



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
(b) (6)

STATISTICAL REVIEW AND EVALUATION EUA

EUA/Supplement Number: 27073

Product Name: COVID-19 vaccine

Authorized Use: For active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older

Sponsor: ModernaTX, Inc.

Date submitted: November 30, 2020

Primary Statistical Reviewer: (b) (6) 12/18/2020

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EXECUTIVE SUMMARY

On November 30, 2020, ModernaTX submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (mRNA-1273) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The proposed use under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is 2 doses, 100 µg each, administered 1 month apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3, randomized, double-blinded and placebo-controlled trial of mRNA-1273 in approximately 30,400 participants. The primary efficacy endpoint is the reduction of incidence of COVID-19 in the period after 14 days post-Dose 2 among participants who do not have evidence of SARS-CoV-2 infection before the first dose. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of 27,817 participants randomized 1:1 to vaccine or placebo with a median follow-up of 7 weeks post-Dose 2 were included in the per-protocol efficacy analysis population. Vaccine efficacy (VE) in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5% (95% CI: 86.5% - 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group and a one-sided p-value of <0.0001 for testing $H_0: VE \leq 30\%$, meeting the prespecified O'Brien-Fleming boundary (nominal alpha = 0.0047). Subgroup analyses of the primary efficacy endpoint showed similar VE point estimates across age groups, sex, and racial and ethnic groups. Analyses on secondary efficacy endpoints suggested possible benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group) and in preventing COVID-19 starting at 14 days following the first dose.

Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cutoff of November 21, 2020, with a median follow-up of >2 months post-Dose 2) demonstrated a VE of 94.1% (95% CI: 89.3% - 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group, which was consistent with results obtained from the interim analysis. A final analysis of a secondary efficacy endpoint also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 case in the vaccine group.

Safety data from the November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo with a median follow-up of 7 weeks after the second dose supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median follow-up of >2 months post-Dose 2. Key safety data from this later submission, including death, other serious adverse events, and unsolicited adverse events of interest were independently verified by the review team and confirmed not to change the safety conclusions from the interim safety analysis.

Overall, the available efficacy and safety data show that mRNA-1273 is effective and safe through a median follow-up of two months post Dose 2. In the Vaccines and Related Biological Products Advisory Committee meeting held on December 17, 2020, 20 committee members voted Yes, 0 voted No and 1 abstained to the voting question "Based on the totality of scientific

evidence available, do the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older?”

This memo was based on the joint clinical and statistical sections of the EUA 27073 review memo, and only contents relevant to the statistical review are presented. The section numbers in the EUA/pre-EUA for an unapproved product CBER review template are used in this memo.

ModernaTX, Inc. EUA- Sections VI - VIII

VI. Summary of Clinical Data

Overview of Clinical Studies

Data from three ongoing clinical studies were included in the EUA submission, which are summarized in Table 1 below. Study mRNA-1273-P301 is a multi-center, Phase 3, randomized, blinded, placebo-controlled study to investigate safety, immunogenicity, and efficacy of mRNA-1273, and is the focus of the EUA review.

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Moderna COVID-19 Vaccine mRNA-1273

Study Number	Type of Study (Efficacy, Safety, Nonclinical)	Participants randomized (N)	Study Design & Type of Control	Test Product(s); Dosing Regimens	Study Status
P301	Efficacy, Safety	30418	A Phase 3, randomized, stratified, observer-blind, placebo-controlled study	mRNA-1273 100 µg	Ongoing- vaccine efficacy demonstrated at the 1st interim analysis
P201	Safety, Immunogenicity	600	A Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study	mRNA-1273 50ug, 100µg	Ongoing- Day 57 primary analysis have completed
20-0003*	Safety, Immunogenicity	120	A Phase 1 Open-label dose-ranging study	mRNA-1273 25ug 50ug, 100ug 250ug	Ongoing- Day 119 (25ug, 100ug, 250ug), Day 57 (50ug)

Source: Adapted from Section 2.5 Clinical Overview submitted to Module 2 of EUA 27073.0

*Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

VII. Human Clinical Efficacy

1. Review of Relevant Individual Trials Used to Support Efficacy

1.1 Study mRNA-1273-P301

Study Design

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. The study took place in 99 sites in the United States. Subjects (N=30,350) were randomized 1:1 and received intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,180) or placebo (n=15,170) on Day 1 and Day 29. Subjects were stratified by age and health risk into one of three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 40.3% of the study population. Subjects were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in subjects with negative SARS-CoV-2 status at baseline (i.e., negative reverse-transcriptase polymerase chain reaction [RT-PCR] and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS-CoV-2 at a central laboratory using RT-PCR, or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the final scheduled efficacy analysis. Two interim analysis timepoints were pre-specified: the first upon accrual of 53 cases and the second upon accrual of 106 cases. The expected duration of study participation is approximately 25 months.

