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Applicant	ModernaTX, Inc.
Established Name	Respiratory Syncytial Virus (RSV) vaccine, mRNA
(Proposed) Trade Name	mRESVIA
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Single dose of 0.5 mL
Indication(s) and Intended Population(s)	Active immunization for the prevention of lower respiratory tract disease (LRTD) (b) (4) caused by RSV in adults 60 years of age and older

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Glossary

ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AESI	Adverse Events of Special Interest
AR	Adverse Reaction
ARD	Acute Respiratory Disease
BLA	Biologics License Application
BMI	Body Mass Index
CHF	Congestive Heart Failure
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendment
COPD	Chronic Obstructive Pulmonary Disease
DSMB	Data and Safety Monitoring Board
eCRF	electronic Case Report Form
FAS	Full Analysis Set
GBS	Guillain-Barré Syndrome
HR	Hazard Ratio
IA	Interim Analysis
IP	Investigational Product
LL	Lower Limit
LRTD	Lower Respiratory Tract Disease
MAAE	Medically Attended Adverse Events
mITT	Modified Intent-to-Treat Set
mRNA	Messenger Ribonucleic Acid
PPE	Per-Protocol Set for Efficacy
RS	Randomization Set
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SS	Safety Set
SSS	Solicited Safety Set
STN	Submission Tracking Number
U.S.	United States
VE	Vaccine Efficacy
YOA	Years of Age

1. Executive Summary

ModernaTX, Inc. submitted a rolling Biologics License Application (BLA) to seek licensure of the messenger ribonucleic acid-1345 (mRNA-1345) vaccine intended to prevent (b) (4) lower respiratory tract disease (LRTD) (b) (4) caused by Respiratory Syncytial Virus (RSV) in adults 60 years of age (YOA) and older. The submission was completed on 12 September 2023. The BLA was designated as Priority Review.

A Phase 1 clinical study, P101, was conducted to determine both the dose level and number of doses for the pivotal Phase 2/3 clinical study, P301. Based on the results of P101, a single dose with a dose level of 50 µg was selected for P301. The BLA is supported primarily by both efficacy and safety data from P301.

P301 is a Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety and efficacy of a single dose of mRNA-1345 vaccine in adults 60 YOA and older. Subjects were randomized to receive either a single dose of mRNA-1345 vaccine or placebo in a 1:1 allocation ratio. Randomization was stratified by both age category (60 to 74 YOA versus ≥75 YOA) and risk factors for LRTD (present versus absent).

The two primary efficacy endpoints were the first episodes of RSV-LRTD with 2 or more or 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection. The two key secondary efficacy endpoints were the first episode of RSV-ARD and the first hospitalization associated with RSV-ARD within the period of 14 days post-injection up to 12 months post-injection. For each primary efficacy endpoint and each key secondary efficacy endpoint, the success criterion was that the lower limit (LL) of the 2-sided confidence interval (CI) for vaccine efficacy (VE) was > 20%.

For both primary efficacy endpoints, two interim analyses (IAs) were pre-specified based on the Lan-DeMets approximation to Pocock stopping boundaries with information fractions of 0.5 and 0.85 out of a target total of 86 and 32 cases, respectively. The success criterion for the trial was the rejection of the null hypothesis for the first primary efficacy endpoint (i.e., RSV-LRTD with 2 or more symptoms). If the success criterion was met, the null hypothesis of the second primary efficacy endpoint (i.e., RSV-LRTD with 3 or more symptoms) was to be tested.

The null hypothesis of the first key secondary efficacy endpoint (i.e., RSV-ARD) was to be tested only once, conditional on the rejection of the null hypotheses for both primary efficacy endpoints. Similarly, the null hypothesis of the second key secondary efficacy endpoint (i.e., hospitalization associated with RSV-ARD) was to be tested only once, conditional on the rejection of the null hypotheses for both primary efficacy endpoints and the first key secondary efficacy endpoint.

At the first IA, the success criterion for the trial was met. The three null hypotheses for both primary efficacy endpoints of RSV-LRTD and the first key secondary efficacy endpoint of RSV-ARD were all rejected. The null hypothesis for hospitalization associated with RSV-ARD was not tested due to an insufficient number of cases. Hence, the second IA was not conducted. The

median duration of follow-up at the IA was 112 days up to the data cutoff of 30 November 2022 in both groups.

For RSV-LRTD with 2 or more symptoms, 15 and 70 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 78.7% with 2-sided 95.04% CI (62.8%, 87.9%). The alpha value of 4.96% for the 2-sided CI was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.99 (85 out of total of 86 cases). Because the LL of the 2-sided CI was above 20%, the success criterion for the first primary efficacy endpoint (and the trial) was met.

For RSV-LRTD with 3 or more symptoms, 5 and 26 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 80.9% with 2-sided 95.10% CI (50.1%, 92.7%). The alpha value of 4.90% for the 2-sided CI was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.97 (31 out of total of 32 cases). Because the LL of the 2-sided CI was above 20%, the success criterion for the second primary efficacy endpoint was met.

For RSV-ARD, 33 and 106 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 69.1% with 95% CI (54.3%, 79.1%). Because the LL of the CI was above 20%, the success criterion for the first key secondary efficacy endpoint was met.

For hospitalization associated with RSV-ARD, only one case (in the placebo group) met the corresponding case definition. Therefore, no meaningful inference could be drawn for the null hypothesis of the second key secondary efficacy endpoint at the IA.

Additional efficacy analyses were conducted up to the data cutoff of 30 April 2023. The median duration of follow-up was 257 days in both groups.

Compared to the IA, for both RSV-LRTD with 2 or more symptoms and 3 or more symptoms, VEs declined from 78.7% with 95.04% CI (62.8%, 87.9%) to 62.5% with 95% CI (47.7%, 73.1%) and from 80.9% with 95.10% CI (50.1%, 92.7%) to 61.1% with 95% CI (34.7%, 76.8%), respectively. For RSV-ARD, VE declined from 69.1% with 95% CI (54.3%, 79.1%) to 54.1% with 95% CI (40.8%, 64.4%). For hospitalization associated with RSV-ARD, only two cases (both in the placebo group) met the corresponding case definition.

Overall, the mRNA-1345 vaccine met the primary efficacy objectives evaluated in P301. No major statistical issues have been identified.

Safety analyses were conducted up to the data cutoff of 24 June 2023. The median duration of follow-up was 311 days in both groups.

Solicited Adverse Reactions (ARs) and unsolicited Adverse Events (AEs) were collected through 7 and 28 days, respectively, post-injection. Unsolicited AEs included Medically Attended Adverse Events (MAAEs), Adverse Events of Special Interest (AESIs), and Serious Adverse Events (SAEs).

Within 7 days post-injection, rates of solicited local and systemic ARs were generally higher in the mRNA-1345 group than the placebo group. Injection site pain was the most frequently reported solicited local AR, while fatigue was the most frequently reported solicited systemic AR.

Within 28 days post-injection, for unsolicited AEs regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs, MAAEs, AESIs, SAEs, and deaths in both groups. For unsolicited AEs considered by the investigator to be related to study vaccination, there were also similar percentages of unsolicited AEs, MAAEs, AESIs, and SAEs in both groups. These findings generally held for the unsolicited AEs collected up to the data cutoff of 24 June 2023. No events of either Guillain-Barré Syndrome (GBS) or acute disseminated encephalomyelitis (ADEM) were reported. As determined by the investigator, no related deaths and no related events of either myocarditis or pericarditis were reported.

The results of both the interim efficacy analysis and additional efficacy analysis and safety analysis were included in the label.

Overall, both the efficacy and safety data support licensure of the mRNA-1345 vaccine in adults 60 YOA and older.

2. Clinical and Regulatory Background

ModernaTX, Inc. submitted a rolling BLA to seek licensure of the mRNA-1345 vaccine intended to prevent ^{(b) (4)} LRTD ^{(b) (4)} caused by RSV in adults 60 YOA and older. The submission was completed on 12 September 2023. The BLA was designated as Priority Review.

