

**RESPONSE TO CBER COMMENTS ON PROPOSED EUA PRE-SUBMISSION PACKAGE
RECEIVED ON NOVEMBER 19, 2020**

The Sponsor acknowledges CBER's comments on the proposed EUA Pre-Submission package.

This document provides the Sponsor's responses to FDA's comments (in **Bold**).

Sponsor Question 2 (from Amendment 63):

Based on the enrollment rates in the Phase 3 study P301, the Sponsor anticipates that the full study cohort of 30,000 subjects may reach a median of 2 months of follow up post-second dose around November 20th, when 15,000 participants have completed Day 85. Once that timeline is met, a safety data snapshot (DS) will be generated. In accordance with the FDA Extended Comments on EUA provided on 05 October 2020, the Sponsor proposes that an appropriate clinical safety data package supporting an initial EUA will include:

- Unblinded safety data for doses 1 & 2 from all cohorts of Phase 1 study (DMID 20-003) from the active vaccination phase provided as TFLs (DMID IND #19635),
- Unblinded safety data for doses 1 & 2 from the Phase 2 study from the active vaccination phase provided as TFLs,
- Unblinded safety data for doses 1 & 2 from the Phase 3 study with ≥ 2 months median follow-up after the 2nd dose (generated at DS) for all enrolled participants, provided as TFLs, and
- Evidence of absence of vaccine-induced enhanced respiratory disease (ERD) based on the analyses described in the DSMB Statistical Analysis Plan.

These data would form the core of the safety package for EUA in the form of tables and listings supporting EUA as outlined in Annex 1 of Attachment 1. Does CBER agree?

FDA Response to Sponsor Question 2:

You propose to include safety data through Day 119 from your Phase 1 study (DMID 20-0003) and through Day 57 from your Phase 2 study (P201). As your Phase 1 study was initiated in March, and your Phase 2 study was initiated in May, please indicate why longer duration safety data will not be available from those studies at the time of your EUA submission.

Sponsor Response:

With regards to the length of duration of safety data available, data cuts were prespecified in the protocols and the data that is being provided is the most recently available data cut. The table

below shows information on when the last participant received their second dose and the dates the data cuts were available. The data that is proposed to be provided in the EUA is the currently available data.

Study	Safety data provided through/ datacut available	First Participant Enrolled	Last Participant Rec'd Dose 2	Next safety data cut available: (Day/Estimated Date)
DMID 20-0003	07Oct2020	16Mar2020	02Jul2020	6 months post Dose 2 Safety 04Feb2021
mRNA-1273-P201	D57 06Nov2020	29May2020	11Aug2020	6-months post Dose 2 Safety 28Feb2021

Sponsor Question 3 (from Amendment 63):

Section III of the FDA Extended Comments on EUA provided 05 October 2020 (Considerations for continuing clinical trials following issuance of an EUA for a COVID-19 vaccine) states that an EUA request should include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated ERD as well as decreased effectiveness as immunity wanes over time) in sufficient numbers of subjects to support vaccine licensure.

The protocol for the P301 trial specifies two years of follow-up after dose 2 of investigational product or placebo. However, as vaccines become available under EUA the sponsor expects that participants may seek vaccination external to the trial, and Moderna has already received feedback from trial participants regarding this intent. At a minimum, the Sponsor would need to enable unblinding of participants who request to be informed of their vaccination status, to prevent a duplicate series of vaccinations. The sponsor's preferred course of action is to proactively reconsent participants and offer unblinding to those study participants that request it. Should mRNA-1273 be authorized, then Moderna proposes that participants who received placebo would be offered mRNA-1273 vaccination and remain in the trial, enabling Moderna to continue to collect the relevant data over the entire two years of follow-up.

This approach will allow the Sponsor to assess COVID-19 incidence rates in the group of subjects originally vaccinated with mRNA-1273 as compared to the group of subjects originally vaccinated with placebo and later vaccinated with mRNA-1273, allowing some indirect comparison of duration of protection. In addition, adverse events among those vaccinated within the trial will be captured, regardless of the treatment group to which the subjects were originally allocated, over the entire clinical trial follow-up period. The Sponsor proposes to complement unblinding and continued open label follow-up with three enhanced pharmacovigilance and

pharmacoepidemiology systems that will be utilized by the Sponsor during the EUA and post-marketing periods (see details in Rationale).

Does CBER agree with the proposal?