Study Objectives/Endpoints Relevant to the EUA

The key objectives and endpoints presented in the EUA are shown in Table 2 below.

Table 2. Study mRNA-1273-P301 Key Objectives and Endpoints

Primary Efficacy Objective	Associated Endpoints
To demonstrate the efficacy of mRNA-1273 to prevent COVID-19 starting 14 days after the second injection.	Vaccine efficacy of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second dose of investigational product (IP), defined as symptomatic disease based on the following criteria: • The participant must have experienced at least TWO of the following systemic symptoms: Fever ($\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR • The participant must have experienced at least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND • The participant must have at least one NP, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
Secondary Efficacy Objectives	Associated Endpoints
To evaluate the efficacy of mRNA-1273 to prevent severe COVID-19 starting 14 days after the second injection.	Vaccine efficacy of mRNA-1273 to prevent severe COVID-19, defined as first occurrence of COVID-19 starting 14 days after the second dose of IP, (as per the primary endpoint) AND any of the following: • Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, $\text{SpO}_2 \leq 93\%$ on room air at sea level or $\text{PaO}_2/\text{FIO}_2 < 300$ mm Hg, OR • Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR • Significant acute renal, hepatic or neurologic dysfunction, OR • Admission to an intensive care unit or death.
To evaluate the efficacy of mRNA-1273 against a secondary definition of COVID-19 starting 14 days after the second injection.	Vaccine efficacy of mRNA-1273 to prevent a secondary case definition of COVID-19 starting 14 days after the second IP dose, defined as having any of the following systemic symptoms: fever (temperature $\geq 38^{\circ}\text{C}$), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR.
To evaluate the efficacy of mRNA- to prevent death due to a cause directly attributed to a complication of COVID-19, starting 14 days after the second injection of IP.	Vaccine efficacy of mRNA-1273 to prevent death during the study with a cause directly attributed to a complication of COVID-19.

Source: P301 Study Protocol

Analysis Populations

Analysis populations used for the efficacy and safety analyses are summarized in Table 3.

Table 3. Analysis Populations

Population	Description
Randomized	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least one dose of IP, analyzed according to the treatment group randomized.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 at Day 1 before the first dose of IP, analyzed according to the treatment group randomized.
Per Protocol Set (PPS)	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to database lock and unblinding, that impact critical or key study data, analyzed according to the treatment group randomized.
Safety Set	All randomized participants who received at least one dose of IP, analyzed according to the treatment group actually received.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction (AR) data, analyzed according to the treatment group actually received.

Source: P301 Study Protocol

Statistical Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in subjects with negative SARS-CoV-2 status at baseline. Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. $VE = 1 - \text{Hazard Ratio (HR)}$. A stratified Cox proportional hazard (PH) model using Efron's method to handle ties and with treatment group as the independent variable was used to estimate the HR, where the same stratification factor used for randomization was applied. The primary objective would be met if the null hypothesis of $H_0: VE \leq 30\%$ is rejected at any of the interim or primary analyses at the respective significance level.

Subjects who have no documented COVID-19 were censored at the last study assessment date. Subjects who discontinue the study, die due to cause unrelated to COVID-19, and subjects with early COVID-19 prior to 14 days after the second dose were censored at the date of discontinuation, death, or documented COVID-19. The documented COVID-19 date was defined as the later date of 1) the earliest systemic and/or respiratory symptoms reported and 2) date of positive RT-PCR test, where the two dates must be within 14 days of each other.