A Phase 1 clinical study, P101, was conducted to determine the dose level and number of doses for the pivotal Phase 2/3 clinical study, P301. Based on the results of P101, a dose level of 50 µg, single dose, was selected for P301. The BLA is supported primarily by both efficacy and safety data from P301.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

During the BLA review process, some inconsistencies were identified among the Study Data Tabulation Model (SDTM) datasets (e.g., flags, dates, etc.) which had to be corrected and the datasets re-submitted. In addition, the datasets were updated with Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) results from samples collected by the respective data cutoff that were previously unavailable in the original efficacy analyses.

To reflect these changes, in amendment 38, Moderna submitted a document entitled “Summary of Changes to Clinical Study Report Data” which included updated efficacy and safety analyses based on a later data extraction date of 13 February 2024. This BLA review memo covers the updated analyses. A comparison between the VE analyses from the original BLA submission and

the updated VE analyses for both the IA and the additional analysis is included in Tables 10 and 11.

3.2 Compliance With Good Clinical Practice and Data Integrity

No data integrity issues were identified during the review.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to reviews of other review disciplines.

5. Sources of Clinical Data and Other Information Considered

5.1 Review Strategy

This review memo focuses on the pivotal Phase 2/3 clinical study, P301, supporting licensure of the single dose mRNA-1345 vaccine for adults 60 YOA and older. The Phase 1 clinical study, P101, is not included in this review memo.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents submitted to the BLA are reviewed:

STN 125796/0.1 (submitted on 9/12/2023)

1. Module 5. Clinical Study Reports
 - P301 Clinical Study Report

STN 125796/0.38 (submitted on 2/26/2024)

1. Module 5. Clinical Study Reports
 - P301 Summary of Changes to Clinical Study Report Data

STN 125796/0.41 (submitted on 3/6/2024)

1. Module 5. Clinical Study Reports
 - P301 FDA RTQ 27 Ad hoc Analysis

STN 125796/0.44 (submitted on 3/8/2024)

1. Module 5. Clinical Study Reports
 - P301 Response to Information Request 29

STN 125796/0.45 (submitted on 3/12/2024)

1. Module 5. Clinical Study Reports
 - P301 FDA RTQ 29 Ad hoc Analysis

5.3 Table of Studies/Clinical Trials

Two clinical studies, P101 and P301, were conducted to support licensure of the mRNA-1345 vaccine and are summarized in Table 1.

Table 1: Clinical Studies Supporting the BLA

Study	N	Age	Description
P101	425	≥ 18 YOA	Phase 1, randomized, observer-blind, placebo-controlled, dose-escalation study to evaluate the safety and immunogenicity of different doses of mRNA-1345 vaccine in adults 18 YOA and older
P301	36557	≥ 60 YOA	Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety and efficacy of a single dose of mRNA-1345 vaccine in adults 60 YOA and older

N = number of enrolled subjects.

Source: Adapted from both P101 and P301 Clinical Study Reports.

6. Discussion of Individual Studies/Clinical Trials

6.1 Clinical Study P301

Title of Study: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in Adults ≥ 60 Years of Age

Dates:

1. Study initiation date (First Subject First Visit): 17 November 2021
2. Data cutoff date for interim efficacy analyses: 30 November 2022
3. Data cutoff date for additional efficacy analyses: 30 April 2023
4. Data cutoff date for safety analyses: 24 June 2023

6.1.1 Objectives

Primary Efficacy Objective:

1. To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.

Key Secondary Efficacy Objectives:

1. To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-ARD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.
2. To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of first hospitalization associated with RSV-ARD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.

Secondary Efficacy Objective:

1. To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of the first episode of RSV-LRTD as compared with placebo by RSV subtype.

Safety Objective:

1. To evaluate the safety and tolerability of the mRNA-1345 vaccine.

6.1.2 Design Overview

P301 initially began as a Phase 2 clinical study to evaluate the safety of the mRNA-1345 vaccine, where 2,000 participants were randomized to either mRNA-1345 vaccine or placebo in a 1:1 allocation ratio. Randomization was stratified by both age category (60 to 74 YOA versus ≥ 75 YOA) and risk factors for LRTD (present versus absent).

Once at least 400 participants were enrolled in Phase 2, the data were submitted to the Data and Safety Monitoring Board (DSMB) for unblinded review and enrollment continued until the review was complete. The DSMB reviewed safety data from the first 400 participants who received the study injection and had at least 28 days of study follow-up. No concerns with respect to the safety data were identified by the DSMB.

As a result, Phase 3 of P301 was cleared for enrollment, where 35,000 additional participants were planned to be enrolled and randomized to either mRNA-1345 vaccine or placebo according to the same allocation ratio and stratification factors as the participants in Phase 2. Both Phases 2 and 3 contributed to both the efficacy and safety analyses, hence the Phase 2/3 study design, with a total target enrollment of 37,000 participants.

Subjects were to be followed for 24 months post-injection. The primary efficacy analyses were case-driven, with a target total accrual of 86 and 32 RSV-LRTD cases with ≥ 2 and ≥ 3 symptoms, respectively, and two pre-specified IAs at 0.5 and 0.85 information fractions. The first IA for the primary efficacy endpoints was conducted when 85 RSV-LRTD cases with ≥ 2 symptoms were accrued and met the success criterion for the trial (i.e., the rejection of the null hypothesis for the first primary efficacy endpoint). As such, the second IA was not conducted. Additional efficacy analyses were conducted after the first IA up to the data cutoff of 30 April 2023, with a median follow-up duration of 257 days post-injection in both groups.

For safety, solicited ARs were collected through 7 days post-injection. Unsolicited AEs (including MAAEs, AESIs, SAEs, and AEs leading to study discontinuation) were collected through 28 days post-injection and up to the data cutoff of 24 June 2023.

6.1.3 Population

Adults 60 YOA and older were enrolled.

6.1.4 Study Treatments or Agents Mandated by the Protocol

A single dose of 50 μ g mRNA-1345 or saline placebo was administered.

6.1.6 Sites and Centers

Phase 2 was conducted at 55 centers in the U.S. Phase 3 was conducted at 269 centers across 22 countries.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review memo.

6.1.8 Endpoints and Study Success Criteria

Primary Efficacy Endpoints:

1. Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection.
 - The LL of the 2-sided CI for VE is > 20%.
2. Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection.
 - The LL of the 2-sided CI for VE is > 20%.

Key Secondary Efficacy Endpoints:

1. 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.
 - The LL of the 2-sided CI for VE is > 20%.
2. Vaccine efficacy of mRNA-1345 to prevent first hospitalization associated with RSV-ARD within the period of 14 days post-injection up to 12 months post-injection.
 - The LL of the 2-sided CI for VE is > 20%.

Secondary Efficacy Endpoint:

1. Vaccine efficacy of mRNA-1345 to prevent the first episode of RSV-LRTD by RSV subtype A and RSV subtype B.

Safety Endpoints:

1. Numbers and percentages of participants with solicited local and systemic ARs up to 7 days post-injection.
2. Unsolicited AEs (including MAAEs, AESIs, SAEs, and AEs leading to study discontinuation) up to 28 days post-injection.
3. Unsolicited AEs (including MAAEs, AESIs, SAEs, and AEs leading to study discontinuation) up to the data cutoff.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Efficacy

For the efficacy analyses, the stratified Cox proportional hazards model with study vaccination group as a fixed effect and stratification factors for both age category (60 to <75 YOA or ≥ 75 YOA) and risk factors for LRTD (present versus absent) was used to estimate the hazard ratio (HR). Efron's method was used to handle ties. VE was estimated as $VE = 100 * (1 - HR)$. Case definitions are displayed in Table 2.

