ORIGINAL ARTICLE

Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) can cause substantial morbidity and mortality among older adults. An mRNA-based RSV vaccine, mRNA-1345, encoding the stabilized RSV prefusion F glycoprotein, is under clinical investigation.

METHODS

In this ongoing, randomized, double-blind, placebo-controlled, phase 2–3 trial, we randomly assigned, in a 1:1 ratio, adults 60 years of age or older to receive one dose of mRNA-1345 (50 μg) or placebo. The two primary efficacy end points were the prevention of RSV-associated lower respiratory tract disease with at least two signs or symptoms and with at least three signs or symptoms. A key secondary efficacy end point was the prevention of RSV-associated acute respiratory disease. Safety was also assessed.

RESULTS

Overall, 35,541 participants were assigned to receive the mRNA-1345 vaccine (17,793 participants) or placebo (17,748). The median follow-up was 112 days (range, 1 to 379). The primary analyses were conducted when at least 50% of the anticipated cases of RSV-associated lower respiratory tract disease had occurred. Vaccine efficacy was 83.7% (95.88% confidence interval [CI], 66.0 to 92.2) against RSV-associated lower respiratory tract disease with at least two signs or symptoms and 82.4% (96.36% CI, 34.8 to 95.3) against the disease with at least three signs or symptoms. Vaccine efficacy was 68.4% (95% CI, 50.9 to 79.7) against RSV-associated acute respiratory disease. Protection was observed against both RSV subtypes (A and B) and was generally consistent across subgroups defined according to age and coexisting conditions. Participants in the mRNA-1345 group had a higher incidence than those in the placebo group of solicited local adverse reactions (58.7% vs. 16.2%) and of systemic adverse reactions (47.7% vs. 32.9%); most reactions were mild to moderate in severity and were transient. Serious adverse events occurred in 2.8% of the participants in each trial group.

CONCLUSIONS

A single dose of the mRNA-1345 vaccine resulted in no evident safety concerns and led to a lower incidence of RSV-associated lower respiratory tract disease and of RSV-associated acute respiratory disease than placebo among adults 60 years of age or older. (Funded by Moderna; ConquerRSV ClinicalTrials.gov number, NCT05127434.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Wilson can be contacted at eleanor.wilson@modernatx.com or at Moderna, 200 Technology Sq., Cambridge, MA 02139.

*A list of the investigators in the ConquerRSV Study Group is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2023;389:2233-44.
DOI: 10.1056/NEJMoa2307079

A Quick Take is available at NEJM.org

The clinical spectrum of respiratory syncytial virus (RSV) disease ranges from mild upper respiratory symptoms to severe lower respiratory tract disease.[1,2] Older adults are at increased risk for RSV-related complications and death owing to age-related immunosenescence and a higher prevalence of underlying conditions.[3-11] In 2019, an estimated 5.2 million cases of RSV infection led to 470,000 hospitalizations and 33,000 in-hospital deaths among adults 60 years of age or older in high-income countries.[12] The annual incidence of RSV infection is estimated to range from 3 to 10% among older adults, depending on underlying risk factors,[13,14] with frail older persons also at risk for severe RSV infection.[10,15] Consequently, the societal burden and health care utilization that are associated with RSV infection in older adults are substantial.[16,17] As the worldwide population ages, the burden of RSV infection is expected to increase[18] — a situation that highlights the need for an RSV vaccine in this population.

Stabilization of the RSV-F glycoprotein in the prefusion (preF) conformation has advanced the development of RSV vaccines, given that the preF conformation is the primary target of potent RSV-neutralizing antibodies and is highly conserved across the two RSV subtypes (A and B).[19-23] Two recently approved vaccines confirm the success of a preF protein–based vaccination strategy for RSV infection.[24-28]

The mRNA-1345 vaccine (Moderna) uses the same preF antigen and is based on the mRNA vaccine platform that was previously shown to be effective in addressing the worldwide burden of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The mRNA-1345 vaccine is a lipid nanoparticle–encapsulated mRNA-based vaccine encoding the membrane-anchored RSV-F glycoprotein, derived from an RSV A strain, and stabilized in the preF conformation. A phase 1 clinical trial of this vaccine did not show safety concerns and showed immunogenicity in younger and older adults; the vaccine induced neutralizing antibodies against both the RSV A and B subtypes, which persisted through 6 months.[29] We initiated this efficacy trial, ConquerRSV, in November 2021 to assess the safety and efficacy of the mRNA-1345 vaccine in preventing a first episode of RSV-associated lower respiratory tract disease in adults 60 years of age or older. Here, we report the primary analyses of this ongoing trial.

Methods

Trial Design and Oversight

We are conducting this phase 2–3, randomized, double-blind, placebo-controlled trial in 22 countries. The trial was approved by the appropriate institutional review boards. Review of initial safety data from phase 2 of the trial by the data and safety monitoring board preceded the transition to phase 3. The trial was conducted according to the principles of the International Council for Harmonisation Technical Requirements for Registration of Pharmaceuticals for Human Use, the E6(R2) Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and all national, state, and local laws or regulations. All the participants provided written informed consent before enrollment. Safety data were periodically monitored by the independent data and safety monitoring board, whose members were aware of the trial-group assignments. The data and safety monitoring board determined when the vaccine met the prespecified success criteria for efficacy on the basis of prespecified case counts as described in the protocol (available with the full text of this article at NEJM.org).

The sponsor, Moderna, was responsible for overall trial design, trial-site selection, monitoring, and data analysis, which was facilitated by Pharmaceutical Product Development (a contract research organization). All the authors had access to the protocol, the statistical analysis plan, and the data and agreed with the decision of the sponsor to submit the manuscript for publication. The authors vouch for accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by medical writers who were funded by Moderna, in conjunction with several authors employed by Moderna. Additional information is provided the Supplementary Methods section of the Supplementary Appendix, available at NEJM.org.

Trial Participants

Eligible participants were adults 60 years of age or older. The trial included persons with stable chronic medical conditions and excluded per-

sons with certain immunocompromising conditions. A full list of the eligibility criteria is provided in the Supplementary Methods section.

TRIAL PROCEDURES

Randomization was performed in a 1:1 ratio with the use of an interactive response technology system. The vaccine (50 μg of mRNA-1345) or placebo (saline) was administered by injection into the deltoid muscle. The mRNA-1345 vaccine was shipped frozen and stored at clinical sites before preparation and injection (Fig. S1 in the Supplementary Appendix, and see the Supplementary Methods section).

Randomization was stratified according to participant age (60 to 74 years vs. ≥75 years) and certain risk factors (presence or absence of congestive heart failure, chronic obstructive pulmonary disease [COPD], or both). Phase 3 of the trial began after approximately 2000 participants had been enrolled in phase 2 and no safety concerns had been found by the data and safety monitoring board in the unblinded review of safety data from the first 400 or more participants through day 28. Subsequently, data from phases 2 and 3 of the trial were analyzed together.

Personnel who were aware of the trial-group assignments performed assessments of investigational product accountability and prepared and administered injections but were not involved in any other aspects of the trial. The investigators, trial staff, participants, site monitors, and sponsor personnel were unaware of the trial-group assignments. In this ongoing trial, we are following participants until 24 months after injection.

EFFICACY ASSESSMENTS

The two primary efficacy objectives were the evaluation of the efficacy of a single dose of the mRNA-1345 vaccine in preventing a first episode of RSV-associated lower respiratory tract disease with at least two lower respiratory signs or symptoms and with at least three lower respiratory signs or symptoms within 14 days to 12 months after injection (Table S1). A key secondary objective was the evaluation of the efficacy of a single dose of the mRNA-1345 vaccine in preventing a first episode of RSV-associated acute respiratory disease with at least one symptom within 14 days to 12 months after injection. Another secondary objective was the evaluation of the efficacy of the vaccine in preventing a first episode of RSV-associated lower respiratory tract disease according to RSV subtype (A or B). All the end points that were investigated and those discussed in this article are listed in Table S2.

RSV-associated lower respiratory tract disease was defined as RSV infection confirmed by reverse transcriptase–polymerase chain reaction (RT-PCR) and new or worsening lower respiratory symptoms for at least 24 hours or as confirmed RSV infection with radiologic evidence of pneumonia (Table S3). RSV-associated acute respiratory disease was defined as RT-PCR–confirmed RSV infection and at least one new or worsening respiratory symptom for at least 24 hours.

Active surveillance for RSV infection was conducted during the trial. Participants were prompted weekly to report potential RSV-associated respiratory or systemic symptoms. Unscheduled visits were arranged if participants reported any new or worsening symptoms. A nasopharyngeal swab was obtained and tested for RSV A, RSV B, and other respiratory pathogens with the use of RT-PCR (see the Supplementary Methods section).

SAFETY ASSESSMENTS

The primary safety objective was to evaluate the safety and side-effect profile of the mRNA-1345 vaccine. Participants used an electronic diary to report solicited local and systemic adverse reactions for 7 days after injection. Unsolicited adverse events were assessed through 28 days after injection. Data on medically attended adverse events, adverse events of special interest (thrombocytopenia, new-onset or worsening neurologic disease, anaphylaxis, and myocarditis or pericarditis) (Table S4), serious adverse events, and adverse events leading to withdrawal are being collected throughout the trial. The adverse events reported here are those that were not present before exposure to the trial vaccine or placebo or that were already present but worsened in intensity or frequency after exposure. Unsolicited adverse events were graded as mild, moderate, or severe. Additional information is provided in the Supplementary Methods section.

STATISTICAL ANALYSIS

On the basis of assumptions of vaccine efficacy and RSV-infection incidence, we planned for the trial to enroll approximately 37,000 participants.

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The primary analyses were to be conducted when at least 50% of the anticipated cases of RSV-associated lower respiratory tract disease had occurred. The two primary efficacy objectives were tested in hierarchical order of vaccine efficacy against RSV-associated lower respiratory tract disease with at least two lower respiratory signs or symptoms followed by vaccine efficacy against cases with at least three lower respiratory signs of symptoms. We determined that success would be met if the lower boundary of the two-sided confidence interval (alpha-adjusted) was more than 20%. Comparing the lower boundary of the alpha-adjusted confidence interval with the prespecified success criterion of 20% is equivalent to comparing the one-sided P value to the adjusted one-sided alpha (threshold) (see the Supplementary Methods section). The overall type I error was controlled at 2.5% (one-sided). The key secondary objective would be tested if the success criterion for the two primary objectives was met. Vaccine efficacy was calculated as 1−the hazard ratio (mRNA-1345 vs. placebo) × 100%. The confidence interval for vaccine efficacy was based on a stratified Cox proportional-hazards model in the per-protocol efficacy population, which included all the participants who had undergone randomization, received vaccine or placebo, completed at least one visit or surveillance contact 14 days after injection, and had no major protocol deviations that would affect the efficacy outcomes.

The current efficacy analysis was performed as planned when at least 43 cases of RSV-associated lower respiratory tract disease with at least two signs or symptoms and at least 16 cases with at least three signs or symptoms were observed. The primary and key secondary efficacy analyses were performed in the per-protocol efficacy analysis population. Subgroup analyses were performed according to age group, the presence or absence of at least one coexisting condition, race, frailty status, risk factors for congestive heart failure or COPD, and World Bank geographic region and income level. Safety analyses included all the participants who had undergone randomization and received the vaccine or placebo (safety analysis population). Summaries of solicited adverse reactions are based on the solicited safety analysis population, which included all the participants who contributed any data regarding solicited adverse reactions.

RESULTS

TRIAL POPULATION

From November 17, 2021, through October 31, 2022, a total of 35,541 participants underwent randomization; 17,793 participants were assigned to the mRNA-1345 group and 17,748 were assigned to the placebo group (Fig. S2 and Table S5). The safety analysis population included 17,734 participants in the mRNA-1345 group and 17,679 participants in the placebo group and the per-protocol efficacy population included 17,572 and 17,516 participants, respectively.

The demographic and other characteristics of the participants at baseline were balanced between the two groups (Table 1 and Table S6). The mean age of the participants at enrollment was 68.1 years, 49.0% were women, 36.1% were non-White, and 34.5% were Hispanic or Latino. One or more coexisting conditions were reported by 29.3% of the participants, with 1.1% reporting a history of congestive heart failure and 5.5% reporting a history of COPD. A total of 21.9% of the participants were assessed as vulnerable or frail, as defined according to the Edmonton Frailty score (see the Supplementary Methods section). Information on the representativeness of the trial participants as compared with the population affected by RSV infection is provided in Table S7.

The primary analyses were conducted when at least 50% of the anticipated cases of RSV-associated lower respiratory tract disease had occurred. As of the data-cutoff date (November 30, 2022), the median follow-up was 112 days (range, 1 to 379), with 7216 participants (20.4%) having been followed for at least 6 months.

VACCINE EFFICACY

The data and safety monitoring board met on December 22, 2022, and determined that the prespecified success criterion for efficacy (lower boundary of the alpha-adjusted confidence interval, >20%) was met for the two primary efficacy end points. For the primary analysis, 64 cases of RSV-associated lower respiratory tract disease with at least two signs or symptoms were confirmed (9 in the mRNA-1345 group and 55 in the placebo group); vaccine efficacy was 83.7% (95.88% CI, 66.0 to 92.2; one-sided P<0.001) (Table 2). Twenty cases of RSV-associated lower respiratory tract disease with at least three signs

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Safety Analysis Population).*

Characteristic	mRNA-1345 (N=17,734)	Placebo (N=17,679)	Total (N=35,413)
Age at enrollment			
Mean — yr	68.1±6.2	68.1±6.2	68.1±6.2
Median (range) — yr	67 (60–95)	67 (60–96)	67 (60–96)
Distribution — no. (%)			
60–69 yr	11,281 (63.6)	11,222 (63.5)	22,503 (63.5)
70–79 yr	5,474 (30.9)	5,460 (30.9)	10,934 (30.9)
≥80 yr	979 (5.5)	997 (5.6)	1,976 (5.6)
Female sex — no. (%)	8,658 (48.8)	8,711 (49.3)	17,369 (49.0)
Race or ethnic group — no. (%)†			
White	11,240 (63.4)	11,216 (63.4)	22,456 (63.4)
Black	2,203 (12.4)	2,158 (12.2)	4,361 (12.3)
Asian	1,540 (8.7)	1,529 (8.6)	3,069 (8.7)
Other	2,682 (15.1)	2,671 (15.1)	5,353 (15.1)
Unknown or not reported	69 (0.4)	105 (0.6)	174 (0.5)
Frailty status — no. (%)‡			
Fit	13,512 (76.2)	13,354 (75.5)	26,866 (75.9)
Vulnerable	2,828 (15.9)	2,899 (16.4)	5,727 (16.2)
Frail	997 (5.6)	1,017 (5.8)	2,014 (5.7)
Missing data	397 (2.2)	409 (2.3)	806 (2.3)
No. of coexisting conditions of interest — no. (%)§			
0	12,496 (70.5)	12,551 (71.0)	25,047 (70.7)
≥1	5,238 (29.5)	5,128 (29.0)	10,366 (29.3)
Risk factors for lower respiratory tract disease — no. (%)			
Present	1,218 (6.9)	1,230 (7.0)	2,448 (6.9)
Congestive heart failure	205 (1.2)	201 (1.1)	406 (1.1)
COPD	960 (5.4)	978 (5.5)	1,938 (5.5)
Congestive heart failure and COPD	53 (0.3)	51 (0.3)	104 (0.3)
Absent	16,516 (93.1)	16,449 (93.0)	32,965 (93.1)

* Plus–minus values are means ±SD. The safety analysis population included all the participants who had undergone randomization and received any trial injection. Numbers were based on the actual injection received. Data on age and risk factors were obtained from electronic case-report forms. Percentages may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease.