The primary analysis was planned when a total of 151 adjudicated cases occurring at least 14 days after the second injection had been accrued. In addition, two interim analyses were planned when 35% (53 cases) and 70% (106 cases) of the total target number of cases had been accrued. The Lan-DeMets spending function was used for approximating the O'Brien-Fleming efficacy boundaries to preserve the overall Type I error rate at a one-sided alpha = 0.025, yielding nominal one-sided alpha of 0.0002, 0.0073, and 0.0227 at the first and second interim and the primary analyses, respectively.

Supportive analyses based on the exact conditional method, the mITT population, analysis with cases counted starting immediately after the second injection, 14 days after the first injection, immediately after the first injection, and after randomization were performed. Subgroup

analyses for the primary endpoint include estimates of VE within each age group (18 to <65 years, ≥65 years), stratification factor at randomization, sex, race, and ethnicity.

In the study as conducted, the first and only interim analysis occurred at 95 adjudicated cases of the primary endpoint corresponding to an efficacy cutoff date of November 7, 2020, where the null hypothesis of $H_0: VE \leq 30\%$ was evaluated at a one-sided alpha of 0.0047. The final analysis occurred at 196 adjudicated cases of the primary endpoint corresponding to an efficacy cutoff date of November 21, 2020.

Secondary Efficacy Endpoints

Vaccine efficacy of each secondary endpoint was estimated based on the Cox PH model when the primary endpoint reached statistical significance. The PPS was the primary analysis set for all secondary endpoints. In addition, VE to prevent symptomatic COVID-19 regardless of prior SARS-CoV-2 infection was estimated based on the FAS using the primary endpoint definition. Estimates were presented with nominal two-sided 95% Confidence Intervals (CIs).

Safety Endpoints

The number and percentage of subjects reporting each individual solicited local and systemic AR within 7 days following each injection were summarized by treatment group, severity grade, and injection based on the Solicited Safety Set. Unsolicited adverse events (AEs) up to 28 days following each injection, including serious AEs (SAEs), medically attended AEs (MAAEs), and AEs leading to withdrawal were summarized descriptively based on the Safety Set.

1.2 Study Results

Subject Disposition

Subject disposition for the PPS based on the November 11, 2020 cutoff is presented below in Table 4. The proportion of subjects excluded from the PPS was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the PPS, 26.3% of vaccine recipients and 25.7% of placebo recipients completed at least 2 months follow-up after dose 2.

Table 2. Efficacy Analysis Population Study Disposition^a, mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Subjects excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the subject was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set	13934 (91.6)	13883 (91.3)	27817 (91.4)
Completed 1 dose**	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses**	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2**	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2**	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study**	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation**			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Subject	18 (0.1)	22 (0.2)	40 (0.1)
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2

^a EUA submission (interim analysis): November 11, 2020 cutoff

*Percentage based on number of subjects in the Safety Set

**Percentage based on number of subjects in the Per-Protocol Set

Demographics and Other Baseline Characteristics

There was a similar distribution of demographic characteristics between the treatment groups in the all randomized population, FAS, and the PPS (Table 5). The PPS included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of subjects considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups. At least one protocol-defined high-risk condition for severe COVID-19 was present in 26.3% of subjects, and 4% of subjects had two or more high risk conditions.

Table 5. Demographic Characteristics^a, Per-Protocol Set

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk*	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition**			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Source: Sponsor's Table 14.1.3.4.2. ^a EUA submission (interim analysis): November 11, 2020 data cutoff.

Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.

** High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m²); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection

*** Age and health risk for severe COVID-19 is used as stratification factor for randomization.

Statistical Reviewer Comment:

A total of 1,007 subjects in the FAS (of which 921 are in the PPS) were randomized under a stratum different from that based on their age group and risk factor as reported in the dataset.

However, based on the demographics summary in Table 5 and the fact that randomization was 1:1 in all strata, this did not have a major impact on the demographic balance between vaccine groups.

Vaccine Efficacy

Interim Primary Efficacy Analysis

The primary efficacy endpoint was VE in preventing protocol defined COVID-19 occurring at least 14 days after dose 2 based on the PPS. Cases were adjudicated by a blinded committee. The primary efficacy success criterion would be met if the null hypothesis of $VE \leq 30\%$ was rejected at the O'Brien Fleming boundary at either the interim or primary analysis. The efficacy analysis presented in Table 6 is based on data at the first pre-specified interim analysis consisting of 95 adjudicated cases. In subjects ≥ 18 years of age, there were 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group, corresponding to a VE of 94.5% (95% CI: 86.5% - 97.8%) and a one-sided $p < 0.0001$ for testing $H_0: VE \leq 30\%$, which met the pre-specified success criterion. In subjects ≥ 65 years of age in the Per-Protocol Set, there were no COVID-19 cases in the vaccine group and 15 COVID-19 cases in the placebo group.

