RESPONSE TO FDA COMMENTS ON INFORMATION REQUEST#37 RECEIVED ON DECEMBER 16, 2021

The Sponsor acknowledges INFORMATION REQUEST#37 dated 16 DECEMBER 2021 in (**BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Revised Data Sets

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have reviewed your revised data sets submitted December 1, 2021 in amendment 27 and have the following requests for information:

ITEM 1:
Only a few of the terms in AE that are synonymous with solicited adverse reactions that began during the 7 day assessment period and of which you have now subcategorized as "wrong category' have a flag in suppae "AR remove flag" indicating it is removed from AE and included in CE analysis. Please indicate the additional steps you have taken with these adverse reactions in the datasets, i.e., should they have been flagged and were they summarized with the events in CE and was this summarization included in the ADCE analysis datasets and final report.

Sponsor Response:
The Sponsor would like to clarify, after the submission of the updated domains per agreement in the (SN0027) dated 30-Nov-2021, we provided further clarification of AESCAT = "WRONG CATEGORY". There are two scenarios, specifically:

1. Solicited adverse reaction flag is incorrect (AESOFL="Y", but AETERM is not one of pre-specified Symptoms).
2. The event is a solicited adverse reaction, however the onset date is after 7 days of an injection (AESOFL="Y", and AETERM is one of pre-specified Symptoms, but the event started date is after day 7).

These above events thus would not be in CE. These events are kept in AE. These issues and updates were discussed during the TC on 29Oct2021 (Item 4).

ITEM 2:
The number of ongoing events in CE does not match the number of ongoing events in AE (AECAT reactogenicity/AESCAT SAE/Ongoing), i.e. we are finding 5937 events (after removing the "ongoing" immediate events and "ongoing" day 6 events) in CE and 3915 events in AE. We also note that many of the events in CE that appear to be ongoing are not flagged as ongoing so the numerical difference between the 2 datasets could be even more significant. Please explain.

Sponsor Response:
We understand the discrepancy and due to the fact that the database is locked, it is not possible to correct the discrepancy. Please see below for a summary of additional findings:

Total Missing ongoing symptoms in AE are:

There is a total of 6721 ongoing symptoms after removing the "ongoing" immediate events in SDTM domain CE (1 record per unique subject id per dose reference per symptom). Out of these 6721 symptoms:

- 1892 of 6721 ongoing symptoms have no investigator assessment. We are reviewing each line item to record the discrepancy, so that we can not repeat these mistakes in future database locks.
- 970 of 6721 ongoing symptoms have investigator assessment, but event ending day is with day 7, this is an known issue and could be due to any of the following: eDiary (participant reported data) cannot be changed once submitted; eDiary and eCRF are two independent systems; investigator assessments does not agree with participate reporting data via eDiary.

In summary there is a total of 2864 ongoing events in CE does not match the number of ongoing events in AE (6721-1892-970=2864).

ITEM 3:
We have identified several instances where events that are synonymous with prespecified reactions, but which began on Day 8 or thereafter are being reported in CE. We also noticed that in the initial CE dataset you had 149 events and in the revised CE dataset you had 228 events where this was the situation. If the event began after the assessment period it should be considered unsolicited and be reported in AE. Please provide a sensitivity analysis of unsolicited events that are synonymous with prespecified reactogenicity events that began on Day 8 or after. If the event occurred on day 7 but was collected on Day 8 (which it appears many of these were) please include this with the summary of the event in CE. This will mean you need to recalculate the duration of the event and update your analysis of duration of SAR using CBER's definition of last day – first day +1.