Cases were counted from 14 days post-injection up to 12 months post-injection. Participants without a case were censored at the earliest date of 12 months post-injection, date of early discontinuation, date of unrelated death, or data cutoff date (30 November 2022 for the IA; 30 April 2023 for the Additional Efficacy Analysis). Participants with a case before 14 days post-injection were censored at the case date.

All cases related to the efficacy endpoints were collected, but only the first case from each subject was considered for the efficacy analyses. Missing data were not replaced.

All primary efficacy analyses were performed on the Per-Protocol Set for Efficacy (PPE), which was a subset of the Modified Intent-to-Treat Set (mITT), which was a subset of the Full Analysis Set (FAS), which was a subset of Randomization Set (RS). All four analysis sets are defined below as:

- RS: All randomized participants regardless of the participant's investigational product (IP) administration status.
 - FAS: Participants in the RS who received any IP. Participants were analyzed according to the vaccination group to which they were randomized.
 - mITT: Participants in the FAS who completed at least 1 visit or surveillance 14 days after the IP administration.
 - PPE: Participants in the mITT who received the assigned IP dose according to protocol, completed at least 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.

Analyses were performed by age category, RSV subtype, sex, race, ethnicity, region, pre-specified comorbid conditions, and other risk factors.

Table 2: Case Definitions of RSV-LRTD and RSV-ARD

Term	Definition
RSV-LRTD with 2 or more or 3 or more symptoms	<p>RT-PCR-confirmed RSV infection^a PLUS new or worsening of 2 or more or 3 or more of the following symptoms, lasting for at least 24 hours:</p> <ul style="list-style-type: none"> • shortness of breath; • cough and/or fever ($\geq 37.8^{\circ}\text{C}$ [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 $\leq 93\%$ or new or increasing use of supplemental oxygen); • pleuritic chest pain.
RSV-ARD	<p>RT-PCR-confirmed RSV infection^a PLUS an acute symptomatic respiratory disease manifesting as new or worsening of 1 or more of the following symptoms, lasting for at least 24 hours:</p> <ul style="list-style-type: none"> • cough; • stuffy nose; • runny nose; • sore throat; • fever ($\geq 37.8^{\circ}\text{C}$ [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 $\leq 93\%$ or new or increasing use of supplemental oxygen); • wheezing; • sputum production; • hoarseness; • sinus pain; • chills; • pleuritic chest pain.

^aCase definition required that eligible symptoms onset occur within 14 days of positive RSV RT-PCR nasopharyngeal swab specimen collection date. The primary analysis required that cases be confirmed by RT-PCR conducted by the study specialty laboratory or in a clinical laboratory improvement amendment (CLIA)-certified or CLIA-equivalent laboratory using an approved RT-PCR assay.

Source: Table 4 of P301 Clinical Study Report.

Analysis of Safety

All safety data were summarized descriptively. Solicited ARs and unsolicited AEs were summarized in the Solicited Safety Set (SSS) and Safety Set (SS), respectively, where the SSS was a subset of the SS. Both analysis sets are defined below as:

- SS: All randomized participants who received any IP. Participants were included in the vaccination group corresponding to the IP that they actually received.
- SSS: Participants in the SS who contributed any solicited AR data.

For both solicited ARs and unsolicited AEs, subgroup analyses were performed by age category, sex, race, ethnicity, U.S. versus non-U.S. region, World Bank region, comorbidities of interest, and frailty status.

Multiplicity Adjustment

The family-wise Type I error rate for testing both primary efficacy endpoints and both key secondary efficacy endpoints was fixed at one-sided $\alpha = 0.025$. For both primary efficacy endpoints, two IAs were pre-specified based on the Lan-DeMets approximation to Pocock stopping boundaries with information fractions of 0.5 and 0.85, respectively. The success criterion for the trial was the rejection of the null hypothesis for the first primary efficacy endpoint of RSV-LRTD with ≥ 2 symptoms. If the success criterion was met, the null hypothesis of the second primary efficacy endpoint of RSV-LRTD with ≥ 3 symptoms was to be tested.

The null hypothesis of the first key secondary efficacy endpoint of RSV-ARD was to be tested only once conditional on the rejection of the null hypotheses for both primary efficacy endpoints. Similarly, the null hypothesis of the second key secondary efficacy endpoint of hospitalization was to be tested only once conditional on the rejection of the null hypotheses for both primary efficacy endpoints and the first key secondary efficacy endpoint.

Sample Size Determination

The planned sample size of 37,000 (18,500 per arm) enrolled subjects, where 90% were expected to be evaluable, was calculated to yield adequate power for both primary efficacy endpoints and both key secondary efficacy endpoints.

For the first primary efficacy endpoint, an attack rate of 0.5% in the placebo group, a VE of 65%, and a target number of 86 cases yielded $\geq 90\%$ power for the log-rank test.

For the second primary efficacy endpoint, an attack rate of 0.2% in the placebo group, a VE of 80%, and a target number of 32 cases yielded $\geq 90\%$ power for the log-rank test.

For the first key secondary efficacy endpoint, an attack rate of 2.0% in the placebo group and a VE of 50% yielded $\geq 90\%$ power for the log-rank test.

For the second key secondary efficacy endpoint, an attack rate of 0.2% in the placebo group and a VE of 75% yielded $\geq 90\%$ power for the log-rank test.

6.1.10 Study Population and Disposition

Study population and disposition are presented for the Additional Efficacy Analysis and Safety Analysis only.

Additional Efficacy Analysis and Safety Analysis

Table 3 displays the sample size in each analysis set for both the mRNA-1345 and placebo groups. Totals of 18074 (98.8%) and 18010 (98.7%) participants in the mRNA-1345 and placebo groups, respectively, met the criteria for inclusion in the PPE.

Table 3: Number of Participants in Each Analysis Set - Additional Efficacy Analysis and Safety Analysis

-	mRNA-1345	Placebo
Randomization Set, n	18290	18250
Full Analysis Set, n (%) ^a	18230 (99.7)	18182 (99.6)
Modified Intent-to-Treat Set, n (%) ^a	18147 (99.2)	18100 (99.2)
Per-Protocol Efficacy Set, n (%) ^a	18074 (98.8)	18010 (98.7)
Safety Set ^{a,b}	18231 (99.7)	18181 (99.6)
Solicited Safety Set, n (%) ^a	18160 (99.3)	18098 (99.2)

^aNumbers were based on planned vaccination group, and percentages were based on the number of randomized participants.

^bThe number of participants in the mRNA-1345 group in the Safety Set is higher than the number in the Full Analysis Set because two participants who were randomized to placebo instead received mRNA-1345 and one participant who was randomized to mRNA-1345 instead received placebo.

Source: Table 14.1.2.1 of P301 Summary of Changes to Clinical Study Report Data.

Table 4 displays the dispositions of the RS for both the mRNA-1345 and placebo groups, where totals of 18290 and 18250 participants were randomized and 18230 (99.7%) and 18182 (99.6%) participants received a study intervention, respectively.

Table 4: Participant Disposition (RS) – Additional Efficacy Analysis and Safety Analysis

-	mRNA-1345 (N=18290) n (%)	Placebo (N=18250) n (%)
Number of participants	-	-
Received IP injection	18230 (99.7)	18182 (99.6)
Discontinued from study	1130 (6.2)	1193 (6.5)
Primary reason for discontinuation	-	-
Adverse event	9 (< 0.1)	13 (< 0.1)
Death	97 (0.5)	116 (0.6)
Lost to follow-up	461 (2.5)	435 (2.4)
Non-compliance with study drug	1 (< 0.1)	2 (< 0.1)
Physician decision	42 (0.2)	68 (0.4)
Protocol deviation	11 (< 0.1)	11 (< 0.1)
Withdrawal of consent by participant	472 (2.6)	509 (2.8)
Other	37 (0.2)	39 (0.2)

Source: Table 14.1.1.1 of P301 Summary of Changes to Clinical Study Report Data.

