28 days after injection, 3,749 (20.5%) participants reported unsolicited AEs in the mRNA-1345 group versus 3,412 (18.8%) in the placebo group. The most reported SOC was Infections and infestations (7.8% in the mRNA-1345 group versus 7.2% in the placebo group), including COVID-19 (2.1% versus 1.8%) and upper respiratory tract infection (1.2% versus 1.1%).

There were 115 (0.6%) participants with SAEs in the mRNA-1345 group versus 111 (0.6%) in the placebo group. There was one ($<0.1\%$) fatal event in the mRNA-1345 group and six ($<0.1\%$) fatal events in the placebo group.

Unsolicited TEAEs up to 28 days after injection were generally reported as mild (12.7% of participants in the mRNA-1345 group versus 11.2% of participants in the placebo group) or moderate (7.2% versus 6.8%) in severity. There were 129 (0.7%) participants with severe/ \geq Grade 3 AEs up to 28 days after injection in the mRNA-1345 group versus 135

(0.7%) in the placebo group. The most frequently reported severe/≥Grade 3 events in the mRNA-1345 group were fatigue, arthralgia, headache, and myalgia.

Unsolicited TEAEs up to 28 days after injection that were considered to be related to study injection and assessed as severe/≥Grade 3 were reported for 53 (0.3%) of participants in the mRNA-1345 group and 52 (0.3%) participants in the placebo group. Incidence of unsolicited TEAEs was numerically higher among female participants and among participants reporting White race. Incidence of unsolicited TEAEs did not differ appreciably between US and non-US regions.

The most commonly reported (≥2% of participants in the mRNA-1345 group) SOC with the first 2 PTs in each were as follows:

- Infections and infestations (7.8% in the mRNA-1345 group versus 7.2% in the placebo group), including COVID-19 (2.1% versus 1.8%) and upper respiratory tract infection (1.2% versus 1.1%).
- General disorders and administration site conditions (4.4% versus 3.3%), including fatigue (2.7% versus 2.2%) and injection site pain (0.7% versus 0.3%)
- Musculoskeletal and connective tissue disorders (4.2% versus 4.0%), including arthralgia (2.3% versus 2.2%) and myalgia (1.7% versus 1.6%).
- Nervous system disorders (2.3% versus 2.0%), including headache (1.7% versus 1.4%) and dizziness (0.1% in each group).

Up to Data Cutoff, there were 114 (6.1%) participants with SAEs in the mRNA-1345 group versus 1,092 (6.1%) in the placebo group. There were 84 (0.5%) fatal events in the mRNA-1345 group and 83 (0.5%) fatal events in the placebo group. There were 37 (0.2%) participants with AESIs in the mRNA-1345 group versus 35 (0.2%) in the placebo group.

According to the SAP, unsolicited TEAEs were analyzed using selected HLGTS and/or selected PTs within a given HLGTS. In particular, within the HLGTS of myocardial disorders events were reported for 31 participants (0.2%) in the mRNA-1345 group versus 17 participants (<0.1%) in the placebo group. The PTs reported more commonly in the mRNA-1345 group were cardiomegaly (8 participants in the mRNA-1345 group versus 3 participants in the placebo group), cardiomyopathy (4 versus 0 participants), and diastolic dysfunction (4 versus 2 participants).

Reviewer comment

Within 7 and 28 days after injection and up to data cutoff, the overall incidence of unsolicited AEs was similar in mRNA-1345 and placebo groups. Up to 28 days after injection, reported AEs were primarily infections and events related to reactogenicity (solicited AR terms).

The percentage of participants with severe/≥Grade 3 TEAEs was balanced between both groups. Also, incidence of AEs up to data cutoff was numerically higher among females and participants who reported “White” race but was similar between the US region and non-US regions.

Up to data cutoff, events within the HLGTS of myocardial disorders were reported more commonly in the mRNA-1345 group than in the placebo group, specifically events with

PTs of cardiomegaly, left ventricular hypertrophy, cardiomyopathy and diastolic dysfunction.

5.2.1.3. Serious Adverse Events

Up to 7 days after injection, SAEs were reported for 0.1% of participants in each group (27 participants in the mRNA-1345 group and 26 participants in the placebo group).

The following SAEs were considered related:

✓ mRNA-1345:

- A 75-year-old female participant with COPD had chills on Day 1 that was reported as a solicited AR. The participant was diagnosed with pneumonia on Day 8; the event of chills required hospitalization and resolved on Day 10.
- A 64-year-old female participant with history of diabetes mellitus type 2 and diabetic gastroenteropathy had dehydration on Day 2. The participant also had vomiting and was diagnosed with a urinary tract infection. The Investigator reported that dehydration symptoms were related to reactogenicity. The event of dehydration resolved on Day 2.
- A 69-year-old female participant with history of hypertension had **facial paralysis** on Day 5. The event was reported as an AESI and resolved on Day 118.

✓ Placebo:

- A 60-year-old female participant with history of asthma, hypertension, and obesity had a seizure on Day 1 that resolved on the same day.
- A 71-year-old male participant had pyrexia on Day 5 that was reported as a solicited AR, assessed by the Investigator as a medically important event, and resolved on the following day.

Up to 28 days after injection (cumulative), SAEs were reported for 0.6% of participants in each group (115 participants in the mRNA-1345 group and 111 participants in the placebo group). The most reported SAEs by PT were COPD (8 participants in the mRNA-1345 group versus 7 participants in the placebo group (each <0.1%)), pneumonia (6 versus 3 participants (each <0.1%)), hypertension (4 versus 1 participant (each <0.1%)), and acute myocardial infarction (3 versus 3 participants [each <0.1%]). In addition to those reported up to Day 7, the SAEs reported as related to injection up to 28 days after injection (cumulative) included:

• mRNA-1345:

- A 72-year-old male participant with history of lower limb varicose veins and concomitant medication of celecoxib as needed had superficial vein thrombosis on Day 11. The event required hospitalization and resolved on Day 44.

• Placebo:

- A 73-year-old male participant with history of chronic COPD had worsening COPD on Day 23 that resolved on Day 27.

Up to data cutoff (cumulative), there were 1114 (6.1%) participants with SAEs in the mRNA-1345 group and 1092 (6.0%) participants with SAEs in the placebo group. The percentage of participants with related SAEs was the same in both groups (refer to Table 3).

Table 3 Overall Summary of Unsolicited TEAEs After Injection Up to Data Cutoff (April 30, 2023) (Safety Set)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Unsolicited TEAEs up to data cutoff date, regardless of relationship to study injection		
Serious	1092 (6.0)	1114 (6.1)
Fatal	83 (0.5)	84 (0.5)
Medically attended	6923 (38.1)	7145 (39.2)
Leading to study discontinuation	105 (0.6)	99 (0.5)
Any AESI	35 (0.2)	37 (0.2)
Unsolicited TEAEs up to data cutoff date, related to study injection		
Serious	5 (<0.1)	4 (<0.1)
Fatal	0	0
Medically attended	60 (0.3)	85 (0.5)
Leading to study discontinuation	0	1 (<0.1)
Any AESI	2 (<0.1)	2 (<0.1)

Abbreviations: AESI=adverse event of special interest; AR=adverse reaction; ER=emergency room; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

A TEAE was defined as any event not present before exposure to study injection or any event already present that worsened in intensity or frequency after exposure.

Medically attended TEAEs included ER/urgent care and outpatient physician visits but did not include per-protocol illness visits.

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

SAEs assessed by the Investigator as related to study injection were reported for 4 participants in the mRNA-1345 group and for 5 participants in the placebo group (each <0.1%):

- In the mRNA-1345 group, the events were chills (onset on Day 1; participant was later diagnosed with pneumonia that was RSV-, influenza-, and COVID negative), dehydration (onset on Day 2; due to vomiting), facial paralysis (onset on Day 5; reported as an AESI), and superficial vein thrombosis (onset on Day 11; in varicose veins).
- In the placebo group, the events were seizure (onset on Day 1), pyrexia (onset on Day 5), COPD (onset Day 23), transient ischemic attack (onset on Day 65), and myelodysplastic syndrome (onset on Day 285). The most reported SAEs by SOC were events in the Infections and infestations SOC (1.3% in the mRNA-1345 group versus 1.4% in the placebo group).

The most commonly reported SAEs were events in the Infections and infestations SOC (1.3% in the mRNA-1345 group versus 1.4% in the placebo group). The most common PTs for SAEs up to data cutoff in both groups were: pneumonia, chronic obstructive pulmonary disease, osteoarthritis, urinary tract infection, coronary artery disease and acute myocardial infarction. All PTs for SAEs developing in $\geq 0.1\%$ of participants were reported with similar frequency between both groups (refer to Table 4).

Table 4. Participant Incidence of Serious TEAEs Regardless of Causality Up to Data Cutoff by PT (Safety Set)

Preferred Term	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
Number of Participants Reporting Serious TEAEs	1092 (6.0)	1114 (6.1)
Number of Serious TEAEs	1630	1634
Pneumonia	56 (0.3)	64 (0.4)
Chronic obstructive pulmonary disease	41 (0.2)	51 (0.3)
Osteoarthritis	28 (0.2)	29 (0.2)
Urinary tract infection	33 (0.2)	29 (0.2)
Coronary artery disease	25 (0.1)	25 (0.1)
Acute myocardial infarction	25 (0.1)	24 (0.1)
Atrial fibrillation	35 (0.2)	23 (0.1)
Ischemic stroke	22 (0.1)	22 (0.1)
Myocardial infarction	22 (0.1)	22 (0.1)
Cerebrovascular accident	21 (0.1)	21 (0.1)
Syncope	20 (0.1)	13 (<0.1)
Cardiac failure congestive	24 (0.1)	11 (<0.1)
Acute kidney injury	23 (0.1)	9 (<0.1)
Cellulitis	21 (0.1)	9 (<0.1)

Note: PTs Reported for $\geq 0.1\%$ of Participants in Either Group

In addition to the related SAEs reported up to Day 28 described above, 2 additional SAEs were reported as related and both occurred in the placebo group:

- A 60-year-old male participant in the placebo group with medical history including hypercholesterolemia, hypertension, hypothyroidism, and type 2 diabetes mellitus had a transient ischemic attack on Day 65 that resolved on Day 141 with sequela of ongoing aspirin use.

