

RESPONSE TO FDA COMMENTS ON SAFETY RECEIVED ON 23 SEPTEMBER 2021

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

Moderna provided revised post-authorization safety protocol P903 version 3.1 and response to CBER's July 14, 2021 Comments. Below are comments regarding your response received August 31, 2021 (EUA27073 Amendment 248).

ITEM 1:

Response to ITEM 1:

ModernaTx Inc., stated: “To understand the potential for bias from time-varying confounders such as healthcare utilization over the study periods, the rates of medical conditions and procedures expected to be consistent over time (e.g. brain surgery, heart attack, revascularization procedure) will be examined over each of the three study time periods. This will provide context on the potential quantity of bias that may be introduced by changes in healthcare resource utilization over time.”

CBER Comments: Brain surgery, heart attack, and revascularization procedure are severe outcomes, which are less susceptible to health seeking behavior. Please add mild and moderate medical conditions and procedures when examining rates over each of the three study time periods.

Sponsor Response

While the severe outcomes are expected to be more similar to the study outcomes, the MAH agrees that they are less susceptible to changes in health seeking behavior. As such, rates of mild and moderate conditions and procedures (e.g., colonic diverticulitis, hypertension, colonoscopies, mammograms, and cervical cancer screenings) will also be characterized.

ITEM 2:

Response to ITEM 2:

ModernaTx Inc., stated: “For the control period, a 183-day window will be applied consistently across all AESIs. This is aligned with the FDA’s COVID-19 vaccine safety surveillance protocol and is documented in Annex 2 of Protocol v3.1.”

CBER Comments: The FDA’s COVID-19 vaccine safety surveillance protocol does not contain a 183-day control window across all AESIs. Please provide reference and rationale for the choice of the 183-day control window. Please clarify how to control for time-varying confounders when using a 183-day control window.

Alternatively, because the limited gain in power when using longer control windows does not justify the potential increase in time-varying confounders risk, please consider using shorter control windows.

ModernaTx Inc., provided SCRI risk window for each AESI, for example, Anaphylaxis 0-11 days, Myocarditis 1-42 days, Pericarditis 1-42 days.

CBER Comment: *Please clarify why a 0-11 day risk window was chosen for Anaphylaxis and a 1-42 day risk window was chosen for Myocarditis and Pericarditis. The choice of risk window is critical for SCRI. Because the onset of myocarditis and pericarditis was typically within several days after mRNA COVID-19 vaccination, please consider shorter risk windows for both anaphylaxis (most cases of anaphylaxis following vaccination occur within one day post-vaccination) and Myocarditis and pericarditis (which has been mostly identified within 7 days post mRNA vaccinations). Similarly, you have chosen a risk period for thrombosis with thrombocytopenia syndrome of days 1-42. However, most cases of thrombosis with thrombocytopenia syndrome identified following COVID-19 vaccinations (specifically following Adenovirus-vectored vaccines) have occurred within 2 weeks post vaccination. Therefore, please consider modifying your risk window for thrombosis with thrombocytopenia syndrome accordingly.*

Sponsor Response

The Sponsor acknowledges the concerns raised in review, and has revised the protocol to shorten the risk windows to 42 days. Risk windows have further been revised as follows:

Anaphylaxis: 1 day

Myocarditis and pericarditis: 1-7 days

Thrombosis with thrombocytopenia syndrome: 1 – 14 days

ITEM 3:

Response to ITEM 7:

ModernaTx Inc., Stated : “Anaphylaxis (Risk Window=0-1 days)” “Note the risk window for anaphylaxis was updated from 2-days in protocol v1.2 to 11 days in protocol v3.1.” In the sample size calculation table, the total risk period (days) for Anaphylaxis was “1”.

Reviewer Comment: *Please clarify why the risk window was updated from 2-days to 11 days for Anaphylaxis.*

In ITEM 2 response, the Anaphylaxis risk window was 0-11 days (i.e., 12-days risk window). In ITEM 7 response, the risk window was 11 days. Please clarify the discrepancy regarding the length of risk windows for Anaphylaxis.

In ITEM 7 sample size calculation table, the risk window was 1 day. Please correct the typographical error.

Sponsor Response

The length of the risk window for anaphylaxis is 0-1 days. The typographical error leading to this point of confusion has been corrected.

ITEM 4:

Response to ITEM 8:

ModernaTx Inc., mentioned: “the sponsor recognizes the remaining list of time-varying covariates may not be applicable given the relatively short length of the risk and control periods and the frequency of data capture in a claims database.”

CBER Comment: *If a 183-day control window is used for SCRI, adjustment for time-varying confounder may be needed for some of the AESIs. The revised post-authorization safety protocol P903 version 3.1 included individuals 0-17 years old, the impact of time-varying confounder could be larger for young children than for adults. Please see the previous comment regarding length of the control window (Response to ITEM 2).*

Sponsor Response

The length of the control windows has been shortened to 42 days.