FDA U.S. FOOD & DRUG ADMINISTRATION

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CBER Responses

Our Reference: EUA 27073

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SUBJECT: CBER Responses to sponsor questions for 11.3.21 telecon

PRODUCT: Human Coronavirus, (2019-nCoV; Pre-fusion Spike protein; Lipid Nanoparticles; messenger RNA-1273) Vaccine

PROPOSED INDICATION: mRNA-1273 is a vaccine for active immunization to induce protective immunity against acute respiratory disease associated with the SARS-COV-2 virus.

Sponsor Question # 1:
Given that large data sets show a rate of myocarditis observed in young males following mRNA-1273 that is consistent with rates used to confirm the benefit-harm of mRNA vaccines, the small sample sizes and off-label, mixed dosing regimens in the recent unpublished report from Norway, and the similar to lower rates of myocarditis observed in adolescent males relative to young adult males in the Sponsor's global safety database, the Sponsor would appreciate to understand from CBER how the small samples from these recent reports could significantly impact prior assessments of benefit-risk - based on much larger datasets – that have been shown for mRNA vaccines previously.

CBER Response to Sponsor Question 1:
CBER's benefit-risk assessment is supported by several lines of evidence that suggest an increased risk of myocarditis following Moderna COVID-19 vaccine compared to the Pfizer COVID-19 vaccine. First, an unpublished Nordic study including data from four countries Demark, Finland, Norway and Sweden, consistently showed higher

myocarditis case rates associated with the Moderna COVID-19 Vaccine when compared to the Pfizer BioNTech COVID-19 Vaccine, with a sample size sufficient to distinguish the difference. Based on these analyses, Nordic countries have recommended to avoid the use of Moderna COVID-19 Vaccine for younger age groups. Second, the US Vaccine Safety Data Link (VSD) study presentation at the October 21,2021, ACIP meeting also suggested a higher risk of myocarditis associated with Moderna's COVID-19 Vaccine compared to Pfizer BioNTech COVID-19 Vaccine. Lastly, the US Vaccine Adverse Event Reporting System (VAERS) was consistent with a higher myocarditis risk from Moderna COVID-19 Vaccine. Although the FDA BEST system has not identified a risk difference between Moderna-and Pfizer- COVID-19 Vaccines, CBER cannot dismiss the multiple evidence sources suggesting an increased risk of myocarditis with the Moderna COVID-19 vaccine. Therefore, the proposed studies in question 2 should help to address three key questions to inform ongoing benefit-risk assessments: 1) are the risks of myocarditis higher after the Moderna vaccine compared to the Pfizer; 2) are there any differences in the benefits of the two vaccines; and 3) Is there a difference in the risk of long-term effects of post-vaccination myocarditis for Moderna vs. Pfizer vaccinees?

Sponsor Question 2:
The sponsor notes that some non-US data may describe uses that are outside of the Moderna Covid-19 vaccine EUA Fact Sheet. Specifically, these data may include a heterologous priming dose schedule as well as flexible dosing intervals. These data may lead to results that differ from the current and proposed label. The sponsor would like to provide additional US population data to augment the large US government sponsored systems including BEST, in order to support the Agency's benefit: risk assessment.

Specifically, the sponsor has already initiated the following activities:

- Comparison of incidence rates in the US PASS using HealthVerity data has been completed and the sponsor has sent a proposed protocol annex for execution of Self-Controlled Risk Interval Analyses for both dose 1 and dose 2 and for other doses.

- The next study phase, case confirmation (through medical chart review) and characterization of myocarditis cases is underway

- Using Health Verity data, the sponsor has the capacity to stratify the 12-17 year old population and assess myocarditis rates in the pre-vaccine period attributable to COVID-19. These rates can be calculated among those with medically attended COVID-19 and among the total population. The sponsor has the ability to identify rates of hospitalization and medically attended COVID-19 within the 12-17 age stratum in the pre-vaccine COVID-19 period and in the post-EUA COVID-19 time period. This would anchor estimates of benefit within the same population in which risks are assessed.

Can the agency provide input on what data/analyses the sponsor can provide to support the most well-informed benefit risk decision in the 12–17-year-old group?

CBER Response to Sponsor Question 2:
Reference is made to the post-authorization safety study mRNA-1273-P903 Protocol v3.2 that incorporated FDA's comments on the previous version of mRNA-1273-P903 protocol, communicated to you 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 and are likely sufficient to inform ongoing benefit-risk assessments. However, 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. Detailed comments regarding mRNA-1273-P903 will be communicated to you in a separate Information Request. Please note the benefit-risk assessments will be considered using the totality of the evidence, which, as appropriate, could include both U.S. and non-US data.