- A 73-year-old male participant in the placebo group without relevant medical history had myelodysplastic syndrome with multilineage dysplasia on Day 285 that was resolving at the time of data cutoff.

In the mRNA-1345 group, incidence of SAEs up to data cutoff increased with increasing age: 5.2% among participants 60 to 69 years of age, 7.4% among participants 70 to 79 years of age, and 8.4% among participants ≥80 years of age. Observations were similar in the placebo group.

In the mRNA-1345 group, incidence of SAEs up to data cutoff was higher among participants in the White race subgroup (6.7%) than among participants in any other race subgroup, including Black (5.2%), Asian (5.1%), or other (5.3%). Observations were similar for race subgroup comparisons in the placebo group.

Comorbidities of interest included CHF, COPD, asthma, chronic respiratory disease, diabetes mellitus, advanced liver and kidney disease. In the mRNA-1345 group, incidence of SAEs was higher among participants with at least one comorbidity of interest (9.6%) than among participants with no comorbidities of interest (4.6%). Similar trends were observed in the placebo group.

Reviewer comment

Up to data cutoff (30 Apr 2023) (cumulative), the types and incidence of SAEs by SOC and PT were similar between the groups. The most reported SAEs were events in the Infections and infestations SOC. The most common SAE by PT in both groups was pneumonia.

Up to data cutoff (30 Apr 2023) (cumulative), incidence of SAEs including those considered to be related to study injection, were balanced between the groups.

5.2.1.4 Deaths

Death within 7 days after injection was reported for one participant in the placebo group who had a fatal TEAE of road traffic accident.

Death within 28 days after injection (cumulative) was reported for 1 participant (<0.1%) in the mRNA-1345 group versus 5 participants (<0.1%) in the placebo group. None of the deaths were considered by the Investigator to be related to study injection.

Up to data cutoff (cumulative), fatal AEs were reported for 84 participants (0.5%) in the mRNA-1345 group versus 83 participants (0.5%) in the placebo group.

None of the deaths up to data cutoff were considered related to study injection per the Investigator.

Incidence of deaths in the 2 SOC with the most reported AEs leading to death was as follows: Cardiac disorders SOC: 24 participants (0.1%) in the mRNA-1345 group and 29 participants (0.2%) in the placebo group and General disorders and administration site conditions SOC: 14 participants (<0.1%) in the mRNA-1345 group and 11 participants (<0.1%) in the placebo group.

The most frequently reported PT for fatal TEAEs was *death* (11 participants in the mRNA-1345 group and 10 participants in the placebo group), which is included in the SOC for General disorders and administration site conditions.

Fatal TEAEs with PT of pneumonia were reported for 7 participants in the mRNA-1345 group and 2 participants in the placebo group (see Table 7). None of these participants had nasopharyngeal swabs collected within 14 days of the event.

The median time to death after injection was 178.0 days (range: 21 to 488 days) in the mRNA-1345 group and 144.0 days (range: 6 to 324 days) in the placebo group)

The incidence of fatal events was balanced between the mRNA-1345 and placebo groups up to data cutoff, and none of the fatal events were considered to be related to study injection by the Investigator. Please refer to Table 6 for incidence of AEs leading to death up to data cutoff.

Table 5 Participant Incidence of TEAEs Leading to Death up to Data Cutoff Date (30 Apr 2023) by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Placebo (N=18184) n (%)	mRNA- 1345 50 µg (N=18245) n (%)
Number of Participants Reporting TEAEs Leading to Death	83 (0.5)	84 (0.5)
Number of TEAEs Leading to Death	83	90
Infections and infestations	9 (<0.1)	12 (<0.1)
Pneumonia	2 (<0.1)	7 (<0.1)
Sepsis	1 (<0.1)	2 (<0.1)
Septic shock	5 (<0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (<0.1)	6 (<0.1)
Lung neoplasm malignant	0	2 (<0.1)
Nervous system disorders	13 (<0.1)	7 (<0.1)
Cerebrovascular accident	5 (<0.1)	2 (<0.1)
Ischemic stroke	0	2 (<0.1)
Hemorrhagic stroke	2 (<0.1)	1 (<0.1)
Brain injury	3 (<0.1)	0

Cardiac disorders	29 (0.2)	24 (0.1)
Myocardial infarction	8 (<0.1)	6 (<0.1)
Acute myocardial infarction	2 (<0.1)	5 (<0.1)
Cardiac arrest	4 (<0.1)	3 (<0.1)
Acute coronary syndrome	0	2 (<0.1)
Cardiac failure	0	2 (<0.1)
Cardio-respiratory arrest	6 (<0.1)	2 (<0.1)
Cardiopulmonary failure	3 (<0.1)	2 (<0.1)
Respiratory, thoracic and mediastinal disorders	7 (<0.1)	11 (<0.1)
Chronic obstructive pulmonary disease	3 (<0.1)	3 (<0.1)
Respiratory failure	1 (<0.1)	3 (<0.1)
General disorders and administration site conditions	11 (<0.1)	14 (<0.1)
Death	10 (<0.1)	11 (<0.1)
Multiple organ dysfunction syndrome	1 (<0.1)	2 (<0.1)
Injury, poisoning and procedural complications	2 (<0.1)	2 (<0.1)
Road traffic accident	2 (<0.1)	0

Note: Table 5 includes SOC with at least 2 reports.

Reviewer comment

Up to data cutoff (30 Apr 2023) (cumulative), incidence of fatal events, including those considered to be related to study injection, were balanced between the groups.

5.2.1.5 Adverse Events of Interest

❖ Protocol-defined Adverse Events of Special Interest

The incidence of AESIs up to 7 days after injection and up to 28 days after injection was <0.1% for each group. The overall incidence of AESIs up to data cutoff was 0.2% for each group. Please refer to Table 6 for Participant Incidence of Unsolicited TEAEs of Special Interest by SOC and PT (Safety Set) up to data cutoff.

Table 6. Participant Incidence of Unsolicited TEAEs of Special Interest up to Data Cutoff Date (30 Apr 2023) as Assessed by Investigator by SOC and PT (Safety Set)

System organ Class Preferred Term	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N= 18245) n (%)
AESIs up to data cutoff date (includes up to 28 days)	35 (0.2)	37 (0.2)
Blood and lymphatic system disorders	15 (<0.1)	9 (<0.1)
Thrombocytopenia	13 (<0.1)	9 (<0.1)
Nervous system disorders	15 (<0.1)	22 (0.1)
Bell's palsy	3 (<0.1)	6 (<0.1)
Seizure	6 (<0.1)	5 (<0.1)
Facial paralysis	2 (<0.1)	3 (<0.1)
Generalized tonic-clonic seizure	0	2 (<0.1)
Epilepsy	2 (<0.1)	1 (<0.1)
Alcoholic seizure	2 (<0.1)	0
Cardiac disorders	2 (<0.1)	4 (<0.1)
Pericarditis	1 (<0.1)	2 (<0.1)

Note: Table 6 includes SOC with at least 2 reports.

✓ **Anaphylactic reaction**

Up to 7 days after injection, no AESIs of anaphylactic reaction were reported.

Up to 28 days after injection, an AESI of anaphylactic reaction was reported for one participant (<0.1%) in the mRNA-1345 group (anaphylactic reaction to bee venom on Day 28). One additional participant in the mRNA-1345 group had an SAE of anaphylactic reaction, also due to insect sting, on Day 11 that was not reported as an AESI.

No additional AESIs of anaphylactic reaction were reported up to data cutoff.

✓ **Myocarditis and pericarditis**

Any case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis was to be reported as an AESI by the Investigator. A blinded and independent group of cardiologists (the CEAC) reviewed Investigator-suspected cases of myocarditis and pericarditis to determine if they met CDC criteria (Gargano et al 2021) of probable or confirmed acute myocarditis or acute pericarditis based on a data package of

clinical history, laboratory testing, imaging findings, and reports of any consultations obtained; the CEAC did not adjudicate causality.

Although onset of myocarditis or pericarditis after COVID-19 vaccination has been reported within 7 days after injection for over 90% of cases (Gargano et al 2021) and myocarditis associated with mRNA COVID-19 vaccination mostly occurred within 1 week according to VAERS data (Shimabukuro 2022), this analysis considers a 42-day risk window.

No CEAC-adjudicated cases of acute myocarditis or acute pericarditis occurred within 42 days after injection in either group:

Up to 28 days after injection there was one AESI of pericarditis in one participant (<0.1%) in the placebo group.

Up to data cutoff (cumulative), pericarditis was reported as an AESI for 2 participants (<0.1%) in the mRNA-1345 group (one of whom had 2 separate events, on Days 48 and 223; onset for the other participant was on Day 81).

Up to data cutoff (cumulative) myocarditis was reported as an AESI for one participant (<0.1%) in the mRNA-1345 group with onset on Day 62. Of note, the AESI of myocarditis in the mRNA-1345 group was adjudicated by CEAC as not a charter-defined event.

Details about the events are as follows:

Events in the mRNA-1345 group

✓ A 65-year-old male participant with medical history including hyperlipidemia and prior cerebral artery occlusion had medically-attended AE (MAAE) of pericarditis (verbatim: acute pericarditis) with onset on Day 48 after receiving mRNA-1345. The participant had had a viral upper respiratory tract infection from Day 8 to 13 (viral respiratory swab sample was collected on Day 16 that was negative for all pathogens tested). The participant experienced a second episode of pericarditis (verbatim: pericarditis with small pericardial effusion) on Day 223. Three days prior to the second episode of pericarditis, on Day 220, the participant had received a second monkeypox vaccine and Tozinameran (bivalent COVID-19) vaccine. The event was ongoing at the time of data cutoff.

✓ A 67-year-old female participant with medical history including dyslipidemia had an MAAE of pericarditis with onset on Day 81. A nonserious TEAE of right bundle branch block had been reported with onset on Day 75. Mild pericardial effusion was observed on ECHO on Day 81. The event resolved on Day 89.

✓ A 70-year-old male participant with no reported relevant medical history had an MAAE of myocarditis (verbatim: mild myocarditis) with onset on Day 62. The event resolved on Day 199.

Events in the placebo group

✓ A 68-year-old female participant with medical history including hyperkalemia and osteoporosis had an SAE of pericarditis with onset on Day 8. The participant was evaluated by a cardiologist on Day 22, and the medications were stopped because there was no further suspicion of pericarditis.