† Race and ethnic group were reported by the participant. Other included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, or multiple.

‡ Frailty status was based on the Edmonton Frailty scoring system and measured by means of the Edmonton Frail Scale across nine domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance.[30] Scores range from 0 to 17 points, with a score of 0 to 3 indicating fit, a score of 4 or 5 indicating vulnerable, and a score of 6 to 17 indicating frail.

§ Coexisting conditions of interest included advanced liver disease, advanced renal disease, asthma, chronic respiratory disease, congestive heart failure, COPD, and diabetes.

or symptoms were reported (3 in the mRNA-1345 group and 17 in the placebo group); vaccine efficacy was 82.4% (96.36% CI, 34.8 to 95.3; one-sided P=0.008) (Table 2).

For RSV-associated acute respiratory disease, 26 cases occurred in the mRNA-1345 group and 82 in the placebo group; vaccine efficacy was 68.4% (95% CI, 50.9 to 79.7) (Table S9). Similar results were obtained for analyses that included all the participants who had undergone random-

Table 2. Vaccine Efficacy against RSV-Associated Lower Respiratory Tract Disease with at Least Two or at Least Three Signs or Symptoms (Per-Protocol Efficacy Population).*

End Point	mRNA-1345		Placebo		Vaccine Efficacy (CI)†
	no. of participants	*no. of events*	*no. of participants*	*no. of events*	%
RSV-associated lower respiratory tract disease with ≥2 signs or symptoms‡					
Overall	17,572	9	17,516	55	83.7 (66.0 to 92.2)
RSV subtype					
RSV A	17,572	3	17,516	36	91.7 (73.0 to 97.4)
RSV B	17,572	6	17,516	19	68.5 (21.1 to 87.4)
Age group					
60–69 yr	11,168	8	11,118	33	76.0 (48.0 to 88.9)
70–79 yr	5,440	1	5,416	22	95.4 (65.9 to 99.4)
≥80 yr	964	0	982	0	NE (NE to NE)
RSV-associated lower respiratory tract disease with ≥3 signs or symptoms§					
Overall	17,572	3	17,516	17	82.4 (34.8 to 95.3)
RSV subtype					
RSV A	17,572	1	17,516	10	90.0 (22.0 to 98.7)
RSV B	17,572	2	17,516	7	71.5 (–37.0 to 94.1)
Age group					
60–69 yr	11,168	3	11,118	11	72.9 (2.8 to 92.4)
70–79 yr	5,440	0	5,416	6	100 (NE to 100)
≥80 yr	964	0	982	0	NE (NE to NE)

* Respiratory syncytial virus (RSV)–associated lower respiratory tract disease with at least two signs or symptoms or at least three signs or symptoms was based on the onset of eligible symptoms within a window of 14 days before or after the date that a positive result for RSV was obtained by reverse transcription–polymerase chain reaction. The time to the first episode of RSV-associated lower respiratory tract disease with at least two or at least three signs or symptoms was calculated as the case date (see the statistical analysis plan) minus the date of randomization plus 1. Data are from the per-protocol efficacy analysis population, which included all the participants who had undergone randomization, received the vaccine or placebo, completed at least one visit or surveillance contact 14 days after injection, and had no major protocol deviations affecting the efficacy outcomes as determined before database lock and unblinding. NE denotes not estimated.

† Vaccine efficacy was defined as 1 – the hazard ratio (mRNA-1345 vs. placebo) × 100%. The confidence interval in the analysis of vaccine efficacy was based on a stratified Cox proportional-hazards model with Efron's method of tie handling and with trial group as a fixed effect, with adjustment for stratification factors at randomization. In the overall analyses, the adjusted confidence interval was 95.88% for RSV-associated lower respiratory tract disease with at least two signs or symptoms and 96.36% for RSV-associated lower respiratory tract disease with at least three signs or symptoms. In the subgroup analyses, the 95% confidence interval was calculated with the use of the exact method (Poisson distribution) and with adjustment for person-years. Person-years were defined as the total years from the randomization date to the date of the earliest of the following events: RSV-associated lower respiratory tract disease with at least two or at least three signs or symptoms, RSV-associated acute respiratory disease, 12 months after injection, early discontinuation, unrelated death, or early RSV-associated acute respiratory disease or the data-cutoff date.

‡ Follow-up for RSV-associated lower respiratory tract disease with at least two symptoms was 6271.06 person-years in the mRNA-1345 group and 6253.55 person-years in the placebo group. The incidence rate (number of events ÷ 1000 person-years) was 1.44 events per 1000 person-years in the mRNA-1345 group and 8.80 events per 1000 person-years in the placebo group. The incidence rate was defined as the number of participants with a case divided by the number of participants at risk, with adjustment for person-years (total time at risk) in each trial group.

§ Follow-up for RSV-associated lower respiratory tract disease with at least three symptoms was 6272.38 person-years in the mRNA-1345 group and 6259.83 person-years in the placebo group. The incidence rate was 0.48 events per 1000 person-years in the mRNA-1345 group and 2.72 events per 1000 person-years in the placebo group.

ization (randomization set; analysis of efficacy starting from day 1) (Table S8). The cumulative incidence of RSV-associated lower respiratory tract disease with at least two and at least three signs or symptoms and of RSV-associated acute respiratory disease showed a steady increase

among placebo recipients, whereas the incidence among vaccine recipients remained low and stable throughout the observation period (median follow-up, 112 days; range, 15 to 379) (Fig. 1).

With regard to RSV subtypes, vaccine efficacy against RSV-associated lower respiratory tract disease with at least two and at least three signs or symptoms was 91.7% and 90.0%, respectively, for RSV A and 68.5% and 71.5%, respectively, for RSV B (Table 2). Vaccine efficacy was 78.5% against RSV-associated acute respiratory disease caused by RSV A and 51.7% against RSV-associated acute respiratory disease caused by RSV B.

The mRNA-1345 vaccine appeared to be efficacious against RSV-associated lower respiratory tract disease with at least two and at least three signs or symptoms and against RSV-associated acute respiratory disease in subgroups defined according to sex, age group, the presence or absence of at least one coexisting condition, race, frailty status, risk factors for congestive heart failure and COPD, and World Bank geographic region and income level (Table 2). No cases of RSV-associated lower respiratory tract disease were reported in adults 80 years of age or older. Among participants with RSV-associated lower respiratory tract disease, a lower incidence of fever and of shortness of breath was reported among mRNA-1345 recipients than among placebo recipients (Table S10).

SAFETY

Most of the solicited adverse reactions were mild to moderate, with an onset 1 to 2 days after injection and with resolution within 1 to 2 days after onset (Table S11). Solicited local adverse reactions were reported in 58.7% of the participants in the mRNA-1345 group and in 16.2% of those in the placebo group (Fig. 2); grade 3 events were reported in 3.2% and 1.7%, respectively. The most common solicited local adverse reaction was injection-site pain (in 56.3% of the participants in the mRNA-1345 group and in 13.7% of those in the placebo group). Solicited systemic adverse reactions were reported in 47.7% of the participants in the mRNA-1345 group and in 32.9% of those in the placebo group (Fig. 2 and Table S12); grade 3 or higher events were reported in 4.0% and 2.9%, respectively. The most common solicited systemic adverse reactions were fatigue, headache, myalgia, and arthralgia. In the mRNA-1345 group, the incidence of solicited adverse reactions decreased with age and was higher among women than among men, higher among participants of White or Asian race than among those of Black race, and higher among participants who identified as not Hispanic or Latino than among those who identified as Hispanic or Latino.

The frequency of unsolicited adverse events, including severe adverse events, serious adverse events (including fatal events), adverse events of special interest, medically attended adverse events, and adverse events leading to trial discontinuation reported up to the data-cutoff date, was balanced between the two groups (Table S13). Unsolicited adverse events within 28 days after injection were reported in 20.4% of the participants in the mRNA-1345 group and in 18.8% of those in the placebo group; these events were considered to be related to the trial injection in 5.8% and 4.5% of the participants, respectively. Numerical differences observed in the incidence of unsolicited adverse events were attributable to solicited adverse reactions that persisted beyond day 7 or other reactogenicity events. Up to the data-cutoff date, serious adverse events regardless of causality were reported in 2.8% of the participants in each group; serious adverse events that were assessed by the investigator as being related to the trial injection were reported in 4 participants (<0.1%) in each group.

The most commonly reported serious adverse events up to 28 days according to system organ class were events in the infections and infestations class (in 0.1% of the participants in the mRNA-1345 group and in <0.1% of those in the placebo group) (Table S14). In an assessment by an independent cardiac adjudication committee, there were no cases of acute myocarditis and two cases of acute pericarditis, each of which occurred more than 42 days after injection and was considered by the investigator to be unrelated to the trial injection (see the Supplementary Methods section). Up to the data-cutoff date, there were no cases of acute disseminated encephalomyelitis or Guillain–Barré syndrome in either group. No other safety concerns were identified on review of the adverse events of special interest up to the data-cutoff date. Trial discontinuation due to adverse events was balanced between the two groups (in 0.2% of the participants) up to the data-cutoff date. Fatal

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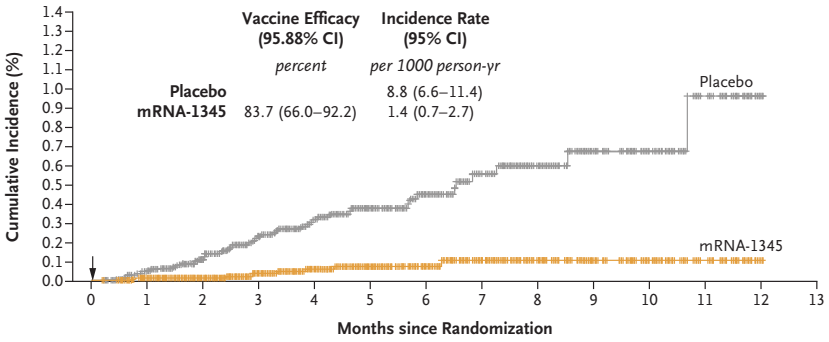
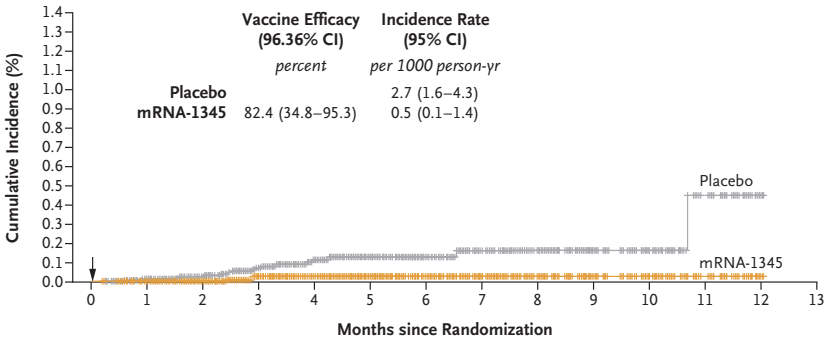
A RSV-Associated Lower Respiratory Tract Disease with ≥2 Signs or Symptoms



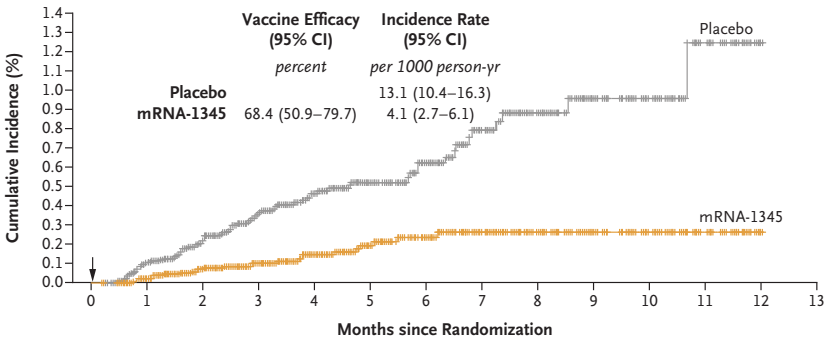
No. at Risk													
Placebo	17,516	17,433	14,735	11,275	7866	5314	3657	2384	1682	1058	629	267	43	0
mRNA-1345	17,572	17,514	14,783	11,293	7892	5333	3648	2389	1694	1062	645	273	47	0

B RSV-Associated Lower Respiratory Tract Disease with ≥3 Signs or Symptoms



No. at Risk													
Placebo	17,516	17,439	14,745	11,292	7877	5322	3663	2388	1686	1063	634	268	44	0
mRNA-1345	17,572	17,516	14,785	11,293	7894	5335	3650	2391	1696	1063	646	274	47	0

C RSV-Associated Acute Respiratory Disease



No. at Risk													
Placebo	17,516	17,423	14,721	11,269	7863	5313	3656	2381	1680	1056	628	266	43	0
mRNA-1345	17,572	17,512	14,774	11,289	7886	5328	3643	2388	1693	1062	645	273	47	0

Figure 1 (facing page). Cumulative Incidence of RSV-Associated Lower Respiratory Tract Disease and RSV-Associated Acute Respiratory Disease (Per-Protocol Efficacy Population).