Table 6. Interim Analysis^a for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person- years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person- years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All subjects	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%***	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1.

COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose. All potential COVID-19 cases starting 14 days after the 2nd dose in the clinical database as of 07-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (07-Nov-2020 is the data cutoff date for efficacy).

* VE is calculated as $1 - \text{hazard ratio (mRNA-1273/placebo)}$ and 95% CI from the stratified Cox proportional hazard model.

**The one-sided p-value is < 0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of $VE \leq 30\%$, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0047 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

***The two-sided 95% CI was not evaluable based on the Cox proportional hazard model.

There were an additional 18 COVID-19 cases which met the protocol-defined primary efficacy endpoint but were not able to be adjudicated in time for the interim analysis. Of these 18 cases, one was in the vaccine group, and 17 were in the placebo group. Vaccine efficacy for the primary efficacy endpoint including these unadjudicated cases was similar to the results presented above.

Statistical Reviewer Comment:

All primary, secondary, and subgroup (see Table 7 below) interim efficacy analyses were verified based on information from the Standard Data Tabulation Model (SDTM), and the results are consistent with those reported by the Sponsor. The Cox PH model and the exact conditional method adjusted for follow-up yielded similar VE estimates, as well as analyses based on the mITT. Case classifications pertaining to the primary and secondary endpoints appear to be, in general, correctly defined according to the Statistical Analysis Plan (SAP) and protocol. One subject in the placebo arm was an adjudicated non-severe case in the interim analysis but did not satisfy the SAP case definition. The subject experienced chills, body aches, nasal congestion, and rhinorrhea, in addition to a positive PCR. However, the latter three symptoms were not qualified symptoms per SAP and protocol. Therefore, this subject was not classified as a per-SAP case. The impact on estimating VE of including or excluding this case is minimal.

Interim Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the primary efficacy endpoint include VE based on age, sex, race and ethnicity, risk factor, and baseline SARS-CoV-2 status and provide additional information on the applicability of these results across the general population. In general, VE among the subgroups are similar to the VE seen in the overall study population. The small number of participants and cases in some subgroups, such as subjects ≥ 75 years of age and subjects in certain racial subgroups, limits the interpretability of the individual VE results, but are displayed in Table 7 for completeness.

Table 7. Subgroup Analyses of Vaccine Efficacy^a, COVID-19 14 Days After Dose 2 Per Adjudication Committee Assessments, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Age (years)			
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)
65 to <75	0 / 2904	12 / 2823 (0.4) 20.883	100%
75 and older	0 / 623	3 / 676 (0.4) 21.726	100%
Age and risk for severe COVID-19**			
18 and <65 and not at risk	4 / 8309 (<0.1) 2.524	57 / 8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1 / 2098 (<0.1) 2.428	18 / 2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥ 65	0 / 3527	15 / 3499 (0.4) 21.046	100%
Sex			
Female	3 / 6661 (<0.1) 2.271	45 / 6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2 / 7273 (<0.1) 1.433	45 / 7369 (0.6) 31.883	95.5% (81.5%, 98.9%)
Race and Ethnicity			
Non-Hispanic white	5 / 8858 (<0.1) 2.657	70 / 8755 (0.8) 37.721	93.0% (82.6%, 97.2%)

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Communities of color	0 / 5054	20 / 5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0 / 2783	12 / 2769 (0.4) 26.346	100%
Not Hispanic or Latino	5 / 11019 (<0.1) 2.243	77 / 10987 (0.7) 34.729	93.6% (84.1%, 97.4%)
Race			
American Indian or Alaska Native	0 / 107	0 / 110	
Asian	0 / 616	3 / 684 (0.4) 26.549	100%
Black or African American	0 / 1369	4 / 1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0 / 33	0 / 30	
White	5 / 11078 (<0.1) 2.215	80 / 11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0 / 293	1 / 304 (0.3)	100%
Other	0 / 298	2 / 293 (0.7) 45.645	100%

Source: Sponsor's Table 14.2.2.1.1.6.1.1, Table 14.2.2.1.1.6.3.1, Table 4.2.2.1.1.6.7.1, Table 14.2.2.1.1.6.10.1, Table 14.2.2.1.1.6.4.1, Table 14.2.2.1.1.6.2.1, Table 14.2.2.1.1.6.5.1, Table 14.2.2.1.1.6.6.1

^a EUA submission (interim analysis): November 7, 2020 data cutoff.

* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥ 40 kg/m²); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection

**used as stratification factor for randomization

Only 2.2% of participants had evidence of prior infection at study enrollment, and there was only one COVID-19 case starting 14 days after dose 2 reported from this subgroup, which was a subject in the placebo group (Table 8).

Statistical Reviewer Comment:

One case in the placebo group had an "unknown" ethnicity and was not included in Table 7.

Table 8. Vaccine Efficacy by Baseline SARS-CoV-2 Status: First COVID-19 From 14 Days After Dose 2 Per Adjudication Committee Assessment, Full Analysis Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6/15180	92/15170	93.5% (85.2, 97.2)
Positive	0/341	1/334 (0.3) 17.038	100%
Negative	6/14312 (<0.1) 2.154	90/14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0/527	1/465 (0.2)	100%

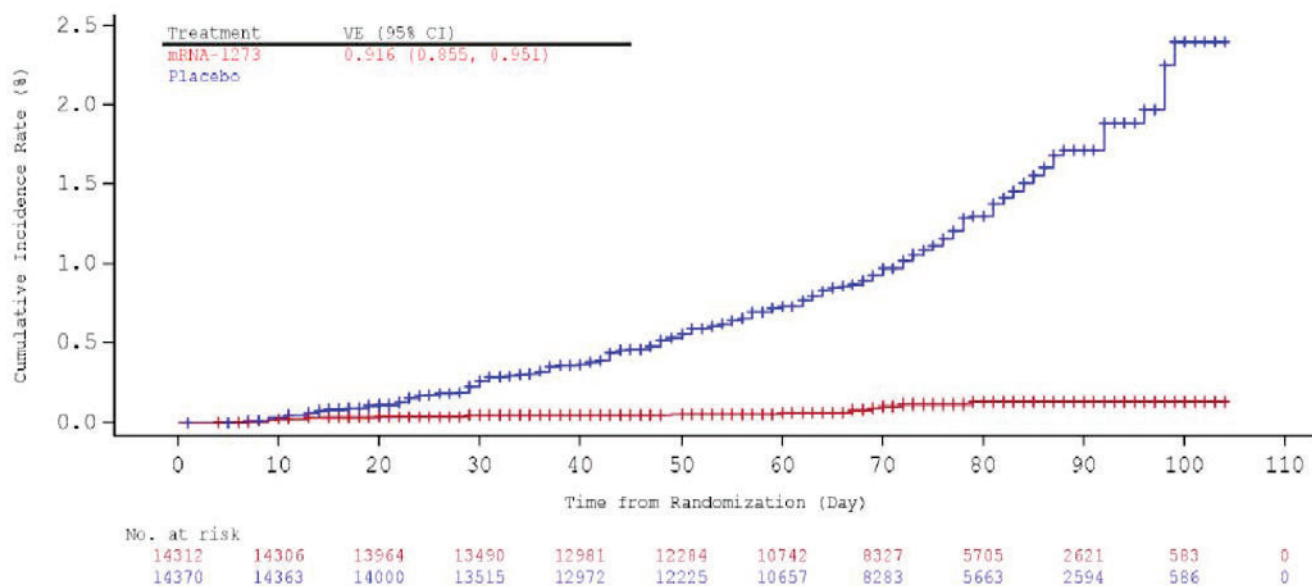
Source: Sponsor's Table 14.2.2.7.1.6.10

* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

Cumulative Incidence Curves – Interim Primary Efficacy Analysis

Based on the cumulative incidence curve for cases in the mITT population after randomization (same as date of dose 1), COVID-19 cases appear to have occurred similarly at low rates for both the mRNA-1273 and placebo groups until Day 14 after Dose 1 (Figure 1). The curves then diverge, with more cases accumulating in the placebo group than the mRNA-1273 group.

