Emergency Use Authorization (EUA) Amendment
for an Unapproved Product
Review Memorandum

Identifying Information

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Established Name/Other Names Used During Development	Moderna COVID-19 Vaccine/mRNA-1273
Dosage Forms/Strengths and Route of Administration	Booster: 0.25 mL suspension for intramuscular injection
Intended Use for EUA	Indication: Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Use: A single booster dose administered at least 6 months after completing a Moderna COVID-19 vaccine primary series
Intended Population	• Individuals 65 years of age and older, • Individuals 18 through 64 years of age at high risk of severe COVID-19, and • Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2.

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Glossary

AE	adverse event
AR	adverse reaction
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls
CNS	central nervous system
COVID-19	coronavirus disease 2019
DVRPA	Division of Vaccines and Related Products Applications
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GLSM	Geometric least squares mean
GM	geometric mean
GMR	geometric mean ratio
GMT	geometric mean titer
HHS	Health and Human Services
ID50	50% inhibitory dose
LL	lower limit
LMP	last menstrual period
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
mRNA	messenger ribonucleic acid
OVRR	Office of Vaccines Research and Review
PVP	Pharmacovigilance Plan
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	Standardized MedDRA Query
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	variant of concern

1. Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to present an extraordinary challenge to global health and, as of October 15, 2021, has caused 239 million cases of COVID-19, including 4.8 million deaths worldwide. In the United States, more than 44 million cases have been reported to the Centers for Disease Control and Prevention (CDC), of which 85% occurred among individuals 18 years and older. Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an Emergency Use Authorization (EUA) for a COVID-19 vaccine after determining that certain statutory requirements are met.

On December 18, 2020, FDA issued an Emergency Use Authorization for the Moderna coronavirus disease 2019 (COVID-19) Vaccine (also known as mRNA-1273), for active immunization to prevent COVID-19 due to SARS-CoV-2 in individuals 18 years of age and older. The vaccine is based on the SARS-CoV-2 spike glycoprotein antigen encoded by modified mRNA and formulated in lipid particles. The authorized regimen is a 2-dose primary vaccination series administered 1 month apart in individuals 18 years of age and older and as a third dose of the primary series in individuals 18 years of age and older with certain immunocompromising conditions. Each 0.5 mL dose in the primary series contains 100 µg mRNA.

On September 3, 2021, Moderna requested an amendment to their EUA to include use of a 50 µg (0.25 mL) booster dose of mRNA-1273 at least 6 months after completion of the primary series in individuals ≥18 years of age. Following the September 22, 2021 emergency use authorization of the Pfizer-BioNTech COVID-19 Vaccine for use as a booster dose, Moderna revised their request to align with the same populations as authorized for the Pfizer-BioNTech COVID-19 Vaccine:

- individuals 65 years of age and older,
- individuals 18 through 64 years of age at high risk of severe COVID-19, and
- individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2.

To support the need for a booster dose, the request referenced real-world effectiveness data that suggest waning of protection against COVID-19 in the setting of the current Delta variant surge among individuals who previously received a primary series.

The EUA amendment includes safety data and immunogenicity data from 171 immunocompetent adults 18 years of age and older in an ongoing Phase 2 study (P201 Part B) who received an open-label 50 µg booster dose of mRNA-1273 administered intramuscularly six months after completion of a 2-dose primary series of 100 µg mRNA-1273 (P201 Part A). Additional safety data were provided for assessment of serious adverse events and other adverse events of interest (e.g., myocarditis, pericarditis, neurologic, neuroinflammatory and thrombotic events*)* among participants in study P201B who received a 50 µg booster dose following a 50 µg mRNA-1273 primary series (a dose that had been investigated for the primary series, but not authorized) (N=173). Efficacy against symptomatic COVID-19 disease was not evaluated for Phase 2 mRNA-1273 booster dose recipients.