Shown is the cumulative incidence of respiratory syncytial virus (RSV)–associated lower respiratory tract disease with at least two signs or symptoms (Panel A) or at least three signs or symptoms (Panel B) and RSV-associated acute respiratory disease (Panel C). Only first episodes occurring between 14 days after injection and up to 12 months after injection were included in the analysis (per-protocol efficacy population). The per-protocol efficacy population included all the participants who had undergone randomization, received the vaccine or placebo, completed at least one visit or surveillance contact 14 days after injection, and had no major protocol deviation that would affect the efficacy outcomes. In each panel, the arrow indicates day 1, when the injection was administered. Vaccine efficacy was defined as 1 – the hazard ratio (mRNA-1345 vs. placebo) × 100%, and the confidence interval was based on a stratified Cox proportional-hazards model with Efron's method of tie handling and with the vaccination group as a fixed effect, with adjustment for stratification factors at randomization. The cumulative incidence based on the Kaplan–Meier method. The incidence rate was defined as the number of participants with a case, divided by the number of participants at risk, with adjustment for person-years. Tick marks indicate censored data.

events were reported in 0.1% of the participants in each group up to the data-cutoff date; none of these deaths were reported by the investigator as being related to the trial injection.

DISCUSSION

The clinical spectrum of RSV disease in older adults ranges from milder upper airway disease to severe RSV-associated lower respiratory tract disease.[1,2] RSV-associated lower respiratory tract disease, particularly in persons with underlying medical conditions, can lead to hospitalization or death.[3,31,32] To capture this clinical spectrum, the efficacy end points in this trial included both RSV-associated lower respiratory tract disease (with at least two or at least three prespecified signs or symptoms of lower respiratory tract disease; i.e., severe disease) and RSV-associated acute respiratory disease (with at least one prespecified sign or symptom; i.e., all RSV disease).

In this international, phase 2–3 trial involving adults 60 years of age or older, a single dose of the mRNA-1345 vaccine showed 83.7% efficacy against RSV-associated lower respiratory tract disease with at least two signs or symptoms, 82.4% efficacy against RSV-associated lower respiratory tract disease with at least three signs or symptoms, and 68.4% against RSV-associated acute respiratory disease. On the basis of the lower boundary of the confidence intervals (alpha-adjusted confidence interval for the primary efficacy end points and 95% confidence intervals for the key secondary efficacy end point) exceeding 20%, the trial met the prespecified success criteria for the primary and key secondary efficacy objectives. Protection was observed against both the RSV A and B subtypes, which may circulate simultaneously or as a dominant subtype during a season.[33,34]

The mRNA-1345 vaccine was 88.4% efficacious against RSV-associated lower respiratory tract disease with at least two signs or symptoms among participants with at least one coexisting condition. Although no cases were reported among adults 80 years of age or older in the current analysis, efficacy was maintained with increasing age (76.0% among adults 60 to 69 years of age and 95.4% among those 70 to 79 years of age). The vaccine also showed efficacy in preventing the clinical spectrum of RSV disease regardless of race, ethnic group, sex, or World Bank geographic region and income level. The vaccine may prevent severe outcomes that contribute to substantial societal and health care burdens.

There was an increase in the cumulative incidence of RSV infection in the placebo group, whereas the incidence in the mRNA-1345 group remained low and stable over the observation period. For RSV-associated lower respiratory tract disease with at least two signs or symptoms, this separation in cumulative incidence was observed from 14 days after injection, a finding consistent with a rapid immune response, and was sustained over the observation period. A similar pattern was observed for RSV-associated lower respiratory tract disease with at least three signs or symptoms and for RSV-associated acute respiratory disease. The time to the onset of protection is supported by the results of the phase 1 study, in which peak RSV neutralizing

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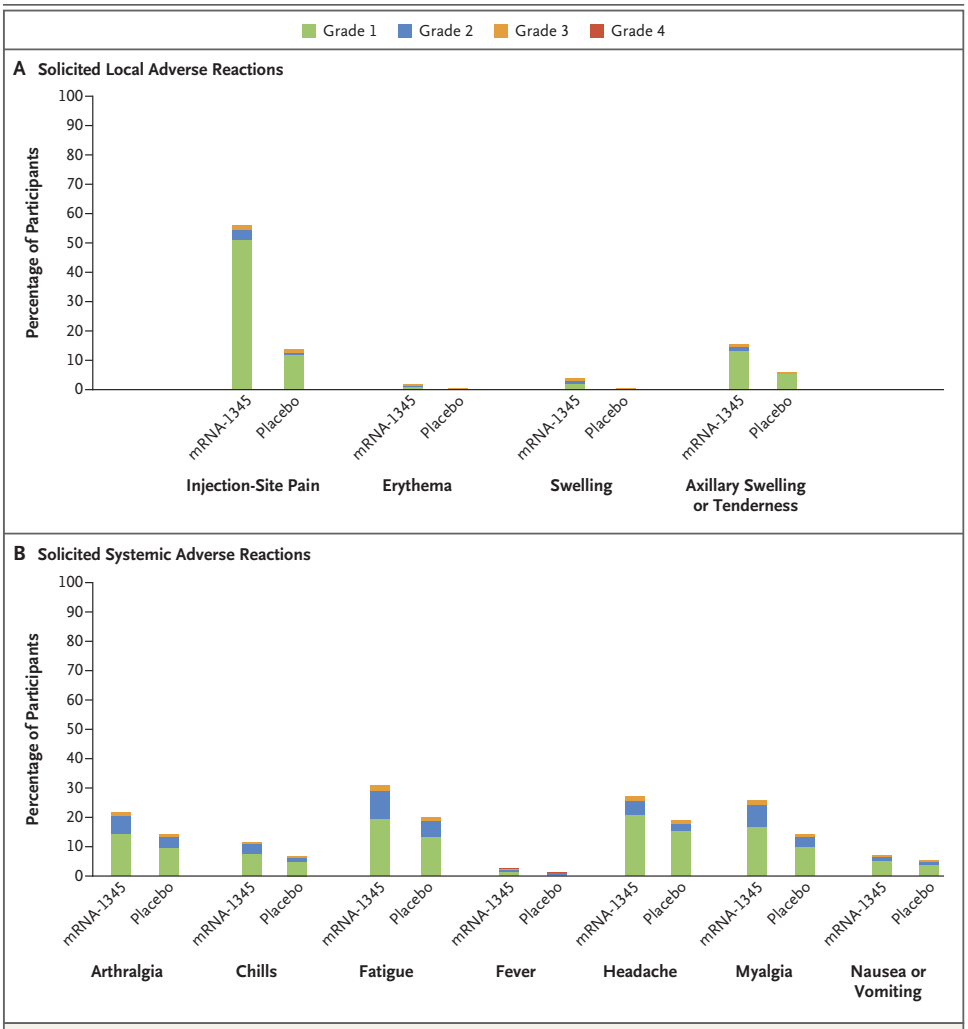

Figure 2. Solicited Local and Systemic Adverse Reactions.

Shown is the percentage of participants who had a local (Panel A) or systemic (Panel B) adverse reaction within 7 days after injection. No grade 4 solicited local adverse reactions were reported. Among participants with solicited systemic adverse reactions, grade 4 fever was reported in 0.2% of the participants in each group.

antibody responses were observed 1 month after injection and persisted through 6 months.[29] The point estimate of efficacy against RSV B infection was lower than that against RSV A infection across all the end points. Whether this result could be due to the biologic characteristics of RSV vaccine protection is unclear. This observation has been reported in trials of other RSV vaccines.[25,28]

The safety profile of the mRNA-1345 vaccine in this trial was consistent with that observed in the phase 1 study[29] and in a study of the variant-specific, mRNA-1273 booster (Moderna) for protection against SARS-CoV-2 infection in older adults.[35] The incidence and severity of solicited adverse reactions were higher in the mRNA-1345 group than in the placebo group. However, the majority of adverse reactions were mild to moderate and transient.

Enrollment of a diverse population across age

groups and risk factors, including frailty and coexisting conditions, highlights that the protection we observed is likely to be generalizable. Limitations of this trial include low case numbers in some subgroups (participants ≥80 years of age, frail adults, and participants with RSV B infection) and the exclusion of persons with certain immunocompromising conditions. In this ongoing trial, the accumulation of additional cases of RSV-associated acute respiratory disease and lower respiratory tract disease, as well as immunogenicity analysis, may allow for additional estimates of vaccine efficacy in subgroups and may also provide data on hospitalizations due to RSV infection. Further follow-up to determine the duration of protection afforded by the vaccine is ongoing, and the appropriateness of and timing of a booster dose is under evaluation.

This phase 2–3 efficacy trial showed that a single 50-μg dose of the mRNA-1345 vaccine in adults 60 years of age or older was efficacious against a spectrum of RSV-confirmed respiratory disease. No safety concerns were evident.

Parts of this research were carried out at the U.K. National Institute for Health and Care Research (NIHR) Newcastle Clinical Research Facility. The views expressed in this article are those of the authors and not necessarily those of the NIHR or the U.K. Department of Health and Social Care.

Supported by Moderna.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participants in the trial and their families; the members of the data and safety monitoring board; Beverly Francis, Ph.D., for helpful discussions; and Jared Mackenzie, Ph.D., Joyce Lee, Ph.D., Meenu Minhas, Ph.D., and Louansha Nandlal, Ph.D., of MEDiSTRAVA, for medical writing and editorial assistance with an earlier version of the manuscript, funded by Moderna and under the direction of the authors, in accordance with Good Publication Practice guidelines.

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Supplementary Appendix

Supplement to: Wilson E, Goswami J, Baqui AH, et al. Efficacy and safety of an mRNA-based RSV PreF vaccine in older adults. N Engl J Med 2023;389:2233-44. DOI: 10.1056/NEJMoa2307079

This appendix has been provided by the authors to give readers additional information about the work.

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Supplementary Methods

Trial Design and Oversight

Moderna was responsible for the overall trial design, site selection, monitoring, and data analysis, which was facilitated by Pharmaceutical Product Development (PPD; North Carolina, USA). All authors had access to the protocol, statistical analysis plan, and collected data, and agreed to submit the manuscript for publication. Medical writers who were funded by the sponsor assisted with the development of the manuscript. The trial is ongoing, and the investigators remain unaware of participant level data. Designated team members within Moderna have unblinded access to the data, to facilitate interface with the regulatory agencies and the data and safety monitoring board; all other trial staff and participants remain unaware of the treatment assignments.

Eligibility Criteria

Inclusion Criteria

All participants were eligible to be included in the study only if all the following criteria applied:

1. Adults ≥60 years of age who were primarily responsible for self-care and activities of daily living. Participants may have had one or more chronic medical diagnoses (including chronic heart failure [including heart failure with preserved ejection fraction] and chronic obstructive pulmonary disease [COPD]), but should have been medically stable as assessed by the following criteria:
    - Absence of changes in medical therapy within 1 month due to treatment failure or toxicity
    - Absence of medical events qualifying as serious adverse events (SAEs) within 1 month of the planned study injection on day 1
    - Absence of known, current, and life-limiting diagnoses which could continue for the duration of the primary efficacy period (12 months from study injection on day 1)

and which, in the opinion of the investigator, would make completion of the protocol unlikely

2. Body mass index ≥18 kg/m^2 to ≤35 kg/m^2
3. Willing and able (on both a physical and cognitive basis) to give informed consent prior to study enrollment
4. Able to comply with study requirements

Exclusion Criteria

Participants were excluded from the study if any of the following criteria applied:

1. Participation in another clinical research study where participant had received an investigational product (drug/biologic/device, with the exception of investigational respiratory syncytial virus products) within 6 months before the planned date of the day 1 study injection. Current participation in another RSV investigational trial was exclusionary
2. History of a diagnosis or condition that, in the judgment of the investigator, was clinically unstable or may have affected participant safety, assessment of safety endpoint, assessment of immune response, or adherence to study procedures. Clinically unstable was defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to screening and included ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition
3. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease

   Note: Human immunodeficiency virus (HIV)-positive participants with CD4 count ≥350 cells/mm^3 and an undetectable HIV viral load within the past year (low-level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy) as determined from participant's medical records, were permitted

Note: To clarify, participants with stable autoimmune diseases that did not require systemic immunosuppressants (per Exclusion Criterion #9) were permitted

4. Dermatologic conditions that could affect local solicited AR assessments (e.g., tattoos, psoriasis patches affecting skin over the deltoid areas)
5. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mRNA-1345 vaccine or any components of the mRNA-1345 vaccine
6. Reported history of bleeding disorder that was considered a contraindication to intramuscular (IM) injection or phlebotomy
7. History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome within 6 weeks of any prior influenza immunization
8. Received or plans 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. Non-study vaccination(s) should not be delayed
9. 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. An immunosuppressant dose of glucocorticoid was defined as a systemic dose ≥10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids was permitted
10. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the study injection or during the study
11. Acute disease at the time of enrollment (defined as the presence of moderate or severe illness with or without fever, or an oral temperature ≥37.8°C (100.0°F) on the planned day of vaccine administration)
12. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results

13. Known history of poorly controlled hypertension (per determination of the investigator), or systolic blood pressure >160 mmHg at the screening or baseline (day 1) visit
14. Known history of hypotension, or systolic blood pressure <85 mmHg at the screening or baseline (day 1) visit
15. Diastolic blood pressure >90 mmHg at the screening or baseline (day 1) visit
16. Known uncontrolled disorder of coagulation

    Note: Participants receiving aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin for cardiovascular prophylaxis or prophylaxis of thromboembolic disease or stroke in the setting of atrial fibrillation and under good control were NOT excluded
17. History of myocarditis, pericarditis, or myopericarditis within 2 months prior to screening. Participants who have not returned to baseline after their convalescent period were also excluded
18. Donated ≥450 mL of blood products <14 days prior to screening
19. Study personnel or immediate family member or household member of study personnel

Participants with LRTD Risk Factors and Comorbidities of Interest

Individuals with Comorbidities

Comorbidities of interest included COPD, asthma, chronic respiratory or pulmonary disease, diabetes, CHF, advanced liver disease, or advanced renal disease. Chronic respiratory disease included chronic pulmonary fibrosis (idiopathic and otherwise), restrictive lung disease, asbestosis, bronchiectasis, cystic fibrosis, pulmonary hypertension, sarcoidosis, and history of tuberculosis.

Individuals with Frailty

Frailty was measured by Edmonton Frail Scale across nine domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and

functional performance [1]. Using the 0- to 17-point scale, participants were categorized as fit (0–3), vulnerable (4–5), or frail (6–17). Frailty status was assessed at baseline, 12 months, and 24 months.

Investigational Product

The mRNA-1345 vaccine is a lipid nanoparticle (LNP) dispersion of mRNA sequences encoding the membrane-anchored RSV fusion glycoprotein (derived from an RSV-A strain (RSV-A A2 strain) stabilized in the prefusion conformation, formulated in LNPs composed of four lipids (one proprietary and three commercially available): the proprietary ionizable lipid heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight of 2000 g/mol.

