RESPONSE TO FDA COMMENTS ON CLINICAL RECEIVED ON 17 SEPTEMBER 2021

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

Our review of your August 24, 2021 submission (STN 125752/0) is ongoing. We have the following requests for additional information:

Please respond to the following request by September 21, 2021:

ITEM 1:

Please submit an analysis of vaccine efficacy against severe COVID-19 cases using the CDC definition (hospitalization, admission to the ICU, intubation or mechanical ventilation, or death).

Sponsor Response

In Study P301, severe COVID-19 requires any of the conditions listed in Section 8.1.1 of the protocol, copied below:

Severe COVID-19:

To be considered severe COVID-19, the following criteria must be met:

- Confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, plus any of the following:
    - Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FIO_2 < 300$ mm Hg, OR
    - Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
    - Significant acute renal, hepatic or neurologic dysfunction, OR
    - Admission to an intensive care unit or death.

Based on the protocol-specified definition, only 2 participants in the mRNA-1273 group had adjudicated severe COVID-19 starting 14 days after second injection in the PP Set (106 cases in the placebo group); the VE point estimate (95% CI) based on the hazard ratio was 98.2% (92.8%, 99.6%; P301 CSR Table 6-4, Table 1 below).

Table 1: Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19* Based on Adjudication Committee Assessments Starting 14 Days After the Second Injection (Per-Protocol Set)

	Placebo (N=14164)	mRNA-1273 (N=14287)
Number of subjects with severe COVID-19, n (%)	106 (0.7)	2 (<0.1)
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.982 (0.928, 0.996)

[a] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

For the two adjudicated severe COVID-19 cases on mRNA-1273, US3742357 was considered as severe COVID-19 based on Oxygen Saturation of SpO_2 <= 93%; and US3772037 was considered as severe COVID-19 based on Oxygen Saturation of SpO_2 <= 93% and respiratory failure. Neither participant would be considered as severe COVID-19 per CDC definition that requires hospitalization, admission to the ICU, intubation or mechanical ventilation, or death.

Therefore, based on the CDC definition of severe COVID-19, that requires hospitalization, admission to the ICU, intubation or mechanical ventilation, or death, the VE against severe COVID-19 starting 14 days after Dose 2 in PP Set would be 100%.

Among the 106 adjudicated severe COVID-19 cases on Placebo per protocol definition, the following 5 would have met CDC definition of severe COVID-19 based on admission to the ICU or mechanical ventilation.

Subject ID	Group	Admission to an intensive care unit due to SARS-CoV-2	Mechanical Ventilation
US3042288	Placebo	Y	
US3272026	Placebo	Y	Y
US3932083	Placebo	Y	
US3932286	Placebo	Y	
US3952094	Placebo		Y

Among the 106 adjudicated severe COVID-19 cases on Placebo per protocol definition, a total of 22 on Placebo would have met CDC definition of severe COVID-19 based on admission to the

ICU, mechanical ventilation, or hospitalization due to COVID-19, and the VE against severe COVID-19 starting 14 days after Dose 2 in PP Set would be 100%.

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