Table 5 displays the distributions of the demographic characteristics of the SS for both the mRNA-1345 and placebo groups, where totals of 18231 and 18181 participants were included, respectively. No meaningful differences in demographic characteristics were observed between the two groups. Demographic characteristics were generally similar in the PPE.

Table 5: Baseline Demographics and Characteristics (SS) – Additional Efficacy Analysis and Safety Analysis

-	mRNA-1345 (N=18231)	Placebo (N=18181)
Age at Enrollment (YOA)	-	-
n	18231	18181
Mean (SD)	68.5 (6.6)	68.5 (6.6)
Median	67.0	67.0
Min, Max	60, 108	60, 105
Age Category 1, n (%) ^a	-	-
60 to 74 YOA	14930 (81.9)	14876 (81.8)
≥ 75 YOA	3301 (18.1)	3305 (18.2)
Age Category 2, n (%) ^a	-	-
60 to 69 YOA	11304 (62.0)	11250 (61.9)
70 to 79 YOA	5490 (30.1)	5482 (30.2)
≥ 80 YOA	1437 (7.9)	1449 (8.0)
LRTD Risk Factors (CHF/COPD), n (%) ^a	-	-
Present	1310 (7.2)	1317 (7.2)
CHF	219 (1.2)	214 (1.2)
COPD	1037 (5.7)	1050 (5.8)
CHF and COPD	54 (0.3)	53 (0.3)
Absent	16921 (92.8)	16864 (92.8)
Gender, n (%)	-	-
Male	9343 (51.2)	9238 (50.8)
Female	8888 (48.8)	8943 (49.2)
Race, n (%)	-	-
White	11266 (61.8)	11252 (61.9)
Black or African American	2197 (12.1)	2158 (11.9)
Asian	2013 (11.0)	1995 (11.0)
American Indian or Alaska Native	905 (5.0)	892 (4.9)
Native Hawaiian or Other Pacific	27 (0.1)	19 (0.1)
Other	994 (5.5)	1009 (5.5)
Multiple	760 (4.2)	751 (4.1)
Unknown	10 (< 0.1)	20 (0.1)
Not Reported	59 (0.3)	85 (0.5)
Race Group, n (%)	-	-
White	11266 (61.8)	11252 (61.9)
Black	2197 (12.1)	2158 (11.9)
Asian	2013 (11.0)	1995 (11.0)
Other ^b	2686 (14.7)	2671 (14.7)
Unknown/Not Reported	69 (0.4)	105 (0.6)
Ethnicity, n (%)	-	-
Hispanic or Latino	6091 (33.4)	6147 (33.8)
Not Hispanic or Latino	11955 (65.6)	11825 (65.0)
Unknown	27 (0.1)	22 (0.1)
Not Reported	158 (0.9)	187 (1.0)
Height (cm)	-	-
n	18217	18161
Mean (SD)	166.2 (10.8)	166.2 (10.8)
Median	166.0	166.0
Min, Max	125.0, 203.5	110.0, 208.3

Table 5: Baseline Demographics and Characteristics (SS) – Additional Efficacy Analysis and Safety Analysis (continued)

-	mRNA-1345 (N=18231)	Placebo (N=18181)
Weight (kg)	-	-
n	18217	18161
Mean (SD)	75.6 (16.1)	75.5 (16.0)
Median	75.1	75.0
Min, Max	31.0, 143.0	30.2, 143.2
Body Mass Index (BMI) (kg/m ²)	-	-
n	18216	18161
Mean (SD)	27.2 (4.2)	27.1 (4.2)
Median	27.2	27.1
Min, Max	16.8, 38.4	11.8, 49.8
BMI Group, n (%)	-	-
< 30 kg/m ²	13155 (72.2)	13167 (72.4)
≥ 30 kg/m ²	5061 (27.8)	4994 (27.5)
Missing	15 (< 0.1)	20 (0.1)
Edmonton Frail Scale Total Score	-	-
n	17341	17286
Mean (SD)	2.3 (1.8)	2.3 (1.8)
Median	2.0	2.0
Min, Max	0, 14	0, 14
Edmonton Frail Scale Total Score Category, n (%)	-	-
0-3: Fit	13501 (74.1)	13359 (73.5)
4-5: Vulnerable	2834 (15.5)	2902 (16.0)
6-7: Mild Frailty	812 (4.5)	826 (4.5)
8-9: Moderate Frailty	169 (0.9)	160 (0.9)
10 or More: Severe Frailty	25 (0.1)	39 (0.2)
Missing	890 (4.9)	895 (4.9)
Frailty Status 1, n (%)	-	-
0-3: Fit	13501 (74.1)	13359 (73.5)
4-5: Vulnerable	2834 (15.5)	2902 (16.0)
6 or More: Frailty	1006 (5.5)	1025 (5.6)
Missing	890 (4.9)	895 (4.9)
Frailty Status 2, n (%)	-	-
0-3: Fit	13501 (74.1)	13359 (73.5)
4 or More: Vulnerable/Frailty	3840 (21.1)	3927 (21.6)
Missing	890 (4.9)	895 (4.9)
World Bank Region, n (%)	-	-
North America/Europe	11099 (60.9)	11064 (60.9)
Central/Latin America/Africa	5174 (28.4)	5163 (28.4)
Asian Pacific	1958 (10.7)	1954 (10.7)
World Bank Income Level 2022, n (%)	-	-
Lower-Middle-Income Economies	1212 (6.6)	1209 (6.6)
Upper-Middle-Income Economies	4841 (26.6)	4826 (26.5)
High-Income Countries	12178 (66.8)	12146 (66.8)
History of COVID-19, n (%)	-	-
No	16299 (89.4)	16364 (90.0)
Yes	1932 (10.6)	1817 (10.0)
History of Hospitalization due to COVID-19, n (%)	-	-
No	18119 (99.4)	18069 (99.4)
Yes	112 (0.6)	112 (0.6)

Table 5: Baseline Demographics and Characteristics (SS) – Additional Efficacy Analysis and Safety Analysis (continued)

-	mRNA-1345 (N=18231)	Placebo (N=18181)
Comorbidities of Interest, n (%) ^c	-	-
0	12824 (70.3)	12886 (70.9)
≥ 1	5407 (29.7)	5295 (29.1)

^aDerived from age and risk collected on eCRFs.

^bOther race includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, or Multiple.

^cComorbidities of Interest include COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease or advanced renal disease.

Source: Table 14.1.3.6 of P301 Summary of Changes to Clinical Study Report Data.

Reviewer's Comment:

- At the Interim Efficacy Analysis, totals of 17561 and 17503 participants in the mRNA-1345 and placebo groups, respectively, met the criteria for inclusion in the PPE. Demographic characteristics were generally similar in the PPE between the Interim and Additional Efficacy Analyses.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Efficacy Endpoints

Interim Efficacy Analysis

For the interim efficacy analysis, the results for both primary efficacy endpoints are displayed in Table 6. The median follow-up was 112 days in both groups.

For RSV-LRTD with 2 or more symptoms, 15 and 70 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 78.7% with 2-sided 95.04% CI (62.8%, 87.9%). The alpha value of 4.96% for the 2-sided CI was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.99 (85 out of total of 86 cases). Because the LL of the 2-sided CI was above 20%, the success criterion for the first primary efficacy endpoint (and the trial) was met.

For RSV-LRTD with 3 or more symptoms, 5 and 26 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 80.9% with 2-sided 95.10% CI (50.1%, 92.7%). The alpha value of 4.90% for the 2-sided CI was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.97 (31 out of total of 32 cases). Because the LL of the 2-sided CI was above 20%, the success criterion for the second primary efficacy endpoint was met.

Additional Efficacy Analysis

For the Additional Efficacy Analysis, the results for both primary efficacy endpoints are displayed in Table 7. The median follow-up was 257 days in both groups.

