



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)**

REAL WORLD EVIDENCE BLA MEMORANDUM

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To: Sudhakar Agnihothram, PhD
Chair of the Review Committee
Office of Vaccines Research and Review

Through: Richard Forshee, PhD
Acting Deputy Director, OBE
CBER, FDA

Subject: Review of Pharmacovigilance Plan, Real World
Postmarketing Effectiveness Protocol mRNA-1273-
P901 RWS, Postmarketing Safety Protocols mRNA-
1273-P903 and mRNA-1273-P904

Sponsor: ModernaTX Inc

Product: SPIKEVAX; Moderna COVID-19 Vaccine*

Application Type/Number: BLA STN 125752/0

Proposed Indication: Prevention of COVID-19 in individuals 18 years of age
and older

Submission Date: August 24, 2021

*The product was also referred to as mRNA-1273 in the clinical development

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the real world vaccine effectiveness protocol mRNA-1273-P901 RWS, postmarketing vaccine safety protocols mRNA-1273-P903 and mRNA-1273-P904 for Moderna coronavirus disease 2019 (COVID-19) Vaccine SPIKEVAX.

Materials Reviewed

- Clinical Overview (STN 125752/0.2; received August 24, 2021)
- Pharmacovigilance Plan (STN 125752/0.37; received December 16, 2021)
- mRNA-1273-P901 RWS: Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine
 - protocol version 3.0 (STN 125752/0.20, received November 10, 2021; also submitted to EUA 27073.293, received November 9, 2021)
 - protocol version 4.0 (EUA 27073.314, received December 20, 2021)
 - 1st Interim Report (EUA 27073.256, received September 14, 2021)
 - 2st Interim Report (EUA 27073.312, received December 14, 2021)
 - response to CBER's July 29, 2021 Comments (EUA 27073.265, received September 28, 2021)
 - response to CBER's October 28, 2021 Comments (EUA 27073.303, received November 17, 2021)
- mRNA-1273-P903: 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
 - protocol version 3.1 (EUA 27073.248, received August 31, 2021)
 - protocol version 3.2 (STN 125752/0.17, received November 5, 2021; also submitted to EUA 27073.285, received October 29, 2021)
 - Interim Report 3 (EUA 27073.285, received October 29, 2021)
 - response to CBER's July 14, 2021 Comments (EUA 27073.248, received August 31, 2021)
 - response to CBER's September 23, 2021 and September 27, 2021 Comments (EUA 27073.285, received October 29, 2021)
- mRNA-1273-P904: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe
 - protocol version 1.2 (STN 125752/0.17, received November 5, 2021; also submitted to EUA 27073.270; received October 6, 2021)

2 PRODUCT INFORMATION

2.1 Product Description

The Moderna COVID-19 Vaccine SPIKEVAX contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The product is a frozen suspension for intramuscular injection.

The product is administered as a series of two doses (0.5 mL) each 28 days apart by intramuscular injection.

2.2 Proposed Indication

The proposed indication for Moderna COVID-19 Vaccine SPIKEVAX in the United States is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

3 POST-MARKETING SAFETY AND EFFECTIVENESS STUDIES

3.1 Executive Summary

3.1.1 Post-Marketing Safety Study mRNA-1273-P903 (US) Summary

Study Title: “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”

Study mRNA-1273-P903 is an ongoing post-marketing safety study in the US. It is a retrospective observational cohort study using historical controls with further signal evaluation using a self-controlled risk interval (SCRI) design.

The study has large source population. HealthVerity’s aggregated database covered >140 million patients. Interim Report 3 identified >15 million individuals receiving at least one dose of mRNA-1273 through June 20, 2021. Among them, about 11 million mRNA-1273 vaccine recipients met study entry criteria, including >1.3 million vaccinated individuals 18 – 29 years of age. With data available through June 20, 2021, a minimum of 1.46 million vaccine recipients <30 years of age are expected to meet all study entry criteria. The post-EUA period (T3) is from December 11, 2020 to December 31, 2022 and we would expect more mRNA-1273 vaccine recipients <30 years of age to evaluate the occurrence of myocarditis and pericarditis following mRNA-1273 vaccination.

