

RESPONSE TO FDA COMMENTS ON CLINICAL RECEIVED ON JULY 29, 2021

The Sponsor acknowledges FDA comments on CLINICAL topics (in **BOLD**)

We have completed the review of the protocol for post-authorization effectiveness study mRNA 1273-P901 RWS submitted in amendment 195 to EUA 27073, and have the following comments:

ITEM 1:

Page 17, Section 5. “The unvaccinated comparator cohort will comprise individuals who have not received Moderna COVID-19 vaccine or any other COVID-19 vaccine as of the index date of their matched vaccinated individual.”

FDA Comment # 1:

People without COVID-19 vaccination code could have received their vaccinations outside of the KPSC health system such as in a State/County facility or fair, or in a pharmacy unaffiliated with KPSC. Please explain how thorough your assessment of such out of the KPSC system vaccination is. Please also see Comment # 9.

The cohort without vaccination code consists of both vaccinated and unvaccinated individuals, and people with COVID-19 vaccination code are most likely vaccinated, so the results are biased toward the null. Please clarify how to mitigate against the risk of bias due to exposure misclassification.

Vaccinated and unvaccinated individuals could have different health seeking behaviors or medical conditions. Please clarify how to mitigate against the risk of confounding bias such as health seeking behaviors.

Sponsor Response

Vaccinations received outside of the health plan are recorded with appropriate documentation to capture exposure that occurred outside of the KPSC system. Specifically for COVID-19 vaccinations, KPSC is receiving regular batch imports of external administrations of COVID-19 vaccine for KPSC members. The external sources include claims (e.g., retail pharmacies), California Immunization Registry (or CAIR, which is California’s immunization information system), CalVax (e.g., Cal Poly Pomona mass vaccination site), (b) (4) (system that allows health care systems on the (b) (4) EHR platform to exchange patient medical information), and member self-report (with valid documentation). Because external COVID-19 vaccination can be captured in the KPSC EHR data by manual entry and automated updates from mechanisms such as CAIR and claims, assessment of vaccination via the KPSC system is thorough and as complete as possible in a pandemic setting.

To mitigate the potential for exposure misclassification, in addition to the above mechanisms for capturing COVID-19 vaccination, we will have at least 3 months follow-up time to allow

vaccination records to be complete for first 3 interim analyses and at least 9 months (6 months follow-up time + 3 months data lag) for the rest of the interim and final analyses.

A potential limitation of this study is that there could be differences between vaccinated and unvaccinated individuals that are difficult to control and measure. Vaccinated and unvaccinated individuals will be matched on the most important risk factors, i.e., age, sex, race/ethnicity, and index date. We will adjust for differences in demographic characteristics, health care utilization, comorbidities, and geographic area, but differences in other unmeasured factors, such as occupational risk exposures and behavioral factors (e.g., masking, distancing, handwashing, test-seeking behavior), could result in residual confounding. 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.

ITEM 2:

Page 17, Section 5. “For the first and second interim analyses, unvaccinated individuals will be randomly selected and n:1 matched to vaccinated individuals by age, sex, and race/ethnicity, and will be assigned an index date based on the vaccination date of their matched vaccinated individual.”

FDA Comment # 2:

Individuals receiving vaccines during different phases could have different level of exposures to SARS-CoV-2 virus and different risks for COVID-19. Please clarify how to control for potential confounding when selecting unvaccinated individuals during different vaccination phases. Geographical factors including community COVID-19 circulation will impact incidence of COVID-19 diagnosis and severe COVID-19 outcomes. Please clarify whether vaccinated and unvaccinated individuals will be matched by geographical factors with sufficient granularity. If geographical factors will not be matched, please specify how to control for those factors in the analysis. Please specify how to handle long-term care residents.

Sponsor Response

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). That is, the vaccination date of the second Moderna

COVID-19 vaccine dose will be assigned as the index date, and individuals who meet the inclusion/exclusion criteria and have not received any COVID-19 vaccine dose by the index date will be randomly selected and matched to the 2-dose vaccinated individuals. This approach ensures that matched vaccinated and unvaccinated individuals are followed over the same calendar time, inherently accounting for vaccination phases, varying levels of exposures to SARS-CoV-2 virus, and differential risks levels over time.

