RESPONSE TO FDA COMMENTS ON CLINICAL DATED NOVEMBER 12, 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. We have the following requests for additional information:

There appear to be inconsistencies in the analysis dates (ADT) for SARS-CoV-2 infection regardless of symptomatology and asymptomatic infection between ADEFF and ADTTEB, on which the final efficacy analyses of these endpoints appear to be based. For example, subject US338-2007 tested positive for serology on both 2021-01-15 and 2021-03-10. However, the analysis dates for the two efficacy endpoints are 2021-01-15 in ADEFF and 2021-03-10 in ADTTEB. Of note, this subject was unblinded on 2021-01-15. Similar observations were made for subjects US340-2153, US397-2129, and among others. In addition, we note that some subjects (e.g. US321-2148, US303-2145, US315-2071, etc) had a positive PCR or serology on the same day (and for some cases e.g. US315-2071 the same time) as the Participant Decision Visit (PDV), but were not considered to have had an infection during the blinded phase even though the endpoints explicitly include infections detected at the PDV.

ITEM 1:
1. Clarify reasons for discrepancies in the analysis dates between the analysis datasets noted above.

Sponsor Response

The Sponsor would like to thank the reviewers for the thorough review and respond to all 3 items together in a systematic way.

The reason for these discrepancies is due to the visit names from the testing/central lab for serology (bAb against SARS-CoV-2 N protein as measured by Roche Elecsys) were different than the visits collected in EDC.

In P301, for serology, the site personnel fill out the sample requisition form on which the site checks the corresponding visit (visit name/label). A barcode is generated, manifest id, and used together with subject id to identify the samples (with subject ID) at the testing lab (PPD vaccine). The testing of serology/Roche Elecsys (samples/aliquot) were sent to the testing lab once they were taken.

Data received from the testing lab, including subject ID and these selected visit names, were reconciled with data from EDC on a regular basis. When the central/testing lab data are merged with EDC data to develop relevant SDTM domains, subject IDs, dates, and visit names are used

as the keys for merging. When the visit names from the two sources do not match, visit names provided by testing labs were used. These visit names are correspondingly captured in SDTM domain IS.VISIT.

Subsequently, in the corresponding analysis dataset, AVISIT is derived using the corresponding SDTM domain, e.g. ADIS.AVISIT vs. IS.VISIT.

For example, Subject 338-2007 had their participant decision visit date (PDV) on 15-Jan-2021 (PDVDT), was unblinded, and the start of the open-label phase for this subject was recorded as 15-Jan-2021 (ADSL.AP02SDT). This participant had positive serology tests on 15-Jan-2021, 10-Mar-2021 and 18-Mar-2021, however in the raw data for serology results from the central lab, PDV was labeled for 10-Mar-2021.

Participants US303-2145, US321-2148 and US338-2007 had positive serology results on PDV visit, but the results on the same date were labeled as visits other than PDV visits from the central/testing lab.

Table 1-1 lists aelect subjects with positive serology results (positive bAb against SARS-CoV-2 N protein as measured by Roche Elecsys) on PDV date with discrepancy on visit name from central lab or with positive result labeled as PDV from central lab with discrepancy on PDV date in EDC.

A similar process was used for RT-PCR results, and Table 1-2 lists US3402153's positive RT-PCR test results, one positive result on 09-Mar-2021 was labeled as 'PDV/OL-D1' which was not on the date of PDV of 06-Jan-2021.

Table 1-3 lists the participants the reviewers had questions. For each participant, the current variables in ADTTEB for infection and asymptomatic infection; the reason for current derivation, and what should be updated is presented.