The sponsor addressed and incorporated FDA’s comments regarding various potential sources of biases. To reduce the risk of bias due to the differences between COVID-19 vaccinated patients in the post-EUA period and unvaccinated patients in the pre-EUA period, the study will additionally estimate background rates in T1 (pre-COVID) among influenza vaccinees and provide descriptive analyses. To understand the potential for bias from time-varying confounders such as healthcare utilization over the study periods, the sponsor will examine rates over the pre-COVID (T1), pre-vaccine active-COVID (T2), and post-EUA period (T3) for mild, moderate, and severe medical conditions and procedures that are not related to COVID-19 vaccines. The SCRI design is less susceptible to bias due to vaccination status misclassification, but time-varying confounder bias is a potential issue and the choice of risk window is critical for SCRI. The sponsor shortened SCRI control windows from 183 days to 42 days, revised risk window for myocarditis and pericarditis from 42 days to 7 days, and revised risk windows for other adverse events of interest (AESIs) such as anaphylaxis and thrombosis with thrombocytopenia syndrome.

The sponsor revised the study protocol to expand beyond the adult population to capture children, adolescents, and adults. The revised protocol includes analyses by dose for all AESIs, characterization of myocarditis events by age, sex, and time since most recent vaccination, dose stratified analyses for the primary endpoint of myocarditis regardless of sample size. The sponsor agreed that FDA may request the implementation of SCRI (and/or other analyses/subanalyses) for AESIs that the agency considers as safety concerns.

The sponsor will submit the final study protocol by January 31, 2022.

The study is adequate as a potential postmarketing requirement (PMR).

3.1.2 Post-Marketing Safety Study mRNA-1273-P904 (EU) Summary

Study Title: “Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe”

Study mRNA-1273-P904 is an ongoing post-marketing safety study in Europe. The study has two stages: the signal detection stage is a cohort study with historical rates from 2017-2019, and the signal evaluation stage will use self-controlled designs and cohort designs with either historical or concurrent unexposed comparators.

The database covered five European countries: Denmark, Norway, Italy, Spain, and UK. The database has very good coverage in Denmark (100%) and Norway (100%), and much lower coverage in Italy (5%), Spain (10%), and UK (6%). The Italian ARS database comprises all information that are collected by the Tuscany Region to account for the healthcare delivered to its around 3.6 million inhabitants. The Spanish SIDIAP database has records for 5.7 million people (80% of the Catalan population) being highly representative of the Catalan population. The UK CPRD database covers 13 million active patients (still alive and registered with the general practitioner (GP) practice) and the dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage. The UK HES database contains details of all admissions to National Health System hospitals in England and approximately 60% of GP practices in the CPRD are linked to the HES database. The low coverage does not create bias concern because the database in each low coverage country either has high regional coverage or is generalizable to the national population.

As of June 1, 2021, 0.43 million SPIKEVAX vaccinees were covered by the database. In the study, SPIKEVAX vaccinees will be identified between January 6, 2021 and December 31, 2022. Considering data through November 19, 2021 on administration and the per protocol assumptions concerning population coverage in the participating countries, the current estimated number of SPIKEVAX recipients expected to be included in the study is approximately 4.39 million. Of these, approximately 0.61 million will be <30 years of age. Because some of the analyses will be conducted by country, study size could be a concern to detect rare adverse event of special interest (AESI) if a country has small number of SPIKEVAX vaccinees covered by the database.

The sponsor will use a triangulation approach in the signal evaluation stage: the self-controlled designs are the preferred methods; if the AESIs have properties not amenable to self-controlled method, the sponsor will use one of more versions of parallel cohort designs with either historical or concurrent unexposed comparators. Each study design has its own potential sources of bias. Self-controlled methods control for time-fixed confounders by design and are less susceptible to exposure misclassification bias. The choice of risk window is critical for self-controlled methods, and the sponsor will conduct sensitivity analysis with alternative risk windows for AESIs without well-known risk windows. Cohort designs using historical controls could be biased by time varying confounders, such as change of health seeking behavior, because the COVID-19 pandemic could have long-term and short-term impact on people's health seeking behavior. Cohort designs using concurrent unexposed comparators could be biased because vaccinated and unvaccinated individuals may not be comparable. Exposure misclassification is less of a concern in this study due to accurate linkage among data sources. The triangulation approach could reduce potential bias to some extent.

The study protocol included analyses by dose number where feasible and for any dose, as well as stratified analyses by country, age, sex, calendar time, and seasonality if applicable.

The study is adequate as a potential postmarketing requirement (PMR).

3.1.3 Real World Effectiveness Study mRNA-1273-P901 RWS (US) Summary

Study Title: "Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine"

Study mRNA-1273-P901 RWS is an ongoing real world effectiveness study in the US. It is an observational cohort study.