Sponsor Response:
The Sponsor would like to take this opportunity to explain the derivation of Event Start Day.
Calculation Programming Logic:
Step 1: check CESTDTC, if time is missing in CESTDTC missing, to impute time using the following logic:

- If Dose Date and Event Date are the same, then set missing time to 23:59 – this is to make sure this event is occurred after dose date time
- if Dose Date and Event Date are not on the same date, then set time to 11:59 – this is to follow e-Diary Window Closing Time

Step 2:
Calculated Event Start Day = [(Event Date Time (in Second) - Dose Date Time (in second)]/(3600*24)
Set Start Day to 7 if the results are <7.5

USUBJID	CETERM	CECAT	CETOXGR	CESTDTC	CERFTDTC	CEENDTC	CESTDY	Calculated Day	CETPTREF
mRNA-1273-P301-US300-2043	Erythema	REACTOGENICITY	1	2020-08-05	2020-07-29T11:55	2020-08-06	8	7.002777778	DOSE 1
mRNA-1273-P301-US300-2159	Arthralgia	REACTOGENICITY	1	2020-08-20T10:42	2020-08-13T11:04	2020-08-20T10:42	8	6.984722222	DOSE 1
mRNA-1273-P301-US300-2331	Nausea/Vomiting	REACTOGENICITY	1	2020-10-05T01:23	2020-09-28T11:08	2020-10-05T01:23	8	6.59375	DOSE 1
mRNA-1273-P301-US301-2149	Fatigue	REACTOGENICITY	1	2020-08-21T10:28	2020-08-14T15:02	2020-08-21T10:28	8	6.809722222	DOSE 1
mRNA-1273-P301-US301-2232	Underarm Gland Swelling or Tenderness	REACTOGENICITY	1	2020-09-02T08:32	2020-08-26T19:23	2020-09-05T08:28	8	6.547916667	DOSE 1
mRNA-1273-P301-US301-2252	Fatigue	REACTOGENICITY	1	2020-09-08T00:19	2020-09-01T14:16	2020-09-09T09:43	8	6.41875	DOSE 1
mRNA-1273-P301-US302-2040	Chills	REACTOGENICITY	1	2020-08-04T09:37	2020-07-28T10:40	2020-08-04T09:37	8	6.95625	DOSE 1
mRNA-1273-P301-US302-2100	Fatigue	REACTOGENICITY	1	2020-08-07T06:25	2020-07-31T15:04	2020-08-07T06:25	8	6.639583333	DOSE 1
mRNA-1273-P301-US304-2023	Nausea/Vomiting	REACTOGENICITY	1	2020-08-05T07:15	2020-07-29T14:34	2020-08-05T07:15	8	6.695138889	DOSE 1
mRNA-1273-P301-US304-2070	Nausea/Vomiting	REACTOGENICITY	1	2020-08-11T01:01	2020-08-04T19:28	2020-08-11T22:31	8	6.23125	DOSE 1

Please see attached excel that included all 228 calculation results. Thus the sponsor respectively propose the suggested sensitivity is not necessary.

ITEM 4:
Many of the lymphadenopathy events (equivalent to axillary swelling) beginning within the 7 day assessment period are still in AE (AECAT=adverse event). Please provide additional information on the steps taken in SDTM to remove these events from the ADAE analysis dataset and include them in the ADCE analysis dataset.

Sponsor Response:
There are a total of 72 lymphadenopathy events with AESOFL="N", i.e. the event is not checked as a solicited adverse reaction on the AE eCRF form (snapshot below).

For the convenience of your review, we are including these 72 data issues as appendix. (attached please find 72 Data Issues, below is a snapshot for demonstration purpose).