Compared to the IA, for both RSV-LRTD with 2 or more symptoms and 3 or more symptoms, VE estimates declined from 78.7% with 95.04% CI (62.8%, 87.9%) to 62.5% with 95% CI (47.7%, 73.1%) and from 80.9% with 95.10% CI (50.1%, 92.7%) to 61.1% with 95% CI (34.7%, 76.8%), respectively. For RSV-LRTD with 2 or more symptoms, 48 and 127 cases were reported in the mRNA-1345 and placebo groups, respectively. For RSV-LRTD with 3 or more symptoms, 20 and 51 cases were reported in the mRNA-1345 and placebo groups, respectively.

Reviewer's Comment:

- *Both the efficacy (Section 6.1.11) and safety (Sections 6.1.12) analyses were verified based on data submitted in the Study Data Tabulation Model format, and the results were consistent with those reported by the Applicant.*

6.1.11.2 Analyses of Secondary Efficacy Endpoints

Interim Efficacy Analysis

For the interim efficacy analysis, the results for the first key secondary efficacy endpoint of RSV-ARD are displayed in Table 8.

For RSV-ARD, 33 and 106 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 69.1% with 95% CI (54.3%, 79.1%). Because the LL of the CI was above 20%, the success criterion for the first key secondary efficacy endpoint was met.

For hospitalization associated with RSV-ARD, only one case (in the placebo group) met the corresponding case definition. Therefore, no meaningful inference could be drawn for the null hypothesis of the second key secondary efficacy endpoint.

Additional Efficacy Analysis

For the Additional Efficacy Analysis, the results for the first key secondary efficacy endpoint of RSV-ARD are displayed in Table 9.

Compared to the IA, for RSV-ARD, VE estimate declined from 69.1% with 95% CI (54.3%, 79.1%) to 54.1% with 95% CI (40.8%, 64.4%) with 87 and 188 cases reported in the mRNA-1345 and placebo groups, respectively.

For hospitalization associated with RSV-ARD, only two cases (both in the placebo group) met the corresponding case definition.

For both RSV-LRTD with 2 or more and 3 or more symptoms, Table 7 displays VE by RSV subtype. For RSV-LRTD with 2 or more symptoms, VE was numerically higher for RSV-A at 68.2% with 95% CI (50.0%, 79.7%) than RSV-B at 56.3% with 95% CI (27.9%, 73.5%). For

RSV-LRTD with 3 or more symptoms, VEs were similar for RSV-A at 63.6% with 95% CI (27.3%, 81.7%) and RSV-B at 59.3% with 95% CI (11.7%, 81.3%).

6.1.11.3 Subpopulation Analyses

Additional Efficacy Analysis

For both RSV-LRTD with 2 or more and 3 or more symptoms, Table 7 displays VE by age category.

For RSV-LRTD with 2 or more symptoms, VE point estimates were > 55% across the age categories of 60 to 74 YOA, 60 to 69 YOA, and 70 to 79 YOA. VE point estimates were generally lower for the older age categories, with VEs < 40% across age categories of ≥ 75 YOA and ≥ 80 YOA.

For RSV-LRTD with 3 or more symptoms, VE point estimates were > 55% across the age categories of 60 to 74 YOA, 60 to 69 YOA, and 70 to 79 YOA. Due to the small numbers of cases across age categories of ≥ 75 YOA and ≥ 80 YOA, findings for these subgroups were limited.

For RSV-ARD, Table 9 displays VE by both RSV subtype and age category. VE was numerically higher for RSV-A at 59.5% with 95% CI (42.5%, 71.5%) than RSV-B at 48.5% with 95% CI (25.3%, 64.5%). For RSV-ARD, VE point estimates were > 45% across all age categories but ≥ 80 YOA, where findings in this subgroup were limited due to the small number of cases.

For both RSV-LRTD with 2 or more and 3 or more symptoms as well as RSV-ARD, across the other subgroups of sex, race, ethnicity, region, pre-specified comorbid conditions, and other risk factors, no meaningful differences in VEs were observed (not shown in tables).

Reviewer's Comment:

- *The Summary of Changes to Clinical Study Report Data document included updated efficacy analyses based on a later data extraction date of 13 February 2024. The updated efficacy analyses identified more cases for both the primary efficacy endpoints of RSV-LRTD and first key secondary efficacy endpoint of RSV-ARD for both the Interim Efficacy Analysis and Additional Efficacy Analysis that were originally unavailable due to operational reasons. For each efficacy endpoint, Tables 10 and 11 display both the original and updated VEs for the Interim Efficacy Analysis and Additional Efficacy Analysis. Each original and updated VE differed at most by five percentage points.*

Table 6: VE based on HR of mRNA-1345 to Prevent First Episode of both RSV-LRTD With 2 or More Symptoms and 3 or More Symptoms Between 14 Days Post-Injection up to 12 Months Post-injection (PPE) – Interim Efficacy Analysis

-	mRNA-1345 N	mRNA-1345 Cases	Placebo N	Placebo Cases	VE ^a (% CI ^b)
RSV-LRTD with 2 or more symptoms	17561	15	17503	70	78.7 (62.8, 87.9)
RSV-LRTD with 3 or more symptoms	17561	5	17503	26	80.9 (50.1, 92.7)

^aVE = 100 * (1 – HR), where HR was estimated from the stratified Cox proportional hazards model with study vaccination group as a fixed effect. For both the overall analyses and analyses by RSV subtype, the stratification factors included both age category (60 to <75 YOA or ≥75 YOA) and risk factors for LRTD (present versus absent). For the subgroup analyses by age category, risk factors for LRTD (present versus absent) was the only stratification factor.

^bFor RSV-LRTD with 2 or more symptoms, 95.04% CI where the alpha value of 4.96% was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.99 (85 out of total of 86 cases). For RSV-LRTD with 3 or more symptoms, 95.10% CI where the alpha value of 4.90% was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.97 (31 out of total of 32 cases).

Source: Adapted from both Tables 10.11.1.1 and 10.11.2.1 of P301 FDA RTQ 29 Ad hoc Analysis.

Table 7: VE based on HR of mRNA-1345 to Prevent First Episode of both RSV-LRTD With 2 or More Symptoms and 3 or More Symptoms Between 14 Days Post-Injection up to 12 Months Post-injection (PPE) – Additional Efficacy Analysis

-	mRNA-1345 N	mRNA-1345 Cases	Placebo N	Placebo Cases	VE ^a (95% CI)
RSV-LRTD with 2 or more symptoms	18074	48 ^b	18010	127 ^c	62.5 (47.7, 73.1)
60 to 74 YOA	14798	37	14733	110	66.7 (51.7, 77.0)
≥ 75 YOA	3276	11	3277	17	35.3 (-38.1, 69.7)
60 to 69 YOA	11193	32	11146	77	58.8 (37.8, 72.7)
70 to 79 YOA	5455	10	5431	45	78.0 (56.3, 88.9)
≥ 80 YOA	1426	6	1433	5	-20.0 (-293.3, 63.4)
RSV-A Only	18074	25	18010	78	68.2 (50.0, 79.7)
RSV-B Only	18074	22	18010	50	56.3 (27.9, 73.5)
RSV-LRTD with 3 or more symptoms	18074	20	18010	51 ^c	61.1 (34.7, 76.8)
60 to 74 YOA	14798	17	14733	46	63.4 (36.1, 79.0)
≥ 75 YOA	3276	3	3277	5	40.0 (-150.9, 85.7)
60 to 69 YOA	11193	14	11146	31	55.1 (15.6, 76.1)
70 to 79 YOA	5455	4	5431	18	77.9 (34.6, 92.5)
≥ 80 YOA	1426	2	1433	2	0.3 (-607.7, 86.0)
RSV-A Only	18074	11	18010	30	63.6 (27.3, 81.7)
RSV-B Only	18074	9	18010	22	59.3 (11.7, 81.3)

^aVE = 100 * (1 – HR), where HR was estimated from the stratified Cox proportional hazards model with study vaccination group as a fixed effect. For both the overall analyses and analyses by RSV subtype, the stratification factors included both age category (60 to <75 YOA or ≥75 YOA) and risk factors for LRTD (present versus absent). For the subgroup analyses by age category, risk factors for LRTD (present versus absent) was the only stratification factor.