Kaiser Permanente Southern California (KPSC) is one of the largest not-for-profit health plans and integrated health care systems in the U.S. KPSC's population includes >4.5 million members, of which 0.70 million adults are aged ≥ 65 years and 0.34 million are between 12 and 17 years old.

The sponsor addressed FDA's comments regarding various potential sources of bias. To address the risk of bias due to exposure misclassification, the sponsor clarified that KPSC is receiving regular batch imports of external administration of COVID-19 vaccine for KPSC members, and the "assessment of vaccination via the KPSC system is thorough and as complete as possible in a pandemic setting." To reduce potential outcome misclassification, the sponsor will ask patients about positive tests conducted outside of KPSC, document in the EHR with internal diagnosis codes, and perform chart review of potential COVID-19 hospitalizations and deaths to confirm severe COVID-19 symptoms. The sponsor will conduct matching for important risk factors such as age, sex, and race/ethnicity in the design stage and control for demographic characteristics,

health care utilization, comorbidities, and geographic area in the analysis stage. The above approach could reduce confounding bias.

There are potential sources of residual confounding: 1) The vaccinated cohort may have different COVID-19 risk or different exposure to SARS-CoV-2 than the unvaccinated cohort, especially for the vaccinated cohort prior to March 31, 2021 in the 1st interim report. The demographics of the vaccinated and unvaccinated cohort could change over time. 2) Unvaccinated person time is significantly shorter than vaccinated person time. Because Covid-19 circulation changes over time, the study could be biased due to secular confounding. 3) Long-term care residents were part of California's Phase 1A for COVID-19 vaccine prioritization. Long-term care residents and community dwelling individuals can be very different. Not controlling for long-term care status could potentially introduce bias. 4) The sponsor mentioned high sensitivity of molecular diagnostic tests among individuals with COVID-19 symptoms, however, false positives due to imperfect specificity of molecular diagnostic tests or COVID-19 diagnosis code could bias the vaccine effectiveness (VE) results, especially for the COVID-19 diagnosis outcome where there is no chart review.

The revised protocol version 3 added VE against SARS-CoV-2 variants: two-dose VE study will use both test-negative and cohort designs, and one-dose VE study will use test-negative design only. The revised protocol version 4 added VE of 3 doses in immunocompromised and booster dose in non-immunocompromised individuals using cohort design.

The two interim reports demonstrated high real-world VE for mRNA-1273 despite potential sources of biases.

The study is adequate as a potential postmarketing commitment (PMC).

3.2 Post-Marketing Safety Studies

In Clinical Overview (STN 125752/0.2; received August 24, 2021), the sponsor listed six Moderna-sponsored studies in the post-authorization development plan, including safety studies mRNA-1273-P903 (US) and mRNA-1273-P904 (EU), and effectiveness study mRNA-1273-P901 (US).

***Reviewer comment:** The study mRNA-1273-P903 (US) has a relatively large source population (over 140 million patients from HealthVerity's aggregated database). The study mRNA-1273-P904 (EU) is an ongoing study to monitor real-world safety of mRNA-1273 in five European countries. It would be useful to include these two safety studies as postmarketing requirements (PMRs).*

The study mRNA-1273-P901 (US) is an ongoing real-world vaccine effectiveness study of mRNA-1273 among Kaiser Permanente Southern California (KPSC) members ≥ 12 years of age. It would be useful to include this effectiveness study as a postmarketing commitment (PMC).

The sponsor submitted mRNA-1273-P903 protocol version 3.1 and response to CBER's July 14, 2021 Comments regarding P903 to the EUA (STN 27073.248, received August 31, 2021).

Below are the comments for mRNA-1273-P903 protocol version 3.1:

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 Advisory Committee on Immunization Practices (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 are important safety concerns for mRNA vaccines. so please describe the information available on the risk of myocarditis and pericarditis following mRNA vaccines, and specifically following mRNA-1273.

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.*
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.

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.

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.*

Below are the comments for response to CBER’s July 14, 2021 Comments regarding P903:

1. Response to ITEM 1,

Reviewer comment: *The sponsor addressed FDA’s comments regarding the risk of bias due to the differences between COVID-19 vaccinated patients and unvaccinated patients in the pre-COVID (T1) and pre-vaccine active-COVID (T2) periods. The sponsor clarified that the study will additionally estimate background rates in T1 (pre-COVID) among influenza vaccinees and provide descriptive analyses.*

The response is acceptable.

2. In Response to ITEM 1, the sponsor 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.”

Reviewer comment: *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.*

3. In Response to ITEM 2, the sponsor 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.”

Reviewer comment: *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.