Table 1-1. Select subjects with positive serology results (positive bAb against SARS-CoV-2 N protein as measured by Roche Elecsys) on PDV date with discrepancy on visit name from central lab or with positive result labeled as PDV from central lab with discrepancy on PDV date in EDC

SUBJID	TRT01P	PDVDT	ISDTC	IS.VISIT	ADIS.ADT	ADIS.AVALC	ADIS.AVISIT
US3032145	mRNA-1273	9-Jan-21	1/9/2021	OL-D29	9-Jan-21	Positive	Open Label Day 29
US3212148	mRNA-1273	4-Mar-21	2021-03-04T11:32	Visit 4 Day 209	4-Mar-21	Positive	Day 209
US3382007	Placebo	15-Jan-21	1/15/2021	OL-D57	15-Jan-21	Positive	Open Label Day 57
US3382007	Placebo		2021-03-10T09:14	Participant Decision Visit / OL-D1	10-Mar-21	Positive	Participant Decision Visit / OL-D1
US3382007	Placebo		2021-03-18T15:47	Visit 4 Day 209	18-Mar-21	Positive	Day 209
US3402153	Placebo	6-Jan-21	2021-03-09T15:17	Participant Decision Visit / OL-D1	9-Mar-21	Positive	Participant Decision Visit / OL-D1
US3972129	Placebo	20-Jan-21	2021-03-04T11:57	Participant Decision Visit / OL-D1	4-Mar-21	Positive	Participant Decision Visit / OL-D1
US3972129	Placebo		2021-04-01T10:48	Visit 4 Day 209	1-Apr-21	Positive	Day 209

Table 1-2 Positive RT-PCR results for Participant US340-3153

SUBJID	TRT01P	PDVDT	MBDTC	MB.VISIT	ADMB.ADT	ADMB.AVALC	ADMB.AVISIT
US3402153	Placebo	6-Jan-21	1/13/2021	Illness Visit Day 1	13-Jan-21	Positive	Illness Visit
US3402153	Placebo		1/14/2021	Illness Visit Day 3 - Day 21	13-Jan-21	Positive	Illness Visit
US3402153	Placebo		2021-03-09T15:12	Participant Decision Visit / OL-D1	9-Mar-21	Positive	Participant Decision Visit / OL-D1

Table 1-3 detailed explanation for each participant

SUBJID	TRT01P	PDVDT	ADTTEB.Paramcd "TTINFB5" all infection		ADTTEB.Paramcd "TASYCRB5" Asymptomatic infection		Comments	Reason
			CNSR	ADT	ADT	CNSR		
US3032145	mRNA-1273	9-Jan-21	1	9-Jan-21	9-Jan-21	1	censored on 09-Jan-2021 (PDV) for all infection and asymptomatic infection for blinded phase; should be event on 09-Jan-2021 (PDV) for all infection and asymptomatic infection	positive serology result on PDV labeled as OL-Day 57, thus were not considered
US3212148	mRNA-1273	4-Mar-21	1	4-Mar-21	4-Mar-21	1	censored on 04-Mar-2021 (PDV) for all infection and asymptomatic infection for blinded phase; should be event on 04-Mar-2021 (PDV) for all infection and asymptomatic infection	positive serology result on PDV labeled as Day 209, thus were not considered. There was no serology result labeled as OL-Day 1
US3152071	mRNA-1273	27-Jan-21	1	27-Jan-21	27-Jan-21	1	censored on 27-Jan-2021 (PDV) for all infection and asymptomatic infection for blinded phase.	Subject had a positive RT-PCR on 27-Jan-2021 with "Illness Day 1"; participants had negative RT-PCR on 27-Jan-2021 "PDV" and negative RT-PCR on 29-Jan-2021, 02-Feb-2021 and 04-Feb-2021. (pls see Table 1-4 below)
US3382007	Placebo	15-Jan-21	0	10-Mar-21	10-Mar-21	0	event on 10-March-2021 for all infection and asymptomatic infection; should be event on 15-Jan-2021 for all infection and asymptomatic infection	subject's positive serology result on PDV (15-Jan-2021) was labeled as 'OL-D57'; positive serology result on 10-March-2021 was labeled as 'PDV/OL-Day1' and was taken into consideration