✓ **New onset or worsening of neurological disorders**

➤ **Guillain-Barre Syndrome**

No AESIs of GBS were reported up to data cutoff.

➤ **Acute Disseminated Encephalomyelitis (ADEM)**

No AESIs of ADEM were reported up to data cutoff. Review of all unsolicited TEAEs up to data cutoff did not identify any events with the following PTs that could suggest an event of ADEM: acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, autoimmune demyelinating disease, demyelinating polyneuropathy, encephalomyelitis, immune mediated neuropathy, leukoencephalomyelitis, and noninfective encephalomyelitis.

➤ **Bell's palsy/facial paralysis**

Up to 7 days after injection, one event of facial paralysis occurred on Day 5 after injection of mRNA-1345 in a 65 year old female with hypertension. The event resolved on Day 118 after treatment with steroids and acyclovir.

Up to 28 days after injection AESIs of Bell's palsy were reported for one participant (<0.1%) in the mRNA-1345 group (onset Day 20) and 2 participants (<0.1%) in the placebo group:

- A 60-year-old female participant with a history of Bell's palsy developed facial and eyelid drooping as she was recovering from COVID-19 infection and was diagnosed with Bell's palsy on Day 20 after mRNA-1345 injection. The event resolved on Day 62 after treatment with valacyclovir and prednisone.
- A 69-year-old male participant with a history of Bell's palsy, type 2 diabetes mellitus and deep vein thrombosis had Bell's palsy on Day 9 after injection of placebo.
- A 66-year-old female participant with a history of hypertension and type 2 diabetes mellitus had Bell's palsy on Day 24 after injection of placebo.

Within a 42-day risk window after injection, AESIs of Bell's palsy/facial paralysis were reported for 2 participants (<0.1%) in each group

Up to data cutoff (cumulative), AESIs of Bell's palsy were reported for a total of 6 participants (<0.1%) in the mRNA-1345 group and 3 participants (<0.1%) in the placebo group and AESIs of facial paralysis were reported for a total of 3 participants in the mRNA-1345 group (<0.1%) and 2 participants in the placebo group (<0.1%) see Table 6)

One additional event of facial paralysis that was not reported as an AESI was reported for a participant in the placebo group. Also, an event of herpes zoster oticus was reported as an AESI for a 67-year-old female participant in the placebo group.

➤ **Seizures**

Up to 7 days after injection, AESIs of seizure were reported for 0 participants in the mRNA-1345 group and 2 participants (<0.1%) in the placebo group . Up to 28 days after injection (cumulative), AESIs of seizure were reported for 0 participants in the mRNA-1345 group and 3 participants (<0.1%) in the placebo group.

Up to data cutoff (cumulative), AESIs with “PTs indicative of seizure” activity were reported for 10 participants (<0.1%) in the mRNA-1345 group and 11 participants (<0.1%) in the placebo group; terms included alcoholic seizure, epilepsy, generalized tonic-clonic seizure, petit mal epilepsy, seizure, seizure like phenomena, and status epilepticus. Event onset ranged from Day 63 to Day 467 in the mRNA-1345 group and from Day 1 to 365 in the placebo group. An event of cerebrovascular accident was reported as an AESI for a 67-year-old female participant in the mRNA-1345 group. The event was an SAE, had a verbatim term of “query CVA or 1st seizure,” and occurred on Day 251. The participant also had internal carotid artery deformity (right ICA kinking) with onset on the same day.

✓ **Thrombocytopenia**

Up to 7 days after injection, no AESIs of thrombocytopenia were reported in either group. Up to 28 days after injection, AESIs of thrombocytopenia were reported for 0 participants in the mRNA-1345 group and 2 participants (<0.1%) in the placebo group.

Up to data cutoff (cumulative), AESIs of thrombocytopenia were reported for 9 participants (<0.1%) in the mRNA-1345 group and 13 participants (<0.1%) in the placebo group. Additional PTs reported as AESI of thrombocytopenia included decreased platelet count for one participant (<0.1%) in the mRNA-1345 group and immune thrombocytopenia and pancytopenia each for one participant (<0.1%) in the placebo group. The time to onset of AESIs of thrombocytopenia events for all reported PTs ranged from Day 61 to 358 in the mRNA-1345 group and from Day 25 to 321 in the placebo group.

✓ **Other AESIs**

Some events that were reported as AESIs did not clearly fall within one of the medical concepts in the preceding subsections as defined in the protocol.

In the mRNA-1345 group, the events included one event each of myasthenia gravis, atrial fibrillation, worsening of a pre-existing essential tremor and encephalopathy. Overall, encephalopathy (including PTs encephalopathy, toxic encephalopathy, septic encephalopathy, and metabolic encephalopathy; not reported as AESIs) were reported in 4 participants in the mRNA-1345 group and 6 participants in the placebo group (<0.1% each).

In the placebo group, additional AESI events included cardiac tamponade and myotonic dystrophy.

❖ **Standardized MedDRA Queries**

The evaluations are presented by SMQ with a focus on the narrow scope queries; the narrow/broad scope queries were included where relevant to ensure a comprehensive review. Please refer to Table 7 for a summary of the evaluations by SMQ. The events described in the table met any of the following criteria: occurred more frequently in the mRNA-1345 group than in the placebo group, were considered to be related to study injection, were of a type with biological plausibility for a relationship with vaccine, and/or that occurred within a relevant risk window, regardless of per-Investigator causality.

Table 7. Summary of evaluations within each SMQ and scope for events up to 28 days and for events up to data cutoff.

	mRNA-1345 group n (%)	placebo group n (%)
Anaphylaxis		
Algorithmic SMQ up to 7 days post injection	--	--
Algorithmic SMQ up to 28 days post injection (cumulative)	3 (<0.1)	4 (<0.1)
Cardiac arrhythmias		
Up to data cutoff (cumulative) narrow/broad scope SMQ	265 (1.5)	286 (1.6)
Cardiomyopathy		
Up to data cutoff (cumulative) narrow scope SMQ **	13 (<0.1)	7 (<0.1)
Cardiac failure		
Up to data cutoff (cumulative) narrow scope SMQ	56 (0.3)	74 (0.4)
Angioedema		
Up to 7 days post injection narrow scope SMQ	10 (<0.1)	2 (<0.1)
Up to 28 days post injection (cumulative) narrow scope SMQ	22 (0.1)	8 (<0.1)
Up to data cutoff (cumulative) narrow scope SMQ	61 (0.3)	52 (0.3)
Hypersensitivity		
Up to 7 days post injection narrow scope SMQ	38 (0.2)	22 (0.1)
Up to 28 days post injection (cumulative) narrow scope SMQ	105 (0.6)	100 (0.5)
Up to data cutoff (cumulative) narrow scope SMQ	328 (1.8)	288 (1.6)
Peripheral neuropathy		
Up to data cutoff (cumulative) narrow scope SMQ	37 (0.2)	36 (0.2)
Guillain-Barre syndrome		
Up to data cutoff (cumulative) narrow scope SMQ	--	--
Demyelination		
Up to data cutoff (cumulative) narrow scope SMQ	2 (0.1)	1 (0.1)
Immune-mediated/Autoimmune disorders		
Up to data cutoff (cumulative) narrow scope SMQ ***	49 (0.3)	32 (0.2)
Embolic and thrombotic events		
Up to data cutoff (cumulative) narrow scope SMQ	201 (1.1)	191 (1.1)

Ischemic heart disease		
Up to data cutoff (cumulative) narrow scope SMQ	154 (0.8)	162 (0.9)
CNS vascular disorders		
Up to data cutoff (cumulative) narrow scope SMQ	98 (0.5)	106 (0.6)
Noninfectious myocarditis and pericarditis		
Up to data cutoff (cumulative) narrow scope SMQ	--	--
Convulsions		
Up to data cutoff (cumulative) narrow scope SMQ	12 (<0.1)	11 (<0.1)
Vasculitis		
Up to data cutoff (cumulative) narrow scope SMQ	11 (<0.1)	4 (<0.1)
Hematopoietic cytopenias		
Up to data cutoff (cumulative) narrow scope SMQ	15 (<0.1)	26 (0.1)

A cell is blank when no participants were identified.

(*) The most commonly reported term within the narrow cardiac arrhythmia SMQ was atrial fibrillation (reported in <0.1% of participants in both groups up to 28 days after injection and in 0.4% of mRNA-1345 participants and 0.5% of placebo participants up to data cutoff).

(**) Eleven of the 13 participants in the mRNA-1345 group and all 7 participants in the placebo group had predisposing conditions considered as risk factors for the event, an alternative etiology was identified, and/or there was long latency from the time of study injection. None of the participants with events identified in the cardiomyopathy SMQ had previously reported myocarditis or pericarditis.

(***) The overall incidence up to data cutoff was balanced between the groups for common immune-mediated conditions including rheumatoid arthritis (8 participants in the mRNA-1345 group and 7 participants in the placebo group), polymyalgia rheumatica (5 and 4 participants), and thyroid conditions (including PTs of autoimmune thyroiditis, autoimmune hypothyroidism, and Basedow's disease; 4 and 3 participants) (each <0.1%).

Reviewer comment

Incidence of AESIs was balanced between the groups up to 7 days after injection, up to 28 days after injection, and up to data cutoff. The review of programmatic searches by SMQ for medical concepts of theoretical clinical interest for vaccines in general and/or mRNA vaccines did not identify safety concerns:

- No vaccine-associated events of anaphylactic reaction were reported up to data cutoff.
- No CEAC-adjudicated cases of acute myocarditis were reported up to data cutoff in either group, and no CEAC-adjudicated cases of acute pericarditis were

reported within the relevant risk window of 42 days after study injection (two participants in the mRNA-1345 group had CEAC-adjudicated cases of acute pericarditis that had onset >42 days after study injection and were considered to be unrelated to study injection). No CEAC-adjudicated cases of acute pericarditis were reported in the placebo group up to data cutoff.