4. In Response to ITEM 2, the sponsor provided SCRI risk window for each AESI, for example, Anaphylaxis 0-11 days, Myocarditis 1-42 days, Pericarditis 1-42 days, Thrombosis with thrombocytopenia syndrome of days 1-42.

Reviewer 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, a risk period of days 1-42 was chosen for thrombosis with thrombocytopenia syndrome. 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 the risk window for thrombosis with thrombocytopenia syndrome accordingly.

The sponsor submitted mRNA-1273-P903 protocol version 3.2 (STN 125752/0.17, received November 5, 2021; also submitted to EUA 27073.285, received October 29, 2021) and response to CBER's September 23 and September 27, 2021 Comments regarding P903 (EUA 27073.285, received October 29, 2021).

Below are the comments for mRNA-1273-P903 protocol version 3.2:

1. *The post-authorization safety study mRNA-1273-P903 Protocol v3.2 incorporated FDA's comments on the previous version of mRNA-1273-P903 protocol, communicated to the sponsor on September 23, 2021 and September 27, 2021. The revised study protocol includes coprimary analyses by dose for all adverse events of interest, characterization of myocarditis events by age, sex, and time since most recent vaccination (1-7 days vs. >7 days), dose stratified analyses for the primary endpoint of myocarditis regardless of sample size and the Self-Controlled Risk Interval Analyses for myocarditis and pericarditis with revised risk window from 1-42 days to 1-7 days.*

The analyses in the revised mRNA-1273-P903 Protocol v3.2 are generally acceptable. Please add language to the protocol to include analyses for pericarditis, as the age, sex, time since vaccination, and dose stratified analyses apply to both myocarditis and pericarditis.

2. *Page 29, Section 9.7. Data Analysis Plan, the sponsor stated that "Descriptive analyses will include stratification by age, sex, dose, and time since most recent*

vaccination (1-7 days vs. >7 days)". Myocarditis and pericarditis may be a systemic inflammatory reaction which could happen on day 0, and the U.S. Vaccine Safety Datalink and other systems have found sufficient numbers of cases with onset on day 0. For the descriptive analyses by time since most recent vaccination, please include 0 day, 1-7 days, 8-21 days, and >21 days. The SCRI study revised risk window is 1-7 days for myocarditis and pericarditis. Other studies have used 0-7 days or 1-7 days as the risk window. The 0 day descriptive analysis could provide useful information to inform the choice of risk window for the SCRI study.

Below are the comments for response to CBER's September 23 and September 27, 2021 Comments regarding P903:

1. To study change in health seeking behavior, in addition to severe outcomes, the sponsor will also characterize rates of mild and moderate conditions and procedures (e.g., colonic diverticulitis, hypertension, colonoscopies, mammograms, and cervical cancer screenings).

The response is acceptable.

2. The sponsor revised the protocol to shorten the control windows to 42 days. Risk windows have been revised to: Anaphylaxis: 1 day; Myocarditis and pericarditis: 1-7 days; Thrombosis with thrombocytopenia syndrome: 1 – 14 days.

The response is generally acceptable. For myocarditis and pericarditis, please also include a secondary 1-21 days risk window to improve compatibility with studies performed by others.

3. The sponsor is working to develop additional studies to follow vaccine associated myocarditis cases longitudinally for at least 5 years to characterize potential long-term sequelae.

The response is acceptable.

The sponsor submitted mRNA-1273-P904 protocol version 1.2: (STN 125752/0.17, received November 5, 2021; also submitted to EUA 27073.270; received October 6, 2021)

Below are the comments for mRNA-1273-P904 protocol version 1.2:

1. Page 29-30, Section 9.5. Study Size. In Table 4, a total of 6,200,539 doses of SPIKEVAX were administered in the participating 5 countries as of June 1, 2021. In Table 6, 431,216 SPIKEVAX vaccinees were covered by the database in the same 5 countries as of June 1, 2021. The database has very good coverage in Denmark (100%) and Norway (100%), and much lower coverage in Italy (5%), Spain (10%), and UK (6%). The Italian ARS database comprises all information that are collected by the Tuscany Region to account for the healthcare delivered to its around 3.6 million inhabitants. The Spanish SIDIAP database has records for 5.7

million people (80% of the Catalan population) being highly representative of the Catalan population. The UK CPRD database covers 13 million active patients (still alive and registered with the general practitioner (GP) practice) and the dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage. The UK HES database contains details of all admissions to National Health System hospitals in England; approximately 60% of GP practices in the CPRD are linked to the HES database. The low coverage does not create bias concern because the database in each country either has high coverage regionally or is generalizable to the national population. Because some of the analyses will be conducted by country, study size could be a concern to detect rare adverse event of special interest (AESI) if a country has small number of SPIKEVAX vaccinees covered by the database.