For the phase 2 segment of the study, the mRNA-1345 vaccine was provided as a sterile liquid for injection and was a white to off-white dispersion, at a concentration of 0.4 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 8.6 mM sodium acetate at pH 7.5. For the phase 3 segment of the study, mRNA-1345 vaccine was provided as in the phase 2 segment, but at a concentration of 0.1 mg/mL in 20 mM Tris containing 87 mg/mL sucrose and 2.2 mM sodium acetate at pH 7.5. The placebo was 0.9% sodium chloride (normal saline) injection. mRNA-1345 or placebo was administered as a 0.5-mL single IM injection on day 1 to participants in both phase 2 and phase 3 segments of the study, according to the study protocol.

The product was shipped frozen, and then either remained frozen (-25 – -15°C) (Phase 2) or was thawed in a refrigerator at 2-8°C (phase 3) until the day of administration. Prior to administration, it was equilibrated at room temperature for 15 minutes, the dose prepared, and administered within 8 hours of preparation.

Safety Assessments

Grading for solicited ARs was based on grading scales modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials.

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life threatening)
Local					
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever >24 hours, or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25–50 mm/ 2.5–5 cm	51–100 mm/ 5.1–10 cm	>100 mm/ >10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	<25 mm/ <2.5 cm	25–50 mm/ 2.5–5 cm	51–100 mm/ 5.1–10 cm	>100 mm/ >10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter pain reliever >24 hours, or some interference with activity	Any use of prescription pain reliever or prevents daily activity	Emergency room visit or hospitalization
Systemic					
Headache	None	No Interference with activity	Repeated use of over-the-counter pain reliever >24 hours, or some interference	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization

			with activity		
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/ vomiting	None	No interference with activity or 1–2 episodes/24 hours	Some interference with activity or >2 episodes/ 24 hours	Prevents daily activity; requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral temperature)	<38.0°C <100.4° F	38.0°C–38.4°C/100.4°F–101.1°F	38.5°C–38.9°C/101.2°F–102.0°F	39.0°C–40.0°C/102.1°F–104.0°F	>40.0°C/>104.0°F

AE, adverse event; eCRF, electronic case report form

Solicited local ARs were injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the side of the injection. Solicited systemic ARs were headache, fatigue, myalgia (muscle aches all over body), arthralgia (aches in several joints), nausea/vomiting, chills, and fever. All solicited ARs were considered causally related to injection. Numerical severity grading is defined above. Solicited ARs that continued beyond 7 days after study injection were captured in the eDiary until no longer reported, not to exceed 28 days, and were reviewed by the investigator. Solicited ARs that met

criteria for an SAE or persisted beyond day 7 were also programmatically summarized as adverse events (AEs).

All unsolicited AEs were collected through 28 days after injection. The intensity of an unsolicited AE was graded as mild, moderate, or severe, and causality was reported as related or not related per investigator assessment.

Severity of unsolicited AEs was determined by the investigator based on medical judgment and defined as mild (events not interfering with the participant's daily activities), moderate (events causing some interference with the participant's daily activities and requiring limited or no medical intervention), or severe (events preventing the participant's daily activity and requiring intensive therapeutic intervention).

Safety assessments included monitoring and recording of the following for each participant:

- Solicited local and systemic adverse reactions (ARs) that occurred during the 7 days following the study injection (i.e., the day of injection and 6 subsequent days)
- Solicited ARs were recorded daily using eDiaries
- Unsolicited AEs observed or reported during the 28 days following the study injection (i.e., the day of injection and 27 subsequent days)
- AEs leading to discontinuation from study participation from day 1 through end of study (EOS) or withdrawal from the study
- Medically attended adverse event (MAAEs) from day 1 through EOS or withdrawal from the study
- Adverse event of special interests (AESIs) from day 1 through EOS or withdrawal from the study
- SAEs from day 1 through EOS or withdrawal from the study
- Vital sign measurements

- Physical examination findings
- Concomitant medications and non-study vaccinations

Due to the very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with COVID-19 vaccines, including mRNA COVID-19 vaccines, the study protocol specifies myocarditis and pericarditis as AESIs and defines these events based on the CDC working case definitions.[2] Any case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis was reported as an AESI by the investigator. The Cardiac Event Adjudication Committee (CEAC), a blinded and independent group of cardiologists, reviewed investigator-suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they met the CDC criteria.[2] The CEAC reviewed the data package for each reported event including the clinical history, laboratory testing, imaging findings, and reports of any consultations obtained; the CEAC did not adjudicate causality.[2] The CEAC determined if any reported event met the CDC criteria for a "probable" or "confirmed" event. Analyzing myocarditis and pericarditis within 42 days post vaccination is supported by temporal associations reported from experience with other vaccines, including COVID-19 vaccines.[2-6]

Laboratory Analyses

Evaluation of RSV Infection and Other Respiratory Pathogens

For the evaluation of RSV and other respiratory pathogens, nasopharyngeal swabs were tested using a US Food and Drug Administration (FDA)-cleared and CE-marked *in vitro* diagnostic multiplexed reverse transcriptase–polymerase chain reaction (RT-PCR) test; GenMark ePlex® Respirator Panel (RP1). This assay is a cartridge-based closed system that is run on the ePlex® system. The assay detects 17 different viruses and bacteria associated with respiratory tract infection (viruses: adenovirus[7], coronavirus [229E, HKU1, NL63, OC43], human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A/H1, influenza A/H12009, influenza A/H3, influenza B, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4,

RSV-A, and RSV-B; bacteria: *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*). Assay result readouts are reported as negative or positive for each pathogen.

Evaluation of SARS CoV2

For the evaluation of SARS-CoV-2 genomic RNA, a lab-developed (LDT) real-time (TaqPath) RT-PCR assay was used. In this assay, oligonucleotide primers hybridize to the ssRNA genome and allow RNA amplification of a short region in the presence of thermostable DNA polymerase (Taq) enzyme and dNTPs. A dual-labeled oligonucleotide probe that is complementary to an internal sequence of the amplification product is also present in the RT-PCR reaction mixture. The 5' exonucleolytic activity of Taq cleaves the FAM at the 5′ end of the dual-labeled probe, thus releasing it from the effects of a fluorescence-quenching molecule (e.g., Black Hole Quencher 1) at the 3′ end of the probe. Additionally, oligonucleotide primers and a TaqMan probe for PCR detection of an internal extraction/amplification control are also present in the SARS-CoV-2 RT-PCR reaction mix for the simultaneous detection of internal extraction/amplification control DNA in a multiplex reaction for each sample. Fluorescence intensity for both SARS-CoV-2 amplification and internal control amplification is measured in individual wells during each of the 40 amplification cycles and a sample is considered positive when the signal intensity exceeds the baseline threshold value.

Sample Size Determination

This phase 2/3 study planned to randomize approximately 37,000 participants (1:1 randomization ratio) to the mRNA-1345 or the placebo groups. Therefore, approximately 18,500 participants will be randomized to each group.

Power Calculation for Primary and Key Secondary Efficacy Endpoints

The sample size was driven by the total number of cases to demonstrate vaccine efficacy (mRNA-1345 vs. placebo) to prevent protocol-defined RSV lower respiratory tract disease (RSV-LRTD).

Under the assumption of proportional hazards and with 1:1 randomization of mRNA-1345 and placebo, a total of 86 RSV-LRTD cases with ≥2 symptoms in the PPE Set will provide at least 90% power to demonstrate vaccine efficacy, i.e., rejecting the null hypothesis H^1_0: vaccine efficacy ≤20%, with two interim analyses (IAs) at 50% and 85% of the target total number of cases using the Pocock boundary for efficacy and a log-rank test statistic with a one-sided type I error rate of 2.5%. The success criterion was set to a lower bound of 20% in agreement with regulatory agencies.

The total number of cases pertains to the PPE Set within the period of 14 days post-injection up to 12 months post-injection. There were 2 planned IAs for this endpoint, which were performed when at least 43 (50%) and at least 74 (85%) RSV-LRTD cases with ≥2 symptoms within the target total number of 86 cases had been observed. Approximately 37,000 participants would provide approximately 90% power, assuming a target vaccine efficacy of 65%, an attack rate of 0.5% in the placebo arm, and a dropout rate ~ 10%. In addition, the sample size, 37,000 participants and a total of 32 RSV-LRTD cases with ≥3 symptoms in the PPE Set, provided approximately 90% power to demonstrate vaccine efficacy, i.e., rejecting the null hypothesis H^2_0: vaccine efficacy ≤20%, with 2 IAs at 50% and 85% of the target total number of cases using the Pocock boundary for efficacy and a log-rank test statistic with a 1-sided type I error rate of 2.5%. This sample size calculation was based on the following assumptions: a target vaccine efficacy of 80%, an attack rate of 0.2% in the placebo arm, and a dropout rate ~ 10%.

The type I error rate will be adjusted using the Pocock boundary. If the IAs were conducted exactly at 50% and 85% of total targeted cases, the nominal 1-sided type I error rate was 1.55%, 1.18%, and 0.91% at IA1, IA2 and primary analysis, respectively.

It was expected the IA 1 for both primary endpoints were conducted at the same time, i.e., IA 1 was conducted when at least 43 RT-PCR confirmed protocol-defined RSV-LRTD cases with ≥2 symptoms and at least 16 RT-PCR confirmed protocol-defined RSV-LRTD cases with ≥3 symptoms were observed in the PPE Set. Similarly, IA 2 for both primary endpoints were conducted at the same time.

Cases was quantified (without unblinding) on an ongoing basis. If the targeted number of cases are not met in the original 37,000 participants, an extension of enrolment would be pursued. As the sample size recalculation will be performed without unblinding the study, no adjustment of the alpha for the primary analysis will be performed.

For the key secondary endpoints, with approximately 18,500 participants per group, provided power of demonstrating vaccine efficacy based on an attack rate of 2.0% for a first episode of RSV-ARD, under different scenarios of true vaccine efficacy and vaccine efficacy criteria at a 1-sided alpha level of 2.5% considering a ~10% ineligibility rate in the PPE Set. The study had at least 95% power to detect a vaccine efficacy = 50% against H^3_0: vaccine efficacy ≤ 20% to prevent a first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection and approximately 90% power to detect a vaccine efficacy = 50% against H^3_0.

Statistical Analyses

The Per-Protocol Efficacy (PPE) Set is the primary population for the primary efficacy analysis in this study. The PPE Set includes participants who receive the assigned investigational product dose according to protocol, and excludes participants who have major protocol deviations, which may impact the participants' immunogenicity response and will further impact the vaccine efficacy endpoints. The protocol deviations were reviewed and determined by blinded team prior to data base lock to avoid bias. Vaccine efficacy estimated based on the PPE Set would provide more accurate description of vaccine efficacy, as it is based on fully compliant participants, with surveillance beginning after vaccination and is expected to have achieved adequate immune response.

Vaccine efficacy was defined as the percent reduction in the hazard, which is calculated as 1 minus the hazard ratio (HR, mRNA-1345 vs. placebo) x 100%. Vaccine efficacy (i.e. 1-HR) and the confidence interval were estimated by a stratified Cox proportional hazard model with study vaccine

group (mRNA-1345 or Placebo) as a fixed effect, adjusting for the same stratification factors used for randomization. The Efron's method was used to handle ties.

The study was powered and designed to conduct a primary analysis when at least 86 RSV-LRTD cases with ≥2 symptoms and at least 32 RSV-LRTD cases with ≥3 symptoms in the PPE Set were observed. Two IAs were planned when at least 50% (at least 43 cases of RSV LRTD with ≥2 symptoms and at least 16 cases with ≥3 symptoms) and at least 85% (at least 74 cases of RSV-LRTD with ≥2 symptoms and at least 28 cases ≥3 symptoms) of the total target RSV-LRTD cases (for each of the two primary endpoints) were observed. The overall type I error rate for the primary efficacy endpoints at the IAs and the primary analysis was strictly controlled at 2.5% (one-sided) based on the Lan-Demets Pocock approximation spending function.

Statistical significance of the primary efficacy endpoints could be achieved at either of the IAs or at the primary analysis. The first primary objective would be met if the two-sided alpha–adjusted confidence interval (CI) for vaccine efficacy of mRNA-1345 compared with placebo to prevent protocol-defined RSV-LRTD with ≥2 symptoms rules out 20% at either of the IAs or at the primary analysis. Subsequently, the second primary efficacy objective would be met if the two-sided alpha–adjusted CI of the vaccine efficacy of mRNA-1345 compared with placebo to prevent protocol-defined RSV-LRTD with ≥3 symptoms rules out 20% at either of the IAs or at the primary analysis after the first primary objective was met. Once the primary efficacy endpoints achieved statistical significance at either one of the IAs, the analysis is automatically considered as primary analysis of this study, and any other subsequential analysis is considered supplemental.

A sequential/hierarchical testing procedure was used to control type I error rate strictly at 2.5% (1-sided) over the primary efficacy endpoints, key secondary efficacy endpoints, and other selected secondary efficacy endpoints . After statistical significance of both primary efficacy endpoints have been achieved, the key secondary efficacy endpoint of ARD would be tested sequentially. The key secondary objective would be met if the two-sided 95% CI of the vaccine

efficacy of mRNA-1345 compared with placebo to prevent a first episode of RSV-ARD rules out 20%, given both primary efficacy endpoints were previously met. The other key secondary efficacy endpoint and selected secondary efficacy endpoints in the multiplicity will be tested at the planned analysis following the predefined order in the fixed-sequence hierarchical testing process. The 95% CIs of vaccine efficacy would be provided according to the pre-defined success criteria. No further testing will be performed once the sequence breaks, that is, further testing stops as soon as an endpoint in the sequence fails to show statistical significance against the null hypothesis.

At the primary analysis with a median follow-up time of approximately 3.7 months after injection, based on a total of 64 RSV-LRTD with ≥2 symptoms cases, the one-sided p value was <0.0001 and the lower bound (LB) of the 2-sided 95.88% CI (alpha adjusted) was 66.0%. The LB of alpha adjusted CI exceeded the prespecified success criterion of 20%. Comparing the lower bound of the alpha adjusted CI to the prespecified success criterion of 20% is equivalent to comparing the 1-sided p value to the adjusted 1-sided alpha (threshold). The one-sided p-value was compared to a one-sided alpha of 0.0206 based on 74.4% information of the target total number (64/86) using the Lan-Demets Pocock approximation spending function. Having successfully established vaccine efficacy against RSV-LRTD with ≥2 symptoms vaccine efficacy was next tested against RSV-LRTD with ≥3 symptoms following prespecified multiplicity testing strategy based on a total of 20 RSV-LRTD with ≥3 symptoms cases, the one-sided p value was 0.0078 and the LB of the 2-sided 96.36% CI (alpha adjusted) was 34.8%. The LB of alpha adjusted CI exceeded the prespecified success criterion of 20%, the one-sided p-value was compared to a one-sided alpha of 1.82% based on 62.5% information of the target total number (20/32) using the Lan-Demets Pocock approximation. Therefore, the pre-specified statistical criteria for study success on both primary endpoints were demonstrated, and any subsequent analysis for both primary endpoints would be considered as supplementary in nature.