- No events of GBS or ADEM or events with potentially associated PTs concerning for events of GBS or ADEM were reported up to data cutoff.
- The incidence of AESIs of Bell's palsy and facial paralysis was balanced between study groups (2 participants in each group) within the relevant risk window of 42 days.
- The incidence of urticaria was higher in the mRNA-1345 group (15 participants) than in the placebo group (5 participants) (each <0.1%) up to 28 days after injection.
- The incidence of cardiac arrhythmias based on the narrow cardiac arrhythmias SMQ was similar (0.9% of participants) in both groups up to data cutoff. The most commonly reported term within the narrow cardiac arrhythmia SMQ was atrial fibrillation (reported in <0.1% of participants in both groups up to 28 days after injection and in 0.4% of mRNA-1345 participants and 0.5% of placebo participants up to data cutoff).

5.2.1.6 Medically Attended Adverse Events

Up to data cutoff (cumulative), MAAEs were reported for 39.2% of participants in the mRNA-1345 group and 38.1% of participants in the placebo group, and the incidence of events by SOC and PT were similar between the groups. The most common SOC for MAAEs was Infections and infestations, in which events were reported for 19.9% of mRNA-1345 participants and 19.1% of placebo participants, and in which the most common PT was COVID-19 (reported for 5.0% and 4.7% of participants).

Reviewer comment

Up to data cutoff (30 Apr 2023) (cumulative), incidence of MAAEs leading to study discontinuation were balanced between the groups.

5.2.1.7 TEAEs To Study Discontinuation

Up to data cutoff, TEAEs that led to study discontinuation were reported for 99 participants in the mRNA-1345 group (0.5%) and 105 participants in the placebo group (0.6%), and the type and incidence of the events were similar between groups. Most of these discontinuations in both groups were due to fatal events. Deaths are described in section 5.3.1.4 of this memorandum.

Reviewer comment

Up to data cutoff (30 Apr 2023) (cumulative), incidence of TEAEs leading to study discontinuation, including those considered to be related to study injection, were balanced between the groups.

5.2.2 mRNA-1345-P301 2-Month Safety Addendum Report (June 24, 2023 data cutoff)

The mRNA-1345-P301 2-Month Safety Addendum Report was received October 24, 2023 (BLA 125796.0.7) and provides additional safety data as follows:

- Participants randomized between November 1, 2022 and December 23, 2022 (N=1021): Note that the data cutoff for the Study P301 CSR (April 30, 2023) was ≤6 months from study injection for these participants. Cumulative safety data up to June 24, 2023 is summarized and includes approximately 2 months of additional safety follow-up with a focus on events reported on or after May 1, 2023 (not previously reported in the Study P301 CSR).
- All participants randomized up to 23 Dec 2022 (N=36,558) with approximately 2 months of additional safety follow-up: the safety data focuses on events reported on or after May 1, 2023 (not previously reported in the Study P301 CSR).

The safety addendum report does not present data previously reported in the Study P301 CSR such as solicited adverse reactions that occurred within 7 days after injection or for unsolicited AEs that occurred within 28 days after injection (which is already presented in Section 5.2.1 of this memo)

5.2.2.1 Unsolicited Adverse Events

For participants Randomized Between November 1, 2022 and December 23, 2022 (N=1021) the incidence of fatal events, SAEs, AEs leading to study discontinuation and MAAEs up to data cutoff (June 24, 2023) (cumulative), was similar to or numerically lower in the mRNA-1345 group than in the placebo group. No AESIs were reported in either group up to data cutoff. See Table8.

Table 8 Overall Summary of Unsolicited TEAEs Up to Data Cutoff (June 24, 2023)
(Safety Set – Participants Randomized Between November 1, 2022 and December 23, 2022)

	Placebo (N=508) n (%)	mRNA-1345 50 µg (N=513) n (%)
Unsolicited TEAEs regardless of relationship to study injection		
Serious	37 (7.3)	28 (5.5)
Fatal	13 (2.6)	1 (0.2)
Medically attended	78 (15.4)	69 (13.5)
Leading to study discontinuation	13 (2.6)	1 (0.2)
Any AESI	0	0

In the overall safety population, up to data cutoff (24 Jun 2023) (cumulative), incidence of SAEs, fatal events, MAAEs, AESIs, and TEAEs leading to study discontinuation were similar between the groups and findings were similar to those presented in Study P301 CSR (presented in Section 5.3.1 of this memorandum).

5.2.2.2 Serious Adverse Events

Participants Randomized Between 01 Nov 2022 and 23 Dec 2022: up to data cutoff (cumulative), SAEs were reported for 28 participants (5.5%) in the mRNA-1345 group and for 37 participants (7.3%) in the placebo group. SAEs reported on or after 01 May 2023 were reported for 3 participants (0.6%) in the mRNA-1345 group and 12 participants (2.6%) in the placebo group, as follows:

- mRNA-1345: femoral neck fracture (Days 141 to 170); cardiovascular disorder (recurrent), dyslipidemia, hemiplegia, aortic arteriosclerosis, and hypertension (Days 152 to 155); humerus fracture (onset Day 187 and ongoing)
- Placebo: hypotension (Days 174 to 175); cerebrovascular accident (Days 190 to 192); acute left ventricular failure (Days 169 to 172); sudden cardiac death (Day 186); respiratory failure (Days 189 to 206); cardiac arrest (Day 192); respiratory tract infection (Days 157 to 198); cardiogenic shock, ischemic cardiomyopathy, septic shock, and respiratory failure (onset Day 169 and ongoing); COPD (Days 160 to 188); dehydration (Days 174 to 175); COPD (Days 188 to 206); ischemic stroke (onset Day 205 and ongoing); COPD (onset Day 201 and ongoing); chronic kidney
Placebo: hypotension (Days 174 to 175); cerebrovascular accident (Days 190 to 192); acute left ventricular failure (Days 169 to 172); sudden cardiac death (Day 186); respiratory failure (Days 189 to 206); cardiac arrest (Day 192); respiratory tract infection (Days 157 to 198); cardiogenic shock, ischemic cardiomyopathy, septic shock, and respiratory failure (onset Day 169 and ongoing); COPD (Days 160 to 188); dehydration (Days 174 to 175); COPD (Days 188 to 206); ischemic stroke (onset Day 205 and ongoing); COPD (onset Day 201 and ongoing); chronic kidney.

Overall safety population: Up to data cutoff (cumulative), SAEs were reported for 1314 participants (7.2%) in the mRNA-1345 group and 1327 participants (7.3%) in the placebo group for the overall safety population. The types and incidence of SAEs by SOC and PT were similar between the groups as reported in Section 5.3.1.3 of this memo. Up to data cutoff, SAEs that were considered to be related were reported for 5 participants in each group (each <0.1%); details of these events are provided in Section 5.3.1.3 of this memo, with exception of one SAE reported on or after May 2023, as follows:

- mRNA-1345: A 73-year-old male participant in the United States had thrombocytopenia on Day 153 that was reported as an SAE and AESI. The participant had prior medical history including factor 5 deficiency, bradycardia, and aortic, mitral, and tricuspid valve regurgitation and previous SAE (considered to be unrelated) of aortic valve incompetence (Day 115 to 153) and congestive cardiac failure (Day 140 to 142). The participant's concomitant medications included apixaban for the clotting disorder. The thrombocytopenia occurred after planned surgery for pacemaker and heart valve replacement on Day 153 and resolved on Day 158. The thrombocytopenia event was considered to be related to study injection; the Investigator's rationale for this assessment was that thrombocytopenia is not expected in an individual with factor 5 clotting disorder.

5.2.2.3 Deaths

Up to data cutoff (June 24, 2023) (cumulative) for participants randomized between 01 Nov 2022 and 23 Dec 2022, fatal AEs were reported for 1 participant (0.2%) in the mRNA-1345 group and 13 participants (2.6%) in the placebo group. Deaths reported on or before 30 Apr 2023 are presented in Section 5.2.1.4 of this memorandum. Deaths reported on or after May 1, 2023 were reported for 5 participants in the placebo group.

In the overall safety population, up to data cutoff (cumulative), fatal TEAEs were reported for 97 participants (0.5%) in the mRNA-1345 group and 112 participants (0.6%) in the placebo group. None of the fatal AEs were considered to be related to study injection. New fatal outcomes (reported on or after 01 May 2023) were reported for 15 participants in the mRNA-1345 group (<0.1%) and 29 participants in the placebo group (0.1%); this included fatal AEs with onset on or after 01 May 2023 and AEs with onset before 01 May 2023 that had a fatal outcome on or after 01 May 2023.

- Deaths due to AEs reported on or after 01 May 2023 were reported for 9 participants in the mRNA-1345 group and 26 participants in the placebo group:
 - mRNA-1345: acute myocardial infarction (onset Day 311; death Day 312); intracranial mass (onset Day 199; death Day 211); cardio-respiratory arrest (onset/death Day 236); cardio-respiratory arrest (onset/death Day 307); septic shock (onset Day 355; death Day 365); malignant neoplasm (onset/death Day 330); stage IV lung carcinoma cell type unspecified (onset/death Day 306); road traffic accident (onset/death Day 392); and death (onset Day 272; death Day 273)
 - Placebo: ventricular arrhythmia (onset/death Day 309); acute respiratory failure (onset/death Day 302); sepsis (onset Day 247; death Day 266); acute myocardial infarction (onset/death Day 265); cardio-respiratory arrest (onset/death Day 235); pneumonia (onset Day 236; death Day 241); cardio-respiratory arrest (onset/death Day 253); hypovolemic shock (onset Day 252; death Day 253); urosepsis (onset Day 238; death Day 251); malignant neoplasm of unknown primary site (onset Day 285; death Day 318); lower gastrointestinal hemorrhage (onset Day 273; death Day 274); cerebrovascular accident (onset Day 297; death Day 311); acute respiratory failure (onset Day 265; death Day 274); bacterial endocarditis (onset Day 247; death Day 250); acute respiratory failure (onset Day 387; death Day 388); death (onset/death Day 330); cardiac arrest (onset/death Day 374); death (onset/death approximately 1 year after injection); death (onset/death Day 356); hypertension (onset/death Day 355); diverticulitis (onset Day 337; death Day 348); cardiorespiratory arrest (onset/death Day 376); acute left ventricular failure (onset Day 169; death Day 172); sudden cardiac death (onset/death Day 186); respiratory failure (onset Day 198; death Day 206); and cardiac arrest (onset/death Day 192).