^bOne case was reported with RSV subtype unknown.

^cOne case was reported with both RSV-A and RSV-B subtype.

Source: Adapted from Table 10 of P301 Summary of Changes to Clinical Study Report Data and Tables 14.2.2.1.10.1, 14.2.2.2.10.1, 14.2.2.9.1, and 14.2.2.10.1 of P301 FDA RTQ 27 Ad hoc Analysis.

Table 8: VE based on HR of mRNA-1345 to Prevent First Episode of RSV-ARD Between 14 Days Post-Injection up to 12 Months Post-injection (PPE) – Interim Efficacy Analysis

-	mRNA-1345 N	mRNA-1345 Cases	Placebo N	Placebo Cases	VE ^a (95% CI)
RSV-ARD	17561	33	17503	106	69.1 (54.3, 79.1)

^aVE = 100 * (1 – HR), where HR was estimated from the stratified Cox proportional hazards model with study vaccination group as a fixed effect. For both the overall analyses and analyses by RSV subtype, the stratification factors included both age category (60 to <75 YOA or ≥75 YOA) and risk factors for LRTD (present versus absent). For the subgroup analyses by age category, risk factors for LRTD (present versus absent) was the only stratification factor.

Source: Adapted from Table 9 of P301 Summary of Changes to Clinical Study Report Data.

Table 9: VE based on HR of mRNA-1345 to Prevent First Episode of RSV-ARD Between 14 Days Post-Injection up to 12 Months Post-injection (PPE) – Additional Efficacy Analysis

-	mRNA-1345 N	mRNA-1345 Cases	Placebo N	Placebo Cases	VE ^a (95% CI)
RSV-ARD	18074	87 ^b	18010	188 ^c	54.1 (40.8, 64.4)
60 to 74 YOA	14798	72	14733	159	55.1 (40.7, 66.0)
≥ 75 YOA	3276	15	3277	29	48.5 (3.9, 72.4)
60 to 69 YOA	11193	57	11146	111	49.2 (30.0, 63.1)
70 to 79 YOA	5455	23	5431	69	67.0 (47.0, 79.4)
≥ 80 YOA	1426	7	1433	8	12.6 (-140.9, 68.3)
RSV-A Only	18074	44	18010	108	59.5 (42.5, 71.5)
RSV-B Only	18074	42	18010	81	48.5 (25.3, 64.5)

^aVE = 100 * (1 – HR), where HR was estimated from the stratified Cox proportional hazards model with study vaccination group as a fixed effect. For both the overall analyses and analyses by RSV subtype, the stratification factors included both age category (60 to <75 YOA or ≥75 YOA) and risk factors for LRTD (present versus absent). For the subgroup analyses by age category, risk factors for LRTD (present versus absent) was the only stratification factor.

^bOne case was reported with RSV subtype unknown.

^cOne case was reported with both RSV-A and RSV-B subtypes.

Source: Adapted from Table 10 of P301 Summary of Changes to Clinical Study Report Data and Tables 14.2.2.3.10.1 and 14.2.2.10.3 of P301 FDA RTQ 27 Ad hoc Analysis.

Table 10: Differences in VEs for Both Primary Efficacy Endpoints and First Key Secondary Efficacy Endpoint for the Interim Efficacy Analysis Between the Original P301 Clinical Study Report and Updated Analyses (PPE)

Efficacy Analysis	Efficacy Endpoint	mRNA-1345 N	mRNA-1345 Cases	Placebo N	Placebo Cases	VE ^a (% CI ^b)
Original Interim	RSV-LRTD with 2 or more symptoms	17572	9	17516	55	83.7 (66.0, 92.2)
Updated Interim	RSV-LRTD with 2 or more symptoms	17561	15	17503	70	78.7 (62.8, 87.9)
Original Interim	RSV-LRTD with 3 or more symptoms	17572	3	17516	17	82.4 (34.8, 95.3)
Updated Interim	RSV-LRTD with 3 or more symptoms	17561	5	17503	26	80.9 (50.1, 92.7)
Original Interim	RSV-ARD	17572	26	17516	82	68.4 (50.9, 79.7)
Updated Interim	RSV-ARD	17561	33 ^c	17503	106 ^c	69.1 (54.3, 79.1)

^aVE = 100 * (1 – HR), where HR was estimated from the stratified Cox proportional hazards model with study vaccination group as a fixed effect. The stratification factors included both age category (60 to <75 YOA or ≥75 YOA) and risk factors for LRTD (present versus absent).

^bFor the original IA for RSV-LRTD with 2 or more symptoms, 95.88% CI where the alpha value of 4.12% was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.74 (64 out of total of 86 cases). For the original IA for RSV-LRTD with 3 or more symptoms, 96.36% CI where the alpha value of 3.64% was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.63 (20 out of total of 32 cases). For the updated IA for RSV-LRTD with 2 or more symptoms, 95.04% CI where the alpha value of 4.96% was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.99 (85 out of total of 86 cases). For the updated IA for RSV-LRTD with 3 or more symptoms, 95.10% CI where the alpha value of 4.90% was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.97 (31 out of total of 32 cases). For both the original and updated IA for RSV-ARD, 95% CI.

^cThere were a total of 31 newly identified cases of RSV-ARD in the 13 February 2024 data extraction. These cases were not identified in the original IA because RT-PCR results were not available at the time.

Source: Adapted from Tables 19 and 23 of P301 Clinical Study Report and Table 9 of P301 Summary of Changes to Clinical Study Report Data.

Table 11: Differences in VEs for Both Primary Efficacy Endpoints and First Key Secondary Efficacy Endpoint for the Additional Efficacy Analysis Between the Original P301 Clinical Study Report and Updated Analyses (PPE)

Efficacy Analysis	Efficacy Endpoint	mRNA-1345 N	mRNA-1345 Cases	Placebo N	Placebo Cases	VE ^a (95% CI)
Original Additional	RSV-LRTD with 2 or more symptoms	18112	47	18045	127	63.3 (48.7, 73.7)
Updated Additional	RSV-LRTD with 2 or more symptoms	18074	48	18010	127	62.5 (47.7, 73.1)
Original Additional	RSV-LRTD with 3 or more symptoms	18112	19	18045	51	63.0 (37.3, 78.2)
Updated Additional	RSV-LRTD with 3 or more symptoms	18074	20	18010	51	61.1 (34.7, 76.8)
Original Additional	RSV-ARD	18112	86	18045	185	53.9 (40.5, 64.3)
Updated Additional	RSV-ARD	18074	87 ^b	18010	188 ^b	54.1 (40.8, 64.4)

^aVE = 100 * (1 – HR), where HR was estimated from the stratified Cox proportional hazards model with study vaccination group as a fixed effect. The stratification factors included both age category (60 to <75 YOA or ≥75 YOA) and risk factors for LRTD (present versus absent).

^bThere were a total of 4 newly identified cases of RSV-ARD in the 13 February 2024 data extraction. These cases were not identified in the original additional analysis because nasopharyngeal swab testing results were not available at the time.

Source: Adapted from Tables 28 and 34 of P301 Clinical Study Report and Table 10 of P301 Summary of Changes to Clinical Study Report Data.

