RESPONSE TO FDA COMMENTS ON CLINICAL RECEIVED ON 22 OCTOBER 2021

The Sponsor acknowledges FDA comments on Clinical topics (in **Bold)**

ITEM 1:

Please submit a sensitivity analysis for the rates of solicited adverse reactions by including all relevant events (occurring within the 7 days post vaccination) from the e-diary captured as COVID-19 symptoms that were negative for SARS-CoV-2. Please perform a similar sensitivity analysis for unsolicited AEs for those events that occurred beyond 7 days of vaccination.

Sponsor Response:

Thank you for the further clarification provided on this request (26-Oct-2021).

> Please submit a sensitivity analysis for the rates of solicited adverse reactions by including all relevant events (occurring within the 7 days post vaccination) reported in the COVID-19 symptom logs from subjects that were ultimately negative for SARS-CoV-2. Please perform a similar sensitivity analysis for unsolicited AEs for those events reported in the COVID-19 symptom logs from subjects that were ultimately negative for SARS-CoV-2 but which are not included in the first sensitivity analysis for solicited reactions.

The Sponsor's question:

> *The Sponsor would like to ask for further clarifications on the reviewers' request on "including all relevant events (occurring within the 7 days post vaccination) from the e-diary captured as COVID-19 symptoms that were negative for SARS-CoV-2". Are the reviewers referring to the "Symptom Log" reported by participants? Is the request for sensitivity analysis of SAR(solicited adverse reactions), to include the following symptoms reported on "Symptom Log" within 7 days post vaccination in those participants reported such symptoms on "Symptom Log" and later had a negative RT-PCR result?*
>
> *Symptoms reported on "Symptom Log":*
>
> *- Fever based on Temperature reported*
>
> *- Chills*
>
> *- Fatigue*
>
> *- Muscle Aches (Myalgia) or Body Aches*
>
> *- Headache*
>
> *- Nausea or Vomiting*

For the request: a sensitivity analysis for the rates of solicited adverse reactions by including all relevant events (occurring within the 7 days post vaccination) reported in the COVID-19 symptom logs from subjects that were ultimately negative for SARS-CoV-2:

The Sponsor first looked at relevant events (select symptoms listed below) reported within 7 days post vaccination from the e-diary COVID-19 "symptoms log" in those participants who ultimately had negative RT-PCR results, defined as, a negative RT-PCR within 28 days after last dose. Those with a positive RT-PCR within 28 days after last dose, or those had no RT-PCR tests were excluded from this analysis.

The below symptoms reported on "Symptom Log":
- Fever based on Temperature reported
- Chills
- Fatigue
- Muscle Aches (Myalgia) or Body Aches
- Headache
- Nausea or Vomiting

The table below summarizes these select symptoms reported on COVID-19 'Symptom Log' within 7 days post vaccination in participants who ultimately had negative RT-PCR results. In general, using the Safety Set, the number of participants reporting these select symptoms within 7 days on 'Symptom Log' who ultimately had negative RT-PCR results is low (<1%). The incidence of these select symptoms was similar in the mRNA-1273 group and the placebo group after Dose 1, and after Dose 2, the incidence of these select symptoms was higher in the mRNA-1273 group than the placebo group.

Table 1-1 Select symptoms reported on COVID-19 'Symptom Log' within 7 days post vaccination in participants who ultimately had negative RT-PCR results – Safety Set

	DOSE 1		DOSE 2	
Symptom	mRNA-1273 (N=15184)	Placebo (N=15162)	mRNA-1273 (N=15184)	Placebo (N=15162)
Fever	4 (<0.1)	3 (<0.1)	33 (0.2)	4 (<0.1)
Headache	55 (0.4)	54 (0.4)	79 (0.5)	35 (0.2)
Fatigue	63 (0.4)	50 (0.3)	87 (0.6)	38 (0.3)
Myalgia	48 (0.3)	30 (0.2)	91 (0.6)	30 (0.2)
Nausea/Vomiting	20 (0.1)	20 (0.1)	28 (0.2)	11 (0.1)
Chills	24 (0.2)	13 (0.1)	61 (0.4)	14 (0.1)

For ease of review, Table 1-2 below summarizes Solicited Systemic Adverse Reactions Within 7 Days After Each Dose as reported in the CSR Table 7-1 and Table 7-2.

