

RESPONSE TO FDA COMMENTS ON P901 INTERIM REPORT DATED OCTOBER 28, 2021

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

ITEM 1:

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.

Please clarify whether the unvaccinated cohort in the interim report also included individuals 18-64 years who do not fall under the above-described categories. If the answer is yes, then the vaccinated cohort may have higher COVID-19 risk or have higher exposure to SARS-CoV-2 than unvaccinated cohort.

Sponsor Response:

Individuals who met the inclusion/exclusion criteria and received 2 doses of mRNA-1273 vaccine at least 24 days apart during study accrual period (December 18, 2020 to March 31, 2021) were included in the vaccinated group. Individuals who met the inclusion/exclusion criteria and had not received any COVID-19 vaccine dose by the index date were randomly selected and matched to the 2-dose vaccinated individuals. For this first interim analysis (IA), unvaccinated individuals were 1:1 matched to vaccinated individuals by age group (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).

In the study design phase, vaccinated and unvaccinated individuals were matched on the most important risk factors, i.e., age, sex, race/ethnicity, and index date. During the statistical analysis phase, we adjusted for differences in demographic characteristics, health care utilization, comorbidities, and geographic area, including: frailty index, history of COVID-19 diagnosis, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, preventive care, Medicaid, neighborhood median household income, KPSC physician/employee status, medical center area.

By design, we followed 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). We also allowed unvaccinated individuals to become vaccinated at any time during follow-up to reduce confounding by indication.

It is possible that differences in other unmeasured factors, such as occupational risk exposures and behavioral factors (e.g., masking, distancing, handwashing), could result in residual confounding. However, we believe the above design and analytical approaches minimize potential difference in COVID-19 risk between vaccinated and unvaccinated cohorts.

ITEM 2:

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.

Sponsor Response:

We have updated the flow chart during manuscript revision and since the submission of this interim analysis (IA) to CBER. Please see updated Supplementary [Figure 1: Flow chart for 2-dose mRNA-1273 vaccine 1st interim analysis cohort](#) (below).

Of the 435,106 individuals excluded from this first IA, 432,206 individuals received only one dose of mRNA-1273 at the time of the IA, and 2,900 individuals received two doses of mRNA-1273 < 24 days apart. Of the 432,206 individuals who received only one dose of mRNA-1273 at the time of the first IA, 395,145 (91.43%) received a second dose after March 31, 2021. They will be captured as fully vaccinated in IA #2 (due to CBER Dec. 14, 2021) and will be included in analyses if they meet study inclusion criteria.

Updated Supplementary Figure 2. Flow chart for 2-dose mRNA-1273 vaccine 1st interim analysis cohort