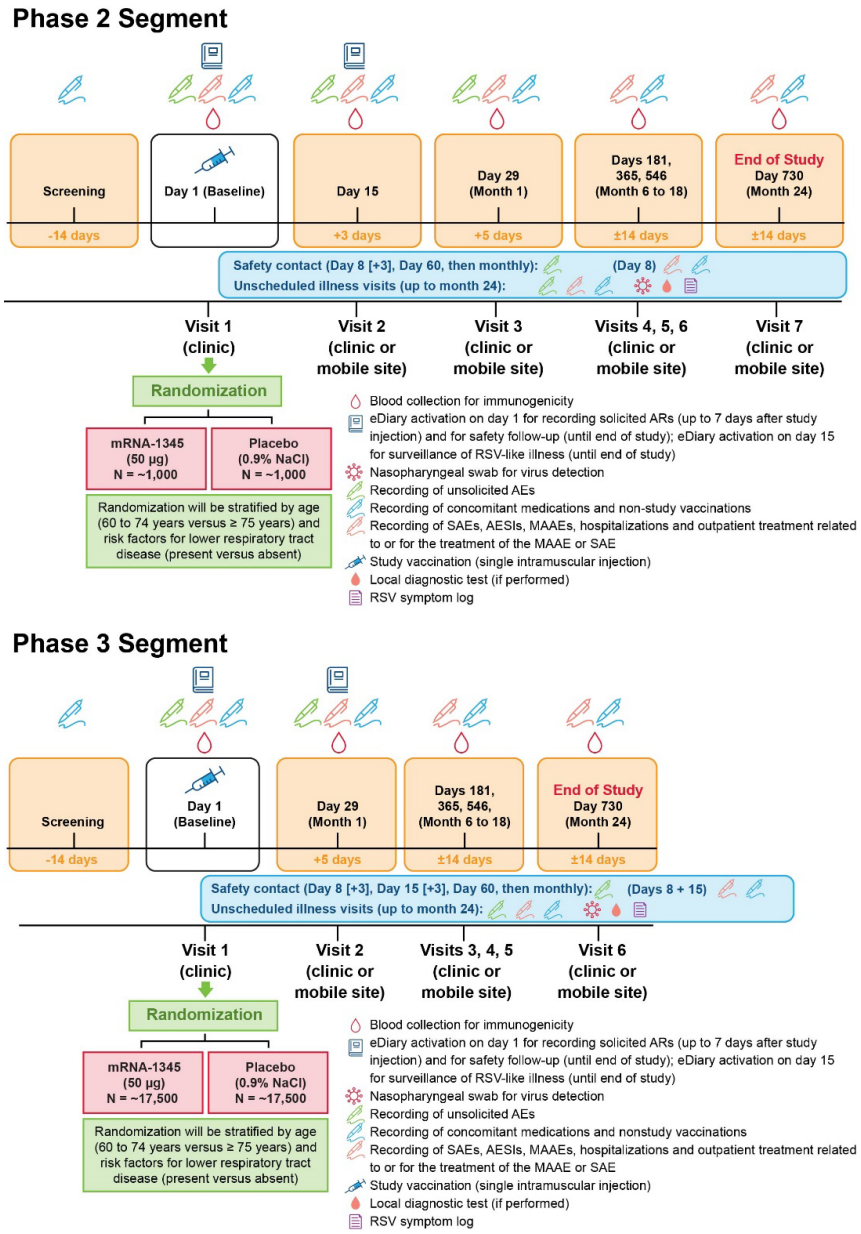
No formal multiplicity adjustments were employed for safety endpoints. All analyses were performed by vaccination group, unless specified otherwise. For categorical variables, frequencies and percentages are presented. Continuous variables were summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum). All statistical analyses were performed using SAS® Version 9.4.

Author Contributions

PG, WH, AK, FS, LL, SM, RM, CAP, SKS, CAS, JMM, RD, and CLD contributed towards the concept and design of the study. EW, JG, AHB, PAD, GPM, KZ, JM, CJAD, MU, MR, LPB, RD, PG, AK, SM, RM, KS, LW, JMM, RD, and GC were involved in data collection. EW, JG, RD, JJ, PG, WH, AK, BJK, FS, LL, SM, RM, CAP, CR, AKS, KS, SKS, LW, CAS, JMM, RD, and GLC analyzed or interpreted the data. All authors provided writing, review, or intellectual contributions and approved the final draft.

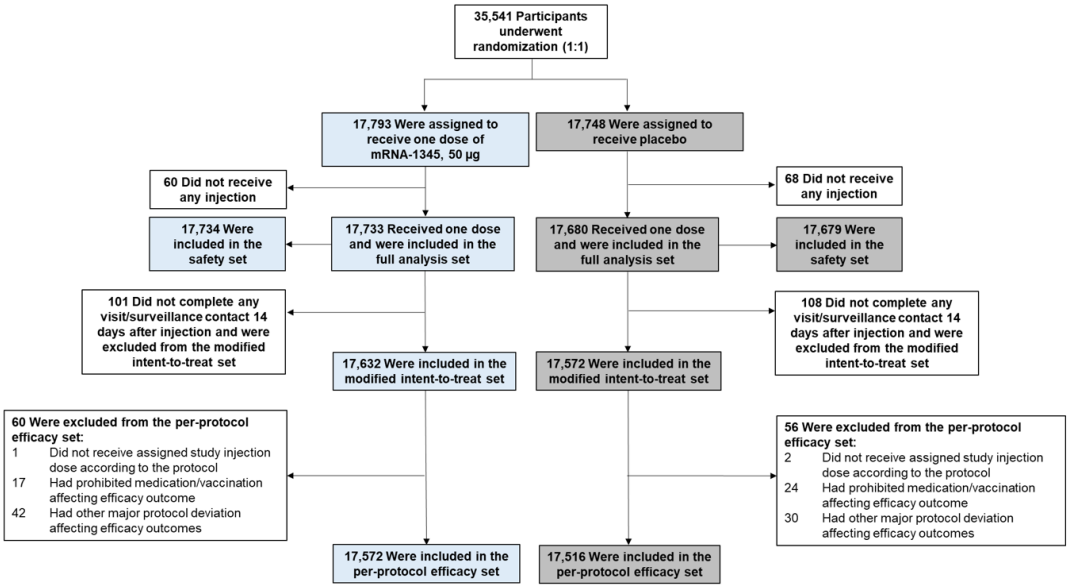
Supplementary Figures

Figure S1. Phase 2 and Phase 3 Study Schema.



AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; MAAE, medically attended adverse event; NaCl, sodium chloride (normal saline); RSV, respiratory syncytial virus; SAE, serious AE.

Figure S2. Randomization and Analysis Populations.
The 35,541 Participants aged ≥60 years who underwent 1:1 randomization were assigned to receive mRNA-1345 or placebo (investigational product; IP). The Safety Set consisted of all randomized participants who received any IP. Numbers were based on actual treatment group. The full analysis set consisted of all randomized participants who received any IP, and the modified intent-to-treat population consisted of all participants in the full analysis set who completed ≥1 visit or surveillance 14 days after the IP administration. The per-protocol efficacy set consisted of all participants in the modified intent-to-treat set who received the assigned IP dose according to protocol, completed ≥1 visit or surveillance contact 14 days after the IP administration, and had no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding.



The full analysis set consisted of all randomized participants who received any investigational product (IP).

The modified intent-to-treat population consisted of all participants in the full analysis set who completed at least one visit or surveillance 14 days after the IP administration.

The per-protocol efficacy population consisted of all participants in the modified intent-to-treat population who received the assigned IP dose according to protocol, completed at least one visit or

surveillance contact 14 days after the IP administration and had no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding.

The Safety Set consisted of all randomized participants who received any IP. Numbers were based on actual treatment group.

Supplementary Tables

Table S1. Study Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
Efficacy Objective	**Efficacy Endpoint**
• 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 post-injection up to 12 months post-injection	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with ≥2 symptoms within the period of 14 days post-injection up to 12 months post-injection • Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with ≥3 symptoms within the period of 14 days post-injection up to 12 months post-injection
Safety Objective	**Safety Endpoint**
• To evaluate the safety and tolerability of the mRNA-1345 vaccine	• Numbers and percentages of participants with solicited local and systemic ARs up to 7 days post-injection • Unsolicited AEs up to 28 days post-injection • MAAEs, AESIs, SAEs, and AEs leading to withdrawal up to 24 months post injection
Key Secondary Efficacy Objectives	**Key Secondary Efficacy Endpoints**

• To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-ARD compared with placebo within the period of 14 days post-injection up to 12 months post-injection	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection
Other Secondary Efficacy Objectives	**Other Secondary Efficacy Endpoints**
• 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 by RSV subtype	• Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD by RSV subtype A and RSV subtype B

AE, adverse event; AESI, adverse event of special interest; AR, adverse reaction; ARD, acute respiratory disease; LRTD, lower respiratory tract disease; MAAE, medically attended adverse event; RSV, respiratory syncytial virus; SAE, serious adverse event

Table S2. Prespecified Endpoints (Primary, Secondary, Exploratory) Included or Omitted from the Manuscript

	Endpoint included or omitted	Reason endpoint was omitted
Primary endpoints		
Solicited local and systemic ARs up to 7 days post-injection	Included	NA
Unsolicited AEs up to 28 days post-injection	Included	NA
MAAEs, AESIs, SAEs, and AEs leading to withdrawal up to 24 months post-injection	Included	NA
Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with ≥2 symptoms within the period of 14 days post-injection up to 12 months post-injection	Included	NA
Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with ≥3 symptoms within the period of 14 days post-injection up 12 months post-injection	Included	NA
Key secondary endpoints		
Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection	Included	NA
Vaccine efficacy of mRNA-1345 to prevent the first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection	Omitted	Not enough cases to reliably assess vaccine efficacy
Other secondary endpoints		
Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD by RSV subtype A and RSV subtype B	Included	NA
Vaccine efficacy of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 12 months post-injection	Omitted	Not enough cases to reliably assess vaccine efficacy

	Endpoint included or omitted	Reason endpoint was omitted
Vaccine efficacy of mRNA-1345 to prevent all-cause LRTD* within the period of 14 days post-injection up to 12 months post-injection	Omitted	Data not yet available
Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with ≥2 symptoms within the period of 14 days post-injection up to 24 months post-injection	Omitted	Data not yet available
Vaccine efficacy of mRNA-1345 to prevent a first episode of RSV-LRTD with ≥3 symptoms within the period of 14 days post-injection up to 24 months post-injection	Omitted	Data not yet available
Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 24 months post-injection	Omitted	Data not yet available
Change in total frailty score from baseline to 12 months and 24 months post-injection, using the Edmonton Frail Scale [1]	Omitted	Data not yet available for 12 and 24 months
GMT of serum RSV neutralizing antibodies and GMC of serum RSV binding antibodies at prespecified study timepoints from baseline up to 24 months post-injection	Omitted	Data not yet available
Seroresponse rate in RSV neutralizing antibodies up to 24 months post-injection.	Omitted	Data not yet available
GMFR from baseline at prespecified study timepoints up to 24 months post-injection	Omitted	Data not yet available
Proportion of participants with ≥ 2-fold increase in antibody titer from baseline at prespecified study timepoints up to 24 months post-injection	Omitted	
Exploratory endpoints		
Number of participants with the first episode of RSV-LRTD by baseline frailty status	Included	NA

	Endpoint included or omitted	Reason endpoint was omitted
Number of participants with the first episode of RSV-ARD by baseline frailty status	Included	NA
Number of participants with the first episode of RSV-LRTD by baseline comorbidities such as COPD, asthma, any chronic respiratory or pulmonary disease, diabetes mellitus type 1 or 2, CHF, and advanced liver or renal disease	Included	NA
Number of participants with the first episode of RSV-ARD by baseline comorbidities such as COPD, asthma, any chronic respiratory or pulmonary disease, diabetes mellitus type 1 or 2, CHF, and advanced liver or renal disease	Included	NA
Immune response biomarkers after dosing with mRNA-1345 vaccine as potential correlates of protection or risk of RSV disease	Omitted	Data not yet available
Additional analyses relating to further understanding of infection and disease associated with RSV and related pathogens, including analyses related to the immunology of vaccination, viral infection, and clinical conduct	Omitted	Analysis not yet conducted, awaiting additional data
Vaccine efficacy of mRNA-1345 to prevent or mitigate RSV-LRTD and all-cause LRTD* with at least 1, 2, 3, 4, or 5 symptoms or signs of lower respiratory tract involvement	Omitted	Analysis not yet conducted, awaiting additional data
Vaccine efficacy of mRNA-1345 to prevent all-cause hospitalizations within the period of 14 days post-injection up to 24 months post-injection.	Omitted	Analysis not yet conducted, awaiting additional data
Vaccine efficacy of mRNA-1345 to prevent all-cause ARD# within the period of 14 days post-injection up to 12 months post-injection	Omitted	Analysis not yet conducted, awaiting additional data

	Endpoint included or omitted	Reason endpoint was omitted
Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-ARD within the period of 14 days post-injection up to 24 months post-injection	Omitted	Data not yet available
Vaccine efficacy of mRNA-1345 to prevent all-cause LRTD* within the period of 14 days post-injection up to 24 months post-injection	Omitted	Data not yet available
Vaccine efficacy of mRNA-1345 to prevent all-cause ARD# within the period of 14 days post-injection up to 24 months post-injection	Omitted	Data not yet available
To describe the effect of a single dose of mRNA-1345 vaccine on level of care required for daily living.	Omitted	Data not yet available
Vaccine efficacy of mRNA-1345 to prevent exacerbations of CHF up to 12 months and 24 months postinjection	Omitted	Analysis not yet conducted, awaiting additional data
Vaccine efficacy of mRNA-1345 to prevent exacerbations of COPD up to 12 months and 24 months post-injection	Omitted	Analysis not yet conducted, awaiting additional data
Number of deaths from all causes at 12 months and 24 months post-injection	Omitted	Data not yet available
Change from baseline in HRQoL using the EQ-5D-5L utility index scores at 12 months and 24 months	Omitted	
Change from baseline in HRQoL for participants with RSV-LRTD or RSV-ARD using the EQ-5D-5L utility index scores at 12 months and 24 months	Omitted	Analysis not yet conducted, awaiting additional data
Work Productivity and Activity Impairment Questionnaire impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with RSV-LRTD or RSV-ARD at the start of the symptoms (baseline), and at 7 days (+1 day) and 14 days (+1 day) after the start of the symptoms	Omitted	Analysis not yet conducted, awaiting additional data