We will account for geographic area through the medical center area variable. The KPSC medical center area is assigned based on each member's location of residence and is where each member receives their usual care. Medical center area will be evaluated as a potential covariate for inclusion in the final adjusted models.

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. Additionally, one of the study's secondary objectives is to evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in frail individuals. This subpopulation will be defined as individuals with a high frailty score during the 1-year prior to index date and aged ≥ 65 years on index date. A frailty index will be calculated for each individual on index date using the method by Kim et al. based on the diagnosis and procedure codes received in the inpatient, outpatient, emergency, and virtual visit settings during the 1 year (-365 to -1 day) prior to index date (Kim et al 2018). The cut-off point of a high frailty score will be determined based on the frailty score distribution. It is possible that matching will not be maintained in the analysis of this secondary objective, if most individuals in long-term care become vaccinated. We will assess the distribution of matching variables and will include them in the adjusted model if needed. For analyses of other objectives, frailty will be evaluated as a potential covariate for inclusion in the final adjusted models.

ITEM 3:

Page 18, Section 6.1. Exclusion criteria "Occurrence of a COVID-19 outcome <14 days after the index date."

FDA Comment # 3:

For the vaccinated individuals, it takes about 14 days to develop immunity after vaccination. Please clarify whether unvaccinated individuals will also be excluded if a COVID-19 outcome occurs <14 days after the index date.

Sponsor Response

We confirm that unvaccinated individuals will also be excluded if a COVID-19 outcome occurs <14 days after the index date (same as for vaccinated individuals).

ITEM 4:

Page 18, Section 6.2. “For the first and second interim analyses, unvaccinated individuals will be randomly selected and n:1 matched to the vaccinated individuals by age (12-17 years, 18-44 years, 45-64 years, 65-74 years, and ≥ 75 years), sex, and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Non-Hispanic Asian, and Other/Unknown).”

FDA Comment # 4:

The age range is very wide for categories 18-44 years, 45-64 years, and ≥ 75 years. To improve the likelihood that subjects are comparable within each age group, please consider using age categories with shorter age intervals, if sample size allows.

Sponsor Response

The age ranges for this study are currently 12-17 years, 18-44 years, 45-64 years, 65-74 years, and ≥ 75 years. The age ranges for this study were selected to align with the age ranges used in Moderna’s pivotal Ph 3 study (the COVE study; [Baden et al 2021](#)) and subsequent adolescent Ph 2 clinical trials (TeenCOVE; [Ali et al 2021](#)). Based on the first interim analysis (IA), the number of COVID-19 cases in the vaccinated group stratified by these age ranges suggests that further age stratification may reduce ability to draw meaningful statistical conclusions: 18-44 years: 93 cases; 45-64 years: 83 cases; 65-74 years: 54 cases; and ≥ 75 years: 59 cases.

ITEM 5:

Page 20, Section 7.2., “The primary outcomes for this study are:

- 1. COVID-19 diagnosis will be defined as a SARS-CoV-2 positive molecular test or a COVID-19 diagnosis code**
- 2. Severe COVID-19 disease includes COVID-19 hospitalization (hospitalization with a SARS-CoV-2 positive test or a COVID-19 diagnosis, or a hospitalization occurring within 7 days after a SARS-CoV-2 positive test) and COVID-19 mortality (death during COVID-19 hospitalization)”**

FDA Comment # 5:

Please clarify how to handle deaths that occur with COVID-19 diagnosis but not during COVID-19 hospitalization. Please provide the sensitivity and specificity of the outcome definition. Please clarify how to mitigate against the risk of bias due to outcome misclassification.

Sponsor Response

Member death status will be identified by death records from KPSC hospitals and EDs, membership termination information, and outside claims. Deaths outside of KPSC will also be captured from the state death file. There is usually a 1- to 2-year delay in receiving and processing the state death file, so this resource will be utilized only if available. Since the study will only include active members during the follow-up period, additional deaths identified from the state death file beyond those identified through KPSC sources is expected to be small (< 5%).