2. *Page 18, Section 9.1.1 Signal detection: cohort study with historical rates. “As increased rates for some AESI might only be expected in a limited time interval after vaccination with Spikevax, the SMRs will be estimated in the following time intervals relative to the date of each dose of the COVID-19 Moderna vaccine: 0-2 days, 0-14 days, 0-28 days, 0-42 days and 0-end of follow-up.”*

Because the onset of myocarditis and pericarditis was typically within several days after mRNA COVID-19 vaccination, please add 0-7 days interval. Please also add 0-21 days interval to improve compatibility with studies performed by others.

3. *The study has two stages: signal detection and signal evaluation. Spikevax vaccinees will be identified between January 6, 2021 and December 31, 2022. For the signal detection phase, country-specific historical background rates of AESI from 2017-2019 will be used, and for the signal evaluation phase, a combination of self-controlled designs and cohort designs using either historical or concurrent unexposed comparators will be used.*

Cohort designs using historical controls could be biased by time varying confounder such as change of health seeking behavior because the COVID-19 pandemic could have long-term and short-term impact on people’s health seeking behavior. To investigate potential biases due to time varying confounders such as change of health seeking behavior, please consider examining rates over the pre-pandemic period and study period for mild, moderate, and severe medical conditions and procedures that are not related to COVID-19 vaccines.

Cohort designs using concurrent unexposed comparators could be biased because vaccinated and unvaccinated individuals may not be comparable. For example, they could have different health seeking behaviors, medical conditions, or exposure to SARS-CoV-2. Please clarify how to mitigate against biases due to the differences between vaccinated and vaccinated cohorts. Exposure misclassification is less of a concern in this study due to accurate linkage among data sources.

The choice of risk window is critical for self-controlled methods. Please provide risk windows for each of the AESIs.

3.3 Real World Effectiveness Study

The sponsor submitted response to CBER's July 29, 2021 Comments regarding the Real World Effectiveness Study mRNA-1273-P901 protocol (EUA 27073.265, received September 28, 2021)

Below are the comments for response to CBER's July 29, 2021 Comments:

5. Response to ITEM 1,

Reviewer comment: *The sponsor addressed FDA's comments regarding the risk of confounding bias due to exposure misclassification. The sponsor clarified that KPSC is receiving regular batch imports of external administration of COVID-19 vaccine for KPSC members, and the "assessment of vaccination via the KPSC system is thorough and as complete as possible in a pandemic setting."*

The response is acceptable.

6. In Response to ITEM 1, the sponsor stated: "Vaccinated and unvaccinated individuals will be matched on the most important risk factors, i.e., age, sex, race/ethnicity, and index date." "By design, we will follow matched individuals over the same calendar time (index date) to minimize bias due to secular confounding (such as the change of COVID-19 incidence rate over time and the timing of COVID-19 vaccine roll-out/patient prioritization approaches taken in the US when vaccine supply was initially limited). Finally, we will allow Moderna COVID-19 unvaccinated individuals to become vaccinated at any time during follow-up to reduce confounding by indication."

Reviewer comment: *The vaccinated and unvaccinated individuals were matched on age, sex, and race/ethnicity, and the index date was defined as the date of receipt of the second dose of mRNA-1273 for vaccinated individuals and their matched unvaccinated counterparts. Even though the study recruited the same number of vaccinated and unvaccinated individuals matched on age, sex, and race/ethnicity, the ratio of unvaccinated vs vaccinated could get smaller with increasing months of follow-up. This would result in significantly shorter unvaccinated person time than vaccinated person time. Because Covid-19 circulation changes over time, the study could be biased due to secular confounding. Please clarify how to control for the secular confounding due to different person time for unvaccinated and vaccinated cohorts.*

7. Response to ITEM 2,

Reviewer comment: *The sponsor addressed FDA's comments regarding geographical factor. The sponsor clarified that geographic area will be accounted for through the medical center area variable.*

The response is acceptable.

8. In Response to ITEM 2, the sponsor stated: “Long-term care residents were part of California’s Phase 1A for COVID-19 vaccine prioritization (started in December 2020).” “To account for the phased roll-out of vaccines in California, vaccinated and unvaccinated individuals will be matched on index date in addition to age, sex, and race/ethnicity.”

