

**RESPONSE TO CBER COMMUNICATION REGARDING EUA 27073 RECEIVED
ON DECEMBER 01, 2020 (EUA IR #0001)**

The Sponsor acknowledges CBER's communication regarding EUA 27073.

This document provides the Sponsor's responses to CBER's requests (in **Bold**).

Item A:

On Page 81 of the 'Clinical Overview' document submitted in the EUA 27073, we note the following:

The vaccine efficacy to prevent COVID-19 starting 14 days after the first dose of vaccine was 95.4%, and to prevent COVID-19 after randomization was 94.6%. However, these analyses must be interpreted with caution because the follow-up period was limited (approximately 28 days), the vast majority (>90%) of participants received a second dose, and cases were not censored from the analysis if they occurred after the second dose.

Please provide the vaccine efficacy starting 14 days after the 1st dose that excludes cases that occurred after the 2nd dose, as well as any other additional data/analyses to describe vaccine efficacy after only a single dose of vaccine.

Sponsor Response:

- For the secondary efficacy endpoint, vaccine efficacy after the first dose, analysis of COVID-19 starting 14 days after dose 1 was performed, and the VE was 95.4% based on 134 total cases in the Per-Protocol Set; a sensitivity analysis of COVID-19 after randomization was also performed with a VE of 94.6% based on 135 total cases in the PP Set. In these analyses, cases after the second dose were included as events as the objective is to assess vaccine efficacy starting from the first dose.
- Moderna would like to acknowledge that the statement that 'the follow-up period was limited (approximately 28 days)' was incorrect, as all cases after 14 days after the first dose, or after randomization were included in the above analyses, respectively. At the first interim analysis (IA1), the median follow-up time after randomization/dose 1 was 78 days.
- Number of COVID-19 cases between 14 days after the 1st dose and up to the 2nd dose is very small, and the case split is provided in the table below using the PP Set.

	Placebo N=13883	mRNA-1273 N=13934
14 days after Dose 1 and before Dose 2	5	0

- An exploratory analysis of vaccine efficacy of only 1 dose was performed using subject in the mITT population who only received 1 dose at IA1 (data snapshot date: 11-Nov-2020). The same stratified Cox proportional hazard model for the primary

efficacy endpoint was used. For COVID-19 starting after randomization, there were 39 cases on Placebo and 7 cases on mRNA-1273, and the VE was 80% with a 95% CI of (55.2%, 91.1%). For COVID-19 starting 14 days after the 1st dose, there were 28 cases on Placebo and 2 cases on mRNA-1273, and the VE was 91.9% with a 95% CI of (66.1%, 98.1%). These subjects had a median follow-up time of 28 days (range: 1 to 108 days) as of 11-Nov-2020. The interpretation has to be made with caution because this is a smaller non-random sample.

Table 1: Vaccine efficacy of mRNA-1273 to prevent COVID-19 in subjects who only received one dose – mITT Set

	Placebo (N=1079)	mRNA-1273 (N=996)	VE (95% CI)
Number of subjects with COVID-19 starting after randomization, n (%)	39 (3.6)	7 (0.7)	80.0% (55.2%, 91.1%)
Number of subjects with COVID-19 starting 14 days after the 1 st dose, n (%)	28 (2.6)	2 (0.2)	91.9% (66.1%, 98.1%)

- Another exploratory analysis was performed as requested by CBER (email from Sudhakar Agnihothram received on 20-Nov-2020). There are two scheduled RT-PCR NP Swab tests in the study: pre-Dose 1 and pre-Dose 2 on Day 29. Based on these scheduled RT-PCR NP Swab tests, 39 subjects on Placebo who had negative RT-PCR at baseline were positive by RT-PCR at pre-Dose 2; 13 subjects on mRNA-1273 who had negative RT-PCR at baseline were positive by RT-PCR at pre-Dose 2. These results indicate mRNA-1273 starts to protect against infection with SARS-CoV-2 after a single dose. The relative strength of this post-hoc analysis is that it is done on a randomized sample.