Reviewer's Comments:

- Between the original BLA submission and the updated VE analyses for the IA, the sample sizes in the PPE decreased from 17572 to 17561 in the mRNA-1345 group and from 17516 to 17503 in the placebo group. Similarly, for the additional analysis, the sample sizes in the PPE decreased from 18112 to 18074 in the mRNA-1345 group and from 18045 to 18010 in the placebo group. This is because some subjects were later excluded due to a mix of newly discovered duplicate enrollment and protocol deviations, while some subjects were later included due to resolution of protocol deviations. Overall, the inclusion/exclusion of subjects resulted in small net decreases in the sample sizes of the PPE for the mRNA-1345 and placebo groups for the IA and additional analysis.
- For the updated VE analyses for both the IA and additional analysis, sensitivity analyses were conducted for the mITT. For the IA, the sample sizes in the mITT were 17634 and 17592 in the mRNA-1345 group and placebo group, respectively. For RSV-LRTD with 2 or more or 3 or more symptoms and RSV-ARD, the numbers of cases reported in both the mRNA-1345 group and placebo group were the same compared to the PPE. For the additional analysis, the sample sizes in the mITT were 18147 and 18100 in the mRNA-1345 group and placebo group, respectively. For RSV-LRTD with 3 or more symptoms, the numbers of cases reported in both the mRNA-1345 group and placebo group were the same compared to the PPE. For both RSV-LRTD with 2 or more symptoms and RSV-ARD, the numbers of cases reported in the mRNA-1345 group were the same, while there was one additional case reported in the placebo group compared to the PPE. The sensitivity analyses in the mITT confirmed the primary analyses in the PPE.

6.1.12 Safety Analyses

Solicited ARs

Overall Analyses

Table 12 displays both solicited local and systemic ARs within 7 days post-injection. Rates of solicited local and systemic ARs were generally higher in the mRNA-1345 group than the placebo group. Injection site pain (55.9%) was the most frequently reported solicited local AR, while fatigue (30.8%) was the most frequently reported solicited systemic AR.

Subgroup Analyses

Compared to the overall analysis, in the mRNA-1345 group, rates of any local and systemic ARs were generally higher among younger age categories, female participants, white participants, not Hispanic or Latino participants, and U.S. participants (not shown in tables). Rates of any local and systemic ARs were generally lower among participants in the Central/Latin America/Africa World Bank region. Across the subgroups of comorbidities of interest and frailty status, no meaningful differences in the rates of local or systemic ARs were observed.

Compared to the overall analysis, in the placebo group, rates of any local and systemic ARs were generally higher among female participants. Across the other subgroups, no meaningful differences in the rates of local or systemic ARs were observed.

Table 12: Summary of Participants With Solicited Adverse Reactions Within 7 Days Post-Injection by Grade (SSS)

Event	mRNA-1345 (N=18160) n (%)	Placebo (N=18098) n (%)
Local ARs, n	18157	18094
Local ARs, Any Grade	10584 (58.3)	2936 (16.2)
Local ARs, Grade 3	560 (3.1)	309 (1.7)
Pain, n	18156	18094
Pain, Any Grade	10155 (55.9)	2497 (13.8)
Pain, Grade 3 ^a	308 (1.7)	194 (1.1)
Axillary swelling/tenderness, n	18154	18093
Axillary swelling/tenderness, Any Grade	2761 (15.2)	1105 (6.1)
Axillary swelling/tenderness, Grade 3 ^a	138 (0.8)	117 (0.6)
Swelling (hardness), n	18155	18093
Swelling (hardness), Any Grade	674 (3.7)	60 (0.3)
Swelling (hardness), Grade 3 ^b	156 (0.9)	18 (< 0.1)
Erythema (redness), n	18154	18093
Erythema (redness), Any Grade	363 (2.0)	103 (0.6)
Erythema (redness), Grade 3 ^b	105 (0.6)	58 (0.3)
Systemic ARs, n	18157	18097
Systemic ARs, Any Grade	8608 (47.4)	5956 (32.9)
Systemic ARs, Grade 3	683 (3.8)	482 (2.7)
Systemic ARs, Grade 4	35 (0.2)	29 (0.2)
Fatigue, n	18153	18093
Fatigue, Any Grade	5586 (30.8)	3616 (20.0)
Fatigue, Grade 3 ^c	315 (1.7)	217 (1.2)
Myalgia, n	18153	18093
Myalgia, Any Grade	4652 (25.6)	2607 (14.4)
Myalgia, Grade 3 ^c	259 (1.4)	153 (0.8)
Arthralgia, n	18153	18092
Arthralgia, Any Grade	3945 (21.7)	2538 (14.0)
Arthralgia, Grade 3 ^c	201 (1.1)	133 (0.7)
Headache, n	18153	18093
Headache, Any Grade	4854 (26.7)	3404 (18.8)
Headache, Grade 3 ^d	277 (1.5)	207 (1.1)
Chills, n	18153	18092
Chills, Any Grade	2113 (11.6)	1226 (6.8)
Chills, Grade 3 ^c	110 (0.6)	78 (0.4)
Nausea/vomiting, n	18153	18092
Nausea/vomiting, Any Grade	1273 (7.0)	949 (5.2)
Nausea/vomiting, Grade 3 ^f	80 (0.4)	74 (0.4)
Fever, n	18146	18092
Fever, Any Grade	499 (2.7)	235 (1.3)
Fever, Grade 3 ^g	76 (0.4)	40 (0.2)
Fever, Grade 4 ^h	35 (0.2)	29 (0.2)

^aGrade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.

^bGrade 3 swelling and erythema: Defined as >100 mm / >10 cm.

^cGrade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

^dGrade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

^eGrade 3 chills: Defined as prevents daily activity and requires medical intervention.

^fGrade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.

^gGrade 3 fever: Defined as $\geq 39.0^{\circ} - \leq 40.0^{\circ}\text{C}$ / $\geq 102.1^{\circ} - \leq 104.0^{\circ}\text{F}$.

^hGrade 4 fever: Defined as $> 40.0^{\circ}\text{C}$ / $> 104.0^{\circ}\text{F}$.

Source: Table 14.3.1.2.1 of P301 Summary of Changes to Clinical Study Report Data.

Unsolicited AEs up to 28 days post-injection

Overall Analyses

Table 13 displays unsolicited AEs up to 28 days post-injection in the SS. For unsolicited AEs regardless of relationship to study vaccination, comparing the mRNA-1345 group to the placebo group, there were similar percentages of unsolicited AEs (20.8% and 19.0%, respectively), MAAEs (9.1% and 8.7%, respectively), AESIs ($< 0.1\%$ and $< 0.1\%$, respectively), SAEs (0.7% and 0.6%, respectively), AEs leading to study discontinuation ($< 0.1\%$ and $< 0.1\%$, respectively), Grade 3 unsolicited AEs (0.7% and 0.8%, respectively), and deaths ($< 0.1\%$ and $< 0.1\%$, respectively).

For unsolicited AEs considered by the investigator to be related to study vaccination, comparing the mRNA-1345 group to the placebo group, there were similar percentages of unsolicited AEs (5.7% and 4.4%, respectively), MAAEs (0.4% and 0.3%, respectively), AESIs ($< 0.1\%$ and $< 0.1\%$, respectively), SAEs ($< 0.1\%$ and $< 0.1\%$, respectively), and Grade 3 unsolicited AEs (0.3% and 0.3%, respectively). For the related AESIs, there was one each reported in the mRNA-1345 group (i.e., facial paralysis which was also reported as a related SAE) and placebo group (i.e., seizure). No related AEs leading to study discontinuation or related deaths were reported in either group.

One case of unrelated (as assessed by the investigator) pericarditis was reported in the placebo group on Day 8 post-injection. No events of either GBS, ADEM, or myocarditis were reported up to 28 days post-injection.

Subgroup Analyses

Up to 28 days post-injection, across the subgroups of age category, sex, race, ethnicity, U.S. versus non-U.S. region, World Bank region, comorbidities of interest, and frailty status, no notable differences in the rates of unsolicited AEs were observed (not shown in tables).