FDA Response to Sponsor Question 3:

After an EUA is issued for your product, subjects in ongoing studies should be informed about the availability of the vaccine under the EUA, including relevant conditions for use under EUA and recommendations for vaccine prioritization and distribution issued by CDC. Study subjects may choose to pursue vaccination under an EUA, and we would not object to unblinding subjects who request to know their treatment assignment to inform their decision-making, on a case-by-case basis provided that those subjects are eligible for vaccination based on the conditions of the EUA, prioritization recommendations, and vaccine availability. However, we do not agree with a proposal to unblind all study participants and to offer vaccine to all placebo recipients immediately following issuance of an EUA. The information obtained from continued blinded, placebo-controlled follow-up, even with a smaller placebo group cohort, would be essential to continued assessment of risk-benefit considerations for your vaccine, including but not limited to duration of protection and risk of vaccine induced enhanced disease. We therefore request that you maintain blinded, placebo-controlled follow-up for as long as feasible, but appreciate the difficulties associated with this request. We also recommend that subjects who choose to pursue vaccination with mRNA-1273 under an EUA should continue follow-up for safety and effectiveness outcomes. Please discuss your plans to encourage ongoing study participation after an EUA issuance, including counseling that emphasizes the value each participant adds to the overall study conclusions whether as a vaccine recipient or placebo recipient, and measures other than vaccination that participants can undertake to protect themselves from SARS-CoV-2 infection. Please also discuss your plans to mitigate and account for loss of follow-up of subjects who choose to withdraw from the study to pursue vaccination under an EUA.

Sponsor Response:

The company's proposal was developed in accordance with our understanding of the planned prioritization of subpopulations for vaccination under the EUA. On November 23, 2020, the Advisory Committee on Immunization Practices (ACIP) presented their Phase 1 plans for vaccine distribution under EUA. Phase 1A includes Health Care Workers and Long-term Residential Care Facility Residents, Phase 1B includes essential workers (examples given at the meeting include people working in the education, food and agriculture, utilities, and transportation sectors, along

with police, firefighters, and corrections officers), and Phase 1C includes adults ≥ 65 years of age and adults with high-risk medical conditions. According to timelines for distribution presented by the COVID-19 Work Group, it is possible that the majority of Phase 1A, 1B, and 1C vaccinations are completed by 15 weeks after EUA.

By design, Study mRNA-1273-P301 enrolled subjects at increased risk for COVID-19 disease. The company collected detailed information about the potential risk factors for COVID-19 disease, including occupational information. According to the demography tables from the November 11, 2020 data snapshot, out of 30,350 subjects included in the Safety Set, there are 7,613 (25.1%) Healthcare Workers, 7,030 (23.2%) Essential Workers (in the P301 study, we have considered the following occupations as Essential Workers: Emergency Responders, Manufacturing and Production workers, Warehouse/ Shipping, Transportation/ Delivery, Border Protection and Military, Pastoral, Social, and Public Health Workers, and Educators and Students), 7,520 (24.8%) subjects ≥ 65 years of age, and 5,065 (16.7%) subjects < 65 years of age with other high-risk medical conditions. The Company estimates that at least 48.3% and as much as 89.8% of the study could be vaccinated as part of the EUA distribution.

In addition, our investigators have received a high volume of calls since the outcome of the first interim analysis of efficacy was announced from subjects requesting to know their treatment groups. Healthcare Workers in particular have stated that they have been informed by their employers that they must provide proof of vaccination against COVID-19 once any vaccine becomes available or they will not be able to continue working in the healthcare setting. Without an option to receive vaccine as part of the study, these subjects will be forced to discontinue our study and be vaccinated through their place of employment.

Therefore, the company believes that the plan to unblind subjects and vaccinate placebo recipients with mRNA-1273, and then follow all subjects who consent for continued safety and effectiveness information in an unblinded manner, is the best retention plan to keep subjects in the study and enabling long-term data to accrue. This plan enables the subjects to receive the mRNA-1273, which many of them are clearly already requesting, and also enables high risk groups to receive vaccine while still continuing to contribute their data to the study. The analysis plan can be adapted to 1) follow all subjects for Medically-Attended Adverse Events (MAAEs) and Serious Adverse Events (SAEs), doubling the size of the safety database for which we will perform active follow-up; and 2) following the continued incidence of COVID-19 in the original mRNA-1273 to the original placebo group. The length of time since completion of the vaccination series can be followed and calculated, and differences in attack rates can be used to infer efficacy over time. Subjects could also be re-randomized from both groups to assess the safety and immunogenicity of a booster vaccination at one year after vaccination. Given the high proportion of subjects who

will qualify for vaccination under EUA, this may be the only feasible option to retain sufficient sample size for further evaluation of study objectives.