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%). Moreover, to mitigate the risk of outcome misclassification, efforts are made to ask patients about positive tests conducted outside of KPSC and to document in the EHR with internal diagnosis codes. In addition, misclassification of the severe COVID-19 disease outcome is possible if hospitalization or death occurs for reasons other than COVID-19. To minimize the risk of this type of misclassification, chart review of potential COVID-19 hospitalizations and deaths will be performed to confirm severe COVID-19 symptoms. Furthermore, this is less of a concern if misclassification of COVID-19 outcomes is non-differential across the vaccinated and unvaccinated groups.

ITEM 6:

Page 21-22, Section 7.3. Table 3. “The covariates included in adjusted analyses will be determined by scientific relevance, association with exposure, and data availability.”

Page 25, Section 8.3. “we may also conduct propensity score analyses with inverse probability of treatment weighting (IPTW) to balance covariates across exposure groups.”

FDA Comment # 6:

Please clarify whether the covariates listed in Table 3 will be included in the outcome model or the propensity score model. Please specify how to determine variables being included in the propensity score model. Please clarify how to handle individuals with extreme weights when using IPTW.

Sponsor Response

The covariates included in adjusted analyses for the outcome model will be determined by scientific relevance, association with exposure, and data availability. Specifically, we will select covariates by following these steps:

1. The distribution of covariates will be reviewed. Some categories of a categorical variable with small sample sizes may be redefined or combined into one category.

2. The association of baseline covariates with exposure will be assessed. We will use standardized difference to assess the balance of covariates between exposed and unexposed cohorts. Unlike p-values, for which magnitude is highly related to sample size, standardized difference is a unified approach to quantifying the magnitude of difference between groups regardless of sample size, where an absolute value less than 0.1 is considered a negligible difference (Austin et al 2011). We will use a SAS macro %stddiff developed by Yang and Dalton (Yang et al 2012) to calculate the standardized differences for continuous and categorical variables. Potential confounders will be determined by absolute standardized difference (ASD) >0.1 (Nguyen et al 2017).
3. All potential confounders from Step 2 will be included in the analyses. Steps 1 and 2 will be repeated for the 2-dose cohort and the 1-dose cohort. Matching variables (age, sex, and race/ethnicity) and index date, which are considered important risk factors, will be kept in the adjusted model for possible imbalance on matching variables due to loss to follow-up or subgroup analysis (e.g., by baseline comorbidities).

For the final analysis of primary objectives, we will conduct propensity score analyses with IPTW to balance covariates across exposure groups. We will estimate the probability of receiving 2 doses of Moderna COVID-19 vaccine (propensity score) as predicted by covariates selected by the above steps using a logistic regression model. The weight for each individual will be calculated as the inverse of the predicted probability of receipt of exposure. The weight will be normalized by dividing by the mean weight of each exposure group to avoid extreme large values and to resize the weighted population to the original sample size for each group (Tartof et al 2016). Baseline characteristics of the weighted 2-dose Moderna COVID-19 vaccine cohort will be described and compared between the vaccinated and unvaccinated groups. Absolute standardized difference scores will be used to assess whether balance of covariates is achieved between the comparison groups after weighting. Separate Cox regression models with IPTW will be used to estimate the HRs and VEs for each outcome. Although we will balance the covariates at baseline, the distributions of covariates could become imbalanced during follow-up due to censoring. To account for this potential bias, we will apply a double-adjustment approach, i.e., control for all covariates included the treatment model in the outcome models (Nguyen et al 2017).

ITEM 7:

Page 25, Section 8.4. There are 15 secondary objectives

FDA Comment # 7:

Please clarify how to handle secondary objectives which do not have enough statistical power.

Sponsor Response

As of Aug. 23, 2021, 1,120,475 KPSC members ≥ 18 years old received 2 doses of Moderna COVID-19 vaccine. The first interim analysis (IA) was based on 352,878 vaccinated individuals 1:1 matched to 352,878 unvaccinated individuals. The first IA showed vaccine effectiveness (VE, and 99.3%CI) against COVID-19 diagnosis, COVID-19 hospitalization, and COVID-19 hospitalized death to be: 87.4% (84.8-89.6%); 95.8% (90.7-98.1%); and 97.9% (66.9-99.9%), respectively. Secondary objectives that do not have sufficient statistical power will be described and contextualized in terms of clinical significance and what is known from the literature.