- Adverse Events reported before 01 May 2023 that had a fatal outcome after 01 May 2023 occurred in 6 participants in the mRNA-1345 group and 3 participants in the placebo group:
 - mRNA-1345: metastatic carcinoma of the bladder with onset on Day 26; biliary obstruction (onset Day 236) and pancreatic mass (onset Day 239) with death on Day 262; pancreatic neoplasm (onset approximately 3 months after injection, death Day 289); pancreatolithiasis (onset Day 75; death Day 227); metastatic breast cancer (onset Day 159; death Day 353); and cardiac failure (onset approximately 11 months after injection [Listing 16.2.5.1]; death Day 342).
 - Placebo: intracranial mass (onset Day 131; death Day 288); abdominal mass (onset Day 288; death Day 375); COPD (onset Day 127; death Day 154).

The timing of death following injection and the type and incidence of fatal events by SOC and PTs were similar between the groups (as presented in Section 5.3.1.4 of this memorandum).

5.2.2.4 Protocol- defined Adverse Events of Special Interest

For participants randomized between 01 Nov 2022 and 23 Dec 2022 no AESIs, including no cases of GBS or ADEM, were reported among participants up to the data cutoff.

In the overall safety population cumulatively up to data cutoff of June 24, 2023), AESIs were reported for 51 participants (0.3%) in the mRNA-1345 group and 47 participants (0.3%) in the placebo group (see Table 9). Findings were similar to those presented in Section 5.3.1.5. AESIs that were considered to be related to study injection were reported for 3 participants in the mRNA-1345 group (thrombocytopenia - Day 153, platelet count decreased - Day 144 and facial palsy - Day 5) and 2 participants in the placebo group (thrombocytopenia – Day 22 and seizure - Day 1).

This addendum includes AESIs reported on or after 01 May 2023 for 11 participants in the mRNA-1345 group and 9 participants in the placebo group. No cases of GBS or ADEM were reported during the additional follow-up in the overall population.

Table 9 Participant Incidence of Unsolicited TEAEs of Special Interest as Assessed by Investigator Up to Data Cutoff Date (24 Jun 2023) by System Organ Class and Preferred Term (Safety Set – Overall Safety Population)

	Placebo (N=18184) n (%)	mRNA-1345 50 µg (N=18245) n (%)
System Organ Class		
Preferred Term		
Number of participants reporting AESIs	47 (0.3)	51 (0.3)

Blood and lymphatic system disorders	17 (<0.1)			17 (<0.1)
Thrombocytopenia	14 (<0.1)			17 (<0.1)
Nervous system disorders	21 (0.1)			26 (0.1)
Seizure	10 (<0.1)			7 (<0.1)
Bell's palsy	4 (<0.1)			5 (<0.1)
Facial paralysis	2 (<0.1)			3 (<0.1)
Generalised tonic-clonic seizure	0			2 (<0.1)
Epilepsy	2 (<0.1)			1 (<0.1)
Alcoholic seizure	2 (<0.1)			0
Cardiac disorders	3 (<0.1)			4 (<0.1)
Pericarditis	2 (<0.1)	2	2	2 (<0.1)
			(<0.1)	(<0.1)

Table 9 includes SOC with at least 2 reports.

✓ **Anaphylactic reaction**

Cumulatively up to data cutoff, AESIs of anaphylactic reaction were reported for 1 participant (<0.1%) in each group. An ESI of drug hypersensitivity was reported in the mRNA-1345 group (Day 394 to 395; considered an SAE and occurred after treatment with amoxicillin clavulanate). An AESI of anaphylactic reaction reported in the placebo group (Day 320 to 333; SAE considered unrelated to study injection per Investigator; occurred after treatment with amoxicillin).

✓ **New onset or worsening of neurological disorders**

No AESIs of GBS or ADEM were reported cumulatively up to data cutoff. Cumulatively up to data cutoff, AESIs of Bell's palsy were reported for 5 participants in the mRNA-1345 group and 4 participants in the placebo group and AESIs of facial paralysis were reported for 3 and 2 participants, respectively (all <0.1%). All participants in the mRNA-1345 group who had AESIs of Bell's palsy or facial paralysis had risk factors for the event other than age. All participants in the mRNA-1345 group who had AESIs of Bell's palsy or facial paralysis had risk factors for the event other than age. Only the previously reported Day 5 facial paralysis event in the mRNA-1345 group was considered to be related to study injection.

✓ **Seizures**

Cumulatively up to data cutoff, AESIs of seizure (and seizure-like PTs) were reported for 14 participants in the mRNA-1345 group and 14 participants in the placebo group (each <0.1%). None of the seizure and seizure-like AESIs in the mRNA-1345 group had onset within 28 days after injection. Among all AESIs of seizure or seizure-like PTs reported cumulatively, onsets in the mRNA-1345 group ranged from Day 63 to 499 and onsets in the placebo group ranged from Day 1 to 532.

✓ **Myocarditis and pericarditis**

Cumulatively up to data cutoff, AESIs of pericarditis were reported for 2 participants in each group and an AESI of myocarditis was reported for 1 participant in the mRNA-1345 group and 0 participants in the placebo group (all <0.1%). Please refer to Section 5.3.1.5 of this memo for further details.

✓ **Thrombocytopenia**

Cumulatively up to data cutoff, thrombocytopenia and associated PTs of pancytopenia, heparin induced thrombocytopenia, immune thrombocytopenia, and decreased platelet count were reported as an AESI for 18 participants in the mRNA-1345 group and 18 participants in the placebo group (each <0.1%). No thrombocytopenia AESIs in the mRNA-1345 group had onset within 28 days after injection (onsets ranged from Day 61 to 368) and onsets in the placebo group, including PTs other than thrombocytopenia, ranged from Day 25 to 372.

5.3.2.5 Medically Attended Adverse Events

Up to data cutoff, MAAEs (excluding per-protocol illness visits) were reported for 7791 participants (42.7%) in the mRNA-1345 group and for 7642 participants (42.0%) in the placebo group in the overall safety population, and the incidence of events by SOC and PT was similar between the groups.

Reviewer comment

Up to data cutoff (24 Jun 2023) (cumulative), incidence of SAEs, fatal events, MAAEs, AESIs, and TEAEs leading to study discontinuation, including those considered to be related to study injection per investigator, were similar between the groups in the overall safety population.

The additional safety follow-up in the overall safety population, including participants randomized between 01 Nov 2022 and 23 Dec 2022 has not identified new safety concerns.

5.3 SAFETY ANALYSIS OF STUDY mRNA-1345-P101 (P101)

Study mRNA-1345-P101 is an ongoing Phase 1, randomized, observer-blind, placebo-controlled, dose escalation study to assess safety and immunogenicity of mRNA-1345.

The primary safety endpoints included:

- Solicited local and systemic ARs through 7 days after each injection.
- Unsolicited AEs through 28 days after the last injection.
- SAEs and MAAEs throughout the entire study period

Study population included the following groups of healthy subjects:

- Adults aged 18 to 49 years: 6 months post last injection (Month 6 for single injection cohorts and Month 10 for 3-injection cohort).
- Adults aged 65 to 79 years: 12 months after the Month 12 injection. Data are included in this report up to Month 14 (approximately 2 months after the booster injection) (Interim analysis). The follow-up for this cohort is up to 24 Months post first injection.
- Adults of Japanese descent aged ≥60 years: 6 months post-injection (Month 6)

Please refer to Appendix C1 for additional study details of study mRNA-1345-P101

5.3.1 Safety Results in Adults Aged 18 to 49 Years

- **Solicited adverse reactions (reactogenicity):**

- Single injection: The incidence and severity of solicited local and systemic ARs was dose-dependent.

Solicited local ARs were reported for 14/19 participants (73.7%), 18/20 participants (90.0%), and 20/20 participants (100%) in the 50 µg, 100 µg, and 200 µg mRNA-1345 groups, respectively, and for 0 participants in the placebo group.

The most frequently reported solicited local AR was injection site pain.

Solicited systemic ARs were reported for 11/19 participants (57.9%), 14/20 participants (70.0%), and 20/20 participants (100%) in the 50 µg, 100 µg, and 200 µg groups, respectively, and for 6 participants (40.0%) in the placebo group. The 4 most frequently reported solicited systemic ARs were fatigue, headache, myalgia, and chills. Solicited ARs were generally Grade 1 or 2 in severity, and of the 9 participants overall who reported any Grade 3 solicited ARs, 7 were in the 200 µg mRNA-1345 group.

Solicited ARs had onset within 2 days after injection and resolved within 2 days.

- Three injections (100 µg mRNA-1345): All participants (20/20; 100%) in the 100 µg mRNA-1345 group had solicited ARs (local and/or systemic) after the first injection. Severity, time to onset, and duration of solicited ARs were similar to observations in the single dose 100 µg mRNA-1345 group. Severity, time to onset, and duration after subsequent injections were similar to characteristics after the first injection, with most solicited ARs having onset on Day 1 or Day 2 and a median duration of 1 to 3 days.

- **Unsolicited adverse events:** No deaths, SAEs, TEAEs leading to discontinuation of study vaccine, TEAEs leading to discontinuation from study participation, or AESIs were reported up to the end of study.

- Single injection: Unsolicited TEAEs up to 28 days after injection were reported in a roughly dose-dependent manner for 2/19 participants (10.5%) in the 50 µg mRNA-1345 group, 2/20 participants (10.0%) in the 100 µg mRNA-1345 group, 15/20 participants (75.0%) in the 200 µg mRNA-1345 group, and 5/15 participants (33.3%) in the placebo group.
- Three injections (100 µg mRNA-1345): Reporting of unsolicited TEAEs up to 28 days after each injection was similar to observations after the first dose of 100 µg mRNA-1345.

5.3.2 Safety Results in Adults Aged 65 to 79 Years

- **Solicited adverse reactions (reactogenicity):**

- First injection: The incidence of solicited local and systemic ARs after one injection

of mRNA-1345 was lower in the 12.5 µg, 25 µg, and 50 µg groups than in the 100 µg and 200 µg mRNA-1345 groups.

The most frequently reported solicited local AR was injection site pain, which was reported for 23/46 participants (50.0%), 29/44 participants (65.9%), 29/47 participants (61.7%), 35/47 participants (74.5%), and 37/47 participants (78.7%) in the 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg mRNA-1345 groups, respectively, and for 7/55 participants (12.7%) in the placebo group.