Table 13: Summary of Unsolicited AEs up to 28 Days Post-Injection (SS)

-	mRNA-1345 (N=18231) n (%)	Placebo (N=18181) n (%)
Unsolicited AEs regardless of relationship to study vaccination	-	-
All	3800 (20.8)	3447 (19.0)
Serious	124 (0.7)	113 (0.6)
Fatal	2 (< 0.1)	6 (< 0.1)
Medically attended	1657 (9.1)	1575 (8.7)
Leading to study discontinuation	2 (< 0.1)	11 (< 0.1)
Grade 3	136 (0.7)	138 (0.8)
Nonserious event	3739 (20.5)	3383 (18.6)
Grade 3	74 (0.4)	76 (0.4)
AESI	3 (< 0.1)	9 (< 0.1)
Unsolicited AEs related to study vaccination	-	-
All	1044 (5.7)	805 (4.4)
Serious	4 (< 0.1)	2 (< 0.1)
Fatal	0	0
Medically attended	65 (0.4)	50 (0.3)
Leading to study discontinuation	0	0
Grade 3	53 (0.3)	54 (0.3)
Nonserious event	1043 (5.7)	803 (4.4)
Grade 3	52 (0.3)	52 (0.3)
AESI	1 (< 0.1)	2 (< 0.1)

Source: Table 14.3.2.1.1.1 of P301 Summary of Changes to Clinical Study Report Data.

Unsolicited AEs up to data cutoff of 24 June 2023

Table 14 displays the unsolicited AEs up to the data cutoff of 24 June 2023 in the SS. The median follow-up was 311 days in both groups.

For unsolicited AEs regardless of relationship to study vaccination, comparing the mRNA-1345 group to the placebo group, there were similar percentages of MAAEs (44.8% and 44.0%, respectively), AESIs (0.3% and 0.3%, respectively), SAEs (7.8% and 7.9%, respectively), AEs leading to study discontinuation (0.6% and 0.8%, respectively), and deaths (0.6% and 0.7%, respectively).

For unsolicited AEs considered by the investigator to be related to study vaccination, comparing the mRNA-1345 group to the placebo group, there were similar percentages of related MAAEs (0.4% and 0.3%, respectively), AESIs (< 0.1% and < 0.1%, respectively), and SAEs (< 0.1% and < 0.1%, respectively). For the related AESIs, in addition to those reported up to 28 days post-injection, there were two more reported in the mRNA-1345 group (i.e., decreased platelet count and thrombocytopenia) and one more reported in the placebo group (i.e., myelodysplastic syndrome). No related AEs leading to study discontinuation or related deaths were reported in either group.

For pericarditis, in addition to the unrelated (as assessed by the investigator) case reported up to 28 days post-injection in the placebo group, one more case of unrelated pericarditis was reported in the placebo group on Day 455 post-injection. Additionally, three cases of unrelated

pericarditis were reported in the mRNA-1345 group for two subjects (one subject had two cases of unrelated pericarditis on Day 48 and Day 233 post-injection, one other subject had one case of unrelated pericarditis on Day 81 post-injection). One case of unrelated myocarditis was reported in the mRNA-1345 group on Day 62 post-injection. No events of either GBS or ADEM were reported up to the 24 June 2023 data cutoff.

Table 14: Summary of Unsolicited AEs up to Data Cutoff of 24 June 2023 Post-Injection (SS)

-	mRNA-1345 (N=18231) n (%)	Placebo (N=18181) n (%)
Unsolicited AEs regardless of relationship to study vaccination	-	-
Serious	1414 (7.8)	1438 (7.9)
Fatal	106 (0.6)	125 (0.7)
Medically attended	8161 (44.8)	8002 (44.0)
Leading to study discontinuation	118 (0.6)	143 (0.8)
AESI	54 (0.3)	51 (0.3)
Unsolicited AEs related to study vaccination	-	-
Serious	5 (< 0.1)	4 (< 0.1)
Fatal	0	0
Medically attended	75 (0.4)	55 (0.3)
Leading to study discontinuation	0	0
AESI	3 (< 0.1)	2 (< 0.1)

Source: Table 14.3.2.1.1.1 of P301 Summary of Changes to Clinical Study Report Data.

7. Integrated Overview of Efficacy

No integrated overview of efficacy was submitted.

8. Integrated Overview of Safety

No integrated overview of safety was submitted.

9. Additional Statistical Issues

There are no additional statistical issues.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

Both efficacy and safety data obtained from the Phase 2/3 clinical study, P301, were the primary support for licensure of the mRNA-1345 vaccine in adults 60 YOA and older.

At the first IA, the success criterion for the trial was met. The three null hypotheses for both primary efficacy endpoints of RSV-LRTD and the first key secondary efficacy endpoint of RSV-ARD were all rejected. The null hypothesis for hospitalization associated with RSV-ARD was not tested due to an insufficient number of cases. Hence, the second IA was not conducted. The

median duration of follow-up at the IA was 112 days up to the data cutoff of 30 November 2022 in both groups.

For RSV-LRTD with 2 or more symptoms, 15 and 70 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 78.7% with 2-sided 95.04% CI (62.8%, 87.9%). The alpha value of 4.96% for the 2-sided CI was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.99 (85 out of total of 86 cases). Because the LL of the 2-sided CI was above 20%, the success criterion for the first primary efficacy endpoint (and the trial) was met.

For RSV-LRTD with 3 or more symptoms, 5 and 26 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 80.9% with 2-sided 95.10% CI (50.1%, 92.7%). The alpha value of 4.90% for the 2-sided CI was derived from the Lan-DeMets approximation to the Pocock stopping boundary with an information fraction of 0.97 (31 out of total of 32 cases). Because the LL of the 2-sided CI was above 20%, the success criterion for the second primary efficacy endpoint was met.

For RSV-ARD, 33 and 106 cases were reported in the mRNA-1345 and placebo groups, respectively, where the estimated VE was 69.1% with 95% CI (54.3%, 79.1%). Because the LL of the CI was above 20%, the success criterion for the first key secondary efficacy endpoint was met.

For hospitalization associated with RSV-ARD, only one case (in the placebo group) met the corresponding case definition. Therefore, no meaningful inference could be drawn for the null hypothesis of the second key secondary efficacy endpoint at the IA.

Additional efficacy analyses were conducted up to the data cutoff of 30 April 2023. The median duration of follow-up was 257 days in both groups.

Compared to the IA, for both RSV-LRTD with 2 or more symptoms and 3 or more symptoms, VEs declined from 78.7% with 95.04% CI (62.8%, 87.9%) to 62.5% with 95% CI (47.7%, 73.2%) and from 80.9% with 95.10% CI (50.1%, 92.7%) to 61.1% with 95% CI (34.7%, 76.8%), respectively. For RSV-ARD, VE declined from 69.1% with 95% CI (54.3%, 79.1%) to 54.1% with 95% CI (40.8%, 64.4%). For hospitalization associated with RSV-ARD, only two cases (both in the placebo group) met the corresponding case definition.

Safety analyses were conducted up to the data cutoff of 24 June 2023. The median duration of follow-up was 311 days in both groups.

Within 7 days post-injection, rates of solicited local and systemic ARs were generally higher in the mRNA-1345 group than the placebo group. Injection site pain was the most frequently reported solicited local AR, while fatigue was the most frequently reported solicited systemic AR.

Within 28 days post-injection, for unsolicited AEs regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs, MAAEs, AESIs, SAEs, and

deaths in both groups. For unsolicited AEs considered by the investigator to be related to study vaccination, there were also similar percentages of unsolicited AEs, MAAEs, AESIs, and SAEs in both groups. These findings generally held for the unsolicited AEs collected up to the data cutoff of 24 June 2023. No events of either GBS or ADEM were reported. As determined by the investigator, no related deaths and no related events of either myocarditis or pericarditis were reported.

The results of both the interim efficacy analysis and additional efficacy analysis and safety analysis were included in the label.

10.2 Conclusions and Recommendations

No major statistical issues have been identified. The pre-specified efficacy objective for P301 was met and no notable imbalances in safety results were identified. Overall, both the efficacy and safety data support licensure of the mRNA-1345 vaccine in adults 60 YOA and older.