

**RESPONSE TO CBER COMMUNICATION REGARDING VACCINE EFFICACY AFTER FIRST DOSE RECEIVED ON DECEMBER 05, 2020 (EUA IR#7)**

The Sponsor acknowledges CBER's communication regarding Vaccine efficacy after first dose.

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

**Item 4:**

**Please fill in the following table using data from the final analysis (Nov 25 snapshot):**

**Sponsor Response:**

At the time of Data snapshot (DS) 2 that occurred on 25-Nov-2020, for efficacy analysis, there were 30 severe COVID-19 cases starting 14 days after the 2nd dose based on adjudication committee assessments using the Per-Protocol (PP) Set, with 0 severe cases on mRNA-1273 and 30 severe cases on Placebo with VE of 100% (Table 14.2.2.2.1.1.1, data snapshot 25-Nov-2020).

Analyses of severe COVID-19 based on the positive RT-PCR results and COVID-19 symptoms as defined in the protocol were also performed using the PP Set for severe COVID-19 starting 14 days after the 2<sup>nd</sup> dose (38 on Placebo and 0 on mRNA-1273; Table 14.2.2.2.2.1.1) and starting from randomization (39 on Placebo and 0 on mRNA-1273; Table 14.2.2.2.1.5.1).

In the PP Set, subjects are included in the group to which they were randomized, subjects with non-negative (positive, or unknown/missing) baseline SARS-CoV-2 status are excluded from the PP Set.

As requested, in the table below, Safety Set is used, in which, subjects are included in the group according to the actual investigational product (IP) received. If a subject was randomized to Placebo but received at least one dose of mRNA-1273, the subject would be included under mRNA-1273 instead of Placebo. Subjects with non-negative baseline SARS-CoV-2 status were included in the Safety Set.

In the Safety Set, there were a total of 49 severe COVID-19 cases based on positive RT-PCR results and COVID-19 symptoms starting from first injection. All the severe COVID-19 cases received the IP according to what they were randomized to.

Two cases in the mRNA-1273 group (US3162078 and US3532279) had baseline negative SARS-CoV-2 status, did not receive the second injection and were excluded from the PP Set.

- Subject US3162078 (49 years old, male, White Hispanic or Latino) received 1<sup>st</sup> injection on 07-Aug, started reporting symptoms on 19-Aug, a positive RT-PCR on 19-Aug, and

had O2 saturation of 93% on 29-Aug. Subject did not receive 2<sup>nd</sup> injection due to COVID-19.

- Subject US3532279 (66 years of age, female, White) received 1<sup>st</sup> injection on 10-Sep, started reporting symptoms on 04-Oct, had a positive RT-PCR on 08-Oct, . The subject had O2 saturation of 80% on 10-Oct. Subject did not receive 2<sup>nd</sup> injection due to COVID-19.

**Summary of severe COVID-19 starting after first injection (Safety Set, DS 2 25-Nov-2020)**

	Vaccine Group N=15185 n (%)	Control Group N=15166 n (%)
Number of subjects with severe COVID-19 starting after first injection, regardless of baseline SARS-CoV-2 status	2 (<0.1)	47 (0.3)
Number of subjects with severe COVID-19 starting after first injection, excluding subjects with baseline positive SARS-CoV-2 status	2 (<0.1)	45 (0.3)

**Item 5:**

**Regarding your response to Items A and B in EUA IR #0001, please present the data regarding vaccine efficacy after dose 1 using the following table:**

**Sponsor Response:**

In our response to Item A submitted on 06-Dec-2020 (EUA SN 0004), an exploratory vaccine efficacy of only 1 dose was performed using subject in the modified intent-to-treat (mITT) population who only received 1 dose at IA1 (data snapshot 1, occurred on: 11-Nov-2020). Subjects are included in the group to which they were randomized, subjects with non-negative (positive, or unknown/missing) baseline SARS-CoV-2 status were excluded from the mITT Set. At IA1 (DS1, 11-Nov-2020), in the mITT population, out of the 14550 subjects in mRNA-1273, 996 subjects only received one dose; out of the 14598 subjects in Placebo, 1079 subjects only received one dose. The VE and 95% CI provided in response to Item A (EUA SN 0004) were based on the stratified Cox proportional hazard model.