The incidence of solicited systemic ARs was approximately 50% in the 12.5 µg, 25 µg, and 50 µg groups compared with 78.7% and 66.0% in the 100 µg and 200 µg groups, respectively, and 45.5% in the placebo group. The 4 most frequently reported solicited systemic ARs in the total mRNA-1345 group were fatigue, headache, myalgia, and arthralgia.

Most solicited ARs were reported at Grade 1 or 2; Grade 3 solicited ARs were more common in the higher mRNA-1345 dose groups (100 µg and 200 µg).

Most solicited ARs had onset within 2 days after injection and most resolved within 2 days.

- Booster injection: A comparison of reactogenicity after a booster injection with reactogenicity after the first injection based on 18 participants who received the 50 µg mRNA-1345/50 µg mRNA-1345 sequence did not reveal substantial differences between results for each injection.

- **Unsolicited adverse events:**

No TEAEs leading to discontinuation of study vaccine, TEAEs leading to discontinuation from study participation, or AESIs were reported up to the data cutoff after either the first injection or the booster injection.

- First injection: No dose-dependent trends were observed in the incidence of unsolicited TEAEs, SAEs, MAAEs, or Grade 3 or higher events.
The proportions of participants who had unsolicited TEAEs in the mRNA-1345 groups ranged from 41.7% (20/48 participants) in the 100 µg group to 66.7% (32/48 participants) in the 12.5 µg group versus 35.6% (21/59 participants) in the placebo group.
Other than 2 participants (2/239, 0.8%) with SAE of pneumonia, both in the 12.5 µg mRNA-1345 group, no SAE by PT was reported for more than one participant overall.
After the first injection and up to the booster injection or end of study (EOS) (whichever is earlier), no AESIs were reported among participants who received a single injection of 12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg mRNA-1345 or placebo.
- Booster injection: No safety concerns were identified in participants who received a booster dose of 50 µg mRNA-1345 approximately 12 months after the first dose of 50 µg mRNA-1345 or in participants who received a booster injection at any mRNA-1345 dose level based on follow-up until Month 14.

Unsolicited TEAEs were reported for 26/99 participants (26.3%) in the mRNA-1345/mRNA-1345 total group, 26/96 participants (27.1%) in the mRNA-1345/placebo total group, and 10/52 participants (19.2%) in the placebo/placebo group.

SAEs were reported for 3/99 participants (3.0%) in the mRNA-1345/mRNA-1345 total group, 4/96 participants (4.2%) in the mRNA-1345/placebo total group, and 1/52 participants (1.9%) in the placebo/placebo group.

No AESIs were reported.

Two participants had fatal events after booster injection (bone sarcoma on Day 162 after booster injection in the 12.5 µg mRNA-1345/placebo group; road traffic accident on Day 63 in the 25 µg mRNA-1345/placebo group).

5.3.3 Safety Results in Adults of Japanese Descent Aged ≥60 Years

The cohort of adults of Japanese descent aged ≥60 years was included to demonstrate safety, tolerability, and immunogenicity in this population and to enable evaluation of mRNA-1345 in subsequent late-stage clinical studies in Japan.

- **Solicited adverse reactions (reactogenicity):**

- Solicited local ARs were reported for 18/21 participants (85.7%) in the mRNA-1345 group and all of these participants reported injection site pain, which was the most frequently reported solicited local AR term.

Most solicited local ARs were Grade 1 and none were Grade 3.

No local ARs were reported by participants in the placebo group.

- Solicited systemic ARs were reported for 15/21 participants (71.4%) in the mRNA-1345 group. The most frequently reported solicited systemic ARs were fatigue (11/21 participants [52.4%]) and myalgia (8/21 participants [38.1%]). Most solicited systemic ARs were mild and none were Grade 3.

Systemic ARs (all Grade 1) were reported in 3/4 participants (75.0%) in the placebo group (fatigue [2 participants] and headache [1 participant]).

- **Unsolicited adverse events:**

Unsolicited TEAEs up to the EOS were reported for 1/21 participants (4.8%) after a single dose of 100 µg mRNA-1345 who reported:

-Injection site swelling (mild) was reported as a solicited AR, and thus by definition assessed as related to study vaccine, which began on Day 1 and resolved on Day 9.

-Diplopia (severe) was reported as a MAAE beginning on Day 4 and resolved on Day 44.

-Intracranial aneurysm (moderate) was reported as a nonserious MAAE beginning on Day 17 and was ongoing (resolving) as of data cutoff.

No deaths, SAEs, AESIs, or TEAEs leading to study discontinuation were reported up to the EOS in the single dose 100 µg mRNA-1345 group or in the placebo group.

Among participants in the placebo group, one participant had a TEAE of headache on Day 7 after injection and one participant had a MAAE of vertigo from Day 36 to Day 42.

Reviewer comment

The incidence and severity of solicited local and systemic ARs was dose-dependent. However, the majority of solicited local and systemic ARs were Grade 1 to Grade 2 in severity.

Among participants aged 18 to 49 years who received 3 injections with 56-day intervals

between doses, the severity, time to onset and duration of reactogenicity events after dose # 2 and # were similar to reactogenicity after the first injection.

Among participants aged 65 to 79 years who received a booster injection 12 months after the first injection (50 µg mRNA-1345/50 µg mRNA-1345), reactogenicity did not differ substantially between the first and booster injections.

There were no AESIS reported and no SAEs up to up to 28 days after any injection were reported.

Two deaths (unrelated to study injection per investigator) were reported after the booster injection among adults aged 65 to 79 years: one participant who received 12.5 µg/placebo died due to bone sarcoma and one participant who received 25 µg /placebo died due to road traffic accident; both deaths were reported >28 days after the booster injection and more than 1 year after the last injection of mRNA-1345.

6 PHARMACOVIGILANCE PLAN

The Core Risk management Plan (RMP) v 1.0 (submitted under BLA 125796) is based on data lock point of April 30, 2023 and comprises a comprehensive review of clinical safety data to identify the important risks of mRNA-1345. Other risks not considered important are also discussed. Additionally, areas of missing information are identified, focusing on populations where there is expected anticipated use of the vaccine and where current exposure is missing or limited.

Moderna's routine pharmacovigilance practices include signal management process (signal detection, validation and evaluation of spontaneous reports from all sources) where data sources will be screened for new safety information related to mRNA-1345. Following initial review of the available data, a determination will be made on the basis of the nature and the quality of the new information whether further investigation is warranted, at which point those topics referred for further investigation are considered "validated signals". Data sources will include safety data from Moderna-sponsored clinical trials as well as non-interventional studies, spontaneous AE reports, published literature, and communications from external sources, including regulatory agencies, and (if applicable) business partners.

Routine PV also includes a periodic review of the literature that involves targeted keyword searches in widely recognized databases (i.e., MEDLINE, EMBASE).

Moderna performs a weekly aggregate quantitative signal detection review of the global safety database in order to identify possible adverse reactions and employs routine pharmacovigilance consistent with that described in the ICH E2F Pharmacovigilance Planning Guideline.

The PVP included in the core RMP sets out specific plans to further characterize and minimize the product safety concerns.

Please refer to Table 10 below for a summary of the sponsor's PVP (included in the core Risk management Plan version 1.0, September 7, 2023)

Table 10 Safety concerns and planned actions for mRNA-1345

Safety Concern	Planned Actions
Important Identified Risks	
N/A	
Important Potential Risks	
Anaphylaxis	<ul style="list-style-type: none"> • Routine pharmacovigilance activities (adverse reactions reporting and signal detection) • Structured collection of clinical details via questionnaire for any spontaneous cases of anaphylaxis reported to Moderna during the post-marketing period • Safety studies * mRNA-1345-P101 mRNA-1345-P301 mRNA-1345-P302 mRNA-1345-P303 mRNA-1345-P304 mRNA-1345-P902 mRNA-1345-P903 • Anaphylaxis is included in Section 4 <i>Contraindications</i> of the proposed USPI
Myocarditis / pericarditis	<ul style="list-style-type: none"> • Routine pharmacovigilance activities (adverse reactions reporting and signal detection) • Structured collection of clinical details via questionnaire for any spontaneous cases of myocarditis or pericarditis reported to Moderna during the post-marketing period • Safety studies * mRNA-1345-P101 mRNA-1345-P301 mRNA-1345-P302 mRNA-1345-P303 mRNA-1345-P304 mRNA-1345-P902 mRNA-1345-P903
Missing Information	
Interaction with other vaccines	<ul style="list-style-type: none"> • Routine pharmacovigilance activities (adverse reactions reporting and signal detection) • Safety studies * mRNA-1345-P302 mRNA-1345-P304

	mRNA-1345-P902 mRNA-1345-P903
Use in immunocompromised individuals	<ul style="list-style-type: none"> • Routine pharmacovigilance activities (adverse reactions reporting and signal detection) • Safety Studies * mRNA-1345-P303 mRNA-1345-P902 mRNA-1345-P903 • Section 5.3 <i>Altered Immunocompetence</i> of the proposed USPI indicates that immunocompromised individuals, including those receiving immunosuppressive therapy, may have a diminished immune response to the vaccine. • The section <i>INFORMATION FOR RECIPIENTS AND CAREGIVERS</i> of the USPI prompts to tell the healthcare provider in case the vaccine recipient is immunocompromised or is on a medicine that affects the immune system.
Use in individuals with autoimmune or inflammatory disorders	<ul style="list-style-type: none"> • Routine pharmacovigilance activities (adverse reactions reporting and signal detection) • Safety Studies mRNA-1345-P902 mRNA-1345-P903
Long-term safety	<ul style="list-style-type: none"> • Routine pharmacovigilance activities (adverse reactions reporting and signal detection) • Safety Studies * mRNA-1345-P101 mRNA-1345-P303 mRNA-1345-P303 mRNA-1345-P902 mRNA-1345-P903

(*) Refer to appendix C1 and C2 for mRNA-1345-P101 and mRNA-1345-P301, respectively.

Refer to Appendix D for mRNA-1345-P302, mRNA-1345-P303 and mRNA-1345-P304. Refer to Appendix E and F for mRNA-1345-P902 and mRNA-1345-P903, respectively.

