RESPONSE TO FDA COMMENTS ON SAFETY DATED NOVEMBER 05, 2021

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

Our review of your pharmacovigilance plan for SPIKEVAX under BLA STN 125752/2 is ongoing. We have the following comments regarding postmarketing studies. Please propose:

For each study, include the following information in your proposal: study designs, sample sizes and justification of sample sizes including number of subjects ≤30 years of age, information to be collected at baseline, frequency and methods for follow-up data collection, plan for duration of long term follow-up and information to be collected in follow-up, study timeline and milestone dates (final protocol submission date, study completion date, and final study report submission date; please provide dates in mm/dd/yyyy format).

ITEM 1:
Postmarketing observational safety study(ies) to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX, to quantify the magnitude of risk of myocarditis and pericarditis by age, sex, and dose.

Sponsor Response

Evaluation of the occurrence of myocarditis and pericarditis following administration of SPIKEVAX and quantification of the magnitude of risk by age, sex and dose will occur primarily in two large secondary database studies conducted in the United States (mRNA-1273-P903) and Europe (mRNA-1273-P904), respectively. These studies have been described in the RMP as follows:

Study Number, Title, and Categories Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 – Required pharmacovigilance activities				
Study mRNA-1273-P903 Post Authorisation 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	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory	Protocol submission	01/31/2021
			Interim updates	4/30/2021, 07/31/2021, 10/31/2021, 01/31/2022, 04/30/2022, 07/31/2022, 10/31/2022, 12/31/2022
			Final study report	06/30/2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study status: Ongoing	-Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	disease (VAERD) Long-term safety AESI and emerging validated safety signals		
Study mRNA-1273-P904 A Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Study status: Planned	The overarching research question of this study is whether the occurrence of adverse events of special interest (AESI) among persons vaccinated with COVID-19 Vaccine Moderna in Europe is higher than expected. Primary objectives: To estimate incidence rates of the AESI among persons receiving COVID-19 Vaccine Moderna overall and in subgroups of interest To assess whether vaccination with COVID-19 Vaccine Moderna (one dose, two doses, any dose) is associated with an increased rates of the AESI compared with expected overall and in subgroups of interest. Secondary objectives: To estimate incidence rates of the AESI among individuals vaccinated with the COVID-19 Vaccine Moderna, using real-world data, in the following specific subpopulations of COVID-19 Vaccine Moderna recipients: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety Interaction with other vaccines Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders	Feasibility assessment	06/30/2021
			Protocol submission	06/30/2021
			Interim Updates	09/30/2021, 03/31/2022, 09/30/2022, 03/31/2023
			Final study report	12/31/2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	with unstable health conditions and morbidities, subjects patients with autoimmune or inflammatory disorders, and in age-specific populations (children, adolescents, adults); To assess whether vaccination with COVID-19 Vaccine Moderna is associated with an increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and morbidities, subjects patients with autoimmune or inflammatory disorders, and in age-specific populations (children, adolescents, adults).			

Updates to each of these protocols have been implemented to enhance characterization of the risk of myocarditis, which will be assessed using both cohort and self-controlled risk interval methods in each study.

Because these studies rely on real-world data where off-label use may be identified, both studies have proactively expanded to include SPIKEVAX recipients of all ages with appropriate stratified analyses planned. Accrual of individuals <30 years of age will vary based on the uptake of SPIKEVAX in this population, however the most recent interim report for the US PASS study included analyses of >1.3 million vaccinated individuals 18 – 29 years of age. For the EU PASS study, it is estimated that the participating databases together will be able to identify at least 431,216 recipients of Spikevax.

Both studies have been further expanded to describe to characterize measured risk factors and sequelae of cases of myocarditis and pericarditis. Exposed and unexposed myocarditis and pericarditis cases will be described with respect to demographic and clinical characteristics. Furthermore, investigative clinical markers, relevant healthcare utilization, and cardiac outcomes will be explored over the available follow-up time after observed myocarditis and pericarditis events.

ITEM 2:
Prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination, including assessment of recovery status, risk factors, and identification of serious cardiovascular outcomes, and analyses by age, sex, and dose.

Sponsor Response

A new observational prospective cohort study, mRNA-1273-P911, is proposed to address the objectives noted in item 2. A synopsis of the proposed protocol follows.

