RESPONSE TO FDA COMMENTS ON INFORMATION REQUEST#36 RECEIVED ON DECEMBER 16, 2021

The Sponsor acknowledges INFORMATION REQUEST#36 dated 16 DECEMBER 2021 in **(BOLD)**

Subject: Safety Data

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing and we have the following request for information:

ITEM 1:
In the 28 day follow-up period after any vaccination,

a. For lymphadenopathy, please provide:
- **i. Median day of onset and range (in days) following dose 1 and dose 2 in mRNA-1273 vs placebo arms**
- **ii. Median duration and range (in days) of lymphadenopathy in mRNA-1273 arm and placebo arm.**

Sponsor Response:
A total of 127 participants in the placebo group and 264 participants in the mRNA-1273 group reported lymphadenopathy up to 28 days after any dose in the Safety Set (Source Table 14.3.1.8.1.1 of CSR section 14.4.1). The table below presents the requested information on these lymphadenopathy events.

Table 1-1 Summary of Onset and Duration of Lymphadenopathy up to 28 days after any Dose, Safety Set

	Dose 1		Dose 2	
	Placebo	mRNA-1273	Placebo	mRNA-1273
	(N=15162)	(N=15184)	(N=15162)	(N=15184)
Number of subjects reporting				
Lymphadenopathy	69	200	61	78
Number of events	72	203	61	80
Onset day				
median (min, max)	6.0 (1, 28)	6.0 (1, 28)	5.0 (1, 28)	2.0 (1, 26)
Duration				
median (min, max)	6.0 (1, 242)	6.0 (1, 216)	7.0 (1, 176)	10.0 (1, 180)

b. For vertigo or positional vertigo, please provide:
- **i. Details of participants reporting vertigo/ positional vertigo in mRNA-1273 arm vs placebo arm, such as onset from dose 1 and dose 2, concomitant medications, concomitant AEs, other underlying conditions.**

ii. Median day of onset and range (in days) following mRNA-1273 dose 1 and dose 2 vs placebo dose 1 or dose 2.
iii. Median duration and range (in days) of vertigo

Sponsor Response:
For Item 2.b.i, an Excel file includes all the requested information is included in this response.

A total of 18 participants in the placebo group and 23 participants in the mRNA-1273 group reported vertigo; 1 in the placebo group and 7 in the mRNA-1273 group reported positional vertigo up to 28 days after any dose in the Safety Set (Source Table 14.3.1.8.1.1 of CSR section 14.4.1). The table below presents the requested information on the vertigo/ positional vertigo events with regards to items ii and iii.

Table 1-2 Summary of Onset and Duration of Vertigo/positional vertigo up to 28 days after any Dose, Safety Set

	Dose 1		Dose 2	
	Placebo (N=15162)	mRNA-1273 (N=15184)	Placebo (N=15162)	mRNA-1273 (N=15184)
Number of subjects reporting **vertigo** or **positional vertigo**	11	12	9	18
Number of events	11	12	10	18
Onset day				
median (min, max)	11.0 (5, 25)	12.5 (3, 24)	8.5 (1, 20)	15.5 (1, 28)
Duration				
median (min, max)	3.0 (1, 25)	2.5 (1, 211)	4.5 (1, 51)	3.5 (1, 184)

ITEM 2:
For Part A of study P301, please provide separate tables for broad with narrow combined and narrow Standardised MedDRA Queries (SMQs) for autoimmune disorders (MedDRA version 24). For each table provide the following information:

a. # of events reported for each term for each group
b. 'n' participants and percentage (%) who reported each term for each group

Sponsor Response:

Unsolicited AEs were coded by SOC and PT according to the MedDRA version 23.0, which is the version used in all of our mRNA-1273 clinical trials. Safety analyses for AEs of clinical interest were performed by using Standardized MedDRA Queries (SMQs) or Custom MedDRA Queries (CMQs) for P301 Part A, blinded phase. At the time of the BLA data cut, the SMQ of autoimmune disorders was not available within MedDRA version 23.0. Therefore, the Sponsor created a CMQ for autoimmune disorders (see CMQ for autoimmune disorders PT list spreadsheet), based on the reference (Da Silva, "Optional approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines").

Although some autoimmune disorders were reported as SAEs in both groups, no cases of autoimmune disease exacerbations were explicitly reported, and no imbalance was evident in analyses using the CMQ for autoimmune disorders. Please refer to Table 14.3.1.22.9 in the P301 Part A Blinded Phase CSR for the detailed data.

ITEM 3:
For each of the SMQs listed below (submitted to CBER under STN 125752) and for the autoimmune disorders SMQ, please provide sensitivity analyses excluding events that occurred after unblinding in Part A of Study P301. Please provide separate tables for broad with narrow combined, and narrow scope.

a. Embolic and Thrombotic events
b. Hearing and vestibular disorders
c. Angioedema events
d. Arthritis events
e. Convulsion
f. CNS vascular disorder
g. Hypersensitivity events
h. Peripheral neuropathy events
i. Demyelination events
j. Thrombophlebitis events
k. Vasculitis events
l. Hematopoietic cytopenia events
m. Cardiomyopathy events
n. Ischemic heart disease, cardiac arrhythmia, cardiac failure

Sponsor Response:
The Sponsor has previously provided the SMQ analyses for each of the requests above (narrow and broad, and narrow only), based exclusively on the Part A blinded phase of P301. Please refer to the CBER shell tables submitted in BLA 125752 SN0011 (08Oct2021) in the document entitled "Moderna_mRNA-1273_BLA_CBER requested tables_FINAL_08Oct2021", Section 5.6, Tables 65-110, including sub-analyses by age and gender, to address 'a-m'. These analyses based only on the narrow scope were also included in the P301 Part A CSR, Tables 14.3.1.22.1-14.3.1.22.16. For 'n', please refer to IR#2 (9/17 group), submitted on 27Sep2021 in SN0007.

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Approval	Honghong Zhou Clinical 18-Dec-2021 21:14:29 GMT+0000

Approval	Michelle Olsen Regulatory 19-Dec-2021 19:57:35 GMT+0000

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