6.1 Assessment of Risk minimization measures

6.1.1 Important Potential Risks

6.1.1.1 Anaphylaxis

Any individual receiving a vaccine is at risk of anaphylaxis, and individuals with a known history of hypersensitivity to any component of the vaccine are at increased risk of

anaphylaxis. As anaphylaxis is a potentially life-threatening hypersensitivity reaction, it is considered an important potential risk of mRNA-1345.

In study mRNA-1345-P101 there were no AESIs of anaphylaxis.

In mRNA-1345-P301 there were no AESIs of anaphylaxis up to 7 days post vaccination.

Up to 28 days post vaccination there was one AESI of anaphylaxis to bee venom in a subject in the vaccine group. There were no additional cases up to data cutoff of April 30, 2023.

The proposed risk minimization activities are acceptable. Also, the proposed postmarketing studies will provide a larger denominator of vaccinees to better characterize this risk.

6.1.1.2 Myocarditis and pericarditis

Rare cases of myocarditis/pericarditis have previously been reported following the COVID-19 mRNA vaccines with higher incidence rates in young males and within a short risk window (7 days) after the second dose.

In study mRNA-1345-P101, no AESIs of myocarditis or pericarditis were reported in either the mRNA-1345 or placebo groups in any of the cohorts.

In study mRNA-1345-P301 no CEAC-adjudicated AESIs of myocarditis or pericarditis were reported within 42 days after injection. Two participants in the mRNA-1345 group had a CEAC-adjudicated AESI of acute pericarditis that had onset >42 days after injection.

The proposed risk minimization activities are acceptable. Also, the proposed postmarketing studies will provide a larger denominator of vaccinees to better characterize this risk.

6.1.1.3 Bell's palsy

In study mRNA-1345-P101, no AESIs of Bell's palsy were reported in either the mRNA-1345 or placebo groups in any of the cohorts.

In study mRNA-1345-P301 there were 2 events of Bell's palsy within 42 days post vaccination in each group. Also, in study mRNA-1345-P301 6 participants (<0.1%) and 3 (<0.1%) participants reported Bell's palsy up to data cut-off in the mRNA-1345 group and placebo group, respectively. Based on these data, DPV considers that Bell's Palsy does not represent a safety risk and will ask the sponsor to provide updates of Bell's palsy and other AESIs from the proposed post-authorization voluntary studies (mRNA-1345-P902 and mRNA-1345-P903), along with an assessment of the cases, in the quarterly periodic safety reports for the first 3 years after approval.

6.1.2 Missing information

6.1.2.1 Interaction with other vaccines

Individuals who received or planned to receive any non-study vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of type of vaccine) within 28 days before or after the Day 1 study injection were excluded from participation in study mRNA-1345- P301.

Due to the exclusion criterion in the clinical program no experience exists with administration of other vaccines within 28 days of mRNA-1345 administration, although it is common medical practice to administer vaccines concurrently. The proposed risk

minimization activities are acceptable. Interactions with other vaccines will be further characterized through study mRNA-1345-P302 and study mRNA-1345-P304 and through planned voluntary post-authorization studies mRNA-1345-P902 and mRNA-1345-P903, in addition to routine pharmacovigilance activities.

6.1.2.2 Use in immunocompromised individuals

It is generally expected that participants with immunocompromised status may not reach the protective antibody level achieved in healthy individuals with vaccines. Therefore, individuals with a reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease were excluded from participation in Study mRNA-1345-P301. Likewise, individuals receiving chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection were excluded.

The proposed risk minimization activities are acceptable. The proposed studies will better characterize this safety concern and provide data to inform guidance for healthcare providers for use of mRNA-1345 in immunocompromised individuals.

6.1.2.3 Use in individuals with autoimmune or inflammatory disorders

Individuals receiving chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection were excluded from study participation in study mRNA-1345-P301. This would have included individuals with autoimmune or inflammatory disorders. While individuals with stable autoimmune diseases that do not require systemic immunosuppressants were permitted in the study, mRNA-1345 exposure is limited in individuals with autoimmune or inflammatory disorders. The proposed risk minimization activities are acceptable.

The proposed studies will better characterize this safety concern and provide data to inform guidance for healthcare providers for use of mRNA-1345 in individuals with autoimmune or inflammatory disorders.

6.1.2.4 Long term safety

The safety profile of mRNA-1345 is based on the ongoing Phase 2/3 clinical study mRNA-1345-P301 in which 18,245 adult participants aged ≥ 60 years received one injection of 50 microgram mRNA-1345; and 17,152 of these participants had at least 6 months of follow-up after injection. At the time of the data cutoff of 30 April 2023, the median study duration from injection (days) in the mRNA-1345 group (N=18245) was 257 days.

In Phase 1 dose-escalation study mRNA-1345-P101 the median study duration from injection (days) in the mRNA-1345 group was 169 days. The proposed risk minimization activities are acceptable. The proposed studies will provide data to support the long-term safety of mRNA-1345.

6.2 Proposed post-approval safety studies

The sponsor included the synopses for the two proposed post-approval safety studies using administrative databases in the United States and Europe, as appendices to the

core RMP, given that it is seeking approval of the vaccine by the FDA and regulatory authorities in Europe. These synopses provide high-level summaries of rationale and background, research question and objectives, study design, study population, variables including a preliminary list of AESI, data source considerations, data analysis and milestones. The summaries of the proposed postmarketing study in the United States (*RSV PASS-902*) and in Europe (*RSV PASS-903*) are depicted in Appendix E and F, respectively. DPV considered that Moderna's proposed post-Authorization studies in the US (*RSV PASS-902*) and in Europe (*RSV PASS-903*) should be kept as voluntary as safety data from supporting studies, P101 and P301, do not merit a PMR/PMC. In response to DPV's IR from April 18, 2024 (received April 22, 2024 under BLA 125796, Sequence #0060) the sponsor committed to conducting these studies upon the approval of mRESVIA in the respective regions. Also, the sponsor committed to providing updates on AESIs from mRNA-1345-P902 and mRNA-1345-P903, along with an assessment of the cases, in the quarterly periodic safety reports for the first 3 years post-approval and to submitting interim study reports for both voluntary studies annually with the periodic study reports.

7 DPV ASSESSMENT AND RECOMMENDATIONS

Should MRESVIA be approved, OBPV/DPV agrees with the sponsor's proposed PVP (included in the core Risk management Plan version 1.0, September 7, 2023) to include routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80.

DPV and Division of Clinical & Toxicology Review concurred that there is no basis to consider a PMC/PMC based on the review of current safety data from supporting studies and agree with the sponsor's plan to conduct the voluntary proposed post-authorization safety studies mRNA-1345-P902 and mRNA-1345-P903. DPV requested the sponsor to provide updates of AESIs from both voluntary studies, along with an assessment of the cases, in the quarterly periodic safety reports for the first 3 years after approval. DPV also requested the sponsor to submit interim study reports for both voluntary studies annually with the periodic safety reports.

The review of current safety data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS). Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

REFERENCES

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Appendix A. Materials Reviewed in Support of this Assessment

Source	Submission Tracking Number	Documents Reviewed
Module 2.2 Sponsor	STN 125796	Module 1.14 - RSV Vaccine, mRNA label draft (annotated)
		Module 1.16 - Core Risk Management Plan (v 1.0 Summary of Clinical Safety Data lock point April 30, 2023), which includes the mRNA-1345 PVP
		Module 2.5 Clinical Overview
		Module 2.7.4 Summary of Clinical Safety
		Module 5.3.5.1 Reports of controlled trials pertinent to the claim indication: Study mRNA-1345-P101 Study mRNA-1345-P301 Study mRNA-1345-P301 2-month Addendum Report
		Module 5.3.5.3 Integrated Summary of safety
Sponsor	STN 125796	Module 1.11.3, Response to Information Request # 41, received April 22, 2024 under BLA 125796, Sequence # 0060

Appendix B. Rolling submission plan for BLA # 125796

Timing	Submission components
Part #1 (CMC &Nonclinical) – Q2 2023	Module 1.1 through 1.9; 1.12
	Module 2.3, 2.4 and 2.6
	Module 3 (complete)
	Module 4 (complete)
Part #1 (Clinical) – Q3 2023	Module 1.11, 1.14, 1.16, 1.18
	Module 2.2, 2.5, 2.7
	Module 5 (complete)

Appendix C1. Study mRNA-1345-P101

Design (status)	Objectives	Study Population / Sample size	Dose, Test Product(s) Regimen Route of Administration
<p>Phase 1 / Phase 1, randomized, observer-blind, placebo- controlled, dose-escalation multicenter study</p> <p>(ongoing)</p>	<p>Safety Objective</p> <p>To evaluate the tolerability and reactogenicity of up to 5 dose levels of mRNA-1345 in adults 18 to 49 years of age, adults 65 to 79 years of age, and adults of Japanese descent ≥60 years of age.</p> <p>To evaluate the tolerability and reactogenicity of 3 injections of the middle dose level of mRNA-1345 given 56 days apart in adults 18 to 49 years of age.</p> <p>To evaluate the tolerability and reactogenicity of a booster injection of mRNA-1345 given approximately 12 months after the primary injection in adults 65 to 79 years of age.</p>	<p>Healthy adults 18 to 49 years of Age</p>	<p>Single IM injection: mRNA-1345 50 µg mRNA-1345 100 µg mRNA-1345 200 µg Placebo (0.9% normal saline)</p> <p>mRNA-1345 N=59 Placebo N=15</p> <p>-----</p> <p>3 IM injections, 2 months apart: mRNA-1345 100 µg Placebo (0.9% normal saline)</p> <p>mRNA-1345 N=20 Placebo N=5</p>

Design (status)	Objectives	Study Population / Sample size	Dose, Test Product(s) Regimen Route of Administration
		Healthy adults 65 to 79 years of age	<p>Single IM injection followed by Month 12 Booster injection</p> <p>mRNA-1345 12.5 µg mRNA-1345 25 µg mRNA-1345 50 µg mRNA-1345 100 µg mRNA-1345 200 µg Placebo (0.9% normal saline)</p> <p><i>First injection</i> mRNA-1345 N=239 Placebo N=59</p> <p><i>Booster injection</i> mRNA-1345/ mRNA-1345 N=99</p> <p>mRNA- 1345/Placebo N=96 Placebo/Placebo N=52</p>