Title	Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273)
Research question and objectives	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (SPIKEVAX). *Primary objectives:* 1. To characterize the presentation, clinical course of acute post-vaccine myocarditis in children and young adults 2. To characterize potential long-term sequelae of post-vaccine myocarditis, and functional outcomes in children and young adults *Secondary objectives:* 3. To compare long-term effects of post-vaccine myocarditis with those of nonvaccine myocarditis, including myocarditis arising in COVID-infected children and young adults 4. To identify possible risk factors for post-vaccine myocarditis in children and young adults including age, sex, race, ethnicity, obesity, lifestyle factors, and medical history
Study design	Observational cohort study
Population	Cases of myocarditis will be followed for up to five years to identify long-term outcomes. <u>Myocarditis cases following vaccination:</u> *Inclusion Criteria:* • Onset within 30 days of Moderna COVID-19 vaccination. • Cardiovascular magnetic resonance imaging or other relevant combination of laboratory and clinical findings consistent with myocarditis • Meeting Brighton or CDC case definition criteria for definite or probable myocarditis. *Exclusion Criteria:* • Plausible alternative diagnosis • Absence of clinical markers consistent with myocarditis Comparison Groups will be defined in the study protocol, with two proposals under current consideration:

	• Contemporaneous patients with definite or probable myocarditis (with or without COVID-19) who have not been vaccinated within 30 days of the event • If needed to obtain unvaccinated, non-COVID-19 associated cases, a historical cohort with definite or probable myocarditis
Variables	Exposures: Individuals will be considered exposed if at least one dose of mRNA-1273 is observed in the 30 days prior to the onset of myocarditis. Outcomes: Results of cardiac imaging and diagnostic procedures will be described at presentation and follow-up. Potential measures include troponins, assessment for the occurrence of arrhythmia, extent of myocardial inflammation, presence of pericardial effusion, and cardiac function indices such as left ventricular ejection fraction. Required medication or related cardiac procedures during and following hospitalization, and cardiac or other hospitalization events will continue across the follow-up period. Functional outcomes derived from secondary data as recorded by healthcare providers, or, if feasible, from the patient will be described.
Data sources	This study will be conducted in a data source such as hospital-based network or similar environment with access to detailed medical record and/or patient reported information.
Study size	Available study size is currently under evaluation and will be described in the study protocol; accrual of at least 100 patients with vaccine associated myocarditis and 50 comparison patients is anticipated. The data source(s) will be selected to ensure capture of SPIKEVAX recipients <30 years of age.
Data analysis	Cases of myocarditis following administration of mRNA-1273 vaccine and comparator group members will be described in terms of demographic characteristics, lifestyle factors, and medical history. Clinical course of the index myocarditis event will be described for myocarditis cases by vaccination status, including analysis of relevant procedures, available data on outcomes, and relevant healthcare utilization, and occurrence of additional cardiac events over the follow-up period. Functional outcomes potentially including patient reported outcomes (and/or other measures of functional capacity) and quality of life may also be described. A predictive modelling approach will be used to identify potential risk factors for myocarditis temporally associated with mRNA-1273 (SPIKEVAX) as well as for potential risk factors associated with long term sequelae, if identified, among myocarditis cases.

Milestones	Protocol submission: 03/31/2022 Interim report 1: 09/30/2022 Interim report 2: 09/30/2023 Interim report 3: 09/30/2024 Interim report 5: 09/30/2025 Interim report 6: 09/30/2026 Interim report 7: 09/30/2027 Final report: 09/30/2028 Protocol submission will include a feasibility analysis, however the results of this feasibility analysis may result in changes to the proposed study timeline.

ITEM 3:
Prospective study to assess the incidence of subclinical myocarditis following SPIKEVAX, including analyses by age, sex, and dose.

Sponsor Response

The sponsor has included the following activities within the ongoing clinical trials for mRNA-1273 for the purpose of increasing the sensitivity of identifying potential cases of myocarditis not rising to full clinical identification during the conduct of the ongoing clinical trials.

Study Title	**Summary of Objectives**		
Ongoing Studies	***Assessing Sub-Clinical Myocarditis***	***LPLV / Final CSR***	***Amendment/ Submission Date***
mRNA-1273- P301 – Part C, Booster Phase Phase 3, Randomized, Stratified, Observer-Blind, Placebo Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Interventional	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 for potential cardiac biomarker testing, in order to evaluate the frequency of subclinical myocarditis amongst individuals >18 years of age. Collection from all participants will allow analysis by age and sex.	29/12/2022 – 01/06/2023	mRNA1273-P301, Amendment 9 (IND19745 SN0189, 14Sep2021)
mRNA-1273-P203 – Part C, Booster Phase Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity,	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	22/12/2022 – Q2 2023	mRNA 1273-P203, Amendment 3*

and Effectiveness of mRNA-1273 SARS-CoV2 Vaccine in Healthy Adolescents 12 to < 18 years of age	~4 days after vaccination for potential cardiac biomarker testing, in order to evaluate the frequency of subclinical myocarditis amongst individuals 12 years to <18 years of age. Collection from all participants will allow analysis by age and sex.		
mRNA-1273-P204 Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV 2 vaccine in healthy children 6 months to less than 12 years of age	Samples will be requested from all participants in Cohort D Part 2 of the study (Optional for 6-<12 yr, required for <6 yrs). Samples will be collected within the first ~4 days after Dose 2 for potential cardiac biomarker testing, in order to evaluate the frequency of subclinical myocarditis amongst individuals 6 months to <12 years of age. Collection from all participants will allow analysis by age and sex.	Estimated Q2 2023	mRNA 1273-P204, Amendment 5 (IND19745 SN0195, 06Oct2021)

*Protocol Amendment #3 has been finalized and is pending submission to IND19745.