RESPONSE TO FDA COMMENTS ON INFORMATION REQUEST#24 DATED NOVEMBER 30, 2021

The Sponsor acknowledges FDA Comments on INFORMATION REQUEST#24 dated 30 NOVEMBER 2021 in (**BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Asymptomatic infection, blinded efficacy follow-up
Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have the following requests for additional information:

ITEM 1:
In your response to the November 12, 2021 clinical information request, you present in Table 1-3 examples of subjects that were incorrectly censored as a result of mis-labeled VISIT in IS and MB, resulting in inappropriate exclusion of cases, inclusion of non-cases, and cases with incorrect event dates for SARS-CoV-2 and asymptomatic infection. Please submit corrected analyses of efficacy against SARS-CoV-2 infection and asymptomatic infection starting 14 days after Dose 2 in the Per-Protocol Set during blinded follow-up. Similarly, please provide the corrected sensitivity analysis for asymptomatic infection from Item 1 of your response to the November 3, 2021 information request, copied below for your reference:
From November 3, 2021 Information Request:
On review of 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 has incorporated the updates presented in Table 1-3 of the SN0024 response to November 12, 2021 IR20 Item 1 and performed the analyses of efficacy against SARS-CoV-2 infection and asymptomatic infection starting 14 days after Dose 2 in the Per-Protocol Set during the blinded follow-up. The results are presented in Table 1-1 and Table 1-2 below; the updated results are consistent with those presented in Table 6-6 (Infections) and Table 6-9 (Asymptomatic infection) in the CSR.

Table 1-1 Analysis of Vaccine Efficacy of mRNA-1273 to Prevent SARS-CoV-2 Infection Regardless of Symptomatology and Severity Starting 14 Days After the Second Injection Including Participant Decision Visit (Per-Protocol Set)

	Placebo (N=14164)	mRNA-1273 (N=14287)
Number of subjects with SARS-CoV-2 infection regardless of symptomatology and severity, n (%)	1338 (9.4)	282 (2.0)
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.819 (0.794, 0.841)
Person-years [b]	5442.1	5755.2
Incidence rate per 1,000 person-years (95% CI) [c]	245.9 (232.9, 259.4)	49.0 (43.4, 55.1)
Vaccine efficacy based on incidence rate (95% CI) [d]		0.801 (0.773, 0.825)

Abbreviations: CI = confidence intervals.

[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.

[b] Person-years is defined as the total years from randomization date to the date of SARS-CoV-2 infection, last date of study participation, or efficacy data cutoff date, whichever is earlier.

[c] Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

[d] VE is defined as 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.

Table 1-2 Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Asymptomatic SARS-CoV-2 Infection Starting 14 Days After the Second Injection Including the Participant Decision Visit Using the Competing Risk Method (Per-Protocol Set)

	Placebo (N=14164)	mRNA-1273 (N=14287)
Number of subjects with asymptomatic SARS-CoV-2 infection, n (%)	498 (3.5)	216 (1.5)
Number of subjects with competing event, n (%)	862 (6.1)	62 (0.4)
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.627 (0.562, 0.682)
Person-years [b]	5442.0	5756.1
Incidence rate per 1,000 person-years (95% CI) [c]	91.5 (83.7, 99.9)	37.5 (32.7, 42.9)
Vaccine efficacy based on incidence rate (95% CI) [d]		0.590 (0.518, 0.652)

	Placebo (N=14164)	mRNA-1273 (N=14287)

RT-PCR test and Elecsys anti-SARS-CoV-2 assay results at post-baseline scheduled visits are considered in case definition. Disease cases (COVID-19 or second definition of COVID-19) are considered as competing events for asymptomatic SARS-CoV-2 infection.

[a] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are estimated using Fine and Gray's sub-distribution hazard model with disease cases as competing events and with the treatment group as a covariate, adjusting for stratification factor.

[b] Person-years is defined as the total years from randomization date to the earliest of the date of symptomatic SARS-CoV-2 infection, the date of asymptomatic SARS-CoV-2 infection, last date of study participation, or efficacy data cutoff date, whichever is earlier.

[c] Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

[d] VE is defined as 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.

As requested, a sensitivity analysis for asymptomatic infection using the same approach as in our response to the Item 1 of the November 3, 2021 information request (IR#15, submitted 09Nov2021 SN0021), was performed. Specifically, 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. For your convenience of review, the results are presented below with the response provided to Item 1 of the November 3, 2021 information request.

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 incorporating updates	184 32.0 (27.5, 36.9)	413 75.9 (68.8, 83.6)	57.9 (49.8, 64.8)	61.4 (54.1, 67.6)
Sensitivity analysis (Response to Item 1 of IR15 [SN0021])	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:

2. Please fill in the following table for blinded follow-up for efficacy (from Dose 2 to PDV/unblinding) in the per protocol set:

Table 1. Blinded Follow-up Duration After Dose 2, Per Protocol Set

	mRNA-1273 (N=14287)	**Placebo (N=14164)**	**Total (N=28451)**
Median blinded follow-up post dose 2, days			
All participants			
≥18 to <65 years			
≥65 years			
Between 2 to <4 months blinded follow-up post dose 2, n(%)			
At least 4 months blinded follow-up post dose 2, n (%)			
Between 4 to <6 months blinded follow-up post dose 2, n(%)			
At least 6 months blinded follow-up post dose 2, n (%)			

Sponsor Response:
Please see below the blinded follow-up for efficacy, from Dose 2 to PDV/unblinding in the Per-Protocol Set. In this analysis, if a participant did not have PDV nor unblinded, the participant was considered to be followed up until the earlier of study discontinuation date, or the data cutoff date of 3/26/2021. In the summary by months, 1 month = 28 days. We also added a row to present number and percentage of participants with '<2 months blinded phase follow-up post dose 2'.

	mRNA-1273 (N=14287)	Placebo (N=14164)	Total (N=28451)
Median blinded follow-up post dose 2, days			
All participants	120	117	119
≥18 to <65 years	120	117	119
≥65 years	119	117	118
<2 months blinded follow-up post dose 2, n (%)	225 (1.6%)	280 (2.0%)	505 (1.8%)
Between 2 to <4 months blinded follow-up post dose 2, n(%)	4970 (34.8%)	5539 (39.1%)	10509 (36.9%)
At least 4 months blinded follow-up post dose 2, n (%)	9092 (63.6%)	8345 (58.9%)	17437 (61.3%)
Between 4 to <6 months blinded follow-up post dose 2, n(%)	8408 (58.9%)	7803 (55.1%)	16211 (57.0%)
At least 6 months blinded follow-up post dose 2, n (%)	684 (4.8%)	542 (3.8%)	12266 (4.3%)