Design (status)	Objectives	Study Population / Sample size	Dose, Test Product(s) Regimen Route of Administration
		Healthy adults of Japanese descent ≥60 years of age	Single IM injection: mRNA-1345 100 µg Placebo (0.9% normal saline) mRNA-1345 N=21 Placebo N=4

Appendix C2. Study mRNA-1345-P301

Design (status)	Objectives	Study Population / Sample size	Dose, Test Product(s) Regimen Route of Administration
<p>Phase 2/3 / Phase 2/3, randomized, observer-blind, placebo- controlled, multicenter, case-driven study</p> <p>(ongoing)</p>	<p><u>Efficacy Objective</u> To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo within the period of 14 days postinjection up to 12months postinjection.</p> <p><u>Safety Objective</u> To evaluate the safety and tolerability of the mRNA-1345 vaccine.</p>	<p>Adults ≥60 years of age with or without underlying medical conditions</p> <p>mRNA-1345 N=18,245 Placebo N=18,184</p>	<p>Single IM injection:</p> <p>mRNA-1345 50 µg Placebo (0.9% normal saline)</p>

Appendix D Other ongoing and planned studies supporting the development of mRNA-1345

Study number / Title	Primary Objectives	Status
mRNA-1345-P302 / A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥ 50 Years of Age	Part A <ul style="list-style-type: none"> • To evaluate the safety and tolerability of mRNA-1345 coadministered with a seasonal influenza vaccine (Afluria® Quadrivalent). • To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A. • To evaluate the impact of coadministered RSV vaccine on the immune response to influenza. Part B <ul style="list-style-type: none"> • To evaluate the safety and tolerability of mRNA-1345 coadministered with mRNA-1273.214. • To evaluate the effect of Coadministered mRNA-1273.214 on the immune response to RSV-A. • To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2. Part C <ul style="list-style-type: none"> • To evaluate the safety and tolerability of a booster dose of mRNA-1345 administered at Year 1 following a primary dose. • To evaluate immune response to RSV-A of a booster dose of mRNA-1345 administered at Year 1 following a primary dose. • To evaluate the safety and tolerability of booster dose of mRNA-1345 administered at Year 2 following a primary dose. • To evaluate immune response 	Ongoing

	to RSV-A of a booster dose of mRNA-1345 administered at Year 2 following a primary dose.	
mRNA-1345- P303 A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥ 50 Years of Age	Part A <ul style="list-style-type: none"> • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the RSV-A and RSV-B nAb GMTs after a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to < 60 years) compared with that in older adults (≥60 years). Part B <ul style="list-style-type: none"> • To evaluate the safety and tolerability of mRNA-1345 • To evaluate the RSV-A and RSV-B nAb responses to 2 doses of 50 µg mRNA-1345 injection administered 57 days apart in immunocompromised participants ≥ 18 years of age. 	Planned
mRNA-1345-P304 A Phase 3, Randomized, Observer-blind Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, When Coadministered With a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥ 65 Years of Age	<ul style="list-style-type: none"> • To evaluate the safety and reactogenicity of mRNA- 1345 RSV vaccine co-administered with a high dose (HD) quadrivalent seasonal influenza vaccine (Fluzone® HD). • To evaluate the impact of coadministered HD quadrivalent seasonal influenza vaccine on the immune response to mRNA-1345 RSV vaccine against RSV-A and RSV-B. • To evaluate the impact of coadministered mRNA-1345 RSV vaccine on the immune response to HD quadrivalent seasonal influenza vaccine against 4 vaccine-matched influenza A and B strains. 	Planned

Appendix E Proposed post-authorization safety study mRNA-1345-P902

Study short name and title: *RSV PASS-902 PASS*

Post- Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in the United States.

Rationale and study objectives:

Although no important identified risks arose from this trial the mRNA-1345-P301, the trial sample size and follow-up time provided insufficient power to monitor safety for rare events and long-term safety. Further, insufficient/missing information for special populations of interest who may have a different risk-benefit profile requires additional assessment. Therefore, a postmarketing observational studies using real-world data is proposed.

Primary Objectives:

- Describe the uptake of the mRNA-1345 vaccine and characterize mRNA-1345 vaccine recipients
- Estimate incidence of pre-defined adverse events of special interest (AESI) among mRNA-1345 vaccine recipients
- For signal detection, compare the observed incidence rates of pre-defined AESI among mRNA-1345 vaccine recipients with expected incidence rates of pre-defined AESI from a similar comparator cohort(s)
- When a safety signal is detected based on pre-defined statistical threshold,
 - o Compare incidence rates of pre-defined AESI in the risk interval with incidence rates in the post-vaccination control interval in a self-controlled risk interval analysis. Or
 - o Compare the observed incidence rates of pre-defined AESI among mRNA-1345 vaccine recipients with incidence rates of pre-defined AESI in a similar matched cohort who did not receive the mRNA-1345 vaccine

Secondary Objectives:

Secondary objectives are identical to the primary, although focused on specific populations considered to have missing information, including but not limited to

- Immunocompromised patients
- Stratification by age group and sex
- Patients who, at cohort entry, had recently received other selected vaccines to prevent diseases other than the mRNA-1345 vaccine
- Patients with autoimmune or inflammatory disorders
- Stratification by country where appropriate

Study design:

Post- Authorization Active Surveillance Safety Study with 2 phases: signal detection and signal evaluation

Study population:

Recipients of mRNA-1345 will be identified in at least one full RSV season in the US. In the event of slow and low uptake of mRNA-1345, we will consider extending data

accrual period to cover more RSV seasons. Historical comparator cohort(s) will be identified in the post COVID-19 era prior to availability of any RSV vaccines

Safety concerns addressed:

- Acute disseminated encephalomyelitis
- Acute myocardial infarction (AMI)
- Anaphylaxis
- Atrial fibrillation
- Bell's palsy
- Guillain-Barré syndrome (GBS)
- Heart failure
- Idiopathic/Immune thrombocytopenia
- Myocarditis
- Non-AMI ischemic coronary artery disease
- Pericarditis
- Seizures
- Transverse myelitis

Data Analysis

For signal detection, observed incidence rates among mRNA-1345 vaccinees, as well as observed-to-expected ratios and 95% confidence intervals (CI) will be estimated compared with the expected number as estimated in the comparator cohort for each AESI.

For signal evaluation using the SCRI design, the ratio between the incidence rate estimate in the risk period and the incidence rate estimate in the control period (incidence rate ratio) and the 95%CI will be computed using conditional Poisson regression.

Milestones*

- Final Protocol: April 2024
- Interim report 1: April 2025
- Interim report 2: April 2026
- Final report (including any additional signal evaluation activities as applicable): July 2027

* The proposed timelines are subject to change depending on the US BLA approval date and real-world database selection. The study period may be extended depending on vaccine uptake to allow for a reasonable sample size to monitor rare AESI.

Appendix F Proposed post-authorization safety study mRNA-1345-P903

<p>Study short name and title: <i>RSV PASS-903 PASS</i></p> <p>Post- Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe</p>
<p>Rationale and study objectives:</p> <p>Although no important identified risks arose from the mRNA-1345-P301, the trial sample size and follow-up time provided insufficient power to monitor safety for rare events and long-term safety. Further, insufficient/missing information for special populations of interest who may have a different risk-benefit profile requires additional assessment. Therefore, a postmarketing observational studies using real-world data is proposed.</p> <p><u>Primary Objectives:</u></p> <ul style="list-style-type: none">• Describe the uptake of the mRNA-1345 vaccine and characterize mRNA-1345 vaccine recipients• Estimate incidence of pre-defined adverse events of special interest (AESI) among mRNA-1345 vaccine recipients• For signal detection, compare the observed incidence rates of pre-defined AESI among mRNA-1345 vaccine recipients with expected incidence rates of pre-defined AESI from a similar comparator cohort(s)• When a safety signal is detected based on pre-defined statistical threshold,<ul style="list-style-type: none">o Compare incidence rates of pre-defined AESI in the risk interval with incidence rates in the post-vaccination control interval in a self-controlled risk interval analysis. Oro Compare the observed incidence rates of pre-defined AESI among mRNA-1345 vaccine recipients with incidence rates of pre-defined AESI in a similar matched cohort who did not receive the mRNA-1345 vaccine <p><u>Secondary Objectives:</u></p> <p>Secondary objectives are identical to the primary, although focused on specific populations considered to have missing information, including but not limited to</p> <ul style="list-style-type: none">• Immunocompromised patients• Stratification by age group and sex• Patients who, at cohort entry, had recently received other selected vaccines to prevent diseases other than the mRNA-1345 vaccine• Patients with autoimmune or inflammatory disorders• Stratification by country where appropriate
<p>Study design:</p> <p>Post- Authorization Active Surveillance Safety Study with 2 phases: signal detection and signal evaluation</p>
<p>Study population:</p> <p>Recipients of mRNA-1345 will be identified in at least one full RSV season in the Europe. In the event of slow and low uptake of mRNA-1345, we will consider extending data accrual period to cover more RSV seasons. Historical comparator cohort(s) will be identified in the post COVID-19 era prior to availability of any RSV vaccines</p>
<p>Safety concerns addressed:</p> <ul style="list-style-type: none">• Acute disseminated encephalomyelitis

- Acute myocardial infarction (AMI)
- Anaphylaxis
- Atrial fibrillation
- Bell's palsy
- Guillain-Barré syndrome (GBS)
- Heart failure
- Idiopathic/Immune thrombocytopenia
- Myocarditis
- Non-AMI ischemic coronary artery disease
- Pericarditis
- Seizures
- Transverse myelitis

Data analysis

For signal detection, observed incidence rates among mRNA-1345 vaccinees, as well as observed-to-expected ratios and 95% confidence intervals (CI) will be estimated compared with the expected number as estimated in the comparator cohort for each AESI.

For signal evaluation using the SCRI design, the ratio between the incidence rate estimate in the risk period and the incidence rate estimate in the control period (incidence rate ratio) and the 95%CI will be computed using conditional Poisson regression.

Milestones*

Final Protocol: October 2024

- Interim report 1: November 2025
- Interim report 2: November 2026
- Interim report 3: November 2027
- Final report (including any signal evaluation activities as applicable): May 2028

* The proposed timelines are subject to change depending on the Marketing Authorization Application approval date and real-world database selection. The study period may be extended depending on vaccine uptake to allow for a reasonable sample size to monitor rare AESI.