Reviewer Comments: Long-term care residents and community dwelling individuals can be very different. Long-term care was not a matching variable. Please clarify how to mitigate against the risk of bias due to confounding by long-term care stay status.

9. In Response to ITEM 5, the sponsor stated: “Misclassification of COVID-19 outcomes is also possible due to imperfect capture and sensitivity of SARS-CoV-2 molecular diagnostic tests.” “However, for patients with COVID-19 symptoms, sensitivity of molecular diagnostic tests is generally high (>90%).” “Furthermore, this is less of a concern if misclassification of COVID-19 outcomes is non-differential across the vaccinated and unvaccinated groups.”

Reviewer Comments: We appreciate the effort that the sponsor made to ask patients about positive tests conducted outside of KPSC and to document in the EHR with internal diagnosis codes, and to perform chart review of potential COVID-19 hospitalizations and deaths to confirm severe COVID-19 symptoms. The sponsor mentioned high sensitivity of molecular diagnostic tests among individuals with COVID-19 symptoms, however, false positives due to imperfect specificity of molecular diagnostic tests or COVID-19 diagnosis code could bias the vaccine effectiveness results, especially for the COVID-19 diagnosis outcome where there is no chart review. Please provide positive predictive value of COVID-19 diagnosis outcome definition.

10. Response to ITEM 6:

Reviewer Comments: For propensity score analyses with IPTW, please clarify how to handle covariates which are strong predictors of Moderna COVID-19 vaccinations but not associated with COVID-19 outcomes.

11. In Response to ITEM 10, the sponsor stated: “Although sensitivity and specificity can vary by factors such as quality of specimen collection, specimen type, and PCR assay, in the KPSC real-world setting, all specimens with positive results are considered positive.” “Of 295,395 individuals with a COVID-19 diagnosis (either positive SARS-CoV-2 RT-PCR test result or COVID-19 diagnosis code), 56,752 (19.2%) did not have a positive SARS-CoV-2 RT-PCR test result at KPSC but had a COVID-19 diagnosis, which likely had a positive SARS-CoV-2 test from an outside lab.”

Reviewer Comments: The sponsor mentioned “all specimens with positive results are considered positive”, however, false positives due to imperfect specificity of molecular diagnostic tests could bias the vaccine effectiveness results. Please provide the range of specificity of molecular diagnostic tests.

Since 56,752 (19.2%) of the individuals with a COVID-19 diagnosis did not have a positive SARS-CoV-2 RT-PCR test result at KPSC, please provide the percentage of individuals with a positive SARS-CoV-2 RT-PCR test result outside of KPSC among those 56,752 individuals (Please refer to response to ITEM 5).

The sponsor submitted real world postmarketing vaccine effectiveness study mRNA-1273-P901 1st interim Report (EUA 27073.256, received September 14, 2021).

Below are the comments for mRNA-1273-P901 1st interim report:

1. *The interim report demonstrated high real-world vaccine effectiveness (VE) for mRNA-1273 despite potential sources of biases.*

This prospective observational cohort study included 352,878 vaccinated and 352,878 unvaccinated individuals matched on age, sex, and race/ethnicity.

High VE was observed against COVID-19 hospitalization (VE 95.8%, [99.3% CI: 90.7-98.1%]) and COVID-19 hospital death (VE 97.9%, [99.3% CI: 66.9-99.9%]). VE was higher against symptomatic (VE 88.3% [98.3% CI: 86.1%-90.2%]) than asymptomatic COVID-19 (VE 72.7% [98.3% CI: 53.4%-84.0%]). The point estimates of VE against COVID-19 diagnosis for individuals with history of COVID-19 were lower (8.2% and 33.6% when using different definitions of COVID-19 reinfection) and the 98.3% CIs included 0%.

2. *The vaccinated cohort may have different COVID-19 risk or different exposure to SARS-CoV-2 than the unvaccinated cohort.*

The vaccinated individuals received vaccines between December 18, 2020 and March 31, 2021. Because vaccination for all individuals aged ≥18 years started in April 2021, the vaccinated individuals in this interim report only included healthcare workers, long-term care residents, individuals aged ≥65 years, workers in education and childcare, emergency services, and food and agriculture, and individuals aged 18–64 years with underlying health conditions.