Below is the table with requested VE and 95% CI by time period. Please note this analysis is an adhoc exploratory analysis. In this analysis, VE and 95% CI are based on the exact method conditional on the total number of cases adjusting for person-years using the Poisson distribution. All cases received dose 1 on the date of randomization. Analyses for each time period were performed separately. In each of the analyses, for the time period, only cases with onset/confirmation date of COVID-19 in that time period are considered cases; subjects who are not at risk for the time period, those, either a case or censored at a time point that is prior to the

time period of interest, are excluded from the analysis. For those subjects who are at risk for the time period and not a case during the time period, their exposure time are truncated at the end of the time period.

The interpretation has to be made with caution because this is a smaller non-random sample, especially for those with small total number of cases.

**Vaccine efficacy of mRNA-1273 to prevent COVID-19 (based on RT-PCR and eligible symptoms) from randomization by Time Period in subjects who only received one dose in mITT Set**

	Vaccine Group N=996 Case n (person-years)	Placebo Group N=1079 Case n (1000-person-years)	VE (%) (95% CI)*
<b>First COVID-19 occurrence after Dose 1</b>			
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all subjects within each group at risk for the endpoint

\* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years

\*\*Subjects who were not at risk (cases or censored at prior time period) are excluded from this analysis

In our response to Item B submitted on 06-Dec-2020 (EUA SN 0004), a breakdown using mutually exclusive time periods in PP Set was provided for COVID-19 based on RT-PCR and eligible symptoms in the Per-Protocol Set. There were 128 COVID-19 cases from randomization on Placebo; 7 on mRNA-1273 in the PP Set.

Below is the table with requested VE and 95% CI by time period. Please note this analysis is an adhoc exploratory analysis. In this analysis, VE and 95% CI are based on the exact method conditional on the total number of cases adjusting for person-years using the Poisson distribution. All cases received Dose 1 on the date of randomization. Analyses for each time period were performed separately. In each of the analyses, for the time period, only cases with onset/confirmation date of COVID-19 in that time period are considered cases; subjects who are not at risk for the time period, those, either a case or censored at a time point that is prior to the time period of interest, are excluded from the analysis. For those subjects who are at risk for the time period and are not a case during the time period, their exposure time are truncated at the end of the time period.

The interpretation has to be made with caution because this is a smaller non-random sample, especially for those with small total number of cases.

**COVID-19 (based on RT-PCR and eligible symptoms) starting from randomization in the Per-Protocol Set by time period (DS1, 11-Nov-2020)**

	<b>Vaccine Group N=13934 n1/n2 (person-years)</b>	<b>Placebo Group N=13883 n1/n2 (person-years)</b>	<b>VE (%) (95% CI)*</b>
<b>First COVID-19 occurrence after Dose 1</b>	<b>7/13934 (2716.8)</b>	<b>128/13883 (2695.6)</b>	<b>94.6% (88.5%, 97.9%)</b>
After dose 1 to before dose 2	1/13934 (1134.0)	5/13883 (1130.8)	80.1% (-78.2%, 99.6%)
After dose 1 to 14 days after dose 1	1/13934 (534.5)	0/13883 (532.4)	-
14 days after dose 1 to dose 2**	0/13933 (1134.0)	5/13883 (1130.8)	100%
Dose 2 to 14 days after dose 2**	0/13100 (1538.0)	16/13045 (1532.5)	100%
>14 days after dose 2**	6/12430 (2597.7)	107/12358 (2575.0)	94.4% (87.5%, 98.0%)

n1=number of subjects meeting endpoint definition

Surveillance time in person-years for given endpoint across all subjects within each group at risk for the endpoint

n2=number of subjects at risk for endpoint

\* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years

\*\*Subjects who were not at risk (cases or censored at prior time period(s)) are excluded from this analysis