RESPONSE TO FDA COMMENTS ON CLINICAL DATED NOVEMBER 03, 2021

The Sponsor acknowledges FDA Comments on CLINICAL (in **BOLD**)

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

ITEM 1:

On review your analysis for VE against asymptomatic infection, we have identified cases classified as asymptomatic infection where the participant was asymptomatic before and during the date of their positive RT-PCR or N-serology but then later went on to develop COVID-19 symptoms days/weeks after. Please conduct a sensitivity analysis for your endpoint of VE against asymptomatic infection excluding all participants who had any documented CDC or protocol-defined COVID-19 symptoms at any time during the entire study through the blinded phase of the study (including symptoms reported both before and after the positive PCR or N-serology result and symptoms reported during both the blinded phase and open-label phase of study).

Sponsor Response:

The Sponsor conducted a sensitivity analysis as requested for vaccine efficacy (VE) against asymptomatic SARS-CoV-2 infection starting 14 days after dose 2 in Per-Protocol (PP) set in the blinded phase of the study. In this sensitivity analysis, participants with positive RT-PCR or N-serology results who had any documented CDC or protocol-defined COVID-19 symptoms at any time during the entire study (including symptoms reported both before and after the positive RT-PCR or N-serology results and symptoms reported during both the blinded phase and open-label phase of study) were censored for asymptomatic cases, with censor variable CNSR=2, considered as COVID-19 disease cases for competing risk. Please note that the median follow-up time of the blinded phase was 5.3 months.

In this sensitivity analysis of VE against asymptomatic infection using competing risk, only the censor variable (ADTTEB.CNSR) values were updated as described above. The time to event/censoring variable was kept unchanged from the original analysis presented in the CSR Section 6.2.6 (ADTTEB.AVAL for ADTTEB.PARAMCD ="TASYCRB1", asymptomatic infection starting 14 days after dose 2, including participant decision visits).

The summary of the sensitivity analysis results is presented in the table below. The analysis of VE based on both 1- incidence rate ratio (1-IRR) adjusting for person-years and 1- hazard ratio (1-HR) adjusting for the competing risk yielded the similar results to the original respective

analysis results submitted in the BLA package, as shown in Table 1-1. The results from the requested sensitivity analysis is consistent with the analysis of asymptomatic COVID-19 presented in CSR section 6.2.9.

Table 1-1: Sensitivity analysis of vaccine efficacy (VE) against asymptomatic SARS-CoV-2 infection starting ≥14 days after dose 2 in the blinded phase, Per-Protocol Set

	mRNA-1273 N=14287 n IR/1000 person-years (95% CI)	**Placebo N=14164 n IR/1000 person-years (95% CI)**	**VE[a] (1- IRR) % (95% CI)**	**VE[b] (1- HR) % (95% CI)**
Sensitivity analysis	182 31.6 (27.2, 36.6)	413 75.9 (68.8, 83.6)	58.3 (50.3, 65.2)	61.8 (54.5, 67.9)
Original analysis (P301 CSR Section 6.2.9)	214 37.2 (32.4, 42.5)	498 91.5 (83.7, 99.9)	59.4 (52.2, 65.5)	63.0 (56.6, 68.5)

IR = incidence rate; 1- IRR = 1- incidence rate ratio; 1-HR= 1- hazard ratio
a: VE is defined as 1 – IRR (mRNA-1273 vs. placebo). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
b: VE = 1- HR and 95% CI were estimated using Fine and Gray's sub-distribution hazard model with COVID-19 disease cases as competing events and with the treatment group as a covariate, adjusting for stratification factor.

ITEM 2:
For each efficacy endpoint presented in Table 6 of the Clinical Overview, please clarify the variables in ADSL used to define the time period considered in the analyses.

Sponsor Response:

In Table 6 of the Clinical Overview, various efficacy endpoints starting 14 days after second injection and 14 days after first injection are presented. The table below clarifies ADSL variables used to define the time period of events.

Time period	**ADSL variables**	**Based on event data (ADT) to determine time period**
14 days after second injection	DOSE2DT for second injection date	ADT ≥ DOSE2DT +14 > .
14 days after first injection	TR01SDT for first injection date	ADT ≥ TR01SDT + 14 > .

ITEM 3:

Please complete the following table for subjects who had suspected COVID-19 (met criteria for illness visit and nasopharyngeal swab collection) starting 14 daysafter Dose 2, but for whom no PCR results are not available:

	mRNA-1273	Placebo
Participants with suspected COVID-19 but no PCR result available		
Reason for no PCR results		
Not collected		
Sample lost		
Sample collected out of window		
Other (please list)		

Please provide narratives for participants who would have met severe COVID-19 criteria, but who did not have PCR results available.

Sponsor Response:

At the time of database lock, P301 had around ~6000 illness visits completed. We took a systematic approach to identify participants who potentially had suspected COVID-19 and met criteria for illness visit and nasopharyngeal swab collection, starting 14 days post dose 2 in Part A of the study, but for whom no PCR results were available at the time of the BLA DBL:

- COVID-19 AE listing of participants who had COVID-19 or suspected COVID-19 symptoms starting at least 14 days post-dose 2 in Part A with no corresponding central or local qualifying PCR result at the time of BLA database lock. [Listing from EDC]
- Listing of distinct participants with illness or convalescent samples collected at least 14 days post-dose 2 in Part A with no results from any samples collected and no other qualifying (CLIA certified/waivered) local result present at the time of BLA database lock. [Listing from Viracor]
- Listing of distinct participants with illness visits showing no sample collected at least 14 days post dose 2 in Part A at the time of BLA database lock. [Listing from EDC]

