RESPONSE TO FDA COMMENTS ON CLINICAL RECEIVED ON 28 SEPTEMBER 2021

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

Clinical: efficacy data; CMC: manufacturing processes

Our review of your August 16, 2021 submission (STN 125752/1) is ongoing.

The following are Priority items requested for additional clinical information regarding efficacy data. A response is requested by October 1, 2021:

ITEM 1:

Please indicate when you expect to submit the remaining shell tables. It would be acceptable to submit them in batches, as you complete them.

Sponsor Response

Batch 2 of the shell tables was submitted on 29 September 2021.

Batch 3 is targeted for submission on 11 October 2020.

ITEM 2:

In your response to IR#2-9.21 (Item 1 of IR sent on Sept 17, 2021), you indicate that neither of the two cases of severe COVID-19 in the mRNA-1273 arm met the definition of severe COVID-19 requiring hospitalization, admission to the ICU, intubation or mechanical ventilation, or death. However, for subject # 3772037, the CIOMS form as well as the narrative we received from you during the EUA review (this was the severe COVID-19 case in the mRNA-1273 arm which had not yet been adjudicated at the time of the primary analysis) stated that this subject was in fact hospitalized for respiratory failure due to COVID-19 (from November 8-12, 2020). Based on the available data, this subject has met the CDC definition for severe COVID-19 based on hospitalization. Please submit a revised analysis of the analysis requested in our IR (VE against severe disease based on CDC definition), counting this subject as a case meeting the CDC severe disease definition in the mRNA-1273 arm.

Sponsor Response

The Sponsor would like to thank the reviewer's guidance on CDC definition of severe COVID-19 (hospitalization, admission to the ICU, intubation or mechanical ventilation, or death). Please see below for the revised analysis of VE of severe COVID-19 using CDC definition starting 14 days after the second injection in the Per-Protocol Set. One mRNA-1273 participant, US3772037 would be considered a severe COVID-19 case using CDC definition based on hospitalization. Among the 106 adjudicated severe COVID-19 cases on Placebo per protocol definition, 23 would have met

CDC definition of severe COVID-19 including one participant, US3032204, who met the definition based on death due to COVID-19 but not meeting other criteria. Subject US3572086, a Placebo participant, was not an adjudicated severe COVID-19 case per protocol definition, but was a case for death due to COVID-19, thus, was included in this analysis as a case. In total, using CDC definition of severe COVID-19, there were 24 severe COVID-19 cases on Placebo and 1 on mRNA-1273 starting 14 days after Dose 2 in the Per-Protocol Set with VE of 96.0% (95% CI: 70.5%, 99.5%).

Table 2-1: Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Based on Adjudication Committee Assessments* using CDC definition 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 (%)	24	1
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.960 (0.705, 0.995)

* One Placebo participant (US3572086) was not an adjudicated severe COVID-19 case but was a case for death due to COVID-19 and thus was included in this analysis as a case based on CDC definition

[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

ITEM 3:

In your primary analysis, there was one case of COVID-19 starting 14 days after Dose 2 as assessed by adjudication committee in the placebo group for the subgroup of participants with positive baseline SARS-CoV-2 status at baseline (Table 14.2.2.7.1.6.10 in EUA submission with data extraction date of Nov 25, 2020). However, in your updated efficacy analysis, there are now 0 cases in the placebo group (Table 14.2.2.7.3.6.10 in BLA submission with data extraction date of May 4, 2021). Please clarify and correct this discrepancy.

Sponsor Response

At the primary analysis (data snapshot date: 25-Nov-2020), for the primary efficacy endpoint, COVID-19 starting 14 days after Dose 2 as assessed by adjudication committee in the group of participants with positive SARS-CoV-2 status at baseline (FAS), there was one case of COVID-19, US3242076, whose onset date of COVID-19 was 11-Oct-2020, 60 days after Dose 1. At the final analysis of blinded phase data (database lock date of 04-May-2020), in the analysis of the primary efficacy endpoint, COVID-19, if there was early infection as detected either by positive

RT-PCR at the scheduled pre-Dose 2 visit, or positive bAb against SARS-CoV-2 nucleocapsid protein (as measured by Roche Elecsys) in the blood samples at the scheduled visits (Day 29, Day 57 and etc.), this primary efficacy endpoint would be censored at the date of early infection. This participant had positive bAb against SARS-CoV-2 nucleocapsid on 16-Sep-2020, D29 visit, thus was censored on 16-Sep-2020 in the analysis presented in Table 14.2.2.7.3.6.10 in BLA submission with data extraction date of May 4, 2021.

Included in this response, we performed a sensitivity analysis of the primary efficacy endpoint COVID-19 starting 14 days after Dose 2 per adjudication committee assessment in participants with positive SARS-CoV-2 status at baseline in FAS, in which, COVID-19 was not censored at the early infection. There were 2 COVID-19 cases, both on Placebo. In addition to US3242076, US3662136, was an adjudicated COVID-19 case with onset date of 31-Dec-2020, 98 days after Dose 1 with positive bAb against nucleocapsid on 23-Oct-2020, D29 visit. The VE is 100%.