Figure 1. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Source: Sponsor Figure 14.2.2.1.2.1.4

Interim Secondary Efficacy Analyses

Severe COVID-19 Cases

All 11 cases of severe COVID-19 at least 14 days after the second dose as assessed by the

adjudication committee were in the placebo group, corresponding to an estimated VE of 100% (95% CI was not estimable from the Cox PH model).

Table 9. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

Source: Sponsor's Table 14.2.1.1.1.1.1

^a EUA submission (interim analysis): November 07 2020 efficacy data cutoff.

* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented when the lower bound was not evaluable by the statistical methods used for the analysis.

One subject in the mRNA-1273 group, a subject >65 years of age who had risk factors for severe COVID-19, was hospitalized due to oxygen saturation of 88% on room air 2 months after receiving the second dose of vaccine. There was a verbal report of a positive SARS-CoV-2 RT-PCR test 3 days prior to hospitalization; however, NP swab collected during hospitalization was negative for SARS-CoV-2. Due to absence of a confirmed RT-PCR result at the time of data snapshot, this case was not referred for adjudication and not captured for analyses. The pre-hospitalization RT-PCR result was later reported to be positive from an external CLIA-certified laboratory and may represent a severe COVID-19 case with hospitalization in the vaccine group.

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

Other Secondary Efficacy Endpoints

The secondary efficacy endpoint of VE of mRNA-1273 for the prevention of COVID-19 disease based on a less restrictive definition of COVID-19 disease from 14 days after Dose 2 showed similar case splits and VE to the primary efficacy endpoints described above. Efficacy against COVID-19 occurring at least 14 days after the first dose of vaccine, including cases that occurred after the second dose, was also similar to the primary endpoint. There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.

Final Scheduled Efficacy Analysis

Vaccine efficacy against COVID-19 starting 14 days after the second dose was 94.1% (95% CI: 89.3% - 96.8%) in the final analysis and was consistent with results obtained from the interim analysis (Table 10). VE in subjects ≥65 years of age appears to be numerically lower than in younger adults 18 to <65 years (86.4% compared to 95.6%) and lower than observed in the interim analysis (100% based on a total of 15 cases).

Table 10. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person- years)*	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person- years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All subjects	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6% (90.6%, 97.9%)	NA
65 years and older	4/3583 (0.1) 4.595	29/3552 (0.8) 33.728	86.4% (61.4%, 95.5%)	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1

All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy). One case (in the vaccine group) was adjudicated as a COVID-19 case by the committee but did not meet the case definition per statistical analysis plan due to documented symptoms and positive PCR being more than 14 days apart.

*Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

**VE and 95% CI from the stratified Cox proportional hazard model

***The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary.

Severe COVID-19 Cases

In the primary efficacy analysis, there were an additional 19 cases of severe COVID-19 (one of which resulted in death from COVID-19), for a total of 30 severe COVID-19 cases starting 14 days after dose 2, per adjudication committee assessment (Table 11). All 30 cases were in the placebo group. The possible severe COVID-19 case in a mRNA-1273 vaccine recipient described with the interim efficacy analysis (negative SARS-CoV-2 PCR per the study central laboratory but reported positive PCR per a CLIA-certified external lab) is not included in the per-protocol analysis below.

Table 11. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All subjects	0	30 (0.2) 9.138	100%

Source: Sponsor's Table 14.2.2.2.1.1.1 submitted to Module 5 of EUA 27073.2

^a EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

Statistical Reviewer Comment:

Final efficacy analyses were verified against raw datasets and found to be consistent. Two additional vaccine recipients developed severe COVID-19 per-SAP between the first and second doses, and as a result, did not receive the second dose and thus were not included in the PPS analysis. The cases were only identified at the November 21, 2020 cutoff. Of note, the total number of severe cases after randomization in the FAS were 47 in the placebo group and 2 in the vaccine group, corresponding to a VE of 95.8% based on the Cox PH model.