	Endpoint included or omitted	Reason endpoint was omitted
Number of participants with healthcare encounters (medical attendance and hospitalizations) associated with RSV-LRTD or RSV-ARD and with all-cause LRTD* or all-cause ARD#	Omitted	Analysis not yet conducted, awaiting additional data
Duration of hospital encounters associated with RSV-LRTD or RSV-ARD and with all-cause LRTD* or all-cause ARD#	Omitted	Analysis not yet conducted, awaiting additional data
Number of participants with new prescriptions for medications including antibiotics associated with RSV-LRTD or RSV-ARD and with all-cause LRTD* or all-cause ARD#	Omitted	Analysis not yet conducted, awaiting additional data
Feasibility of linking patient-level data to real-world electronic health databases to extend the duration of monitoring for healthcare encounters such as cardiorespiratory hospitalizations or respiratory hospitalizations, or death from all causes (United States sites only).	Omitted	Analysis not yet conducted, awaiting additional data

AE, adverse event; AESI, adverse events of special interest; AR, adverse reaction; ARD, acute respiratory disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EQ-5D-5L, 5 level EuroQol 5 Dimension; GMC, geometric mean concentration; GMFR, geometric mean-fold rise; GMT, geometric mean titer; HRQoL, health-related quality of life; LRTD, lower respiratory tract infection; MAAE, medically-attended adverse event; NA, not applicable; RSV, respiratory syncytial virus**;** RT-PCR, real time polymerase chain reaction; SAE, serious adverse event; WPAI, Work Productivity and Activity Impairment Questionnaire

*All-cause LRTD was defined as new or worsening of at least 2 of the following symptoms: shortness of breath, cough and/or fever (≥37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥20 breaths per minute or increase of ≥2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause LRTD.

#All-cause ARD was defined as an acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of the following symptoms: cough, stuffy nose, runny nose, sore throat, fever (≥37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥20 breaths per minute or increase of ≥2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤93% or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours with any or no RT-PCR result. In case of

inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm all-cause ARD.

Table S3. Efficacy Endpoint Definitions for RSV-ARD and RSV-LRTD.

Endpoint	Definition
RSV-LRTD with ≥2 symptoms	• RT-PCR–confirmed RSV infection plus new or worsening of at least 2 of the following symptoms: shortness of breath, cough and/or fever (≥37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥20 breaths per minute, or increase of ≥2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours • In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR–confirmed RSV infection can also be used to confirm RSV-LRTD
RSV-LRTD with ≥3 symptoms	• RT-PCR–confirmed RSV infection plus new or worsening of at least 3 of the following symptoms: shortness of breath, cough and/or fever (≥37.8°C [100.0°F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥20 breaths per minute, or increase of ≥2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤93% or new or increasing use of supplemental oxygen), pleuritic chest pain for at least 24 hours • In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR–confirmed RSV infection can also be used to confirm RSV-LRTD

RSV-ARD	• RT-PCR–confirmed RSV infection plus an acute symptomatic respiratory disease manifesting as new or worsening of one or more of cough, stuffy nose, runny nose, sore throat, fever (≥37.8°C [100.0°F]), shortness of breath, observed tachypnea (≥20 breaths per minute, or increase of ≥2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤93%, or new or increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for at least 24 hours • In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR–confirmed RSV infection can also be used to confirm RSV-ARD

ARD, acute respiratory disease; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

Note: The source of the clinical symptomology that supports the case definition can be participant reported and/or from a clinical assessment.

Table S4. Adverse Events of Special Interest.

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts < 150×10^9 cells per liter • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome
New onset of or worsening of neurologic diseases	Neurologic diseases include the following: • Guillain-Barré syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures, including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis as defined per the protocol
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

Table S5. Number of Participants Randomized by Country (Randomization Set[a]).

Country	Number of cases, %		
	mRNA-1345, 50 µg (N=17,793)	Placebo (N=17,748)	Total (N=35,541)
Argentina	1798 (10.1)	1791 (10.1)	3589 (10.1)
Australia	127 (0.7)	129 (0.7)	256 (0.7)
Bangladesh	748 (4.2)	752 (4.2)	1500 (4.2)
Belgium	207 (1.2)	206 (1.2)	413 (1.2)
Canada	354 (2.0)	352 (2.0)	706 (2.0)
Chile	339 (1.9)	340 (1.9)	679 (1.9)
Columbia	1311 (7.4)	1314 (7.4)	2625 (7.4)
Costa Rica	100 (0.6)	103 (0.6)	203 (0.6)
Finland	49 (0.3)	47 (0.3)	96 (0.3)
Germany	237 (1.3)	234 (1.3)	471 (1.3)
Japan	414 (2.3)	408 (2.3)	822 (2.3)
Mexico	371 (2.1)	362 (2.0)	733 (2.1)
New Zealand	147 (0.8)	152 (0.9)	299 (0.8)
Panama	774 (4.4)	777 (4.4)	1551 (4.4)
Poland	173 (1.0)	173 (1.0)	346 (1.0)
Singapore	4 (<0.1)	4 (<0.1)	8 (<0.1)
South Africa	493 (2.8)	489 (2.8)	982 (2.8)
South Korea	5 (<0.1)	6 (<0.1)	11 (<0.1)
Spain	112 (0.6)	108 (0.6)	220 (0.6)
Taiwan	43 (0.2)	41 (0.2)	84 (0.2)
United Kingdom	227 (1.3)	223 (1.3)	450 (1.3)
United States	9760 (54.9)	9737 (54.9)	19497 (54.9)

[a]Percentages are based on the number of randomized participants.

Table S6. Baseline Demographics and Clinical Characteristics (Safety Set).

	mRNA-1345, 50 µg (N=17,734)	Placebo (N=17,679)	Total (N=35,413)
Age at enrollment, years			
Mean (SD)	68.1 (6.2)	68.1 (6.2)	68.1 (6.2)
Median (min, max)	67.0 (60, 95)	67.0 (60, 96)	67.0 (60, 96)
Age group, n (%)*			
60 to 69 years	11,281 (63.6)	11,222 (63.5)	22,503 (63.5)
70 to 79 years	5474 (30.9)	5460 (30.9)	10,934 (30.9)
≥80 years	979 (5.5)	997 (5.6)	1976 (5.6)
Sex, n (%)			
Male	9076 (51.2)	8968 (50.7)	18,044 (51.0)
Female	8658 (48.8)	8711 (49.3)	17,369 (49.0)
Race, n (%)			
White	11,240 (63.4)	11,216 (63.4)	22,456 (63.4)
Black	2203 (12.4)	2158 (12.2)	4361 (12.3)
Asian	1540 (8.7)	1529 (8.6)	3069 (8.7)
Other†	2682 (15.1)	2671 (15.1)	5353 (15.1)
Unknown/Not Reported	69 (0.4)	105 (0.6)	174 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	6086 (34.3)	6141 (34.7)	12,227 (34.5)
Not Hispanic or Latino	11,463 (64.6)	11,329 (64.1)	22,792 (64.4)
Unknown	27 (0.2)	22 (0.1)	49 (0.1)
Not reported	158 (0.9)	187 (1.1)	345 (1.0)
BMI mean ± SD, (kg/m^2)‡	27.3±4.1	27.3±4.2	27.3±4.2
World Bank region, n (%)			
North America/Europe	11,077 (62.5)	11,029 (62.4)	22,106 (62.4)
Central/Latin America/Africa	5171 (29.2)	5161 (29.2)	10,332 (29.2)
Asian Pacific	1486 (8.4)	1489 (8.4)	2975 (8.4)
Frailty status, n (%)			
Fit (0-3)	13,512 (76.2)	13,354 (75.5)	26,866 (75.9)
Vulnerable (4-5)	2828 (15.9)	2899 (16.4)	5727 (16.2)
Frailty (≥6)	997 (5.6)	1017 (5.8)	2014 (5.7)
Missing	397 (2.2)	409 (2.3)	806 (2.3)
Comorbidities of interest, n (%)§			
0	12,496 (70.5)	12,551 (71.0)	25,047 (70.7)
≥1	5238 (29.5)	5128 (29.0)	10,366 (29.3)

	mRNA-1345, 50 µg (N=17,734)	Placebo (N=17,679)	Total (N=35,413)
LRTD risk factors (CHF/COPD), n (%)*			
Present	1218 (6.9)	1230 (7.0)	2448 (6.9)
CHF	205 (1.2)	201 (1.1)	406 (1.1)
COPD	960 (5.4)	978 (5.5)	1938 (5.5)
CHF and COPD	53 (0.3)	51 (0.3)	104 (0.3)
Absent	16,516 (93.1)	16,449 (93.0)	32,965 (93.1)

BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IP, investigational product; LRTD, lower respiratory tract disease.

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

Baseline value for BMI was defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the date of IP injection.

Frailty status based on the Edmonton Frailty scoring system measured by Edmonton Frail Scale across 9 domains: Cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. A 0-17 point scale was used: fit (0-3); vulnerable (4-5); frail (6-17) [1].

*Derived from age and risk collected on eCRFs.

†Other race included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, or Multiple.

‡Some participants had missing data for height or weight.

§Comorbidities of interest included COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease.

Table S7. Race, Ethnicity, Age, and Risk Factors Within the Broader Population.

Category	Details
Disease, problem, or condition under investigation	RSV in adults aged ≥60 years
Special considerations related to	
RSV disease	RSV is a highly contagious virus which circulates globally and is a major cause of upper and lower respiratory tract disease
Age	Older adults, young children, and infants are at highest risk of severe RSV disease. In older adults, decline in immunity and a higher prevalence of certain underlying conditions are thought to place them at higher risk of severe disease[8-10]
Sex	Male infants and young children may be more likely to be hospitalized with severe RSV disease than females.[9,11-13] In older adults, disparity by sex is less clear
Race or ethnic group	Further research describing racial and ethnic disparities, and elucidating the factors that contribute to them, are needed. Certain indigenous populations are disproportionality impacted by RSV. In general, respiratory infections disproportionately affect persons of color[9,14-18]
Geography	Worldwide, RSV often causes annual epidemics, generally during the winter season in temperate climates and during the rainy season in tropical regions. In equatorial regions, year-round circulation of RSV activity occurs[19,20]
Comorbidities	The incidence of RSV and severe outcomes from RSV increases with young and old age, and certain underlying conditions, particularly chronic heart and lung conditions. In patients with these conditions, RSV can cause exacerbations of the underlying condition and lead to severe outcomes such as pneumonia, hospitalization, and death[8,10]
Overall representativeness of this trial	This trial focused on older adults who are all at increased risk of developing severe RSV disease due to age-related decline in immunity and a higher prevalence of certain underlying conditions. It included participants across six continents with different patterns of RSV circulation. It further emphasized inclusion of persons with important known risk factors, such COPD and congestive heart failure. In the United States, although the proportion of Asian participants was lower than the United States population in 2021, the proportion of Black participants and Hispanic or Latino participants were similar to the United States population

COPD, chronic obstructive pulmonary disease; RSV, respiratory syncytial virus

Table S8. Vaccine Efficacy against RSV-LRTD with ≥2 or ≥3 Symptoms and RSV-ARD (Randomization Set)*.

End Point	mRNA-1345		Placebo		Vaccine Efficacy % (95% CI)[§]
	Number of Participants	Number of Events[†,‡]	Number of Participants	Number of Events[†,‡]	
RSV-LRTD with ≥2 symptoms	17,793	10	17,748	62	83.9 (68.7, 91.8)
RSV-LRTD with ≥3 symptoms	17,793	3	17,748	20	85.0 (49.7, 95.6)
RSV-ARD	17,793	29	17,748	95	69.6 (53.9, 79.9)

ARD, acute respiratory disease; CI, confidence interval; LRTD, lower respiratory; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine efficacy

*Data are from the randomization set analysis population.

[†]RSV-LRTD with ≥2 symptoms or ≥3 symptoms and RSV-ARD were based on eligible symptoms onset within a timeframe of ±14 days from positive RSV RT-PCR collection date.

[‡]The time to first episode of RSV-LRTD with ≥2 symptoms or ≥3 symptoms and RSV-ARD were calculated as date of case −date of randomization + 1.

[§]Vaccine efficacy is defined as 100% × (1 − hazard ratio [mRNA-1345 vs. placebo]). The CI for VE is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the study vaccination group as a fixed effect, adjusting for stratification factors at randomization.