Sponsor Question 3:
As suggested by CBER, the Sponsor has considered a lower dosage of 50 µg for the primary immunization series in adolescents.

The Sponsor's opinion is that:
1) The 100 µg primary series has a favorable BR profile in adolescents

2) Safety data from the 100 µg primary series in adolescents can be used to support the safety of the 50 µg series in adolescents

3) Immunogenicity data from 50 µg primary series are available from the younger (6-11 years of age) and older (18+) age groups immediately adjacent to the 12-<18 years age group, allowing for a bracketing approach to infer vaccine efficacy from the available immunogenicity data from studies P301 and P204, as well as efficacy data from P301. Should the development of a 50 µg primary series for adolescents be warranted, does CBER agree with the Sponsor's proposed approach for bracketing (interpolation) using the 50 µg primary series data from 18+ and children <12 years old to adolescents?

CBER Response to Sponsor Question 3:
We do not agree with your assessment that the current risk-benefit analysis would support use of the 100 µg dose in adolescents 12 to <18 years, and we continue to recommend that you pursue development of a 50 µg dose in this age group. We do not consider your proposed approach of extrapolation of the immune responses from the 50 µg primary series data in an older and younger age group, without any available safety and immunogenicity data on the 50 µg dose in adolescents 12 to <18 years, to be sufficient to support a regulatory decision on the use of the 50 µg dose in the adolescent age group. At minimum,

data to support the use of the 50 µg dose in this age group will need to include clinical immunogenicity data with a successful formal immunobridging analysis (see below) and sufficient safety data to characterize the reactogenicity of the 50 µg primary series (i.e., in at least 300 vaccine recipients 12 to <18 years of age).

We recommend that you conduct a placebo-controlled study, which could be designed with a 1:1 or 2:1 randomization scheme of vaccine: placebo, with rapid cross-over of the placebo recipients to receive the active vaccine (i.e., at 28 days post Dose 2) to enhance recruitment and retention, ensuring minimal delays for placebo recipients to have the option to receive vaccination. A placebo-controlled study could potentially be conducted in regions where COVID vaccines are not routinely recommended or available for use in this age group. Safety and immunogenicity data from this study through 28 days post Dose 2, along with the larger safety database and the longer follow-up available from P203 evaluating a higher dose in this age group, may support use of the 50 ug primary series in adolescents. Similar to your ongoing pediatric studies, your new study should assess clinical efficacy as a secondary or exploratory endpoint, and the breadth of neutralizing-antibody responses against circulating variants of concern. We encourage you to include follow up for as long as feasible, to enhance the characterization of safety, immunogenicity and exploratory effectiveness. A more optimal and desirable approach, if feasible, would be to conduct a larger clinical study (~3000 participants, as you had done in P203), with an ultimate follow up period of 1 year, to allow for more robust safety, immunogenicity, and efficacy data of the 50 ug primary series in this adolescent age group.

We agree with your assessment that given the neutralizing antibody GMT observed with the 100 ug dose level in younger adults 18-25 years of age, it may be difficult to achieve the previously recommended immunobridging success criteria for GMT ratio and difference in seroresponse in adolescents who received 50 µg primary series compared to adults 18-25 years of age who received the 100 ug primary series. We acknowledge that in study P301, similarly high clinical efficacy was observed for participants ≥65 years compared to adults 18-64 years, despite overall lower neutralizing antibody titers in the older age cohort. Thus, we agree it would be reasonable for your adolescent and pediatric studies using lower doses to immunobridge to a reference group of adults ≥65 years from P301, instead of to the 18-25 years cohort, provided that adequate measures are taken to mitigate against risk of bias when selecting the samples to generate immunogenicity data for the reference group.

With regards to study P204, as communicated to you previously, the concern that the risk of vaccine-associated myocarditis could be dose related and the need to first evaluate the 50 µg dose level in the next higher age group (12 to <18 years) precludes authorization of the 50 µg dose for use in children 6 to <12 years of age. As you evaluate the 50 µg primary series in adolescents 12 to <18 years of age, we strongly advise that you evaluate a lower dose level (e.g., 25 µg) in the age group of 6 to <12 years, using the same considerations as outlined above for

the study of 50 µg in participants 12 to <18 years. For participants 6 to <12 years in P204 who initially received placebo and are now invited to be unblinded and crossed over to receive active vaccine due to availability of an authorized COVID-19 vaccine, you may consider providing the option to receive the 25 µg dose, instead of 50 µg as currently specified in the protocol.

For the younger age cohorts in study P204 (6 months to <2 years, 2 to <6 years), based on all the considerations outlined above, we recommend you consider changes to your clinical development plan to evaluate a dose level lower than the 25 µg dose as currently planned.