RESPONSE TO FDA COMMENTS ON CLINICAL DATED NOVEMBER 19, 2021

The Sponsor acknowledges FDA Comments on CLINICAL in **BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Datasets

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing.
Please refer to amendment #18 (seq 0020), submitted in response to the teleconference held between Moderna and CBER on October 29, 2021. We have the following comments/responses:

ITEM 1:
Regarding the Response to Comments on Clinical: o 4a - Moderna proposes to re-submit the following domains with application of the updated lookup table: • CE, • FACE, • FAAE and • AE; and to re-submit the analysis of duration of SAR using CBER's definition of last day-first day+1. As the impact on other SAR analyses is minimum, the Sponsor propose not to re-run other analyses of SAR.

CBER Response:
We agree with this proposal.

Sponsor Response:
Thank you. We have submitted the updated domains on 30Nov2021 (SN 0027). As a follow-up to that, in this response, we are providing an updated analysis of duration of SAR using CBER's definition of last day – first day +1 using the updated domains.

The summary results are provided in Table 1-1 for after Dose 1 and Dose 2, and the complete tables are provided in the appendix with this response. Please note that in this analysis, for SAR not yet resolved, duration is calculated using the earlier of (Date of most recent Dose + 28, data cutoff date) – first day +1.

Table 1-1

	First Injection Solicited Safety Set		Second Injection Solicited Safety Set	
Solicited Adverse Reaction **Category** **Statistic**	**Placebo (N=15162)**	**mRNA-1273 (N=15184)**	**Placebo (N=14631)**	**mRNA-1273 (N=14729)**
Solicited Adverse Reactions				
n	7286	13318	6255	13556
Mean (SD)	3.9 (5.59)	3.9 (4.56)	4.2 (7.99)	4.4 (5.72)
Median	2	3	2	3
Min, Max	1, 192	1, 193	1, 212	1, 176
Solicited Local Adverse Reactions				
n	3011	12766	2757	13029
Mean (SD)	2.3 (3.18)	2.8 (2.73)	2.5 (6.83)	3.3 (2.93)
Median	1	2	1	3
Min, Max	1, 55	1, 86	1, 212	1, 156
Solicited Systemic Adverse Reactions				
n	6397	8316	5343	11678
Mean (SD)	3.9 (5.69)	3.5 (5.02)	4.1 (7.75)	3.6 (5.79)
Median	2	2	2	2
Min, Max	1, 188	1, 193	1, 175	1, 176

Source: Table Adhoc 1-1, Adhoc 1-2

Table Adhoc 1-1
Summary of Duration (Days) of Solicited Adverse Reaction After First Injection
First Injection Solicited Safety Set

Solicited Adverse Reaction Category / Statistic	Placebo (N=15162)	mRNA-1273 (N=15184)	Total (N=30346)
Solicited Adverse Reactions			
n	7286	13318	20604
Mean (SD)	3.9 (5.59)	3.9 (4.56)	3.9 (4.95)
Median	2.0	3.0	3.0
Min, Max	1, 192	1, 193	1, 193
Solicited Local Adverse Reactions			
n	3011	12766	15777
Mean (SD)	2.3 (3.18)	2.8 (2.73)	2.7 (2.82)
Median	1.0	2.0	2.0
Min, Max	1, 55	1, 86	1, 86
Pain			
n	2665	12688	15353
Mean (SD)	1.9 (2.46)	2.5 (1.75)	2.4 (1.90)
Median	1.0	2.0	2.0
Min, Max	1, 55	1, 70	1, 70
Erythema (Redness)			
n	79	450	529
Mean (SD)	4.4 (6.31)	3.0 (4.71)	3.2 (5.00)
Median	1.0	2.0	2.0
Min, Max	1, 28	1, 45	1, 45

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

Table Adhoc 1-1
Summary of Duration (Days) of Solicited Adverse Reaction After First Injection
First Injection Solicited Safety Set

Solicited Adverse Reaction Category Statistic	Placebo (N=15162)	mRNA-1273 (N=15184)	Total (N=30346)
Swelling (Hardness)			
n	65	935	1000
Mean (SD)	7.0 (8.91)	2.2 (2.79)	2.5 (3.71)
Median	2.0	1.0	1.0
Min, Max	1, 33	1, 36	1, 36
Axillary Swelling or Tenderness			
n	723	1553	2276
Mean (SD)	2.4 (3.29)	2.7 (4.75)	2.6 (4.34)
Median	1.0	1.0	1.0
Min, Max	1, 35	1, 82	1, 82
Solicited Systemic Adverse Reactions			
n	6397	8316	14713
Mean (SD)	3.9 (5.69)	3.5 (5.02)	3.7 (5.32)
Median	2.0	2.0	2.0
Min, Max	1, 188	1, 193	1, 193
Fever			
n	44	112	156
Mean (SD)	1.4 (0.65)	1.3 (1.04)	1.3 (0.94)
Median	1.0	1.0	1.0
Min, Max	1, 3	1, 9	1, 9

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

Table Adhoc 1-1
Summary of Duration (Days) of Solicited Adverse Reaction After First Injection
First Injection Solicited Safety Set

Solicited Adverse Reaction Category Statistic	Placebo (N=15162)	mRNA-1273 (N=15184)	Total (N=30346)
Headache			
n	4026	4950	8976
Mean (SD)	2.7 (3.11)	2.5 (2.71)	2.6 (2.90)
Median	1.0	1.0	1.0
Min, Max	1, 85	1, 47	1, 85
Fatigue			
n	4133	5636	9769
Mean (SD)	3.3 (4.57)	3.1 (4.13)	3.2 (4.32)
Median	2.0	2.0	2.0
Min, Max	1, 131	1, 93	1, 131
Myalgia			
n	2069	3442	5511
Mean (SD)	3.1 (4.20)	2.6 (3.76)	2.8 (3.94)
Median	1.0	1.0	1.0
Min, Max	1, 56	1, 74	1, 74
Arthralgia			
n	1784	2510	4294
Mean (SD)	3.8 (7.57)	3.1 (6.80)	3.4 (7.14)
Median	2.0	1.0	1.0
Min, Max	1, 188	1, 193	1, 193