Table S9. Vaccine Efficacy against RSV-LRTD with ≥2 or ≥3 Symptoms and RSV-ARD (Per-Protocol Efficacy Set).*

End Point	mRNA-1345		Placebo		Vaccine Efficacy % (95% CI)‖
	Number of Participants	Number of Events†,‡	Number of Participants	Number of Events†,‡	
RSV-LRTD with ≥2 symptoms§,¶					
Overall	17,572	9	17,516	55	83.7 (66.0, 92.2)**
Sex					
Male	8974	4	8875	25	84.1 (54.4, 94.5)
Female	8598	5	8641	30	83.4 (57.3, 93.6)
Comorbidities of interest††					
0	12,377	7	12,431	38	81.6 (58.8, 91.8)
≥1	5195	2	5085	17	88.4 (49.9, 97.3)
Race					
White	11,144	8	11,121	39	79.5 (56.1, 90.4)
Black	2163	0	2111	2	100.0 (NE, 100.0)
Asian	1533	1	1521	6	83.6 (−36.0, 98.0)
Other	2665	0	2661	8	100.0 (NE, 100.0)
World Bank region					
North America/Europe	10,945	7	10,896	34	79.5 (53.7, 90.9)
Central/Latin America/Africa	5148	1	5139	14	92.9 (45.9, 99.1)
Asian Pacific	1479	1	1481	7	85.7 (−16.3, 98.2)
Risk factors: COPD/CHF					
Absent	16,365	8	16,299	53	85.0 (68.4, 92.9)
Present	1207	1	1217	2	49.4 (-457.9, 95.4)
Frailty status					
Fit (0–3)	13,396	8	13,250	45	82.3 (62.5, 91.7)
Vulnerable (4–5)	2799	0	2859	3	100.0 (NE, 100.0)
Frailty (≥6)	982	0	999	3	100.0 (NE, 100.0)
Ethnicity					
Hispanic or Latino	6043	1	6105	15	93.3 (48.9, 99.1)
Not Hispanic or Latino	11,347	6	11,203	40	85.2 (65.0, 93.7)
History of COVID-19					
Yes	1902	0	1801	7	100.0 (NE, 100.0)
No	15,670	9	15,715	48	81.3 (61.9, 90.8)
History of Hospitalization due to COVID-19					
Yes	109	0	111	0	NE (NE, NE)
No	17,463	9	17,405	55	83.7 (67.0, 91.9)
World Bank Income Level 2022					
Lower-Middle	747	0	751	5	100 (NE, 100.0)
Upper-Middle	4820	1	4804	13	92.3 (41.5, 99.0)
High	12,005	8	11,961	37	78.4 (53.7, 90.0)
RSV-LRTD with ≥3 symptoms §,¶					
Overall	17,572	3	17,516	17	82.4 (34.8, 95.3)**

End Point	mRNA-1345		Placebo		Vaccine Efficacy % (95% CI)[‖]
	Number of Participants	Number of Events[†,‡]	Number of Participants	Number of Events[†,‡]	
Sex					
Male	8974	1	8875	6	83.4 (−37.8, 98.0)
Female	8598	2	8641	11	81.7 (17.5, 95.9)
Comorbidities of interest[††]					
0	12,377	1	12,431	10	90.1 (22.7, 98.7)
≥1	5195	2	5085	7	71.8 (−35.9, 94.1)
Race					
White	11,144	3	11,121	14	78.5 (25.3, 93.8)
Black	2163	0	2111	1	100.0 (NE, 100.0)
Asian	1533	0	1521	1	100.0 (NE, 100.0)
Other	2665	0	2661	1	100.0 (NE, 100.0)
World Bank region					
North America/Europe	10,945	2	10,896	13	84.7 (32.0, 96.5)
Central/Latin America/Africa	5148	1	5139	3	66.7 (−219.7, 96.5)
Asian Pacific	1479	0	1481	1	100.0 (NE, 100.0)
Risk factors: COPD/CHF					
Absent	16,365	2	16,299	17	88.3 (49.4, 97.3)
Present	1207	1	1217	0	NE (NE, NE)
Frailty Status					
Fit (0–3)	13,396	3	13,250	13	77.0 (19.2, 93.4)
Vulnerable (4–5)	2799	0	2859	1	100.0 (NE, 100.0)
Frailty (≥6)	982	0	999	2	100.0 (NE, 100.0)
Ethnicity					
Hispanic or Latino	6043	1	6105	4	74.6 (-127.2, 97.2)
Not Hispanic or Latino	11,347	1	11,203	13	92.4 (41.7, 99.0)
History of COVID-19					
Yes	1902	0	1801	3	100 (NE, 100.0)
No	15,670	3	15,715	14	78.6 (25.4, 93.8)
History of Hospitalization due to COVID-19					
Yes	109	0	111	0	NE (NE, NE)
No	17,463	3	17,405	17	82.4 (40.0, 94.8)
World Bank Income Level 2022					
Lower-Middle	747	0	751	1	100.0 (NE, 100.0)
Upper-Middle	4820	1	4804	3	66.8 (-219.4, 96.5)
High	12,005	2	11,961	13	84.7 (32.0, 96.5)
RSV-ARD [§,¶]					
Overall	17,572	26	17,516	82	68.4 (50.9, 79.7)[**]
RSV subtype					
RSV-A	17,572	11	17,516	51	78.5 (58.8, 88.8)
RSV-B	17,572	15	17,516	31	51.7 (10.6, 73.9)
Sex					
Male	8974	14	8875	37	62.5 (30.7, 79.7)
Female	8598	12	8641	45	73.5 (49.9, 86.0)

End Point	mRNA-1345		Placebo		Vaccine Efficacy % (95% CI)[‖]
	Number of Participants	Number of Events[†,‡]	Number of Participants	Number of Events[†,‡]	
Age group					
60-69 years	11,168	20	11,118	44	54.9 (23.5, 73.4)
70-79 years	5440	6	5416	37	83.6 (61.1, 93.1)
≥80 years	964	0	982	1	100.0 (NE, 100.0)
Comorbidities of interest[††]					
0	12,377	19	12,431	62	69.6 (49.2, 81.8)
≥1	5195	7	5085	20	65.7 (18.9, 85.5)
Race					
White	11,144	18	11,121	51	64.7 (39.6, 79.4)
Black	2163	1	2111	2	52.3 (−426.0, 95.7)
Asian	1533	5	1521	14	64.9 (2.6, 87.4)
Other	2665	2	2661	15	86.8 (42.2, 97.0)
World Bank region					
North America/Europe	10,945	16	10,896	45	64.6 (37.3, 80.0)
Central/Latin America/Africa	5148	4	5139	23	82.7 (50.0, 94.0)
Asian Pacific	1479	6	1481	14	57.3 (−11.1, 83.6)
Risk factors: COPD/CHF					
Absent	16,365	25	16,299	79	68.5 (50.6, 79.9)
Present	1207	1	1217	3	66.1 (−225.7, 96.5)
Frailty Status					
Fit (0–3)	13,396	20	13,250	65	69.5 (49.6, 81.5)
Vulnerable (4–5)	2799	1	2859	5	79.7 (−73.4, 97.6)
Frailty (≥6)	982	1	999	3	62.1 (−265.1, 96.1)
Ethnicity					
Hispanic or Latino	6043	5	6105	25	79.8 (47.2, 92.3)
Not Hispanic or Latino	11,347	18	11,203	57	68.8 (47.0,81.6)
History of COVID-19					
Yes	1902	2	1801	9	78.8 (1.8, 95.4)
No	15,670	24	15,715	73	67.2 (48.0, 79.3)
History of Hospitalization due to COVID-19					
Yes	109	0	111	1	100 (NE, 100.0)
No	17,463	26	17,405	81	68.0 (50.3, 79.4)
World Bank Income Level 2022					
Lower-Middle	747	4	751	12	67.1 (-2.0, 89.4)
Upper-Middle	4820	3	4804	22	86.5 (54.9, 96.0)
High	12,005	19	11,961	48	60.5 (32.9, 76.8)

ARD, acute respiratory disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine efficacy.

[*]Data are from the per-protocol efficacy set analysis population.

[†]RSV-LRTD with ≥2 symptoms or ≥3 symptoms and RSV-ARD were based on eligible symptoms onset within a timeframe of ±14 days from positive RSV RT-PCR collection date.

[‡]The time to first episode of RSV-LRTD with ≥2 symptoms or ≥3 symptoms and RSV-ARD were calculated as date of case − date of randomization + 1.
[§]Follow-up in person-years for the mRNA-1345 group was 6271.06, 6272.38, and 6268.28 for RSV-LRTD with ≥2 symptoms, RSV-LRTD with ≥3 symptoms, and RSV-ARD, respectively. Follow-up in person-years for the placebo group was 6253.55, 6259.83, and 6250.26 for RSV-LRTD with ≥2 symptoms, RSV-LRTD with ≥3 symptoms, and RSV-ARD, respectively. Person-years was defined as the total years from randomization date to the date of RSV-LRTD with ≥2 symptoms or ≥3 symptoms and RSV-ARD, 12 months post-injection, date of early discontinuation, date of unrelated death, date of early RSV-ARD, or data cutoff date, whichever was the earliest.
[¶]Incidence rate (number of events/1000 person-years) for the mRNA-1345 group was 1.44, 0.48, and 4.15 for RSV-LRTD with ≥2 symptoms, RSV-LRTD with ≥3 symptoms, and RSV-ARD, respectively. Incidence rate (number of events/1000 person-years) for the placebo group was 8.80, 2.72, and 13.12 for RSV-LRTD with ≥2 symptoms, RSV-LRTD with ≥3 symptoms, and RSV-ARD, respectively. Incidence rate was defined as the number of participants with a case divided by the number of participants at risk-adjusted by person-years (total time at risk) in each vaccination group. The 95% CI was calculated using the exact method (Poisson distribution) and adjusted by person-years.
[‖]Vaccine efficacy is defined as 100% × (1 − hazard ratio [mRNA-1345 vs. placebo]). The CI for VE is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the study vaccination group as a fixed effect, adjusting for stratification factors at randomization.
[**]Adjusted CIs: RSV-LRTD with ≥2 symptoms, 95.88%; RSV-LRTD with ≥3 symptoms, 96.36%; RSV-ARD, 95%.
[††]Comorbidities of interest include COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease.

Table S10. Summary of Symptom Assessment for First Occurrence of RSV-LRTD[*]

	Number of Events[†] n (%)	
	mRNA-1345 (N=17,572)	Placebo (N=17,516)
RSV-LRTD with ≥2 symptoms		
Number of participants with first occurrence of RSV-LRTD cases[‡, §]	9 (<0.1)	55 (0.3)
Shortness of breath	2 (22.2)	15 (27.3)
Cough and/or fever (≥37.8°C)	9 (100)	55 (100)
Cough	9 (100)	54 (98.2)
Fever	0	13 (23.6)
Wheezing and/or rales and/or rhonchi	3 (33.3)	15 (27.3)
Sputum production	7 (77.8)	38 (69.1)
Observed tachypnea (≥20 breaths per minute or increase of ≥2 breaths per minute from baseline in those who have baseline tachypnea)	0	2 (3.6)
Hypoxemia (New oxygen saturation ≤93% or new or increasing use of supplemental oxygen)	0	1 (1.8)
Pleuritic chest pain	1 (11.1)	9 (16.4)
Number of participants with radiologic evidence of pneumonia[§]	0	1 (<0.1)
RSV-LRTD with ≥3 symptoms		
Number of participants with first occurrence of RSV-LRTD cases[‡, §]	3 (<0.1)	17 (<0.1)
Shortness of breath	1 (33.3)	12 (70.6)
Cough and/or fever (≥37.8°C)	3 (100)	17 (100)
Cough	3 (100)	16 (94.1)
Fever	0	6 (35.3)
Wheezing and/or rales and/or rhonchi	2 (66.7)	10 (58.8)
Sputum production	3 (100)	11 (64.7)
Observed tachypnea (≥20 breaths per minute or increase of ≥2 breaths per minute from baseline in those who have baseline tachypnea)	0	2 (11.8)
Hypoxemia (New oxygen saturation ≤93% or new or increasing use of supplemental oxygen)	0	1 (5.9)
Pleuritic chest pain	1 (33.3)	6 (35.3)
Number of participants with radiologic evidence of pneumonia[§]	0	1 (<0.1)

PPE, Per Protocol Set; RSV LRTD, respiratory syncytial virus-associated lower respiratory tract disease.

[*]Data are from the per-protocol efficacy set analysis population

[†]Only RSV-LRTD cases with 2 or more symptoms or 3 or more symptoms between 14 days postinjection up to 12 months postinjection (PPE Set) were included in the summary. Cough and/or fever was counted as 1 eligible symptom for RSV-LRTD.

[‡]Participants could be counted in more than 1 category.

[§]Percentage was calculated based on the number of participants in PPE Set (N). For the individual symptom, the percentage was calculated based on the number of participants with any RSV-LRTD symptom.

Table S11. Number of Days Reporting Solicited Adverse Reactions within 7 Days after Vaccination (Solicited Safety Set).

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Solicited adverse reactions – N1*	17,665	17,598
Any	12,119 (68.6)	6782 (38.5)
Day of onset		
Mean (SD)	1.8 (1.07)	2.4 (1.70)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	3.7 (4.77)	3.9 (5.38)
Median	2.0	2.0
Min, Max	1, 184	1, 117
Persisted beyond 7 days	1200 (6.8)	915 (5.2)
Solicited local adverse reactions – N1*	17,662	17,593
Any	10,367 (58.7)	2845 (16.2)
Day of onset		
Mean (SD)	1.8 (0.92)	2.2 (1.65)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.4 (2.24)	2.2 (2.71)
Median	2.0	1.0
Min, Max	1, 69	1, 48
Persisted beyond 7 days	307 (1.7)	120 (0.7)
Pain – N1*	17,661	17,593
Any	9942 (56.3)	2407 (13.7)
Day of onset		
Mean (SD)	1.8 (0.86)	2.2 (1.57)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.2 (1.93)	2.0 (2.26)
Median	2.0	1.0
Min, Max	1, 69	1, 29
Persisted beyond 7 days	179 (1.0)	83 (0.5)
Erythema (Redness) – N1*	17,659	17,592

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Any	357 (2.0)	101 (0.6)
Day of onset		
Mean (SD)	2.7 (1.46)	3.4 (2.07)
Median	2.0	3.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.9 (3.67)	1.8 (2.19)
Median	1.0	1.0
Min, Max	1, 29	1, 16
Persisted beyond 7 days	47 (0.3)	7 (<0.1)
Swelling (Hardness) – N1*	17,660	17,592
Any	662 (3.7)	59 (0.3)
Day of onset		
Mean (SD)	2.2 (1.11)	2.6 (1.81)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.2 (2.26)	3.6 (6.30)
Median	1.0	1.0
Min, Max	1, 24	1, 31
Persisted beyond 7 days	32 (0.2)	8 (<0.1)
Axillary (underarm) swelling or tenderness – N1*	17659	17592
Any	2711 (15.4)	1091 (6.2)
Day of onset		
Mean (SD)	2.4 (1.42)	2.7 (1.84)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.1 (2.36)	2.2 (3.03)
Median	1.0	1.0
Min, Max	1, 28	1, 48
Persisted beyond 7 days	120 (0.7)	49 (0.3)
Solicited systemic adverse reactions – N1*	17,662	17,597
Any	8432 (47.7)	5798 (32.9)
Day of onset		

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Mean (SD)	2.2 (1.40)	2.6 (1.74)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	3.7 (5.36)	4.0 (5.61)
Median	2.0	2.0
Min, Max	1, 184	1, 117
Persisted beyond 7 days	1034 (5.9)	866 (4.9)
Fever – N1*	17,651	17,593
Any	501 (2.8)	234 (1.3)
Day of onset		
Mean (SD)	2.7 (1.54)	3.4 (1.96)
Median	2.0	3.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	1.5 (1.80)	1.5 (1.82)
Median	1.0	1.0
Min, Max	1, 27	1, 24
Persisted beyond 7 days	17 (<0.1)	6 (<0.1)
Headache – N1*	17,658	17,592
Any	4764 (27.0)	3332 (18.9)
Day of onset		
Mean (SD)	2.5 (1.58)	2.9 (1.82)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.6 (3.50)	2.6 (3.15)
Median	1.0	1.0
Min, Max	1, 146	1, 53
Persisted beyond 7 days	315 (1.8)	264 (1.5)
Fatigue – N1*	17,658	17,592
Any	5470 (31.0)	3518 (20.0)
Day of onset		
Mean (SD)	2.4 (1.46)	2.7 (1.75)
Median	2.0	2.0
Min, Max	1, 7	1, 7

