RESPONSE TO FDA COMMENTS ON INFORMATION REQUEST#31 RECEIVED ON DECEMBER 10, 2021

The Sponsor acknowledges INFORMATION REQUEST#31 dated 10 DECEMBER 2021 in (**BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Post-marketing Requirement/Commitment (PMR/PMC) studies

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have the following request for additional information Post-marketing Requirement/Commitment (PMR/PMC) studies:

Should this product be approved, we have determined that an analysis of spontaneous post-marketing adverse events reported under section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) will not be sufficient to identify:

- **known serious risks of myocarditis and pericarditis**
- **an unexpected serious risk of subclinical myocarditis**

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

ITEM 1:

Therefore, should this product be approved, we have determined that you will be required to conduct the following studies as postmarketing requirements (PMRs) under Section 505(o) of FDCA:

1.1 Study mRNA-1273-P903, entitled "Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity", to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.

1.2 Study mRNA-1273-P904, entitled "Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe," to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.

1.3 Study mRNA-1273-P911, entitled "Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273)," to evaluate long-term sequelae of myocarditis after vaccination with at least 5 years of follow-up.

1.4 Study mRNA-1272-P301 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 18 years of age and older.

1.5 Study mRNA-1273-P203 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 12 to <18 years of age.

1.6 Study mRNA-1273-P204 substudy to prospectively assess the incidence of subclinical myocarditis following administration of SPIKEVAX in a subset of participants 6 months to <12 years of age.

Sponsor Response:

1.1 Study mRNA-1273-P903, entitled "Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity", to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX will be conducted as a postmarketing requirement (PMR) under Section 505(o) of FDCA.

1.2 Study mRNA-1273-P904, entitled "Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe," to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX will be conducted as a postmarketing requirement (PMR) under Section 505(o) of FDCA.

1.3 Study mRNA-1273-P911, entitled "Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273)," to evaluate long-term sequelae of myocarditis after vaccination with at least 5 years of follow-up will be conducted as a postmarketing requirement (PMR) under Section 505(o) of FDCA.

1.4 Study mRNA-1272-P301 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 18 years of age and older will be conducted as a postmarketing requirement (PMR) under Section 505(o) of FDCA. As described in IR#17 (SN0022) serum samples will be requested from all study participants who sign the consent for Part C to receive a booster dose. Samples will be collected within the first ~4 days after vaccination, from all participants who agree to provide the sample, and banked for potential cardiac biomarker testing. The changes were reflected in Protocol Amendment 9, submitted to IND19745 SN0189, on 14Sep2021.

1.5 Study mRNA-1273-P203 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 12 to <18 years of age will be conducted as a postmarketing requirement (PMR) under Section 505(o) of FDCA. As described in IR#17 (SN0022) serum samples will be requested from all study participants who sign the consent for Part C to receive a booster dose. Samples will be collected within the first ~4 days after vaccination and banked for potential cardiac biomarker testing. The changes were reflected in Study P203 Protocol Amendment 3, submitted to IND19745 SN0200 on 12Nov2021.

1.6 Study mRNA-1273-P204 substudy to prospectively assess the incidence of subclinical myocarditis following administration of SPIKEVAX in a subset of participants 6 months to <12

years of age will be conducted as a postmarketing requirement (PMR) under Section 505(o) of FDCA. As described in IR#17 (SN0022) samples will be requested from all participants in Cohort D Part 2 of the study. Samples will be collected within the first ~4 days after Dose 2, from all participants who agree to provide the sample for ages 6-12 years, and all participants from 6 months to 6 years, and banked for potential cardiac biomarker testing. The changes were reflected in Study P204 Protocol Amendment 5, submitted to IND19745 SN0195, on 06Oct2021.