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

Table Adhoc 1-1
Summary of Duration (Days) of Solicited Adverse Reaction After First Injection
First Injection Solicited Safety Set

Solicited Adverse Reaction Category Statistic	Placebo (N=15162)	mRNA-1273 (N=15184)	Total (N=30346)
Nausea/Vomiting			
n	1075	1262	2337
Mean (SD)	2.0 (2.31)	1.9 (1.93)	1.9 (2.11)
Median	1.0	1.0	1.0
Min, Max	1, 35	1, 24	1, 35
Chills			
n	878	1251	2129
Mean (SD)	1.9 (2.15)	1.7 (1.90)	1.8 (2.01)
Median	1.0	1.0	1.0
Min, Max	1, 35	1, 28	1, 35

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

Table Adhoc 1-2
Summary of Duration (Days) of Solicited Adverse Reaction After Second Injection
Second Injection Solicited Safety Set

Solicited Adverse Reaction Category Statistic	Placebo (N=14631)	mRNA-1273 (N=14729)	Total (N=29360)
Solicited Adverse Reactions			
n	6255	13556	19811
Mean (SD)	4.2 (7.99)	4.4 (5.72)	4.3 (6.52)
Median	2.0	3.0	3.0
Min, Max	1, 212	1, 176	1, 212
Solicited Local Adverse Reactions			
n	2757	13029	15786
Mean (SD)	2.5 (6.83)	3.3 (2.93)	3.2 (3.91)
Median	1.0	3.0	3.0
Min, Max	1, 212	1, 156	1, 212
Pain			
n	2486	12964	15450
Mean (SD)	2.1 (5.38)	3.1 (1.82)	2.9 (2.75)
Median	1.0	3.0	3.0
Min, Max	1, 165	1, 65	1, 165
Erythema (Redness)			
n	68	1279	1347
Mean (SD)	4.0 (5.50)	2.8 (2.92)	2.9 (3.11)
Median	1.0	2.0	2.0
Min, Max	1, 30	1, 40	1, 40

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

Table Adhoc 1-2
Summary of Duration (Days) of Solicited Adverse Reaction After Second Injection
Second Injection Solicited Safety Set

Solicited Adverse Reaction Category Statistic	Placebo (N=14631)	mRNA-1273 (N=14729)	Total (N=29360)
Swelling (Hardness)			
n	60	1807	1867
Mean (SD)	4.5 (5.57)	2.6 (2.17)	2.6 (2.38)
Median	1.0	2.0	2.0
Min, Max	1, 32	1, 32	1, 32
Axillary Swelling or Tenderness			
n	571	2092	2663
Mean (SD)	3.4 (11.83)	2.7 (5.49)	2.9 (7.33)
Median	1.0	2.0	1.0
Min, Max	1, 212	1, 156	1, 212
Solicited Systemic Adverse Reactions			
n	5343	11678	17021
Mean (SD)	4.1 (7.75)	3.6 (5.79)	3.7 (6.48)
Median	2.0	2.0	2.0
Min, Max	1, 175	1, 176	1, 176
Fever			
n	43	2276	2319
Mean (SD)	1.5 (1.92)	1.1 (0.48)	1.1 (0.54)
Median	1.0	1.0	1.0
Min, Max	1, 13	1, 10	1, 13

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

Table Adhoc 1-2
Summary of Duration (Days) of Solicited Adverse Reaction After Second Injection
Second Injection Solicited Safety Set

Solicited Adverse Reaction Category Statistic	Placebo (N=14631)	mRNA-1273 (N=14729)	Total (N=29360)
Headache			
n	3427	8637	12064
Mean (SD)	2.9 (5.24)	2.7 (3.34)	2.7 (3.98)
Median	1.0	2.0	2.0
Min, Max	1, 175	1, 117	1, 175
Fatigue			
n	3418	9607	13025
Mean (SD)	3.6 (6.90)	2.9 (5.12)	3.1 (5.65)
Median	2.0	2.0	2.0
Min, Max	1, 175	1, 176	1, 176
Myalgia			
n	1825	8529	10354
Mean (SD)	4.0 (9.45)	2.2 (3.64)	2.5 (5.20)
Median	2.0	1.0	1.0
Min, Max	1, 175	1, 169	1, 175
Arthralgia			
n	1579	6303	7882
Mean (SD)	4.5 (10.29)	2.4 (4.39)	2.9 (6.11)
Median	2.0	1.0	1.0
Min, Max	1, 175	1, 169	1, 175

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.

Table Adhoc 1-2
Summary of Duration (Days) of Solicited Adverse Reaction After Second Injection
Second Injection Solicited Safety Set

Solicited Adverse Reaction Category Statistic	Placebo (N=14631)	mRNA-1273 (N=14729)	Total (N=29360)
Nausea/Vomiting			
n	941	2794	3735
Mean (SD)	2.2 (6.06)	1.8 (1.95)	1.9 (3.48)
Median	1.0	1.0	1.0
Min, Max	1, 175	1, 29	1, 175
Chills			
n	813	6500	7313
Mean (SD)	2.5 (7.69)	1.5 (2.37)	1.6 (3.42)
Median	1.0	1.0	1.0
Min, Max	1, 175	1, 159	1, 175

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection.
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of injection.