RESPONSE TO FDA COMMENTS ON CLINICAL RECEIVED ON 24 SEPTEMBER 2021

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

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have several requests for additional information regarding your datasets.

Priority Group #1: Comments 1-10

Please respond to these comments by October 7, 2021. These comments pertain to the following:

- **Missing ongoing reactogenicity in the AE dataset (improperly excluded) due to multiple reasons.**
- **Request for revised AE dataset, and safety analyses if applicable, that should include ongoing reactogenicity events.**
- **Event duration- not determined as typically done**
- **Request to recalculate event duration by sensitivity analyses**
- **Improper Categorization of AEs**
- **Incorrect filename**

ITEM 1:

The SDTM define file stylesheet has an incorrect filename ('define1-0-0.xsl'). Please change the file name to 'define2-0-0.xsl' and resubmit the file.

Sponsor Response

The Sponsor would like to apologize for any inconvenience this brings to review. The file name of the SDTM define file stylesheet was automatically renamed by the publishing tool, renamed the file name from 'define2-0-0.xsl' to 'define1-0-0.xsl' in tabulation \sdtm location. Please rename the file name back to 'define2-0-0.xsl'. This would be a more straightforward approach.

ITEM 2:

In study P301, 25 subjects had AEs with an AEOUT= RECOVERED/RESOLVED or RECOVERED/RESOLVED WITH SEQUELAE, but an end date or collected duration is not provided. Please clarify if AEOUT is correctly reported (in which case an end date should be provided) or if AEOUT is incorrectly reported. Please correct the dataset accordingly.

Sponsor Response

The Sponsor would like to thank the reviewers' thorough review. The Sponsor has examined the 25 AE records with an AEOUT=RECOVERED/RESOLVED but an end date not provided. Out

of these 25 AE records, 3 have been removed by the site personnel; 1 record has been updated with an end date provided; 1 record has been updated with AEOUT=NOT RECOVERED/NOT RESOLVED; sites have responded/provided comments for 4 records but were not able to update either AEOUT or provide end date; data queries are open for 2 records. The rest 14 AE records had issues on raw data handling, such partial dates were populated inconsistently. We will discuss how to fix this specific raw data issue.

ITEM 3:

In study P301, 6 subjects had AEs with an AEOUT= NOT RECOVERED/NOT RESOLVED, but an end date is provided. Please explain and correct where appropriate.

Sponsor Response

Data queries have been sent to the sites, one record has been updated to RECOVERED after data extraction for BLA.

ITEM 4:

Regarding ongoing solicited events:

a. We have found 2428 records in P301 in which reactogenicity events reported in CE and lasting longer than the 7-day evaluation period (CERFTDTC + 6) were not reported in the AE dataset, e.g. subject 300-2231 had myalgia from Day 3-16 as reported in CE, but myalgia was not reported in AE for this subject's ongoing event following dose 1. Please update the AE dataset if these events should have been reported as ongoing. Please also provide revised summary safety data tables accordingly.

b. 'Ongoing' was not flagged in CE as requested. Instead you flagged an event in SUPPAE with Y for 'solicited adverse reaction' and N for 'AR remove flag' (please notify us if this is incorrect), which impacts our analysis of this data. Please update the CE dataset by including 'ongoing' in CENRTPT with CEENTPT of 'Day 7.'

c. Events are listed in AE that were neither an ongoing solicited event nor an SAE, but which were categorized as 'reactogenicity' in AECAT. We acknowledge that you may have categorized events that were reported by the investigator which were synonymous with solicited events and which occurred during the 7-day evaluation period and which may have been merged into the CE dataset as such, but this negatively impacts out ability to analyze the data. These events should have been reported in CE from the start of the study. Please note that we requested reporting of this data in this way in our September 28, 2020 advice under your IND submission,

but since this was not implemented in your November 2020 EUA submission, we agreed that you could flag these events in SUPPAE as 'removed' from AE analysis and instead were included in the CE dataset and ultimately the reactogenicity analysis. As these events are already flagged, please revise the category for these events back to 'Adverse Event' so that they are not confused with ongoing events.

d. We have identified events that are reported in the 'Events' datasets and 'Findings About' datasets but are not connected to provide a combined assessment for the event., e.g., subject 300-2215 had lymphadenopathy reported in CE (on Days 2-null), FACE (on Days 2 and 7), AE (on Days 7-9) and FAAE (2 rows provided for event but no days are indicated). In ADARSUM the number of days for underarm gland swelling or tenderness is 2 days, which appears to be incorrect. Please correct all events in which this situation may have occurred.

