

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 4:

For review purposes, please complete the following safety overview table for participants ≥ 65 years of age only following any dose.

Subjects reporting at least one	Vaccine Group n/N (%)	Placebo Group n/N (%)
Subjects reporting at least one	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Adverse Reactions after any injection (ALL)	14,338 / 15,176 (94.5)	9,027 / 15,162 (59.5)
Solicited local adverse reaction (ALL)	13,962 / 15,176 (92.0)	4,381 / 15,161 (28.9)
Grade 3 solicited injection site reaction (ALL)	1,386 / 15,176 (9.1)	143 / 15,161 (0.9)
Solicited systemic adverse reaction (ALL)	12,553 / 15,176 (82.7)	8032 / 15,162 (53.0)
Grade 3 or 4 solicited systemic adverse reaction (ALL)	2,501 / 15,176 (16.5)	560 / 15,162 (3.7)
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Safety Set	N=15184	N=15165
Unsolicited Adverse Event up to 28 days after any	3325 (21.9)	2949 (19.4)
Baseline SARS-COV-2 negative	3204 / 14316 (22.4)	2846 / 14366 (19.8)
Baseline SARS-COV-2 positive	49 / 341 (14.4)	56 / 334 (16.8)
Unsolicited non-serious adverse event	3283 (21.6)	2902 (19.1)
Grade 3 non-serious unsolicited adverse event	187 (1.2)	148 (1.0)
Related unsolicited adverse events	1127 (7.4)	609 (4.0)
Baseline SARS-COV-2 negative	1095 / 14316 (7.6)	585 / 14366 (4.1)
Baseline SARS-COV-2 positive	16 / 341 (4.7)	14 / 334 (4.2)
Related Grade 3 non-serious unsolicited adverse	69 (0.5)	28 (0.2)
Medically Attended Adverse Event	1215 (8.0)	1276 (8.4)
Baseline SARS-COV-2 negative	1167 / 14316 (8.2)	1243 / 14366 (8.7)
Baseline SARS-COV-2 positive	19 / 341 (5.6)	18 / 334 (5.4)
Related medically attended adverse events	122 (0.8)	73 (0.5)
Baseline SARS-COV-2 negative	118 / 14316 (0.8)	68 / 14366 (0.5)
Baseline SARS-COV-2 positive	0 / 341	5 / 334 (1.5)
Serious Adverse Event	82 (0.5)	86 (0.6)
Baseline SARS-COV-2 negative	79 / 14316 (0.6)	82 / 14366 (0.6)

Baseline SARS-COV-2 positive	0 / 341	3 / 334 (0.9)
Related serious adverse event	5 (<0.1)	4 (<0.1)
Baseline SARS-COV-2 negative	5 / 14316 (<0.1)	4 / 14366 (<0.1)
Baseline SARS-COV-2 positive	0 / 341	0 / 334
Death*	4 (<0.1)	4 (<0.1)
Related deaths	0	0
AE leading to discontinuation of the vaccine	41 (0.3)	71 (0.5)
Baseline SARS-COV-2 negative	34 / 14316 (0.2)	68 / 14366 (0.5)
Baseline SARS-COV-2 positive	4 / 341 (1.2)	3 / 334 (0.9)

Sponsor Response: Please see the requested table below. Please note that only 2% of the subjects were SARS-CoV-2 positive overall in the study, and there were only 68 subjects who were ≥65 years of age and were SARS-CoV-2 positive at baseline (Table 14.1.3.1.2); therefore, further breakdown by baseline SARS-CoV-2 status are not provided.

Subjects reporting at least one	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Adverse Reactions after any injection (ALL)	3497 / 3766 (92.9)	2010 / 3750 (53.6)
Solicited local adverse reaction (ALL)	3337 / 3766 (88.6)	859 / 3750 (22.9)
Grade 3 solicited local adverse reaction (ALL)	279 / 3766 (7.4)	66 / 3750 (1.8)
Solicited systemic adverse reaction (ALL)	2922 / 3766 (77.6)	1754 / 3750 (46.8)
Grade 3 or 4 solicited systemic adverse reaction (ALL)	444 / 3766 (11.8)	119 / 3750 (3.2)
Safety Set		
Unsolicited Adverse Event up to 28 days after any	872 / 3770 (23.1)	734 / 3750 (19.6)
Related unsolicited adverse events	261 / 3770 (6.9)	138 / 3750 (3.7)
Medically Attended Adverse Event	336 / 3770 (8.9)	376 / 3750 (10.0)
Related medically attended adverse events	22 / 3770 (0.6)	13 / 3750 (0.3)
Serious Adverse Event	36 / 3770 (1.0)	42 / 3750 (1.1)
Related serious adverse event	2 / 3770 (<0.1)	1 / 3750 (<0.1)
Death	1 / 3768 (<0.1)	2 / 3752 (<0.1)
Related deaths	0	0
AE leading to discontinuation of the vaccine	12 / 3770 (0.3)	17 / 3750 (0.5)
Related AE leading to discontinuation of the vaccine	3 / 3370 (<0.1)	4 / 3750 (0.1)

