

## RESPONSE TO FDA COMMENTS ON SAFETY RECEIVED ON 27 SEPTEMBER 2021

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

**Below, please find our comments on the Moderna Post-Authorization Protocol P903 Version 3.1 received, August 26, 2021.**

### ITEM 1:

**Page 10, Section 7, Rationale and Background. In this section, there is no mention of the risk of myocarditis and pericarditis following mRNA-1273 vaccination. This important omission should be corrected.**

**The risk of myocarditis and pericarditis following mRNA COVID-19 vaccines has been explicitly discussed at numerous meetings, including at the ACIP, and are disclosed in the Fact Sheets. Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk of myocarditis and pericarditis is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Information is not yet available about potential long-term sequelae.**

**Myocarditis and pericarditis is an important safety concern for mRNA vaccines. so please describe the information available on the risk of myocarditis and pericarditis following mRNA vaccines, and specifically following mRNA-1273.**

### Sponsor Response

Additional detail concerning the important identified risk of myocarditis has been added to the background section of the protocol.

### ITEM 2:

**Page 29, Section 9.7, Data Analysis Plan, “Objective 3...As a secondary analysis, dose-specific effects will be evaluated.” “Sensitivity analyses that may be performed pending availability of a sufficient sample size include consideration of ..., stratification by dose,...”. For vaccines in general, and specifically for the mRNA-1273 vaccine, the risk of adverse events often vary by dose. For example, postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. Thus, a primary analysis that only includes “any vaccine dose” could potentially bias the results towards the null. Therefore, we suggest that you explicitly include a coprimary analysis by dose for all adverse events, including myocarditis and pericarditis.**

### Sponsor Response

Planned stratification by dose has been elevated to a co-primary analysis as suggested. This will include analysis of the primary series (overall, following dose 1, and following dose 2) and any booster doses observed.

### ITEM 3:

**Specifically for myocarditis and pericarditis, given the available information, please specify that a primary/coprimary analysis for myocarditis and pericarditis will be performed by dose, age group, and sex. Please consider extending the study period to investigate potential long-term sequelae. Please clarify in the protocol that, given the importance of myocarditis and pericarditis in association with mRNA vaccines, descriptive analyses of these events by age and sex and time interval since vaccination will also be provided, regardless of study size.**

#### Sponsor Response

The protocol has been modified to include characterization of myocarditis events by age, sex and time since vaccination, and to specify that dose stratified analyses for the primary endpoint of myocarditis will be included regardless of sample size.

The Sponsor recognizes that there are limitations to administrative claims data, including potentially insufficient long-term data capture given the nature of open and closed claims. To ensure that natural history and long-term outcomes of vaccine associated myocarditis are fully characterized, the Sponsor is working to develop additional observational studies and exploring suitable data sources in the United States and Europe.

The overarching goal of the first study in development is to characterize the natural history, clinical course, outcomes and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination.

#### *Primary objectives:*

1. To characterize the natural history and clinical course of myocarditis, including Moderna vaccine associated myocarditis and myocarditis not associated with COVID vaccines
2. To identify possible risk factors for post-vaccine myocarditis including demographic characteristics (e.g., age, sex, race/ethnicity) lifestyle factors, medical history, and vaccination characteristics

#### *Exploratory objectives:*

3. To identify whether there are differences in the clinical course or risk factor profile between vaccine associated myocarditis and myocarditis not associated with COVID-19 vaccines
4. If severe cases or cases with sequelae are identified, identify risk factors for severe vaccine associated myocarditis

The second will follow cases of vaccine associated myocarditis longitudinally for a minimum of five years. The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of mRNA-1273.

#### *Primary objectives:*

1. To characterize the 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

**ITEM 4:**

**Page 26, Section 9.5, Study Size, Table 2, Example sample size estimates. The sample size estimate does not mention myocarditis and pericarditis. Because of the importance of this safety concern, and the complexities of its analysis, please consider including sample size estimates for the analyses of myocarditis and pericarditis, by dose, age and sex.**

**Sponsor Response**

In alignment with elevation of myocarditis as a primary endpoint, the section on sample size has been revised to explicitly include these items.

**ITEM 5:**

**Page 28, Section 9.7, Data Analysis Plan, “For Objective 3, when the pre-specified criteria are met for a particular AESI, the risk ratio (RR) of each AESI triggered in Objective 2 will be estimated using a self-controlled risk interval (SCRI) design and fitting a conditional Poisson regression model.” Please clarify in your submission that FDA may request the implementation of SCRI (and/or other analyses/subanalyses) for AESIs that the agency considers as safety concerns.**

**Sponsor Response**

The text has been modified to indicate that regulatory agencies may request the implementation of SCRI and/or other analyses for AESI that the agency considers as safety concerns.