Please see below completed table. Please note the total number of Participants in each Part A treatment group do not total of the individual reasons for no PCR results, as some Participants may have had multiple reasons.

	mRNA-1273	Placebo
Participants with suspected COVID-19 but with no PCR result available	**21**	**39**
Reason for no PCR results*:		
1. Sample not collected at Illness Visit	10	9
2. No Illness Visit completed and/or COVID-19 case occurred outside of study clinic	9	22

3. Local sample only, with no supporting source available and/or not CLIA certified/CLIA waivered	1	12
4. Sample lost	0	0
5. Sample out of stability window	1	6
6. Other – Specify	0	1 – see narrative below
7. COVID-19/Suspected COVID-19 AE with no supporting COVID-19 forms or narrative	8	10
8. Expired sample tube	0	1
9. Two Biofire samples sent, no COVID-19 PCR sent	1	0

*Subjects with multiple reasons:

- 1,2 and 3 – 1 placebo
- 2 and 3 – 10 placebo and 1 mRNA-1273
- 2 and 7 – 10 placebo and 8 mRNA-1273

Please see below narratives for participants who would have met severe COVID-19 criteria, but who did not have PCR results available at the time of BLA DBL (please note these participants are also included in the total count above):

Subject ID	**Reason for no PCR result available**	**Date of Dose 2 in Part A**	**Treatment Assignment Part A**	**Narrative**
US3302472	No Illness Visit completed/COVID-19 case occurred outside of study clinic and local sample only, with no supporting source available and/or not CLIA certified/CLIA waivered	11Nov20	Placebo	Subject was hospitalized due to COVID-19 from 22Dec2020-30Dec2020. This case is severe due to acute respiratory failure with hypoxia. Subject did not report hospitalization to site staff until 02Feb2021. PCR result unavailable due to lack of available comprehensive medical record.
US3572086	Other – see narrative	23Sep20	Placebo	Subject was hospitalized and later died due to COVID-19 (12Feb21). COVID -19 SAE onset date of 03Jan21. Medical records indicate COVID-19 PCR negative and respiratory panel negative, but subject was admitted to COVID unit based on

Subject ID	Reason for no PCR result available	Date of Dose 2 in Part A	Treatment Assignment Part A	Narrative
				respiratory status. Chest CT showed moderate to severe COVID pneumonia.
US3642333	No Illness Visit completed/COVID-19 case occurred outside of study clinic and local sample only, with no supporting source available and/or not CLIA certified/CLIA waivered	18Nov20	Placebo	This subject was hospitalized/in the ICU in a hospital in Mexico for 14 days (19Dec2020-01Jan2021) due to COVID-19. Though the site staff reports the subject tested positive via PCR - the result is not from a CLIA certified laboratory and site staff does not have a copy of the result.

ITEM 4:

Regarding your data on variants and Genotyping Report (Appendix 16.5):

a. On page 6 of your Genotyping Report, you indicate of the total adjudicated COVID-19 cases starting 14 days after Dose 2 in the PPS with sequencing data, there were 2 cases attributable to B1.117 variant in the placebo group compared to none in the mRNA-1273 group. However, B1.117 (or B.1.1.7) is not listed in any of the tables (Table 14.2.1.1.2.1.4.1 or 14.2.1.1.2.1.4.2). Please clarify this discrepancy and provide updated tables if applicable.

b. Please provide summary table similar to Table 14.2.1.1.2.1.4.1 for number of variants by lineage when only including adjudicated cases starting after 14 days after Dose 2 in the PP set.

c. Please provide summary table similar to Table 14.2.1.1.2.1.4.1 for sequencing data from all available SARS-CoV-2 RT-PCR positive NP samples collected from July 2020 through May 2021 from participants in the blinded portion of the study, regardless of symptoms.

d. For Table 14.2.1.1.2.1.4.1, in the number of events by lineage, only 17 events are listed out of the 56 mRNA-1273 participants with COVID-19 and only 545 events are listed out of the 769 placebo participants. Please update the table to classify the remaining events so that all 56 cases in mRNA-1273 participants and all 769 cases in placebo participants are accounted for (e.g., other variant—if this would be different than your "none" classification, no sequencing data available, inconclusive sequencing data).

Sponsor Response:

a. The Sponsor would like to acknowledge and apologize for the typos on the Genotyping Report (p.9). it should state that "There were also 2 P.2 variants in the placebo group and none in the mRNA-1273 group" after randomization using the PP. There was no B1.117 (or B.1.1.7) variant as indicated by the source table (copied below) that was included in CSR section 14 and was used for Table S1 of the Genotyping Report.

Ad Hoc Table 14.2.1.1.2.1.4.1	Summary of COVID-19* based on Adjudication Committee Assessments Starting After Randomization by Variant Groups - Per-Protocol Set

b. The requested summary table in number of events by variants /lineage when only including adjudicated cases starting from 14 days post dose 2 in the PP set is provided (Table IR15.B - 14.2.1.1.2.1.4.1).

c. The requested summary table (Table IR15.C -14.2.1.1.2.1.4.1) is provided for sequencing data from available SARS-CoV-2 RT-PCR positive NP samples collected from July 2020 through May 2021 from participants in the blinded portion of the study, regardless of symptoms.

d. As requested, an updated table (Table IR15.D -14.2.1.1.2.1.4.1) is provided to classify events including all 56 cases in mRNA-1273 participants and all 769 cases in placebo participants, with an additional category for "other variant - no sequencing data available" added.