For background information, assumptions for power calculations were made based on COVID-19 incidence rates as of December 2020 and COVID-19 vaccine uptake as of end of January 2021. The actual sample size and power will depend on Moderna COVID-19 vaccine implementation, uptake, and the number of individuals meeting criteria for comparable vaccinated and unvaccinated cohorts.

We estimated that a total of 80,000 individuals would receive 2 doses of Moderna COVID-19 vaccine from December 2020 through March 2021, assuming 80% series completion (first interim analysis). We estimated an incidence of 30 COVID-19 diagnoses per 1,000 unvaccinated adult KPSC members during an average 4-month follow-up period (accounting for possible censoring). We expected to have $>99.9\%$ power to detect a VE of 70%, with various sample sizes in the unvaccinated group (Table 1), using a 2-sided test with $\alpha=0.007$ (0.05 adjusted for 6 interim analyses and 1 final analysis). The calculation was performed using SAS software package (version 9.4) PROC POWER procedure.

Table 1. Power calculations for 1st interim analysis of Primary Objective 1 for various sample sizes and vaccine effectiveness estimates

Sample Size Ratio (Vaccinated vs Unvaccinated)	Incidence rate in unvaccinated group (cases/1000 persons)	VE (%) (reduction rate)	Power
1 vs 0.5	30	90	$>.999$
	30	80	$>.999$
	30	70	$>.999$
1 vs 1	30	90	$>.999$
	30	80	$>.999$
	30	70	$>.999$
1 vs 5	30	90	$>.999$
	30	80	$>.999$
	30	70	$>.999$

For the first interim analysis of Primary Objective 2, we estimated an incidence of 2 COVID-19 hospitalizations and 0.3 deaths per 1,000 unvaccinated adult KPSC members during an average 4-month follow-up period. We expected to have >99.9% power to detect a 70% VE against COVID-19 hospitalizations, with various sample sizes in the unvaccinated group (Table 2).

Table 2. Power calculations for 1st interim analysis of Primary Objective 2 for various sample sizes and vaccine effectiveness estimates

Sample Size Ratio (Vaccinated vs Unvaccinated)	Incidence rate in unvaccinated group (cases/1000 persons)	VE (%) (reduction rate)	Power
1 vs 0.5	2	90	>.999
	2	80	>.999
	2	70	>.999
1 vs 1	2	90	>.999
	2	80	>.999
	2	70	>.999
1 vs 5	2	90	>.999
	2	80	>.999
	2	70	>.999
1 vs 0.5	0.3	90	0.84
	0.3	80	0.69
	0.3	70	0.51
1 vs 1	0.3	90	0.93
	0.3	80	0.81
	0.3	70	0.62
1 vs 5	0.3	90	0.99
	0.3	80	0.97
	0.3	70	0.82

Based on Moderna COVID-19 vaccine implementation plan and anticipated uptake, we expected to accrue 500,000 to 1,000,000 individuals receiving 2 doses of Moderna COVID-19 vaccine for analyses of primary objectives by the end of 2021, which has already been achieved.

ITEM 8:

Page 28-29, Section 9. “We estimate an incidence of 30 COVID-19 diagnoses per 1,000 unvaccinated adult KPSC members during an average 4-month follow-up period.” “For the first interim analysis of Primary Objective 2, we estimate an incidence of 20 COVID- 19 hospitalizations and 0.3 deaths per 1,000 unvaccinated adult KPSC members during an average 4-month follow-up period.”

FDA Comment # 8:

According to Table 2 on Page 15, during 01/01/2020 and 12/31/2020, there were 295,395 patients with COVID-19 diagnosis, 18,938 patients were admitted to hospital with a COVID-19 diagnosis, and 2,754 patients died within 31 days after the first COVID-19 diagnosis. There were more than 4.5 million KPSC members. The estimated incidence of 30 COVID-19 diagnoses, 20 COVID-19 hospitalizations, and 0.3 deaths per 1,000 unvaccinated adult KPSC members during an average 4-month follow-up period did not reflect the incidence rate observed in 2020. The power of the study might be overestimated for hospitalizations and deaths.