Table 2: Summary of RT-PCR NP Swab Results for SARS-CoV-2 – Per-Protocol Set

	Placebo	mRNA-1273
RT-PCR NP Swab Results and Serostatus at Different Time Points	N= 13,883 n (%)	N=13,934 n (%)
Pre-Dose 1 SARS-CoV-2 RT-PCR (NP swab)		
Positive	0	0
Negative	13,883 (100)	13,934 (100)
Pre-Dose 2 SARS-CoV-2 RT-PCR (NP swab)		
Positive	39 (0.3)	13 (0.1)
Negative	12,667 (91.2)	12,791 (91.8)

Subjects with negative PCR pre-dose 1 and positive PCR pre-dose 2	39	13
Subjects with documented COVID-19 symptoms between dose 1 and 2	2	1
Subjects with no documented COVID-19 symptoms between dose 1 and 2	37	12

Item B:

In addition to the above, please also provide the confirmed COVID cases that occurred at:

- a) Any time after Dose 1**
- b) Any time between Dose 1 and Dose 2**
- c) Any time after Dose 2**

Please present this information for all COVID confirmed cases and for those categorized as severe, according to the periods listed above.

Sponsor Response:

In this study, subjects were to be randomized and receive the first dose on the same day. For COVID-19 based on RT-PCR and eligible symptoms in the Per-Protocol Set, all subjects who had COVID-19 received the first dose on the day of randomization. There were 128 COVID-19 cases from randomization on Placebo; 7 on mRNA-1273 in the PP Set.

- Any time after randomization/dose 1²: 128 on Placebo, 7 on mRNA-1273
- Any time between Dose 1 and Dose 2: 5 on Placebo, 1 on mRNA-1273
- Any time after Dose 2: 123 on Placebo, 6 on mRNA-1273

A breakdown using mutually exclusive time periods in PP Set is provided below:

COVID-19	Placebo N=13883	mRNA-1273 N=13934
Randomization to 14 days after Dose 1	0	1
14 days after Dose 1 and before Dose 2	5	0
Dose 2 to 14 days after Dose 2	16	0
starting 14 days after Dose 2 ¹	107	6
Starting from Randomization ² (Total: any time after Randomization)	128	7

¹Table 14.2.2.1.2.1.1 Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days after Second Injection - Per-Protocol Set

²Table 14.2.2.1.2.5.1 Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting After Randomization - Per-Protocol Set

For severe COVID-19, there were 16 severe COVID-19 cases from randomization in the PP Set, all on Placebo.

- Any time after randomization/dose 1²: 16 on Placebo, 0 on mRNA-1273
- Any time between Dose 1 and Dose 2: 1 on Placebo, 0 on mRNA-1273
- Any time after Dose 2: 15 on Placebo, 0 on mRNA-1273

A breakdown using mutually exclusive time periods in PP Set is provided below:

Severe COVID-19	Placebo N=13883	mRNA-1273 N=13934
Randomization to 14 days after Dose 1	0	0
14 days after Dose 1 and before Dose 2	1	0
Dose 2 to 14 days after Dose 2	0	0
starting 14 days after Dose 2 ¹	15	0
Starting from Randomization ² (Total: any time after Randomization)	16	0

¹Table 14.2.2.2.2.1.1 Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Starting 14 Days After Second Injection – Per-Protocol Set

²Table 14.2.2.2.2.5.1 Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Starting After Randomization - Per-Protocol Set

Item C:

In your harm monitoring table (Table 6) submitted on Nov 27, there were 2 subjects in the vaccine arm who developed severe COVID-19 from the time period starting after first injection. Please provide narratives for these 2 cases.

Sponsor Response:

Participant US3162078 is a 49 year-old Hispanic male who received the first injection of mRNA-1273 on 07 August 2020. Baseline RT-PCR at screening was negative for SARS-CoV-2. The participant was exposed to infected co-worker on 11 August and developed symptoms of COVID-19 (rhinorrhea, myalgia, loss of sense of taste and smell) on 14 August. An RT-PCR test done by his employer on 17 August was positive and study NP swab taken at illness visit on 19 August was positive. Oxygen saturation of 93% was reported on 29 August. The event was considered resolved on 3 September. The participant did not receive the second dose of IP due to symptomatic COVID-19.