Sponsor Response

The Sponsor would like to thank the reviewers' thorough review and the guidance/discussions provided through a series of IR correspondence of SDTM mapping (Reference: IND 19745 SN0052 provided on 06-Oct-2020) as well as a teleconference held on 23-Oct-2020 between Moderna and CBER to discuss this topic.

The Sponsor has proactively taken actions to redesign the eCRF forms for future studies at the time of discussions with CBER on these related topics. A newly designed separate reactogenicity eCRF page has been added for new studies (other than P201 and P301) to streamline data collection and mapping to desired SDTM domains.

Response to a:

The Sponsor acknowledges this comment. Please note that:

- The e-Diary data (subsequently mapped to CE domain) were entered by study participants via electronic devices. Once the eDiary data was submitted, no change could be made.
- For study P301, the study sites have been instructed to enter the solicited ARs persisting beyond 7 days into the AE eCRF page (per Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review Guidance for Industry Technical Specifications Document).
- The records identified by CBER resulted from no corresponding AE eCRF entries for SAR persisting beyond 7 days. For each planned database lock, the study team tried very hard to clean the eCRF data as much as possible. However, given that the eDiary and eCRF are two independent systems, it may be possible that the entries into the 2 systems when needed do not match perfectly.

Response to b:

We first would like to explain SUPPAE.REMOVEFL=Y. In this study, participants reported SAR using eDiary after each injection. If an AR is collected on AE eCRF but not satisfies criteria of SAE or last beyond 7 days after injection, such AR would be mapped to CE and FACE domains and flagged as removed in SUPPAE (SUPPAE.REMOVEFL=Y). This mapping logic was implemented after a series of IR correspondence of SDTM mapping (Reference: IND 19745 SN0052 provided on 06-Oct-2020) as well as a teleconference held on 23-Oct-2020 between Moderna and CBER to discuss this topic.

Ongoing flag is not utilized in CE domain as there is no clear definition of 'ongoing', i.e. whether 'ongoing' refers to an SAR ongoing on Day 7 or an SAR ongoing at the time of data snapshot. Per Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review Guidance for Industry Technical Specifications Document, the ongoing information is suggested to be collected; however, in study P301, such information is not collected. In study P301, an ongoing SAR meant a SAR was reported on both D7 and D8. In eDiary data, there could be cases where SAR was reported by a study participant,

- on D7 and D9 (but not reported on D8 or no event on D8), or
- on D6 and D8 (but not reported on D7).

Due to this fact, there was no robust logic to assign "ongoing" in CEENRTPT.

Response to c:

a. AECAT="reactogenicity" is based on answer to the SAR question on AE eCRF form (please refer to response to Item 5 too);

b. Independently, remove flag = "Yes" in SUPPAE if the AE preferred term is pre-identified solicited AR symptom terms but the event not satisfying either lasting beyond 7 days nor SAE criteria.

a) and b) above are assessed independently. Would you please disregard AECAT?

Response to d:

In Study P301, SAR event captured on AE eCRF was identified through clinical review of AE preferred terms in correspondence of AR symptoms as collected on eDiary. For subject 300-2215, Lymphadenopathy was reported on Days 7-9 (AEDECOD="Lymphadenopathy"), but such preferred term was not identified in correspondence of the pre-defined SAR symptoms.

ITEM 5:

We have identified several instances where events reported in AE were erroneously categorized as 'Reactogenicity'. For example, subject 305-2061 had a left knee torn meniscus with AECAT= Reactogenicity. Please ensure that all events in AE are

characterized correctly and resubmit the AE dataset. Please note that none of the events correctly categorized as 'reactogenicity' should be included in ADAE.

Sponsor Response

The Sponsor would like to thank the reviewers for the thorough review. The value "reactogenicity" in AECAT was assigned based on the following question on the AE eCRF page (screenshot below) if the answer to the question is 'Yes':

Part of the data review and cleaning was to identify if an event should be mapped to the CE when it was marked as SAR on the AE eCRF page. If there wasn't enough detail provided to support the mapping to CE domain, sites were queried to provide more details or to make updates. At the time of the database lock and analyses, if queries were not fully resolved, the corresponding events were left in AE domain.

ITEM 6:

We have identified instances where CE was not updated with the investigator collected information. For example, subject 301-2023 had severe underarm gland tenderness on Day 29 (Dose 1 day 1) in AE, and in CE the event was reported as occurring Days 30-33 with moderate severity. In ADARSUM underarm gland tenderness number of days is reported as 4 instead of 5, and the worst analysis toxicity grade is moderate. Please correct all datasets where this may have occurred and update the safety analyses results where appropriate.