The company proposes to submit a protocol amendment detailing these revised study plans to CBER for review. After an EUA is potentially authorized, participants will be encouraged to continue in the ongoing study which will include counseling that emphasizes the value each participant adds to the overall study conclusions whether as a vaccine recipient or placebo recipient, and measures other than vaccination that participants can undertake to protect themselves from SARS-CoV-2 infection.

Sponsor Question 4 (from Amendment 63):

An extended Table of Contents of the proposed complete EUA package can be found in Attachment 1. Does CBER have any comments on the proposed contents, beyond the specific points raised in Questions 1-3 above?

Does CBER agree with the proposal?

FDA Response to Sponsor Question 4:

We agree with the overall proposed contents of your EUA package as presented by your Table of Contents. You will also need to submit the following information in your EUA package:

CMC:

Please clarify the timelines and information to be submitted for Scale B PPQ for the (b) (4) mRNA, (b) (4), and mRNA-1273 LNP provided in SN 63 (Nov. 4, 2020 briefing package, pages 14-16) and SN 65 (Nov 6, 2020):

1. Regarding the Scale B (b) (4) in SN 65, please clarify what PPQ data are available or will be available for the (b) (4) scale and provide the submission dates. Please distinguish availability of 1 PPQ lot vs. 2/3 PPQ lots per site and scale and provide a table with the lot numbers of the PPQ lots which were already produced or are being produced.

2. For the final Scale B (b) (4) package in SN 63 to be submitted on November 30:

- Please clarify whether 3 PPQ lots using (b) (4) and 1 PPQ lot using (b) (4) will be submitted and provide the lot numbers.**
- Please describe (b) (4) contents and manufacturing and clarify the DS scale and manufacturing sites where they will be used. Specifically, please clarify if the DNA template (b) (4) produced at Moderna will be used to supply both the Moderna and Lonza DS manufacturing sites. Please include this information in Module 3.**

3. For the Scale B (b) (4) and mRNA-1273 LNP (SN 63 and 65), please clarify what PPQ data are available or will be available for the initial and final scales and provide the submission dates. Please distinguish availability of 1 PPQ lot vs. 2/3 PPQ lots per site and scale and provide a table with the lot numbers of the PPQ lots which were already produced or are being produced.

Sponsor Response:

The following table outlines the information that will be available by November 30, 2020. Applicable lots and manufacturing locations are provided.

Drug Substance Final Scale B	Manufacturing Location	IND 19745 Sequence	Lot Number	(b) (4)
(b) (4)	Moderna TX	SN0066	4007420001* 4007420002*	(b) (4)
	Moderna TX	November 30	4007420003	
	Lonza	November 30	4007420010 * (Lonza Lot 943122)	
(b) (4)	mRNA-1273 LNP	Moderna TX	SN0070	(b) (4)
	mRNA-1273 LNP	Moderna TX	November 30	
	mRNA-1273 LNP	Lonza	November 30	
			5007520001*	
			5007520002	
			5007520016 * (Lonza Lot 94858)	

Lots denoted with a “*” are GMP comparability lots. Comparability assessments for pre-PPQ/GMP batches encompass the same evaluations as PPQ batches. This includes evaluation of all process parameters (PPs) and IPCs including CPPS, and critical IPCs (CIPCs). For pre-PPQ/GMP batches, comparability reports include tables for CPPs, CIPCs, and select IPCs, while all PPs and IPCs are reviewed during batch disposition.

The Sponsor is actively conducting PPQ activities for all process trains at both ModernaTX and Lonza through the month of December. Complete PPQ information for (b) (4) (ModernaTX) and (b) (4) (Lonza) will be submitted in January.

ModernaTX, Inc. is providing the linearized plasmid DNA template for manufacture at both ModernaTX, Inc. and Lonza. Please note that ModernaTX, Inc. has transferred all manufacturing activities for linearized plasmid DNA template to Aldevron (Fargo, ND), as mention in IND 19745 SN0077 (November 24, 2020). Information concerning the manufacture of the linearized plasmid DNA template will be submitted to IND 19745 on December 8, 2020. Please note that lots manufactured with Aldevron linearized plasmid DNA template have not been submitted to IND 19745.

CLINICAL ASSAYS FOR EVALUATION OF STUDY ENDPOINTS:

Regarding the clinical bioassay for assessment of efficacy endpoints, please provide the estimated date for submission of the SOPs and validation reports for the RT-PCR

(b) (4) and the (b) (4)

Sponsor Response:

The SOPs and Validation reports were submitted on 18 Nov 2020, SN0073.