

**RESPONSE TO CBER COMMUNICATION REGARDING CLINICAL TOPICS (IR#9)
RECEIVED ON DECEMBER 07, 2020**

The Sponsor acknowledges CBER's communication regarding Clinical topics (IR #9).

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

Item 1:

Please complete the shell table below with the proportion of participants experiencing the specified solicited adverse reaction following any dose based on baseline SARS CoV-2 status- Solicited Safety Set.

Sponsor Response:

The requested data has been added to the table shell. The incidence of solicited adverse reactions and severe solicited adverse reactions after any dose were generally similar when comparing participants who were negative or positive for SARS-CoV-2 status at baseline.

Safety Overview: Solicited Adverse Events after ANY Dose for All Participants – Solicited Safety Set

Subjects reporting at least one	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Adverse Reactions after any injection (ALL)	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 (ALL)	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 local adverse reaction	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 (ALL)	12553 / 15176 (82.7)	8032 / 15162 (53.0)
Baseline SARS-COV-2 negative	11893 / 14309 (83.1)	7628 / 14363 (53.1)

Subjects reporting at least one	Vaccine Group n/N (%)	Placebo Group n/N (%)
Baseline SARS-COV-2 positive	237 / 340 (69.7)	137 / 334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction (ALL)	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)

Based on data snapshot 1 (11-Nov-2020)

Item 2:

Please fill in the following table:

Sponsor Response:

At IA1 (data snapshot 11-Nov-2020), there were 113 COVID-19 protocol defined cases starting 14 days after dose 2 in the Per-Protocol Set. The COVID-19 cases are based on eligible symptoms confirmed by positive RT-PCR, not considering the scheduled RT-PCR test at Dose 2 (Day 29). There was 1 subject (US3592197 in mRNA-1273 group, 44 years of age, male, White) who had positive RT-PCR at Dose 2 and later became a COVID-19 case. This subject is excluded from the requested analysis below.

Demographic Characteristics, Participants with Protocol Defined Case (Without Evidence of Infection Prior to 14 Days After Dose 2) Starting 14 Days After Dose 2, Per-Protocol Set

Characteristic	mRNA-1273 (N ^a =5) n ^b (%)	Placebo (N ^a =107) n ^b (%)	Total (N ^a =112) n ^b (%)
Sex: Female	3 (60)	55 (51.4)	58 (51.8)
Sex: Male	2 (40)	52 (48.6)	54 (48.2)
Age at Vaccination: Mean years (SD)	42.8 (12.9)	46.1 (15.7)	45.9 (15.6)
Age at Vaccination: Median (years)	42	43	43
Age at Vaccination: Min, max (years)	29-60	19-77	19-77
Age Group: 18 to < 65 years	5 (100)	91 (85.0)	96 (85.7)
Age Group: ≥ 65 to < 75 years	0	13 (12.1)	13 (11.6)
Age Group: ≥ 75 years	0	3 (2.8)	3 (2.7)
Race: American Indian or Alaska Native	0	0	0
Race: Asian	0	4 (3.7)	4 (3.6)
Race: Black or African American	0	4 (3.7)	4 (3.6)

Race: Native Hawaiian or Other Pacific Islander	0	0	0
Race: White	5 (100)	96 (89.7)	101 (90.2)
Race: Multiracial	0	1 (0.9)	1 (0.9)
Race: Other/Not reported	0	2 (1.9)	2 (1.8)
Ethnicity: Hispanic or Latino	0	14 (13.1)	14 (12.5)
Ethnicity: Not Hispanic or Latino	5 (100)	92 (86.0)	98 (86.6)
Ethnicity: Not reported	0	1 (0.9)	1 (0.9)
At risk^a: Yes	1 (20.0)	26 (24.3)	27 (24.1)
At risk^a: No	4 (80.0)	81 (75.7)	85 (75.9)

^a N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.

^b n = Number of participants with the specified characteristic.

*At risk for severe COVID-19.

Item 3:

To clarify the comment in Item F from IR EUA #0001, what we mean by potential COVID-19 case is when a subject has recorded eligible signs or symptoms per case definition, but who had either a negative or unknown PCR result, so was not confirmed to be a COVID-19 case. Please submit a summary table by study arm of all participants who had a potential COVID-19 illness.

Sponsor Response: In this study, COVID-19 is defined as symptomatic disease based on the following criteria in addition to a positive RT-PCR:

- At least TWO of the systemic symptoms: Fever ($\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- At least ONE of the respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.

The RT-PCR test must be symptom-prompted (i.e. not from scheduled test at Dose 2 [Day 29]), and the eligible symptom(s) and the positive PCR test must be within 14 days to be considered as a case for the efficacy endpoint as defined in SAP.

Based on data snapshot 1 (11-Nov-2020), in the Per-Protocol Set, starting from randomization, there were 1057 subjects (515 on mRNA-1273 and 542 on Placebo) who had eligible symptom(s) but who had no positive RT-PCR test result within the 14 days of the symptom(s), and thus they were not considered as cases for the efficacy endpoint COVID-19 (i.e. not among the 135 COVID-19 cases based on positive RT-PCR and eligible symptoms starting from randomization in the PP Set, Table 14.2.2.1.2.5.1).

Of these 1057 subjects:

- 1 subject on Placebo had a positive unscheduled RT-PCR result, but there were no eligible symptoms within 14 days of that positive RT-PCR result;
- 4 (3 on mRNA-1273 and 1 on Placebo) only had a positive RT-PCR at the scheduled Dose 2 [Day 29] visit that were not considered for the efficacy endpoint COVID-19;
- 3 subjects (1 on mRNA-1273 and 2 on Placebo) did not have any post-baseline RT-PCR data; and
- 511/515 (99%) on mRNA-1273 and 538/542 (99%) on Placebo had negative RT-PCR results.

Summary of number of participants with a potential COVID-19 illness or eligible symptom(s) not meeting per-protocol case criteria, starting from randomization, Per-Protocol Set

	Vaccine Group N=515 n (%)	Placebo Group N=542 n (%)	Total N=1057 n (%)
Only having a positive RT-PCR at Day 29 visit (not symptom-prompted) ^a	3 (0.6)	1 (0.2)	4 (0.4)
Only having a positive RT-PCR test (local, unscheduled) ^b	0	1 (0.2)	1 (0.1)
Without a positive RT-PCR	512 (99.4)	540 (99.6)	1052 (99.5)
RT-PCR negative (other than Day 29)	492 (95.5)	501 (92.4)	993 (93.9)
Only RT-PCR negative at Day 29	19 (3.7)	37 (6.8%)	56 (5.3)
No RT-PCR result post Baseline ^c	1 (0.2)	2 (0.4)	3 (0.3)

a: US3162182, US356-2081, and US358-2081 on mRNA-1273, and US3042062 on Placebo

b: US3872253 on Placebo only had a positive RT-PCR on 29OCT2020 (day 70)

c: US3162286 on mRNA-1273, US3632140 and US3992114 on placebo, ongoing, with the 2nd injection not received yet by the data snapshot 1 (11NOV2020)