If the unvaccinated cohort in the interim report also included individuals 18-64 years who do not fall under the above-described categories, then the vaccinated cohort may have different COVID-19 risk or different exposure to SARS-CoV-2 than unvaccinated cohort. For example, individuals aged 18-64 years with underlying health conditions could have higher baseline COVID-19 risk comparing with healthy individuals in the same age group, and healthcare workers could have higher exposure to SARS-CoV-2.

Page 24-25, Table 1 showed baseline characteristics of vaccinated and unvaccinated cohorts. Compared with unvaccinated, vaccinated cohort included more KPSC physician/employee (26,234 vs. 6,356), vaccinated individuals also had more outpatient/virtual visits in the year prior to index date. The baseline characteristics comparison suggested that vaccinated and unvaccinated cohort may not be comparable with regards to baseline risk and exposure to SARS-CoV-2.

3. *The vaccinated and unvaccinated cohort could have different health-seeking behavior.*

Page 24-25, Table 1 showed baseline characteristics of vaccinated and unvaccinated cohorts. Compared to unvaccinated individuals, fewer vaccinated individuals had a history of COVID-19 diagnosis (23,152 vs. 35,876), but more vaccinated individuals had a history of molecular SARS-CoV-2 test (133,865 vs. 116,859), and vaccinated individuals also had more preventive care visits (294,962 vs. 234,773) in the year prior to index date.

The two cohorts could have different health seeking behaviors, and results could be biased towards the null.

4. *Health care utilization and vaccination exclusion criteria may not accurately reflect the health seeking behavior for the vaccinated individuals.*

One of the exclusion criteria was about health seeking behavior: on Page 6, Study Population “Individuals who ... had no health care utilization and no vaccination from the 2 years prior to the index date through the index date...were excluded.”

The index date was the date of receipt of the second dose of mRNA-1273 for vaccinated individuals and their matched unvaccinated counterparts (matched by age group, sex, and race/ethnicity). For vaccinated individuals, we would expect them to have at least a first dose of mRNA-1273 from 2 years prior to the index date through the index date. Then this exclusion criteria would not exclude anyone from the vaccinated cohort (Page 35, Flow chart for this 1st interim report showed that 0 vaccinated individual was excluded). Unvaccinated counterparts, on the contrary, would need to either have health care utilization or vaccinations other than Covid-vaccines in the past two years. This exclusion criteria may not accurately reflect the health seeking behavior for the vaccinated individuals.

5. *Significantly shorter unvaccinated person time than vaccinated person time*

The interim report included 352,878 vaccinated and 352,878 unvaccinated individuals matched on age, sex, and race/ethnicity. However, Figure 1 on page 22 showed that number at risk with ≥ 1 month of follow-up was much smaller for the unvaccinated cohort than the vaccinated cohorts, and the ratio of unvaccinated vs vaccinated gets smaller with increasing months of follow-up (e.g., for COVID-19 hospitalization, at 1 month follow-up, number at risk was 351,383 and 216,375 for

vaccinated and unvaccinated, respectively; and at 3 months follow-up, number at risk was 286,701 and 121,706 for vaccinated and unvaccinated, respectively). Because Covid-19 circulation changes over time, the study could be biased due to secular confounding.

6. Significant number of vaccinated individuals were excluded from the interim report analysis

Page 35, Flow chart for this 1st interim report showed that among 883,248 individuals who received mRNA-1273 vaccine between 12/18/2020 and 3/31/2021, 448,142 received 2 doses of mRNA-1273 vaccines ≥ 24 days apart.

For the 435,106 individuals excluded from the study, please clarify how many of them only received one dose of mRNA-1273, and how many of them received 2 doses of mRNA-1273 < 24 days apart.

The sponsor submitted response to CBER's October 28, 2021 Comments regarding the 1st Interim Report for Real World Effectiveness Study P901 (EUA 27073.303, received November 17, 2021)

Below are the comments for response to CBER's October 28, 2021 Comments:

1. Response to ITEM 1

The sponsor conducted 1:1 matching for important risk factors such as age, sex, and race/ethnicity in the design stage and controlled for demographic characteristics, health care utilization, comorbidities, and geographic area in the analysis stage. The above approach could reduce confounding bias.

There are potential residual confounding:

- 1) The vaccinated cohort may have different COVID-19 risk or different exposure to SARS-CoV-2 than the unvaccinated cohort, especially for the vaccinated cohort prior to March 31, 2021 in this interim report. The demographics of the vaccinated and unvaccinated cohort could change overtime.*
- 2) Significantly shorter unvaccinated person time than vaccinated person time. Because Covid-19 circulation changes over time, the study could be biased due to secular confounding.*

2. Response to ITEM 2

The sponsor revised cohort flow chart and provided clarification regarding the 435,106 individuals excluded from this first interim report: 432,206 received only one dose of mRNA-1273 at the time of the interim report (395,145 (91.43%) received a second dose after March 31, 2021) and 2,900 individuals received two doses of mRNA-1273 < 24 days apart.