Sponsor Response

In Study P301, SAR event captured on AE eCRF was identified through clinical review of AE preferred terms in correspondence of AR symptoms as collected on eDiary. For subject 301-2023, AEDECOD="Lymph node pain" and such preferred term was not identified in correspondence of the pre-defined SAR symptoms.

ITEM 7:

We have identified 3290 records where 'Reactogenicity' events reported in the AE dataset have either the start date or the end date not equal to the dates reported in CE. This impacts our ability to determine the actual dates/days of occurrence, and also becomes problematic in discerning which events are ongoing. For example, erythema was reported for subject 300-2107 in which the days of the event are 31-37 in CE and 31-36 in AE (Dose 2). Please ensure consistency of the dates/days reported for each reactogenicity event in CE and AE and correct where necessary.

Sponsor Response

As explained to response to Item 4 and 5, such "Reactogenicity" events in AE domain represent data collected on AE eCRF form; while CE domain includes topline events collected in eDiary. Given that the eDiary and eCRF are two independent systems, it may be possible that the entries into the 2 systems when needed do not match perfectly.

ITEM 8:

The duration of solicited adverse reactions appear to be calculated based on the number of unique days in which the event is reported. We are concerned that this underestimates the event duration (e.g. an event reported on Day 1 and Days 3 and 5 likely had lasted 5 days as opposed to 3). Please provide an analysis of solicited adverse reaction duration (as presented in Tables 14.3.1.4.1.1 and 14.3.1.4.1.2 of the CSR) where duration is calculated assuming that the event occurred continuously from the first day to the last day the event was reported (i.e. duration = last day – first day + 1), regardless of how many days the event was documented in between.

Sponsor Response

The duration of solicited adverse reaction (SAR) was calculated as the cumulative number of days that the solicited AR was reported, including the day of injection. We would like to use this opportunity to further explain/clarify the data derivation on duration of SAR. In this study, participants reported SAR using eDiary after each injection started within 7 days until the end of the SAR. If an AR is collected on AE eCRF but does not satisfies criteria of SAE or last beyond 7 days after injection, such AR would be mapped to CE and FACE domains, and flagged as removed in SUPPAE (SUPPAE.REMOVEFL=Y), correspondingly in ADAR and ADARP7D (section 5.2.3 and 5.2.4 of ADRG). If an AR is collected on AE eCRF and either satisfies criteria of SAE or last beyond 7 days after injection, such AR would be included in AE, CE, FAAE and FACE domains, and correspondingly in ADAE, ADAR and ADARP7D. These mapping logics have been implemented after a series of IR correspondence of SDTM mapping (Reference: IND 19745 SN0052 provided on 06-Oct-2020) as well as a teleconference held on 23-Oct-2020 between Moderna and CBER to discuss this topic.

ADaM dataset ADARSUM includes summary data of ADAR and ADARP7D, contains total number of days with symptom grade > 0 that are derived from both ADAR andADARP7D. ADARSUM is one record per subject (SUBJID), per symptom(PARAMCD), and per vaccine/injection (ATPTREF), please refer to Section 4.2 Data Dependencies and Section 5.2.5 ADARSUM of ADRG). ADARSUM is the ADaM dataset that supports Summary of number of days of solicited adverse reaction after each injection provided in the CSR (Tables 14.3.1.4.1.1 and 14.3.1.4.1.2).

We believe the provided summary of number of days (duration) of SAR in CSR presents the reported duration of SAR in this study. In this response, we are providing the requested analysis of summary of duration of SAR using the suggestion of the reviewer which represent a conservative approach of calculating the duration of SAR, in which duration = last date – first date +1 (tables 8-1 and 8-2). The results are summarized in Table 8-1 below with the source tables provided in in Module 5.3.5.1. Using this conservative approach, the results are consistent with the duration of SAR reported in CSR section 7.1.3: The solicited ARs in participants who received mRNA-1273 persisted for a median of 1 to 3 days after the first and second injection, with no apparent difference noted between the first and second injection. For ease of review, results reported in P301 CSR Section 7.1.3 on summary of duration (number of days) of SAR are also provided in Table 8-2.