US3402153	Placebo	6-Jan-21	0	9-Mar-21	13-Jan-21	2	event on 09-Mar-2021 for all infection; cnsr=2 (had other competing event) on 13-Jan-2021 for asymptomatic infection Subject should be censored 6-Jan-2021 for infection and asymptomatic infection for the blinded phase.	Subject had a positive RT-PCR on 09-Mar-2021 labeled as 'PDV/OL-Day 1' thus was considered as event on 09-Mar-2021. Subject had positive serology and RT-PCR result on 13-Jan-2021
US3972129	Placebo	20-Jan-21	0	4-Mar-21	20-Jan-21	2	event on 04-Mar-2021 for all infection; cnsr=2 (had other competing event) on 20-Jan-21 for asymptomatic infection; should be event on 20-Jan-2021 for all infection, cnsr=2 on 20-Jan-21 for asymptomatic infection	Subject had positive serology on 04-Mar-2021 labeled as 'PDV/OL-Day 1' Subject had positive RT-PCR on 20-Jan-2021 'Illness visit' and positive RT-PCR on 22-Jan, 25-Jan, 28-Jan 'Illness visit'

Table 1-4 list of RT-PCR results for Participant US3152071

SUBJID	MBTESTCD	MBORRES	VISIT	MBDTC
US3152071	SARSCOV2	Detected	Illness Visit Day 1	2021-01-27T15:22
US3152071	SARSCOV2	Not Detected	Participant Decision Visit / OL-D1	2021-01-27T15:22
US3152071	SARSCOV2	Not Detected	Illness Visit Day 3 - Day 21	1/29/2021
US3152071	SARSCOV2	Not Detected	Illness Visit Day 3 - Day 21	1/31/2021
US3152071	SARSCOV2	Not Detected	Illness Visit Day 3 - Day 21	2/2/2021
US3152071	SARSCOV2	Not Detected	Illness Visit Day 3 - Day 21	2/4/2021

ITEM 2:
2. Clarify why the later infection date in ADTTEB was used in the analysis for some participants even though the participants had documented infections at earlier time points.

Sponsor Response
Some of the later infection dates were considered in ADTTEB to take into consideration positive infection data labeled as 'PDV/OL-Day 1' but the date is after AP02SDT. In addition to use the date of PDV/unblinding, we have taken this conservative approach to use AVISIT for the positive infection results to ensure positive infection results at PDV were taken into considerations. For example, for all infection Regardless of Symptomatology and Severity in the mITT Set after randomization, there were 80 participants with ADT later than the PDV/unblinding date (AP02SDT) in ADTTEB, and all of them were infection cases with 59 on Placebo and 21 on mRNA-1273. The condition used for the ADTTEB dataset is provided below for your convenience.

```
where adt>. and adt>ap02sdt and ap02sdt>. and mittfl="Y" and
paramcd="TTINFB5";
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We acknowledge that, in the (rare) situation the label of 'PDV/OL-Day' is not correct, this conservative approach may lead to questionable derivation, as noted for Participant US3402153.

ITEM 3:
3. Explain your rationale for excluding positive PCR/serology results from subjects noted above collected on the same day as the PDV for the analyses of SARS-CoV-2 or asymptomatic infection during the blinded phase, despite IS.EPOCH or MB.EPOCH indicating that the sample was collected during blinded follow-up. We also note that some participants' MB.VISIT or IS.VISIT labeled as "Participant Decision Visit / OL-D1" do not appear to correspond to the start of the PDV or the unblinding date for those participants (e.g. US338-2007).

Sponsor Response
Please see explanations in response to Item 1. We use the collected visit information other than the derived EPOCH. For MB.VISIT and IS.VISIT, both visits captured in EDC as well as visits included in the data transfer from central/testing labs for RT-PCR and Elecsys were considered. On top of the data reconciliation explained in Item 1, when the visit name/labels between the two sources still don't match, for P301, the visit name/label from the central/testing labs are used in the SDTM mapping of MB.VISIT and IS.VISIT. We acknowledge that there were still visits labeled as 'PDV/Open-Label Day 1' not matching the PDV date in the final EDC (clinical database). We will continue to look into this.

Participant US338-2007 had a positive serology result on PDV (15-Jan-2021), however it was labeled as 'OL-D57'; the participant's positive serology result on 10-March-2021 was labeled as 'PDV/OL-Day1' and thus was taken into consideration.