Item 5:

Please complete the following safety overview table for the participants at (following any dose)

- Site 387 Dr Levine only
- Site 393 Dr Sheth only

Subjects reporting at least one	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited adverse reactions after any injection (ALL)	14,338 / 15,176 (94.5)	9,027 / 15,162 (59.5)
Solicited local adverse reaction (ALL)	13,962 / 15,176 (92.0)	4,381 / 15,161 (28.9)
Grade 3 solicited injection site reaction (ALL)	1,386 / 15,176 (9.1)	143 / 15,161 (0.9)
Solicited systemic adverse reaction (ALL)	12,553 / 15,176 (82.7)	8032 / 15,162 (53.0)
Grade 3 or 4 solicited systemic adverse reaction (ALL)	2,501 / 15,176 (16.5)	560 / 15,162 (3.7)
Safety Set	N=15184	N=15165
Unsolicited adverse event up to 28 days after any	3325 (21.9)	2949 (19.4)
Unsolicited non-serious adverse event	3283 (21.6)	2902 (19.1)
Grade 3 non-serious unsolicited adverse event	187 (1.2)	148 (1.0)
Related unsolicited adverse events	1127 (7.4)	609 (4.0)
Related Grade 3 non-serious unsolicited adverse	69 (0.5)	28 (0.2)
Medically attended adverse event	1215 (8.0)	1276 (8.4)
Related medically attended adverse events	122 (0.8)	73 (0.5)
Serious adverse event	82 (0.5)	86 (0.6)
Related serious adverse event	5 (<0.1)	4 (<0.1)
Death*	4 (<0.1)	4 (<0.1)
Related deaths	0	0
AE leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)

Sponsor Response:

The Safety Overview for Site 387 is summarized below:

Subjects reporting at least one	Vaccine Group n (%)	Placebo Group n (%)
	N=244	N=247
Solicited adverse reactions after any injection (ALL)	224 (91.8)	148 (59.9)
Solicited local adverse reaction (ALL)	220 (90.2)	73 (29.6)
Grade 3 solicited injection site reaction (ALL)	20 (8.2)	2 (0.8)
Solicited systemic adverse reaction (ALL)	181 (74.2)	136 (55.1)
Grade 3 or 4 solicited systemic adverse reaction (ALL)	41 (16.8)	7 (2.8)
Safety Set	N=244	N= 247
Unsolicited adverse event up to 28 days after any	35 (14.3)	37 (15.0)
Unsolicited non-serious adverse event	34 (13.9)	37 (15.0)
Grade 3 non-serious unsolicited adverse event	2 (0.8)	6 (2.4)
Related unsolicited adverse events	11 (4.5)	4 (1.6)
Related Grade 3 non-serious unsolicited adverse	0	0
Medically attended adverse event	4 (1.6)	20 (8.1)
Related medically attended adverse events	1 (0.4)	0
Serious adverse event	2 (0.8)	0
Related serious adverse event	0	0
Death	1 (0.4)	0
Related deaths	0	0

AE leading to discontinuation from study vaccine	0	1 (0.4)
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The incidence and severity of reactogenicity and safety events reported at Site 387 are comparable to the overall study safety profile of mRNA-1273 compared with placebo. Of note the death reported at this site was a 62 year old male (subject US3872318) with a history of depression and suicidal ideation who received one dose of mRNA-1273 and committed suicide 20 days after receiving IP. The other SAE was a 63 year old male (subject US3872090) who reported diarrhea on study day 5 assessed as unrelated to IP.

The Safety Overview for Site 393 is summarized below:

Subjects reporting at least one	Vaccine Group n (%)	Placebo Group n (%)
	N=130	N=131
Solicited adverse reactions after any injection (ALL)	120 (92.3)	73 (55.7)
Solicited local adverse reaction (ALL)	117 (90.0)	41 (31.3)
Grade 3 solicited injection site reaction (ALL)	17 (13.1)	2 (1.5)
Solicited systemic adverse reaction (ALL)	100 (76.9)	63 (48.1)
Grade 3 or 4 solicited systemic adverse reaction (ALL)	23 (17.7)	6 (4.6)
Safety Set	N=130	N= 132
Unsolicited adverse event up to 28 days after any	14 (10.8)	16 (12.1)
Unsolicited non-serious adverse event	14 (10.8)	15 (11.4)
Grade 3 non-serious unsolicited adverse event	0	0
Related unsolicited adverse events	11 (8.5)	7 (5.3)
Related grade 3 non-serious unsolicited adverse	0	0
Medically attended adverse event	1 (0.8)	4 (3.0)
Related medically attended adverse events	0	0
Serious adverse event	0	2 (1.5)
Related serious adverse event	0	0
Death	0	0
Related deaths	0	0
AE leading to discontinuation from study vaccine	0	1 (0.8)

The incidence and severity of reactogenicity and safety events reported at Site 393 are comparable to the overall study safety profile of mRNA-1273 compared with placebo.