Participant US3532279 is a 66 year-old white female who received the first injection on 10 September with a negative baseline RT-PCR. On 04 October the participant reported symptoms of COVID-19 (chills, cough, shortness of breath, body aches, fatigue, rhinorrhea, and sore throat). An NP swab collected on 8 October was positive for SARS-CoV-2 by RT-PCR. An oxygen saturation of 80% was reported on 10 October but was 99% on 13 October.

The event was considered resolved on 21 October. The participant did not receive the second dose of IP due to symptomatic COVID-19.

It is important to note that since both subjects received only one dose of IP they are excluded from the Per Protocol analysis set. They are included as severe COVID-19 cases in the analysis for harm, based on the Safety Set starting from the time of randomization, in addition the mITT Set and FAS in secondary/sensitivity analyses for efficacy.

Item D:

In the vaccine arm, there was an SAE of COVID-19 infection in one subject (US3772037). Please provide the narrative for this case, if different from the 2 cases mentioned above.

Sponsor Response:

Participant US3772037 is a 72 year-old white female with medical history significant for hypertension, hyperlipidemia, asthma, hypothyroidism, hypokalemia and peripheral neuropathy due to ankle fracture who received first injection of mRNA-1273 on 11 August 2020 and second injection on 8 September. On 5 November participant was diagnosed with sinusitis and, by verbal report, tested positive for SARS-CoV-2 infection. Home oxygen saturation was 88% on 8 November which led to hospitalization until 12 November. Since discharge the O2 sat was 91% on 18 Nov but as of 20 November the participant's O2 saturation is 94% with no other COVID-19 symptoms. An NP swab was collected by the site on 11 November and was reported negative on 13 November. The Investigator has assessed this as an SAE with a verbatim term of "acute hypoxic respiratory failure due to COVID-19 infection."

This case was captured as a serious adverse event but in the absence of a confirmed RT-PCR result confirming the diagnosis of SARS-COV-2 did not meet the protocol definition of COVID-19 and was not referred for adjudication prior to the 11 November data snapshot. On 3 December, the Investigator confirmed the 6 November positive RT-PCR result from the external CLIA-certified laboratory.

Item E:

Please submit a table with demographic characteristics for the Safety Set, similar to Table 3 submitted as part of the 'CBER Requested Tables' document on 11/25/2020.

Sponsor Response:

Please see the summary of demographics and baseline characteristics table (Table 14.1.3.2.2) based on the Safety Set in the Appendix. Demographics and baseline characteristics are generally balanced between the 2 study groups.

Item F:

Please provide a summary table by study arm of all participants who had a potential COVID-19 illness that was not confirmed to be COVID-19. Please provide this information based on the timepoints outlined in comments A and B above.

Sponsor Response:

In this study, COVID-19 is defined as cases with at least two eligible systemic symptoms or one eligible respiratory symptom, confirmed by positive RT-PCR (central or local). The primary efficacy endpoint is COVID-19 starting 14 days after dose 2 and the primary analysis is based on the Per-Protocol Set.

A secondary case definition of COVID-19 is used in this study as a broader definition of COVID-19 with any eligible symptom confirmed by positive RT-PCR. .

Participants who are potential cases for COVID-19, i.e. with any symptom and positive RT-PCR are cases for secondary definition of COVID-19. The table below summarizes the number of cases for COVID-19 and secondary definition of COVID-19 (i.e. potential cases) starting from randomization in the Per-Protocol Set.

Table 3: Summary of participants who were cases for COVID-19, or secondary definition of COVID-19 starting from randomization – Per-Protocol Set

Time period	COVID-19		Secondary Def. COVID-19	
	Placebo	mRNA-1273	Placebo	mRNA-1273
from Randomization to 14 days after Dose 1	0	1	0	1
14 days after Dose 1 and before Dose 2	5	0	5	0
Dose 2 to 14 days after Dose 2	16	0	17	0
starting 14 days after Dose 2	107	6	121	6
Starting from Randomization (Total: any time after randomization)	128	7	143	7

The numbers of participants who were cases for secondary definition of COVID-19 (i.e. potential cases) but not COVID-19 cases are provided below.