Table 1-2. Summary of Participants With Solicited Systemic Adverse Reactions Starting Within 7 Days After Each Dose (Solicited Safety Set)

Event	mRNA-1273 N=15166 Dose 1 n (%)	Placebo N=15151 Dose 1 n (%)	mRNA-1273 N=14691 Dose 2 n (%)	Placebo N=14578 Dose 2 n (%)
Fever (≥38.0°C)	112 (0.7)	44 (0.3)	2276 (15.5)	43 (0.3)
Headache	4950 (32.6)	4026 (26.6)	8637 (58.8)	3427 (23.5)
Fatigue	5636 (37.2)	4133 (27.3)	9607 (65.4)	3418 (23.5)
Myalgia	3442 (22.7)	2069 (13.7)	8529 (58.1)	1824 (12.5)
Arthralgia	2510 (16.6)	1784 (11.8)	6303 (42.9)	1579 (10.8)
Nausea/vomiting	1262 (8.3)	1075 (7.1)	2794 (19.0)	941 (6.5)
Chills	1251 (8.3)	878 (5.8)	6500 (44.3)	813 (5.6)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 7-1 and Table 7-2 (Source: Table 14.3.1.1.1.1, Table 14.3.1.1.1.2, Table 14.1.5.5.1, Table 14.1.5.5.2). Part of CBER requested Table 38 (Table W) submitted BLA125752 Sequence 0011 08Oct2021.

As the number of participants reporting select symptoms is relatively low (Table 1-1) as compared to those reporting Solicited Systemic Adverse Reactions within 7 days as summarized in CSR Tables 7-1 and 7-2 (Table 1-2), the requested sensitivity analysis including the select symptoms would have yielded similar results as currently reported in CSR.

For the request: Please perform a similar sensitivity analysis for unsolicited AEs for those events reported in the COVID-19 symptom logs from subjects that were ultimately negative for SARS-CoV-2 but which are not included in the first sensitivity analysis for solicited reactions.

For the request, the SPONSOR considered, **all** symptoms reported on "Symptom Log" beyond 7 days post vaccination in those who ultimately had a negative RT-PCR result are considered. As the symptoms captured by the Covid-19 "Symptom Log" are not MedDRA Preferred Terms, the Sponsor would like to first provide a summary of all symptoms reported on the eDiary Covid-19 "Symptom Log" occurred beyond 7 days of vaccination (started on Day 8 or later) and had a negative RT-PCR result within 14 days window, defined as:
- the symptom start date was on Day 8 or later
- there was a negative RT-PCR result within 14 days (± 14 days) of the symptom start date
Participants who had any symptom satisfying the above conditions are included in the below summary.

Table 1-3. Summary of all symptoms reported on COVID-19 "Symptom Log" beyond 7 days post vaccination – Safety Set

	Dose 1		Dose 2	
	mRNA-1273 (N=15184)	Placebo (N=15162)	mRNA-1273 (N=15184)	Placebo (N=15162)
Participant reporting any symptom	299 (2.0)	344 (2.3)	1630 (10.7)	1523 (10.0)
Body Aches	82 (0.5)	84 (0.6)	523 (3.4)	491 (3.2)
Chills	62 (0.4)	59 (0.4)	359 (2.4)	353 (2.3)
Clinical Evidence of Pneumonia				1 (0.0)
Cough	141 (0.9)	157 (1.0)	972 (6.4)	924 (6.1)
Diarrhea	77 (0.5)	77 (0.5)	335 (2.2)	305 (2.0)
Difficulty Breathing	31 (0.2)	34 (0.2)	216 (1.4)	200 (1.3)
Fatigue	170 (1.1)	175 (1.2)	895 (5.9)	835 (5.5)
Headache	167 (1.1)	193 (1.3)	932 (6.1)	879 (5.8)
Myalgia	86 (0.6)	93 (0.6)	468 (3.1)	467 (3.1)
Nasal Congestion	139 (0.9)	162 (1.1)	1048 (6.9)	906 (6.0)
Nausea	63 (0.4)	75 (0.5)	341 (2.2)	328 (2.2)
New Loss of Smell	27 (0.2)	23 (0.2)	123 (0.8)	167 (1.1)
New Loss of Taste	33 (0.2)	29 (0.2)	138 (0.9)	181 (1.2)
Oxygen Saturation of SpO2 <=93% on room air at sea level	1 (0.0)			2 (0.0)
Radiographical Evidence of Pneumonia				1 (0.0)
Rhinorrhea	133 (0.9)	157 (1.0)	940 (6.2)	807 (5.3)
Shortness of Breath	56 (0.4)	55 (0.4)	331 (2.2)	324 (2.1)
Sore Throat	127 (0.8)	148 (1.0)	841 (5.5)	727 (4.8)
Systolic Blood Pressure < 90 mmHg, Diastolic Blood Pressure < 60 mmHg	1 (0.0)			
Vomiting	20 (0.1)	21 (0.1)	120 (0.8)	96 (0.6)

Please note that the COVID-19 "Symptom Log" were reported on daily basis, and AE events were collected on event basis; in addition, the symptoms are not MedDRA Preferred Terms, thus, it would be very challenging to perform a sensitivity analysis combining the two. The Sponsor would like to discuss further with the reviews for guidance.