Sponsor Response

The incidence of COVID-19 hospitalizations was 2 per 1,000 unvaccinated adults. The incidence of 20 COVID-19 hospitalizations in the protocol was a typo and has been corrected in the most recent protocol amendment. The actual power calculation was based on the correct incidence rate. In KPSC, there are approximately 3.6 million adult members. According to protocol Table 2, there were 279,588 adult patients (≥ 18 years old) with COVID-19 diagnosis, 18,851 adult patients were admitted to hospital with a COVID-19 diagnosis, and 2,753 adult patients died within 31 days after the first COVID-19 diagnosis between March 1, 2020 and December 31, 2020 (total 10 months). Hence, the incidence of COVID-19 diagnosis, hospitalization, and death was 30 ($=279,588/3.6M/10$ months $\times 4$ months), 2 ($=18,851/3.6M/10$ months $\times 4$ months), and 0.3 ($=2,753/3.6M/10$ months $\times 4$ months) per 1000 unvaccinated adult members, respectively.

ITEM 9:

Page 32, Section 12. “However, external COVID-19 vaccination can be captured in the KPSC EHR data by manual entry and electronic updates from the California Immunization Registry (CAIR) (for which KPSC has a proactive mechanism in place for obtaining regular updates from CAIR).”

FDA Comment # 9:

Please provide information about the percentage of COVID-19 vaccination being captured in the EHR data by manual entry and the percentage of COVID-19 vaccination being captured by electronic updates from CAIR. Are all external vaccinations, including those at mass vaccination centers, included in CAIR?

Sponsor Response

By September 17, 2021, there were 2,793,502 Moderna COVID-19 vaccine doses in the KPSC EHR system (including those administered to non-members). Among them, 1,221,060 (44%)

doses were administered outside KP: 746,391 (27%) from CAIR, 304,973 (11%) by entry into the EHR based on valid documentation, and 169,696 (6%) from claims.

COVID-19 providers, including those at mass vaccination centers, must document COVID-19 vaccine administration data daily to CAIR (<https://eziz.org/assets/docs/COVID19/IMM-1329.pdf>).

ITEM 10:

Page 32, Section 12. “Misclassification of COVID-19 outcomes is also possible due to imperfect capture and sensitivity of SARS-CoV-2 molecular diagnostic tests. For patients with COVID-19 symptoms, sensitivity of molecular diagnostic tests is generally high (>90%). Efforts are made to ask patients about positive tests conducted outside of KPSC and to document in the EHR with internal diagnosis codes.”

FDA Comment # 10:

For patients with COVID-19 symptoms, please provide specificity of molecular diagnostic tests. For patients without COVID-19 symptoms, please provide sensitivity and specificity of molecular diagnostic tests. Please provide percentage of individuals conducting tests outside of KPSC.

Sponsor Response

For patients with COVID-19 symptoms, sensitivity of molecular diagnostic tests is generally high (>90%). As of July 2021, the (b) (4) on the Thermo Fisher Scientific Amplitude Solution is used for the majority of SARS-CoV-2 molecular tests. A small proportion of tests are conducted using the Roche cobas® SARS-CoV-2 assay on the Roche cobas® 8800 System or the Roche cobas® SARS-CoV-2 & Influenza A/B assay on the Roche cobas® Liat® System.

As of July 2021, asymptomatic individuals who receive a COVID-19 test at KPSC may include individuals without COVID-19 symptoms who require or request testing. Both vaccinated and unvaccinated individuals are required to be tested for SARS-CoV-2 prior to KPSC procedures or admission. In addition, asymptomatic individuals can request testing (regardless of vaccination status) for any of the following reasons: travel, exposure to or close contact with a COVID-19-positive individual, residents or employees of congregate living facilities, employment (e.g., healthcare workers, first responders, essential workers, or any others who require testing for workplace), school or daycare, or any other reason. In addition, asymptomatic individuals who are physicians or other employees of KPSC can receive voluntary weekly saliva testing. Testing for asymptomatic individuals most commonly uses saliva samples rather than nasal/oropharyngeal

swabs and are tested by PCR. 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.