Table 3-1: Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Dose 2 in Participant with positive SAS-CoV-2 Status at baseline in Full Analysis Set

	Placebo (N=337)	**mRNA-1273 (N=347)**
Number of subjects with COVID-19, n (%)	2	0
Vaccine efficacy based on hazard ratio (95% CI) [a]		1.0 (NE, 1.0)

[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

ITEM 4:

Please provide the following subgroup analysis for the updated VE analysis, based on the Full Analysis Set (March 26 data cut):

Time period	**mRNA-1273 Cases/N (%) Incidence rate per 1,000 person-years**	**Placebo Cases/N (%) Incidence rate per 1,000 person-years**	**Vaccine Efficacy (%) (95% CI)**
Any time after Dose 1			
Baseline SARS-CoV-2 status: negative			
Baseline SARS-CoV-2 status: positive			
Starting 14 days after Dose 1			
Baseline SARS-CoV-2 status: negative			

Baseline SARS-CoV-2 status: positive

Sponsor Response

Please see below for the requested analyses in the subgroups of VE against COVID-19 based on adjudication committee assessment by baseline SARS-CoV-2 Status at baseline in Full Analysis Set. To help review, subgroup analysis of VE against COVID-19 starting 14 days after Dose 2 is added to the table. In addition, as described in response to Item 3, sensitivity analyses in the baseline positive SARS-CoV-2 group with no censoring of early infection are also provided in the table below. Due to the small sample size of participants with positive SARS-CoV-2 status at baseline, and the number of COVID-19 cases are too small in these participants, the results can not be interpreted in a meaningful way.

Table 4-1: Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments by baseline SAS-CoV-2 Status at baseline in Full Analysis Set

Time period	**mRNA-1273 (N=15180) Cases /N (%) Incidence rate per 1,000 person-years**	**Placebo (N=15166) Cases / N (%) Incidence rate per 1,000 person-years**	**Vaccine Efficacy[a] (%) (95% CI)**
Any time after Dose 1			
Baseline SARS-CoV-2 status: negative	69 / 14746 (0.5) 11.8	834 / 14745 (5.7) 148.8	92.3 (90.1, 93.9)
Baseline SARS-CoV-2 status: positive	5 / 347 (1.4) 129.3	4 / 337 (1.2) 128.9	-24.3 (-365.5, 66.8)
Baseline SARS-CoV-2 status: positive*	5 / 347 (1.4) 129.3	6 / 337 (1.8) 129.1	18.6 (-167.7, 75.3)
Starting 14 days after Dose 1			
Baseline SARS-CoV-2 status: negative	63 / 14746 (0.4) 10.7	823 / 14745 (5.6) 137.0	92.9 (90.8, 94.5)
Baseline SARS-CoV-2 status: positive	1 / 347 (0.3) 7.7	0 / 337 (0) 0	-2.6E9 (NE, 100)
Baseline SARS-CoV-2 status: positive*	1 / 347 (0.3) 7.7	2 / 337 (0.6) 15.5	54.9 (-397.0, 95.9)
Starting 14 days after Dose 2			
Baseline SARS-CoV-2 status: negative	58 / 14746 (0.4) 9.9	751 / 14745 (5.1) 134.0	92.8 (90.6, 94.5)
Baseline SARS-CoV-2 status: positive	0 / 347 (0) 0	0 / 337 (0) 0	

Baseline SARS-CoV-2 status: positive*	0 / 347 (0) 0	2 / 337 (<0.1) 15.5	100 (NE, 100)

[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

* in baseline positive SARS-COV-2 status group, no censoring of early infection at the date of early infection.

ITEM 5:

Please provide the following subgroup analysis for the updated VE analysis (March 26 data cut), for COVID-19 cases starting 14 days after Dose 2 as assessed by adjudication committee:

Subgroup	**mRNA-1273 Cases/N (%) Incidence rate per 1,000 person-years**	**Placebo Cases/N (%) Incidence rate per 1,000 person-years**	**Vaccine Efficacy (%) (95% CI)**
Obesity (BMI>30 kg/m2) and age			
18-64 years and obese			
18-64 years and not obese			
>65 years and obese			
>65 years and not obese			

Sponsor Response

Please see below for the requested analysis of vaccine efficacy against COVID-19 starting 14 days after Dose 2 based on adjudication committee in the Per-Protocol Set by the age and obesity groups. Please note that age groups (18-64, ≥65) and obesity groups (<30, ≥30 kg/m^2) are used in the below analyses to be consistent with the age groups used in the study, the BMI groups in previous requests and the definition of obesity. Vaccine efficacy estimated based on both the stratified Cox proportional model and the exact method upon the total number of cases adjusting for person-years are provided. High vaccine efficacy is observed in each of the 4 subgroups defined by the cross-classification of age groups and obesity groups.

Table 5-1: Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Dose 2 by Age and Obesity Groups (Per-Protocol Set)

	mRNA-1273 (N=14287)	**Placebo (N=14164)**		
Subgroup	**Cases /N (%) Incidence rate per 1,000 person-years**	**Cases / N (%) Incidence rate**	**Vaccine Efficacy[a]**	**Vaccine Efficacy[b]**

		per 1,000 person-years	(%) (95% CI)	(%) (95% CI)
Obesity (BMI≥30 kg/m^2) and age				
18-64 years and obese	22 / 4188 (0.5) 12.9	284 / 4134 (6.9) 177.5	92.9 (89.1, 95.4)	92.7 (88.8, 95.5)
18-64 years and not obese	24 / 6415 (0.4) 9.4	358 / 6379 (5.6) 147.4	93.8 (90.6, 95.9)	93.6 (90.4, 96.0)
≥65 years and obese	7 / 1271 (0.6) 13.7	42 / 1231 (3.4) 86.9	84.3 (65.1, 93.0)	84.2 (64.5, 94.0)
≥65 years and not obese	2 / 2327 (0.1) 2.2	57 / 2340 (2.4) 63.2	96.7 (86.4, 99.2)	96.6 (87.1, 99.6)

[a] 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
[b] VE, based on 1 — ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.