The response is acceptable.

The sponsor submitted real world postmarketing vaccine effectiveness study mRNA-1273-P901 2nd interim Report (EUA 27073.312, received December 14, 2021).

Below are the comments for mRNA-1273-P901 2nd interim report:

1. *The interim report demonstrated high real-world vaccine effectiveness (VE) for mRNA-1273 despite potential sources of biases.*

This prospective observational cohort study included 927,004 mRNA-1273 vaccinated and 927,004 unvaccinated individuals matched on age, sex, and race/ethnicity.

High VE was observed against COVID-19 hospitalization (VE 96.1%, [95% CI: 95.5-96.6%]) and COVID-19 hospital death (VE 97.2%, [95% CI: 94.8-98.4%]). VE against SARS-CoV-2 infection was 82.8% [95% CI: 82.2-83.3%], was similar by age, sex, and race/ethnicity, and was 86.5% [95% CI: 84.8-88.0%] during the Delta period. VE against SARS-CoV-2 infection decreased by 88.0% at 0-2 months, to 75.5% at 6-8 months.

2. *The vaccinated cohort may have different COVID-19 risk or different exposure to SARS-CoV-2 than the unvaccinated cohort.*

The vaccinated individuals received vaccines between December 18, 2020 and June 30, 2021. Because of vaccination tiers, the vaccinated individuals in the 2nd Interim Report included fewer individuals without underlying health conditions and without higher exposure to SARS-CoV-2, even though to a lesser extent than in the 1st Interim Report where vaccinated individuals received vaccines between December 18, 2020 and March 31, 2021.

The vaccinated cohort may have different COVID-19 risk or different exposure to SARS-CoV-2 than unvaccinated cohort.

Page 19-20, Table 1 showed baseline characteristics of vaccinated and unvaccinated cohorts. Compared with unvaccinated, the vaccinated cohort included more KPSC physician/employee (31,111 vs. 15,132), vaccinated individuals also had more outpatient/virtual visits in the year prior to index date. The baseline characteristics comparison suggested that vaccinated and unvaccinated cohort may not be comparable with regards to baseline risk and exposure to SARS-CoV-2.

3. *The vaccinated and unvaccinated cohort could have different health-seeking behavior.*

Page 19-20, Table 1 showed baseline characteristics of vaccinated and unvaccinated cohorts. Compared to unvaccinated individuals, fewer vaccinated individuals had a history of COVID-19 diagnosis (92,461 vs. 113,396), but more vaccinated individuals had a history of molecular SARS-CoV-2 test (364,575 vs.

337,279), and vaccinated individuals also had more preventive care visits (691,389 vs. 568,154) in the year prior to index date.

The two cohorts could have different health seeking behaviors, and results could be biased towards the null.

4. *Significantly shorter unvaccinated person time than vaccinated person time*

The interim report included 927,004 vaccinated and 927,004 unvaccinated individuals matched on age, sex, and race/ethnicity. However, Figure 2 showed that number at risk with ≥ 1 month of follow-up was much smaller for the unvaccinated cohort than the vaccinated cohorts, and the ratio of unvaccinated vs vaccinated gets smaller with increasing months of follow-up (e.g., for COVID-19 hospitalization, at 1 month follow-up, number at risk was 920,453 and 518,477 for vaccinated and unvaccinated, respectively; and at 3 months follow-up, number at risk was 895,584 and 400,333 for vaccinated and unvaccinated, respectively). Because Covid-19 circulation changes over time, the study could be biased due to secular confounding.

4 OBE REAL WORLD EVIDENCE RECOMMENDATIONS

Postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis, using real world evidence study design:

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.”
2. Study mRNA-1273-P904, entitled “Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe.”

OBE will review the final protocols for mRNA-1273-P903 when available (please see approval letter for study milestone dates).

Postmarketing commitment (PMC) vaccine effectiveness study agreed upon by FDA and the sponsor:

1. Study mRNA-1273-P901 RWS, entitled “Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine.”

Note that PMR/PMC studies, in addition to the above listed studies, have been described in OBE/Division of Epidemiology pharmacovigilance plan (PVP) review memo and addendum memo.