Efficacy Summary

The data from the planned interim efficacy analysis, with a cutoff date of November 7, 2020, and a median follow-up for efficacy of 7 weeks post-Dose 2, met the prespecified success criteria. Efficacy of the vaccine to prevent COVID-19 occurring at least 14 days after Dose 2 was 94.5%, (95% CI 86.5%; 97.8%) in participants without prior evidence of SARS-CoV-2 infection or major protocol deviations. VE was >93% in the group of participants with or without prior infection. There was very limited data in subjects with positive SARS-CoV-2 status at baseline, so no conclusions can be drawn about this subgroup. Efficacy outcomes across demographic subgroups were consistent with the efficacy seen in the overall study population. All 11 cases of severe COVID-19 occurring 14 days after the second dose were in the placebo group, although one severe COVID-19 may have occurred in the vaccine group but did not meet criteria for the protocol-specified case definition.

Data from the final efficacy analysis (November 21, 2020 cutoff) was submitted as an amendment after the initial EUA request. The final efficacy analysis on the primary endpoint, demonstrating a VE point estimate of 94.1% (95% CI: 89.3% - 96.8%), appears to align with the data obtained from the interim analysis, except for a lower efficacy observed in participants ≥65 years of age compared to that in younger adults 18 to <65 years of age and compared to the efficacy estimate from the interim analysis.

VIII. Human Clinical Safety

Subject Disposition

Based on the November 11, 2020 safety data cutoff, an overview of subject disposition is presented in Table 12 below. The proportion of randomized participants who discontinued from the study was 0.9% (288 participants) across study groups, with a greater number in the placebo group (168) compared with the vaccine group (120). The most frequently reported reason was withdrawal of consent (67 participants in the vaccine group, 120 in the placebo group). In addition, 51 participants were lost to follow-up (20 in the vaccine group, 31 in the placebo group). In the vaccine group, 3 participants withdrew due to an adverse event (<0.1%, including 1 participant who withdrew due to a SAE) and 3 participants died during the study. In the placebo group, no subjects withdrew due to an adverse event, and 4 subjects died during the study.

Table 12. Safety Analysis Population Study Disposition^a, mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184 (99.8)	15166 (99.7)	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Subject	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10 (<0.1)	19 (<0.1)
Completed ≥1 month f/up*	14354 (94.5)	14345 (94.6)	28700 (94.6)
Completed ≥2 months f/up*	12021 (79.2)	11974 (79.0)	23995 (79.1)
Completed ≥1 month f/up after dose 2*	11717 (77.2)	11559 (76.2)	23276 (76.7)
Completed ≥2 months f/up after dose 2*	3894 (25.7)	3773 (24.9)	7667 (25.3)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2.

^a EUA submission (interim analysis): November 11, 2020 cutoff

Demographics and Other Baseline Characteristics

The demographic characteristics among vaccine and placebo participants in the safety population were similar (Table 13). There were no significant imbalances in demographic and other baseline characteristics between the per-protocol population and the safety population, with a median follow-up of 7 weeks.

Table 13. Demographic Characteristics^a, Safety Set

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Sex			
Female	7255 (47.8)	7100 (46.8)	14355 (47.3)
Male	7929 (52.2)	8065 (53.2)	15995 (52.7)
Age (years)			
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.55)
Median	53.0	52.0	52.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
≥18 to <65	11414 (75.2)	11415 (75.3)	22830 (75.2)
65 and older	3770 (24.8)	3750 (24.7)	7520 (24.8)
Race			
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
Native Hawaiian or other Pacific islander	34 (0.2)	32 (0.2)	66 (0.2)
White	12032 (79.2)	11990 (79.1)	24023 (79.2)
Other	321 (2.1)	315 (2.1)	636 (2.1)
Multiracial	315 (2.1)	319 (2.1)	634 (2.1)
Ethnicity			
Hispanic or Latino	3121 (20.6)	3112 (20.5)	6234 (20.5)
Not Hispanic or Latino	11920 (78.5)	11914 (78.6)	23834 (78.5)
Race and Ethnicity			
Non-Hispanic White	9534 (62.8)	9458 (62.4)	18992 (62.6)
Communities of color	5624 (37.0)	5680 (37.5)	11305 (37.2)
Occupational Risk*	12420 (81.8)	12487 (82.3)	24907 (82.1)
Healthcare worker	3787 (24.9)	3826 (25.2)	7613 (25.1)
High Risk Condition**			
One high risk condition present	3360 (22.1)	3382 (22.3)	6742 (22.2)
No high risk condition	11824 (77.9)	11783 (77.7)	23608 (77.8)
Age and Health Risk for Severe COVID-19***			
≥18 to <65 years and not at risk	8889 (58.5)	8884 (58.6)	17773 (58.6)
≥18 to <65 years and at risk	2530 (16.7)	2534 (16.7)	5065 (16.7)
≥65 years	3765 (24.8)	3747 (24.7)	7512 (24.8)
Baseline SARS CoV-2 status****			
Negative	14316 (94.3%)	14366 (94.7)	26862 (94.5%)
Positive	341 (2.2%)	334 (2.2%)	675 (2.2%)
Missing	527 (3.5%)	465 (3.5%)	993 (3.3%)