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Duration (days)		
Mean (SD)	3.3 (5.37)	3.7 (5.11)
Median	2.0	2.0
Min, Max	1, 184	1, 91
Persisted beyond 7 days	606 (3.4)	503 (2.9)
Myalgia – N1*	17,658	17,592
Any	4574 (25.9)	2542 (14.4)
Day of onset		
Mean (SD)	2.4 (1.40)	3.0 (1.83)
Median	2.0	3.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.9 (4.18)	3.7 (5.58)
Median	1.0	2.0
Min, Max	1, 106	1, 116
Persisted beyond 7 days	410 (2.3)	368 (2.1)
Arthralgia – N1*	17,658	17,591
Any	3867 (21.9)	2477 (14.1)
Day of onset		
Mean (SD)	2.6 (1.49)	3.0 (1.84)
Median	2.0	3.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	3.5 (4.88)	4.2 (5.96)
Median	2.0	2.0
Min, Max	1, 106	1, 108
Persisted beyond 7 days	511 (2.9)	459 (2.6)
Nausea/vomiting – N1[a]	17,658	17,591
Any	1248 (7.1)	933 (5.3)
Day of onset		
Mean (SD)	3.0 (1.71)	3.2 (1.94)
Median	2.0	3.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.1 (2.49)	2.4 (4.72)
Median	1.0	1.0

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Min, Max	1, 27	1, 116
Persisted beyond 7 days	77 (0.4)	63 (0.4)
Chills – N1*	17,658	17,591
Any	2045 (11.6)	1181 (6.7)
Day of onset		
Mean (SD)	2.6 (1.49)	3.0 (1.90)
Median	2.0	2.0
Min, Max	1, 7	1, 7
Duration (days)		
Mean (SD)	2.0 (2.57)	2.4 (2.80)
Median	1.0	1.0
Min, Max	1, 60	1, 28
Persisted beyond 7 days	85 (0.5)	79 (0.4)

Max, maximum; min, minimum; SD, standard deviation.
Any refers to grade 1 or above.
Percentages were based on the number of exposed participants who submitted any data for the event (N1).
Duration was calculated as the last day − the first day + 1, when the solicited adverse reaction was reported starting within the 7 days of injection. Symptoms that persisted beyond 7 days were those that were ongoing at day 7 and persisted, continuously, beyond day 7.
*N1, number of exposed participants who submitted any data for the event.

Table S12. Summary of Participants with Solicited Adverse Reactions within 7 Days after Vaccination by Grade (Solicited Safety Set).

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Solicited adverse reactions – N1*	17,665	17,598
Grade 1	8299 (47.0)	4544 (25.8)
Grade 2	2716 (15.4)	1524 (8.7)
Grade 3	1069 (6.1)	685 (3.9)
Grade 4	35 (0.2)	29 (0.2)
Grade 3 or Grade 4	1104 (6.2)	714 (4.1)
Solicited local adverse reactions – N1*	17,662	17,593
Grade 1	9044 (51.2)	2386 (13.6)
Grade 2	765 (4.3)	154 (0.9)
Grade 3	558 (3.2)	305 (1.7)
Grade 4	0	0
Grade 3 or Grade 4	558 (3.2)	305 (1.7)
Pain – N1*	17,661	17,593
Any	9942 (56.3)	2407 (13.7)
Grade 1	9064 (51.3)	2098 (11.9)
Grade 2	571 (3.2)	117 (0.7)
Grade 3	307 (1.7)	192 (1.1)
Grade 4	0	0
Grade 3 or Grade 4	307 (1.7)	192 (1.1)
Erythema (Redness) – N1*	17,659	17,592
Any	357 (2.0)	101 (0.6)
Grade 1	181 (1.0)	32 (0.2)
Grade 2	71 (0.4)	12 (<0.1)
Grade 3	105 (0.6)	57 (0.3)
Grade 4	0	0
Grade 3 or Grade 4	105 (0.6)	57 (0.3)
Swelling (Hardness) – N1*	17,660	17,592
Any	662 (3.7)	59 (0.3)
Grade 1	365 (2.1)	33 (0.2)
Grade 2	143 (0.8)	9 (<0.1)
Grade 3	154 (0.9)	17 (<0.1)
Grade 4	0	0

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Grade 3 or Grade 4	154 (0.9)	17 (<0.1)
Axillary (underarm) swelling or tenderness – N1*	17,659	17,592
Any	2711 (15.4)	1091 (6.2)
Grade 1	2357 (13.3)	921 (5.2)
Grade 2	216 (1.2)	55 (0.3)
Grade 3	138 (0.8)	115 (0.7)
Grade 4	0	0
Grade 3 or Grade 4	138 (0.8)	115 (0.7)
Solicited systemic adverse reactions – N1*	17,662	17,597
Grade 1	5137 (29.1)	3799 (21.6)
Grade 2	2585 (14.6)	1491 (8.5)
Grade 3	675 (3.8)	479 (2.7)
Grade 4	35 (0.2)	29 (0.2)
Grade 3 or Grade 4	710 (4.0)	508 (2.9)
Fever – N1*	17,651	17,593
Any	501 (2.8)	234 (1.3)
Grade 1	270 (1.5)	99 (0.6)
Grade 2	119 (0.7)	65 (0.4)
Grade 3	77 (0.4)	41 (0.2)
Grade 4	35 (0.2)	29 (0.2)
Grade 3 or Grade 4	112 (0.6)	70 (0.4)
Headache – N1*	17,658	17,592
Any	4764 (27.0)	3332 (18.9)
Grade 1	3701 (21.0)	2723 (15.5)
Grade 2	787 (4.5)	399 (2.3)
Grade 3	276 (1.6)	210 (1.2)
Grade 4	0	0
Grade 3 or Grade 4	276 (1.6)	210 (1.2)
Fatigue – N1*	17658	17592
Any	5470 (31.0)	3518 (20.0)
Grade 1	3425 (19.4)	2354 (13.4)
Grade 2	1735 (9.8)	949 (5.4)
Grade 3	310 (1.8)	215 (1.2)

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Grade 4	0	0
Grade 3 or Grade 4	310 (1.8)	215 (1.2)
Myalgia – N1*	17,658	17,592
Any	4574 (25.9)	2542 (14.4)
Grade 1	2941 (16.7)	1731 (9.8)
Grade 2	1378 (7.8)	658 (3.7)
Grade 3	255 (1.4)	153 (0.9)
Grade 4	0	0
Grade 3 or Grade 4	255 (1.4)	153 (0.9)
Arthralgia – N1*	17,658	17,591
Any	3867 (21.9)	2477 (14.1)
Grade 1	2558 (14.5)	1680 (9.6)
Grade 2	1112 (6.3)	661 (3.8)
Grade 3	197 (1.1)	136 (0.8)
Grade 4	0	0
Grade 3 or Grade 4	197 (1.1)	136 (0.8)
Nausea/vomiting – N1*	17,658	17,591
Any	1248 (7.1)	933 (5.3)
Grade 1	902 (5.1)	679 (3.9)
Grade 2	266 (1.5)	179 (1.0)
Grade 3	80 (0.5)	75 (0.4)
Grade 4	0	0
Grade 3 or Grade 4	80 (0.5)	75 (0.4)
Chills – N1*	17,658	17,591
Any	2045 (11.6)	1181 (6.7)
Grade 1	1335 (7.6)	839 (4.8)
Grade 2	602 (3.4)	263 (1.5)
Grade 3	108 (0.6)	79 (0.4)
Grade 4	0	0
Grade 3 or Grade 4	108 (0.6)	79 (0.4)

*N1, number of exposed participants who submitted any data for the event.

Any refers to Grade 1 or above.

Percentages were based on the number of exposed participants who submitted any data for the event (N1).

The only solicited systemic adverse reaction reported in any participant at Grade 4 was fever, which was defined as oral temperature >40.0°C/>104.0°F. Grade 4 fever was reported for 35 participants in the mRNA-1345 group versus 29 participants in the placebo group (0.2% of participants in each group).

Table S13. Overall Summary of Unsolicited AEs within 28 Days after Injection (Safety Set).

	mRNA-1345, 50 µg (N=17,734) n (%)	Placebo (N=17,679) n (%)
Unsolicited AEs up to 28 days after vaccination, regardless of relationship to study vaccination		
All unsolicited AEs	3624 (20.4)	3331 (18.8)
Serious	102 (0.6)	93 (0.5)
Fatal[*]	2 (<0.1)	4 (<0.1)
Medically attended	1842 (10.4)	1739 (9.8)
AEs leading to study discontinuation	2 (<0.1)	9 (<0.1)
Severe/≥Grade 3	124 (0.7)	119 (0.7)
Non-serious[†]	3522 (19.9)	3238 (18.3)
Severe/≥Grade 3[†]	63 (0.4)	65 (0.4)
≥1 non-serious event[‡]	3570 (20.1)	3273 (18.5)
Severe/≥Grade 3[‡]	70 (0.4)	66 (0.4)
Any AESI	3 (<0.1)	8 (<0.1)
Unsolicited AEs up to 28 days after vaccination, related to study vaccination		
All unsolicited AEs	1033 (5.8)	803 (4.5)
Serious	4 (<0.1)	3 (<0.1)
Fatal	0	0
Medically attended	71 (0.4)	56 (0.3)
AEs leading to study discontinuation	1 (<0.1)	0
Severe/≥Grade 3	52 (0.3)	48 (0.3)
Non-serious[†]	1029 (5.8)	800 (4.5)
Severe/≥Grade 3[†]	50 (0.3)	46 (0.3)
≥1 non-serious event[‡]	1032 (5.8)	800 (4.5)
Severe/≥Grade 3[‡]	51 (0.3)	46 (0.3)
Any AESI	1 (<0.1)	1 (<0.1)

AESI, adverse event of special interest; AR, adverse reaction; COPD, chronic obstructive pulmonary disease; ER, emergency room; MAAE, medically attended adverse event; SAE, serious adverse event; AE, adverse event.
Percentages were based on the number of participants in the Safety Set.
An AE was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
Severe AEs included both unsolicited severe AEs and ≥Grade 3 solicited ARs that met SAE criteria or lasted beyond 7 days after injection.
Medically attended AEs included ER/urgent care, outpatient physician visits, and per-protocol illness visits.
[*]In the mRNA-1345 group, a fatal event of bronchial aspiration was reported with onset on day 21 in one participant. One participant in the mRNA-1345 group had a non-serious event of gingivitis with onset on day 13 and resolution on day 26 that was erroneously reported as a fatal event. In the placebo group, the fatal events were road traffic accident reported on day 6, pneumonia with onset on day 13, COPD exacerbation

with onset on day 12, and unknown cause of death with onset on day 27. None of the deaths were considered by the investigator to be related to study injection.

[†]Participants who did not report any serious AE were included in the summary of "non-serious" and "severe/≥grade 3 non-serious."

[‡]Participants with at least one non-serious AE were included.

Table S14. Participant Incidence of Serious AEs Regardless of Causality Up to 28 Days after Injection by System Organ Class and Preferred Term (PTs Reported for ≥2 Participants in Either Group [Safety Set]).

System Organ Class Preferred Term	mRNA-1345, 50 µg (N=17734) n (%)	Placebo (N=17679) n (%)
Number of participants reporting serious AEs	102 (0.6)	93 (0.5)
Number of serious AEs	117	120
Infections and infestations	22 (0.1)	7 (<0.1)
Pneumonia	6 (<0.1)	2 (<0.1)
Gastroenteritis	2 (<0.1)	0
Influenza	2 (<0.1)	0
Urinary tract infection	2 (<0.1)	1 (<0.1)
Cellulitis	0	2 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (<0.1)	13 (<0.1)
Malignant melanoma	2 (<0.1)	1 (<0.1)
Breast cancer	1 (<0.1)	2 (<0.1)
Blood and lymphatic system disorders	0	2 (<0.1)
Anemia	0	2 (<0.1)
Immune system disorders	2 (<0.1)	1 (<0.1)
Anaphylactic reaction	2 (<0.1)	0
Metabolism and nutrition disorders	7 (<0.1)	2 (<0.1)
Dehydration	3 (<0.1)	0
Hyperglycemia	2 (<0.1)	0
Psychiatric disorders	3 (<0.1)	2 (<0.1)
Nervous system disorders	4 (<0.1)	11 (<0.1)
Syncope	2 (<0.1)	0
Cerebrovascular accident	0	3 (<0.1)
Ischemic stroke	0	4 (<0.1)
Seizure	0	2 (<0.1)
Cardiac disorders	12 (<0.1)	12 (<0.1)
Acute myocardial infarction	3 (<0.1)	3 (<0.1)
Coronary artery disease	2 (<0.1)	0
Cardiac failure congestive	1 (<0.1)	2 (<0.1)
Atrial fibrillation	0	3 (<0.1)
Vascular disorders	6 (<0.1)	4 (<0.1)
Hypertension	3 (<0.1)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	9 (<0.1)	10 (<0.1)
Chronic obstructive pulmonary disease	4 (<0.1)	6 (<0.1)

System Organ Class Preferred Term	mRNA-1345, 50 µg (N=17734) n (%)	Placebo (N=17679) n (%)
Gastrointestinal disorders	13 (<0.1)	10 (<0.1)
Peptic ulcer	2 (<0.1)	0
Hepatobiliary disorders	3 (<0.1)	2 (<0.1)
Cholecystitis acute	2 (<0.1)	1 (<0.1)
Renal and urinary disorders	4 (<0.1)	5 (<0.1)
Nephrolithiasis	2 (<0.1)	1 (<0.1)
General disorders and administration site conditions	2 (<0.1)	6 (<0.1)
Non-cardiac chest pain	0	3 (<0.1)
Injury, poisoning and procedural complications	8 (<0.1)	13 (<0.1)
Femur fracture	2 (<0.1)	1 (<0.1)
Humerus fracture	1 (<0.1)	2 (<0.1)
Foot fracture	0	2 (<0.1)
Wrist fracture	0	2 (<0.1)

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; AE, adverse event.

An AE was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.

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

Adverse events were coded using MedDRA, version 25.0.

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