Table 4: Summary of participants who were cases for secondary definition of COVID-19 but not for COVID-19 starting from randomization – Per-Protocol Set

Time period	Placebo	mRNA-1273
from Randomization to 14 days after Dose 1	0	0
14 days after Dose 1 and before Dose 2	0	0
Dose 2 to 14 days after Dose 2	1	0
starting 14 days after Dose 2 ¹	14	0
Starting from Randomization ² (Total: any time after randomization)	15	0

Item G:

Regarding the efficacy outcomes stratified by risk factors, with the purpose of obtaining more COVID-19 specific risks and meaningful information, we request that you provide analyses by each of the following protocol-defined risk factors for severe COVID-19 disease:

- **Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma**
- **Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)**
- **Severe Obesity (body mass index ≥ 40 kg/m²)**
- **Liver disease**
- **Diabetes (Type 1, Type 2 or gestational)**
- **Human Immunodeficiency Virus (HIV) infection**

Please also provide efficacy analyses for the following additional risk factors:

- **Obesity (defined as BMI >30 kg/m²)**
- **Hypertension**

Sponsor Response:

Analyses of vaccine efficacy of mRNA-1273 to prevent COVID-19 in subgroups defined by the protocol-defined risk factor for severe COVID-19 based on adjudication committee assessments using the Per-Protocol Set. The number of subjects with any, or each of the risk factor for severe COVID-19 are balanced between the two groups. The vaccine efficacy of mRNA-1273 are consistent across subgroups with any risk factor for severe COVID-19, without any risk factor, or with each of the risk factor for severe COVID-19 (please refer to Table 14.2.2.1.1.6.7.1, IND19745 SN0071).

Table 5: Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Risk for Severe COVID-19 at Screening - Per-Protocol Set

	Placebo	mRNA-1273	VE (95% CI)
Subjects with any protocol-defined risk for Severe COVID-19			
Number of subjects with COVID-19, n (%)	24 / 3075 (0.8)	1 / 3116 (<0.1)	95.9% (69.7%, 99.4%)
Subjects without protocol-defined risk for Severe COVID-19			
Number of subjects with COVID-19, n (%)	66 / 10808 (0.6)	4 / 10818 (<0.1)	94.0% (83.5%, 97.8%)
Subjects with Chronic Lung Disease			

Number of subjects with COVID-19, n (%)	6 / 673 (0.9)	0 / 661	100%
Subjects with Significant Cardiac Disease			
Number of subjects with COVID-19, n (%)	3 / 678 (0.4)	0 / 686	100%
Subjects with Severe Obesity			
Number of subjects with COVID-19, n (%)	11 / 884 (1.2)	1 / 901	91.2% (32.0%, 98.9%)
Subjects with Diabetes			
Number of subjects with COVID-19, n (%)	7 / 1309 (0.5)	0 / 1338	100%
Subjects with Liver Disease			
Number of subjects with COVID-19, n (%)	0 / 90	0 / 93	-
Subjects with Human Immunodeficiency Virus Infection			
Number of subjects with COVID-19, n (%)	1 / 76	0 / 80	100%

Of note, among the 11 participants with severe COVID-19 cases (based on adjudication committee assessment) starting 14 days after dose 2 in the Per-Protocol Set (all in the placebo group), 5 reported risk factors for severe COVID-19 and 6 did not.