Effectiveness of a booster dose of the Moderna COVID-19 Vaccine in adults ≥18 years of age was based on neutralizing antibody titers (ID50) against a pseudovirus expressing the SARS-CoV-2 Spike protein from the USA_WA1/2020 isolate carrying the D614G mutation (D614G

strain). Immunobridging analyses compared the neutralizing antibody titers 1 month following the booster dose (N=149) to the corresponding titers 1 month after completion of the primary series in a random subset of participants 18 years of age and older from the Phase 3 efficacy study (P301; N=1055). Immunobridging analyses included hypothesis testing for:

- Geometric mean titers (GMTs) of SARS-CoV-2 neutralizing antibodies at 1 month after the booster dose vs. those values 1 month after the primary series, using a 1.5-fold immunobridging margin for the lower bound of the 95% confidence interval around the GMT ratio (P201B/P301 adjusted for age group, <64 years and ≥65 years, via an Analysis of Covariance model) and a point estimate of the GMT ratio ≥1.0 as the success criteria.
- Percentage of participants with seroresponse (defined as ≥4-fold rise of neutralizing antibody titers from baseline, where baseline titers <LLOQ are set to LLOQ for the analysis), using a -10% immunobridging margin as the success criterion for the lower bound of the 95% confidence interval around the difference between seroresponse rates (P201B – P301). Baseline for the booster dose was defined as titers immediately prior to booster vaccination; baseline for the primary series was defined as pre-dose 1 titers.

Immunobridging analyses against the D614G strain met the pre-specified GMT ratio success criteria for a booster response. While 87.9% (95% CI 81.6, 92.7) of 100 µg-primed booster dose participants achieved at least a 4-fold rise in neutralizing antibody titers, the difference in seroresponse rates (among 100 µg-primed participants) did not meet the pre-specified immunobridging success criterion. The lower limit of the 95% confidence interval for the difference in seroresponse rate (booster dose – primary series) was <-10% (-16.7%). In post-hoc analyses, participants with lower pre-booster neutralizing antibody titers were more likely to achieve a 4-fold rise in neutralizing antibody titers after booster vaccination compared to participants with higher pre-booster neutralizing antibody titers. Moderna proposes to infer effectiveness of the booster dose against the Delta variant from exploratory descriptive analyses of ID50 titers against this variant evaluated among booster dose recipients from study P201 Part B.

Solicited and unsolicited safety data from study P201 Part B 100 µg-primed booster recipients (N=171) were reviewed and compared to safety data from study P201 Part A participants who completed the 100 µg mRNA-1273 primary series (N=198). Safety following the booster dose was assessed for a median of 5.7 months (range 3.1, 6.4). Reported frequencies and severities of local and systemic solicited adverse reactions following the 50 µg booster dose when given 6 months after the 2-dose 100 µg primary series were assessed by age groups 18 to <65 years (N=129) and ≥65 years (N=38). Among 100 µg-primed booster dose recipients 18 to <65 years of age, rates of axillary swelling or tenderness of the vaccination arm (indicating presence of lymphadenopathy), mostly mild in severity and transient, were higher (24.8%) compared to after the second primary series dose (11.6%). Among 100 µg-primed booster dose recipients ≥65 years of age, rates of myalgia and arthralgia were numerically higher after the booster dose (47.4% and 39.5%, respectively) compared to after the second primary series dose (34.9% and 25.6%, respectively). However, these rates after the booster dose were similar to the frequencies of lymphadenopathy, myalgia and arthralgia following the second dose of the primary series (16.2%, 47.1%, and 35.0% respectively) among the corresponding age groups in the larger P301 efficacy trial (overall N=14,691). There were no other notable differences in the frequency or severity of local and systemic adverse reactions following the booster dose compared to after the second dose of the primary series. Severe solicited adverse reactions occurred in 0% to 7.9% of booster dose recipients. Among unsolicited AEs, headache (2.3%) and fatigue (2.3%) were the most commonly reported. There were no other notable patterns or

numerical imbalances between P201B and P201A for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

On October 14, 2021 a VRBPAC meeting was held to discuss if available data support the safety and effectiveness of Moderna COVID-19 Vaccine for use under EUA as a booster dose (50 mcg mRNA-1273) at least 6 months after completion of a primary series in the populations requested by Moderna, as listed above. VRBPAC members voted 19-0 in favor of this EUA amendment.