ITEM #2
Additionally, should this product be approved, your proposed studies listed below will be postmarketing commitments (PMCs) as agreed upon between FDA and the applicant:

2.1 Study mRNA-1273-P901, entitled "Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine."

2.2 Study mRNA-1273-P902, entitled "Moderna mRNA-1273 Observational Pregnancy Outcome Study."

2.3 Study mRNA-1273-P905, entitled "Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries."

Sponsor Response:
The sponsor agrees to the listed PMCs.

ITEM 3:
B. Please populate the table below with your study milestone dates (mm/dd/yyyy) for final protocol submission, study completion and final study report submission for each PMR/PMC study. Note that comments on Study mRNA-1273-P903 protocol have been previously communicated to Moderna, and the final study protocol submission should address FDA recommendations and comments.

	Final protocol submission date	**Study completion Date**	**Final study report submission date**
Study mRNA-1273-P903	01/31/2022	12/31/2022	06/30/2023
Study mRNA-1273-P904	11/04/2021	3/31/2023	12/31/2023
Study mRNA-1273-P911	04/30/2022	10/31/2027	10/31/2028
Study mRNA-1273-P901	12/20/2021	01/31/2024	04/14/2025
Study mRNA-1273-P902	07/31/2022	9/30/2023	06/30/2024
Study mRNA-1273-P905	11/04/2021	3/31/2023	12/31/2023
Study mRNA-1273-P301 substudy	09/14/2021	12/31/2022	06/30/2023
Study mRNA-1273-P203 substudy	Protocol related to myo/peri: 11/12/2021 Next PA related to addition of lower dose: 01/31/2022	04/30/2024	07/31/2024

Study mRNA-1273-P204 substudy	Protocol related to myo/peri: 10/06/2021 Next PA related to addition of lower dose: 02/28/2022	12/31/2023	03/31/2024

Sponsor Response:
Please see the table above with completed milestone dates.

The final protocol submission date for study mRNA-1273-P903 reflects the new protocol submission which will occur in January.

The final protocol submission date for Study mRNA-1273-P911 has been adjusted to enable evaluation of additional data sources in order to reach the target enrollment specified in ITEM 4.

Final protocols for P904 and P905 were submitted to the BLA on 11/04/2021 in response to IR#14.

Protocols for P301, P203, P204 reflecting changes to capture subclinical myocarditis have already been submitted as indicated in the response to Item 2. The protocol dates for P203 and P204 reflect the next protocol amendment that is planned, with regards to EUA 27073 SN310.

ITEM 4:
C. Please refer to study mRNA-1273-P911: We have the following requests:

1. Enroll at least 300 subjects with myocarditis after vaccination with SPIKEVAX

2. Modify inclusion criteria from "Onset within 30 days of Moderna COVID-19 vaccination" to "Onset within 7 days of Moderna COVID-19 vaccination"
Please acknowledge that the final study protocol mRNA-1273-P911 will address the above FDA requests.

Sponsor Response:
The mRNA-1273-P911 study will be revised to target enrollment of at least 300 myocarditis cases with onset within 7 days of Moderna COVID-19 vaccination as referenced in ITEM 4. Given this requirement to enroll a larger sample size with a shorter time to onset for case ascertainment, the timeline for submission of the study protocol has been extended by one month. This will allow time to investigate additional data sources that may be required to support a feasible approach.

ITEM 5:
D. Please include the PMRs and PMCs (listed in section A of this information request) in your updated Pharmacovigilance Plan (PVP) and submit an updated PVP (tracked change and clean versions) to the BLA.

Sponsor Response:
For the initial BLA submission, it was agreed with the Agency to submit the EU RMP instead of a PVP. Currently, an updated RMP is under review with EMA/PRAC. As the review timelines for PRAC are rather lengthy and creation of another updated RMP would result in version control issues, we have requested to revert to a US specific PVP. A PVP will be created based upon EU RMP V2.2 (submitted in SN0003). A track change version will be generated by updating the PVP with the information relevant to this IR. The PVP will be provided no later than Thursday, 16Dec2021.