Table 8-1 Ad-hoc summary of duration of SAR using last date- first date+1

	First Injection Solicited Safety Set		**Second Injection Solicited Safety Set**	
Solicited Adverse Reaction	**Placebo**	**mRNA-1273**	**Placebo**	**mRNA-1273**
Category	**(N=15151)**	**(N=15166)**	**(N=14578)**	**(N=14691)**
Statistic				
Solicited Adverse Reactions				
n	7285	13317	6255	13556
Mean (SD)	3.9 (5.51)	3.9 (4.33)	4.2 (8.86)	4.4 (7.83)
Median	2	3	2	3
Min, Max	1, 191	1, 193	1, 212	1, 198
Solicited Local Adverse Reactions				
n	3009	12765	2757	13029
Mean (SD)	2.2 (3.07)	2.8 (2.37)	2.4 (6.54)	3.3 (3.35)
Median	1	2	1	3
Min, Max	1, 55	1, 72	1, 212	1, 155
Solicited Systemic Adverse Reactions				
n	6397	8316	5343	11678
Mean (SD)	3.8 (5.63)	3.5 (4.97)	4.2 (8.91)	3.7 (8.00)
Median	2	2	2	2
Min, Max	1, 188	1, 193	1, 204	1, 198

Source: Table 14.3.1.4.1.4.1 and Table 14.3.1.4.1.4.2

Table 8-2. Summary of Duration (Number of Days of) Solicited Adverse Reactions After First and Second Injection (reported in P301 CSR)

	First Injection Solicited Safety Set		Second Injection Solicited Safety Set	
Solicited Adverse Reaction	**Placebo**	**mRNA-1273**	**Placebo**	**mRNA-1273**
Category	**(N=15151)**	**(N=15166)**	**(N=14578)**	**(N=14691)**
Statistic				
Solicited adverse reactions				
n	7285	13317	6255	13556
Mean (SD)	3.3 (5.35)	3.5 (4.18)	3.7 (8.69)	4.2 (7.76)
Median	2	3	2	3
Min, Max	1, 189	1, 193	1, 212	1, 198
Solicited local adverse reactions				
n	3009	12765	2757	13029
Mean (SD)	2.0 (2.88)	2.7 (2.22)	2.2 (6.40)	3.2 (3.28)
Median	1	2	1	3
Min, Max	1, 51	1, 71	1, 212	1, 154
Solicited systemic adverse reactions				
n	6397	8316	5343	11678
Mean (SD)	3.3 (5.47)	3.1 (4.81)	3.7 (8.73)	3.4 (7.91)
Median	2	2	2	2
Min, Max	1, 188	1, 193	1, 204	1, 198

Source: CSR Table 7-3 (Table 14.3.1.4.1.1) and
Table 7-4 (Table 14.3.1.4.1.2).

ITEM 9:

Please provide a rationale for reporting in the MH dataset a 'New onset type 2 diabetes' for subject US326-2100 in P301 in which the subject was vaccinated on Aug 5, 2020 and the start date of the event was Mar 26, 2021; and 'Depression' for subject US325-2195 in which the subject was vaccinated on Aug 15, 2020 and the start date of the event was Nov 3, 2020. Please report these events in the AE dataset if the dates are correct and update the safety analyses results where appropriate.

Sponsor Response

Thank you for your comments on the MH records.

For participant US3262100, this new diagnosis of type 2 diabetes was indeed already recorded in AE eCRF and is included in AE domain with AE start date 26-Mar-2021. Queries have been issued regarding the MH record of the new diagnosis of type 2 diabetes but have not yet resolved. The SPONSOR will continue to work on resolving the open query on the MH record.

SUBJID	TRT01P	TRT01A	AEDECOD	AESOC	AESTDTC	AEENRF	ASTDT
US3262100	mRNA-1273	mRNA-1273	Type 2 diabetes mellitus	Metabolism and nutrition disorders	2021-03-26	ONGOING	26MAR2021

Subject US3252195 had 'Depression' on medical history (MH) eCRF form with start date of 03-Nov-2020. No further information can be provided at this time, the PI signed off on March 5, 2021 stating that the participant did not experience any Adverse Events.

ITEM 10:

We have identified instances where the start date or end date of an event is missing in CE even though FACE and FAAE had each day reported. For example, 301-2053 had underarm gland swelling on Day 2, 5, 6, and 7 in FACE and on Days 9-15 in FAAE. The event for this subject was also reported in AE from Days 6-16. This event is also inappropriately reported in ADAE (note that in addition to this event not being appropriate for reporting in ADAE, it is also reported from the subject's diary as indicated in FAAE). Please update the CE dataset with the appropriate dates/days.

Sponsor Response

Per CDISC VXUG1-1, CE START Date/END Date should be set to missing if they cannot be determined due to missing event report date. For subject 301-2053, we cannot determine the end date for this event. There were 2 records in FAAE on Day 16 and 17 with missing report. Therefore, the Sponsor couldn't tell which date is the end date.