U.S. FOOD & DRUG ADMINISTRATION

Information Request

Our Reference: STN: 125752/1

Information Request #6

Date: September 28, 2021

To: **Michelle Olsen, Ph.D.**
ModernaTX, Inc.
Email: Michelle.Olsen@modernatx.com

From: **Joseph Kulinski, Ph.D.**
DVRPA/OVRR/CBER
Email: Joseph.Kulinski@fda.hhs.gov

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Clincal: efficacy data; CMC: manufacturing processes

Our review of your August 16, 2021 submission (STN 125752/1) is ongoing.

The following are **Priority items** requested for additional clinical information regarding efficacy data. **A response is requested by October 1, 2021**:

1. Please indicate when you expect to submit the remaining shell tables. It would be acceptable to submit them in batches, as you complete them.

2. In your response to IR#2-9.21 (Item 1 of IR sent on Sept 17, 2021), you indicate that neither of the two cases of severe COVID-19 in the mRNA-1273 arm met the definition of severe COVID-19 requiring hospitalization, admission to the ICU, intubation or mechanical ventilation, or death. However, for subject # 3772037, the CIOMS form as well as the narrative we received from you during the EUA review (this was the severe COVID-19 case in the mRNA-1273 arm which had not yet been adjudicated at the time of the primary analysis) stated that this subject was in fact hospitalized for respiratory failure due to COVID-19 (from November 8-12, 2020). Based on the available data, this subject has met the CDC definition for severe COVID-19 based on hospitalization. Please submit a revised analysis of the analysis requested in our IR (VE against severe disease based on CDC definition), counting this subject as a case meeting the CDC severe disease definition in the mRNA-1273 arm.

3. In your primary analysis, there was one case of COVID-19 starting 14 days after Dose 2 as assessed by adjudication committee in the placebo group for the subgroup of participants with positive baseline SARS-CoV-2 status at baseline (Table 14.2.2.7.1.6.10 in EUA submission with data extraction date of Nov 25, 2020). However, in your updated efficacy analysis, there are now 0 cases in the placebo group (Table 14.2.2.7.3.6.10 in BLA submission with data extraction date of May 4, 2021). Please clarify and correct this discrepancy.

4. Please provide the following subgroup analysis for the updated VE analysis, based on the Full Analysis Set (March 26 data cut):

Time period	mRNA-1273 Cases/N (%) Incidence rate per 1,000 person-years	Placebo Cases/N (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (%) (95% CI)
Any time after Dose 1			
Baseline SARS-CoV-2 status: negative			
Baseline SARS-CoV-2 status: positive			
Starting 14 days after Dose 1			
Baseline SARS-CoV-2 status: negative			
Baseline SARS-CoV-2 status: positive			

5. Please provide the following subgroup analysis for the updated VE analysis (March 26 data cut), for COVID-19 cases starting 14 days after Dose 2 as assessed by adjudication committee:

Subgroup	mRNA-1273 Cases/N (%) Incidence rate per 1,000 person-years	Placebo Cases/N (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (%) (95% CI)
Obesity (BMI≥30 kg/m^2) and age			
18-64 years and obese			
18-64 years and not obese			
≥65 years and obese			
≥65 years and not obese			

The following are **Non-Priority items** requested for additional clinical information regarding efficacy data. **A response is requested by October 5, 2021**:

6. For the 13 COVID-19 cases (at the time of March 26 data cut) which ***did meet the protocol COVID-19 definition but which were not assessed*** to meet the primary endpoint case definition by the adjudication committee, please provide a summary for why each case was not considered a primary endpoint case by the adjudication committee.

7. For the 6 COVID-19 cases (at the time of the March 26 data cut) which ***did not meet the protocol COVID-19 definition but which were assessed*** to meet the primary endpoint case definition by the adjudication committee, please provide a summary for why each case did not meet the protocol definition and why the adjudication committee assessed each as meeting the primary endpoint.

The following are **Non-Priority items** requested for additional CMC information regarding your manufacturing process. **A response is requested by October 8, 2021**:

8. In the Master Specification tables provided for non-compendial raw materials used in the manufacture of CX-024414 mRNA Drug Substance (e.g., Tables 18 – 42 in section 3.2.S.2.3 *Control of Materials {CX-024414} Raw Materials*), please confirm that the tests listed in those tables are performed at the ModernaTX and Lonza manufacturing sites prior to raw material use in manufacture. In addition, please confirm that Moderna has release and quality testing in place for the raw materials used for the manufacture of (b) (4), mRNA-1273 LNP DS and mRNA-1273 DP. If Moderna is not performing additional release testing for any raw materials used in the manufacture of the products listed here, please revise the Control of Materials sections for (b) (4) DS and the DP to specify the tests performed by the respective product vendors.

9. The linearized pDNA template was initially manufactured at the (b) (4) facility. This manufacturing step has now been transferred to Aldevron to supply the linearized pDNA template for the manufacture of EUA and commercial vaccine product. In your BLA, release data and a Certificate of Analysis were provided for pDNA batch (b) (4) manufactured at (b) (4). We acknowledge that the quality release criteria are the same at (b) (4) and Aldevron; however, please provide quality data for a representative linear pDNA batch produced at Aldevron.

10. Residual DNA was defined as a Critical Quality Attribute of CX-024414 mRNA in multiple sections of Module 3, and the residual DNA template test by qPCR was performed for release of CX-024414 mRNA during clinical development and validation across the process scales and sites. In addition, results from residual DNA testing were included in all the CoAs provided in section 3.2.S.4.4 *Batch*

Analyses. However, we note in the BLA, that residual DNA was not listed among the CX-024414 specifications (Table 1 in section 3.2.S.4.1 *Specification*) and is no longer considered a Critical Quality Attribute (Table 1, section 3.2.S.4.5 *Justification of specification*). Please provide a justification for this change in your quality assessment of the product and for not performing the test. In addition, if you intend to omit this test, please provide product characterization data and validation data showing consistent removal of DNA below the previously specified limit.

Please confirm your receipt of this request, and provide your responses as an amendment to STN 125752 at your earliest convenience but no later than the dates requested above.

Please contact me if you have questions and include Sudhakar Agnihothram (sudhakar.agnihothram@fda.hhs.gov) and Josephine Resnick (josephine.resnick@fda.hhs.gov) on all communications.