USUBJID	AETERM	AEDECOD	AESTDTC	AEENDTC	AESEVSTD	AESOFL
mRNA-1273-P301-US300-2135	RIGHT AXILLARY LYMPHADENOPATHY	Lymphadenopathy	2020-08-07	2020-10-08T00:00	Grade 1/Mild	N
mRNA-1273-P301-US301-2083	SWELLING, LYMPH NODES IN NECK	Lymphadenopathy	2020-09-06	2020-09-09	Grade 1/Mild	N
mRNA-1273-P301-US301-2149	LEFT SIDE SWOLLEN NECK GLAND	Lymphadenopathy	2020-09-15	2020-09-30	Grade 1/Mild	N
mRNA-1273-P301-US303-2267	UNDERARM GLAND SWELLING	Lymphadenopathy	2020-08-20T08:01	2020-09-02T08:15	Grade 1/Mild	N
mRNA-1273-P301-US315-2035	ENLARGED ANTERIOR CERVICAL CHAIN LYMPHNODES	Lymphadenopathy	2020-07-29T19:00	2020-07-30T09:30	Grade 1/Mild	N
mRNA-1273-P301-US315-2067	LEFT ENLARGED SUPRACLAVICULAR LYMPHADENOPATHY, IPSILATERAL	Lymphadenopathy	2020-08-04	2020-08-31	Grade 2/Moderate	N
mRNA-1273-P301-US315-2214	RIGHT INGUINAL LYMPHADENOPATHY	Lymphadenopathy	2020-09-16T14:17		Grade 1/Mild	N
mRNA-1273-P301-US315-2404	BILATERAL CERVICAL LYMPHADENOPATHY	Lymphadenopathy	2020-10-13	2020-10-15	Grade 1/Mild	N

There are 199 lymphadenopathy events started on or after Day 8, we are including these 199 data issues as appendix, and below is a snapshot as example.

USUBJID	AETERM	AEDECOD	AECAT	AESTDTC	AESTDY	AEENDY	AETPTREF	AEREFDTC	EVTSTDY
mRNA-1273-P301-US300-2135	IPSILATERAL LEFT AXILLARY LYMPHADENOPATHY	Lymphadenopathy	ADVERSE EVENT	2020-10-08	63	139	DOSE 2	9/9/2020	30
mRNA-1273-P301-US301-2010	SWOLLEN LYMPH NODES (LYMPHADENITIS), LEFT SIDE OF NEC	Lymphadenopathy	ADVERSE EVENT	2020-08-13	17	24	DOSE 1	7/28/2020	17
mRNA-1273-P301-US301-2070	LYMPHADENOPATHY BILATERAL NECK	Lymphadenopathy	ADVERSE EVENT	2020-12-23	140	147	DOSE 2	9/3/2020	112
mRNA-1273-P301-US302-2065	RIGHT ANTERIOR CERVICAL CHAIN LYMPHADENOPATHY	Lymphadenopathy	ADVERSE EVENT	2020-10-26	90	104	DOSE 2	9/2/2020	55
mRNA-1273-P301-US302-2171	ENLARGEMENT OF LEFT BEAST LYMPH NODE	Lymphadenopathy	ADVERSE EVENT	2021-03-22	216		DOSE 2	9/15/2020	189
mRNA-1273-P301-US302-2223	RIGHT ANTERIOR CERVICAL CHAIN LN	Lymphadenopathy	ADVERSE EVENT	2020-10-12	54	89	DOSE 2	9/17/2020	26
mRNA-1273-P301-US302-2223	LEFT ANTERIOR CHAIN LYMPH NODE, IPSILATERAL TO LYMPH	Lymphadenopathy	ADVERSE EVENT	2020-12-22	125		DOSE 2	9/17/2020	97
mRNA-1273-P301-US302-2223	LEFT POSTERIOR-CHAIN LYMPH NODE IPSILATERAL TO LYMPH	Lymphadenopathy	ADVERSE EVENT	2020-12-22	125		DOSE 2	9/17/2020	97
mRNA-1273-P301-US302-2233	POSTERIOR CERVICAL LYMPHADENOPATHY	Lymphadenopathy	ADVERSE EVENT	2021-02-20	185	191	DOSE 2	9/24/2020	150
mRNA-1273-P301-US302-2239	LEFT CERVICAL LYMPHADENOPATHY	Lymphadenopathy	ADVERSE EVENT	2020-10-20	62		DOSE 2	9/22/2020	29
mRNA-1273-P301-US302-2336	IPSILATERAL-SAME ANTERIOR CHAIN CERVICAL LYMPHADEM	Lymphadenopathy	ADVERSE EVENT	2020-11-04	27		DOSE 1	10/9/2020	27