Source: Sponsor's Table 14.1.3.2.2^a EUA submission (interim analysis): November 11 2020 cutoff.

* Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.**

**High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m²); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human immunodeficiency virus (HIV) infection

Safety Analysis

The safety analyses presented in this review are largely derived from the November 11, 2020

dataset. The safety analyses from the November 25, 2020 cutoff date, as presented by the Sponsor, appear to align with results from the interim analysis in terms of overall rates and types of solicited and unsolicited adverse events. No additional safety concerns were raised based on the additional data reviewed by FDA or analyses presented by the Sponsor.

Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity reported within 7 days following each dose of vaccine (Table 14). A higher frequency of unsolicited adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local and systemic reactogenicity following vaccination. The proportions of participants with SAEs, deaths, and withdrawals due to adverse events were balanced across the study groups. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. Table 14 below provides an overview of the rates of AEs by treatment group and baseline SARS-CoV-2 status.

Statistical Reviewer Comment:

All safety analyses from both the November 11, 2020 and November 25, 2020 data cutoffs were verified to be consistent with the information presented in the raw data.

Table 14. Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)^a

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	N=15176	N=15162
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13962/15176 (92.0)	4381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction ^a	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2501/15176 (16.5)	560/15162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)
Safety Set	N=15184	N=15165
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7

^a There were no reports of Grade 4 injection site adverse reactions

^a EUA submission (interim analysis)-November 11, 2020

**Related as assessed by investigator

The review of the imbalance of specific solicited and unsolicited events, such as Bell's Palsy, is deferred to the clinical reviewer.

Safety Summary

The number of participants in the Phase 3 safety population (N=30,350; 15,184 vaccine, 15,166 placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA submission was based on data from the pre-specified interim analysis (November 11, 2020 data cutoff) with a median follow-up duration of 7 weeks after Dose 2; the interim analysis data are the primary basis of this EUA review and conclusions. Data and analyses from a November 25, 2020 data cut with a median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series were submitted as an amendment to the EUA on December 7, 2020. No new safety concerns have been identified. The rates and types of solicited adverse reactions and unsolicited adverse events are unlikely to change significantly with an additional 2 weeks of follow-up. The totality of the data package submitted to the EUA meets the Agency's expectations on the minimum duration of follow-up.

There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there have been three reports of Bell's palsy in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events. As of December 3, 2020, there were a total of 13 deaths reported in the study (6 vaccine, 7 placebo). None of the deaths were considered by the investigator to be related to the study vaccine. The frequency of non-fatal serious adverse events was low and without meaningful imbalances between study arms (1% in the mRNA-1273 group and 1% in the placebo group).

Conclusion

Based on the interim efficacy analysis from the November 7, 2020 cutoff, mRNA-1273 is effective in preventing confirmed COVID-19 (VE = 94.5%, 95% CI: 86.5% - 97.8%) and confirmed severe COVID-19 occurring at least 14 days after the second dose of the vaccine. This conclusion was further confirmed at the final analysis based on a November 21, 2020 data cut. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses further supported benefit of the vaccine in preventing severe COVID-19.

No major safety concerns have been identified to date. Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity (solicited AEs) reported within 7 days following each dose of vaccine. The proportions of participants with SAEs, death, and withdrawals due to adverse events were balanced across the study groups.

Overall, the available efficacy and safety data show that mRNA-1273 is effective and safe through a median follow-up of two months post Dose 2.