Results of analyses of vaccine efficacy of mRNA-1273 in subgroups of subjects with or without obesity are provided below. The vaccine efficacy of mRNA-1273 is consistent in subjects with or without obesity, defined as BMI >30 kg/m²

	Placebo	mRNA-1273	VE (95% CI)
Subjects with Obesity (BMI >30 kg/m²)			
Number of subjects with COVID-19, n (%)	46 / 5207 (0.9)	2 / 5269 (<0.1)	95.8% (82.6%, 99.0%)
Subjects without Obesity (BMI >30 kg/m²)			
Number of subjects with COVID-19, n (%)	44 / 8517 (0.5)	3 / 8494 (<0.1)	93.2% (78.1%, 97.9%)

The diagnosis of hypertension was not collected in a pre-specified way as for other risk factors for complication of COVID-19. Therefore, conducting such a post hoc analysis is unlikely to yield meaningful results.

Item H:

A Form FDA 483 was issued after inspection of study site 387 (Dr. Michael Levine, Las Vegas, NV) by FDA's Bioresearch Monitoring team. Given the concern for data integrity at this site, please conduct a sensitivity analysis for the primary efficacy endpoint (overall and by the protocol specified age and risk subgroups) excluding all data from this study site, along with data from study site 393 as we previously requested. This should be done both for the interim analysis (Nov 11 snapshot) as well as for the primary analysis.

Sponsor Response:

As requested, sensitivity analyses of the primary efficacy endpoint (COVID-19 starting 14 days after the 2nd injection) were performed excluding all data from study site 393 and site 387 based on the adjudication committee assessments using Per-Protocol Set using the data snapshot occurred on 11-Nov-2020 are listed below. Sensitivity analyses excluding site 393 data have been submitted to IND19745 SN0083 on 03-Dec-2020. Sensitivity analyses excluding site 393 and site 387 based on data snapshot occurred on 25-Nov-2020 will be submitted on 07 December-2020 with other information based on 25-Nov-2020 data snapshot.

- Sensitivity analysis of vaccine efficacy of mRNA-1273 to prevent COVID-19 based on adjudication committee assessments starting 14 days after second injection excluding site 393 data
- Subgroup analysis of vaccine efficacy of mRNA-1273 to prevent COVID-19 based on adjudication committee assessments starting 14 days after second injection by age group (≥ 18 and < 65 years, ≥ 65 years) excluding site 393 data
- Subgroup analysis of vaccine efficacy of mRNA-1273 to prevent COVID-19 based on adjudication committee assessments starting 14 days after second injection by age and health risk for severe COVID-19 (≥ 18 and < 65 years and no risk, ≥ 18 and < 65 years and at risk, ≥ 65 years) excluding site 393 data

There was one COVID-19 case starting 14 days after the 2nd injection based on the adjudication committee assessment in participants enrolled at site 393. There was no case in participants enrolled at site 387. The results are summarized in the table below. The sensitivity analyses results excluding all data from site 393 and site 387 are consistent with the primary analysis and subgroup analysis of the primary efficacy endpoint.

Table 6: Sensitivity analyses excluding data from Site 393 and Site 387: Primary Efficacy Endpoint: COVID-19 starting 14 days after the 2nd dose – Per-Protocol Set

	Placebo N=13587 Cases n (%)	mRNA-1273 N=13648 Cases n (%)	Vaccine Efficacy (VE) % (95% CI)*
Sensitivity Analyses of COVID-19 starting 14 days after 2nd injection per adjudication committee assessment excluding data from Site 387 and Site 393			
All subjects	89 (0.7)	5 (<0.1)	94.4% (86.3%, 97.7%)
In Age subgroups			
18 to <65 years	74 / 10181 (0.7)	5 / 10217 (<0.1)	93.3% (83.5%, 97.3%)
65 years and older	15 / 3406 (0.4)	0 / 3431	100%

In Age and health risk for severe COVID-19 (used as stratification factor for randomization)			
18 and <65 and not at risk	56 / 8159 (0.7)	4 / 8161 (<0.1)	92.9% (80.5%, 97.4%)
18 and <65 and at risk	18 / 2022 (0.9)	1 / 2056 (<0.1)	94.5% (59.2%, 99.3%)
≥65	15 / 3406 (0.4)	0 / 3431	100%

*VE and 95% Confidence Interval (CI) from the stratified Cox proportional hazard model