Based on the totality of the scientific evidence available at this time to support the conclusion that the Moderna COVID-19 vaccine booster dose may be effective and that the known and potential benefits outweigh the known and potential risks associated with the booster dose, the review team recommends authorization of the Moderna COVID-19 vaccine under EUA for use as a booster dose administered at least 6 months after the primary series in:

- individuals 65 years of age and older,
- individuals 18 through 64 years of age at high risk of severe COVID-19, and
- individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2.

2. SARS-CoV-2 Virus and COVID-19 Disease

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of October 15, 2021, has caused approximately 239 million cases of COVID-19, including 4.8 million deaths worldwide. In the United States, more than 44 million cases have been reported to the Centers for Disease Control and Prevention (CDC), of which 85% have occurred in individuals 18 years of age or older. While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2, and emerging variants (such as the highly transmissible Delta variant that is now predominant in the US) have caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

Following emergency use authorization of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals are major factors in the recent resurgence of COVID-19. While recently reported cases appear to be declining relative to the Delta variant-associated peak globally and in the US, the future course of the pandemic is uncertain.

2.1 Vaccines Licensed for SARS-CoV-2

On August 23, 2021, FDA approved COMIRNATY (COVID-19 vaccine, mRNA) as a 2-dose series for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. COMIRNATY is the only vaccine or medical product that is FDA approved for prevention of COVID-19.

2.2 Authorized Vaccines and Therapies for COVID-19

At the time of this review, FDA had issued EUAs for three COVID-19 vaccines as shown in Table 1 below.

Table 1. Emergency Use Authorized Vaccines to Prevent COVID-19

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
Pfizer	2-dose primary series (3 weeks apart)	Individuals ≥16 years of age	December 11, 2020
		Individuals ≥12 years of age	May 10, 2021
Pfizer	3rd primary series dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021
Pfizer	Booster dose (at least 6 months after completing a primary series of COMIRNATY and/or Pfizer-BioNTech COVID-19 Vaccine)	• Individuals 65 years of age and older • Individuals 18 through 64 years of age and at high risk of severe COVID-19 • Individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19	September 22, 2021
Moderna	2-dose series (4 weeks apart)	2-dose primary series in adults ≥18 years of age	December 18, 2020
Moderna	3rd dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021
Janssen	Single dose	Adults ≥18 years of age	February 27, 2021

Remdesivir is the only product currently approved by the FDA for use in adults and pediatric patients 12 years of age and older for treatment of COVID-19 requiring hospitalization. Prior to its approval, remdesivir was authorized for emergency use in adults and pediatric patients and remains authorized for emergency use in hospitalized pediatric patients who are not included in the indicated population under licensure.

Emergency use authorizations of COVID-19 pharmacological products for post-exposure prophylaxis and/or treatment of COVID-19 are as follows:

Table 2. Emergency Use Authorized Pharmacological Products for Post-exposure Prophylaxis and/or Treatment of COVID-19

Product	Date of EUA	Authorized Use and Population
SARS-CoV-2-targeting Monoclonal Antibodies		
• Bamlanivimab/etesevimab • Sotrovimab • Casirivimab/imdevimab	Reissued September 16, 2021 May 26, 2021 Reissued September 9, 2021	All three products are indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years and older at high risk for progressing to severe COVID-19[a] Casirivimab/imdevimab is also authorized for post-exposure prophylaxis (prevention) for COVID-19 in patients at high risk for progressing to severe COVID-19[b]
Antiviral Drugs		
• Remdesivir	Reissued October 22, 2020 (following FDA approval in adults and some pediatric patients)	Treatment of COVID-19 in hospitalized pediatric patients weighing at least 3.5 kg to <40 kg, or <12 years of age weighing at least 3.5 kg, or ≥12 years and weighing at least 40 kg
Immune Modulators		
• Baricitinib • Actemra	Reissued July 29, 2021 June 24, 2021	Treatment of COVID-19 in hospitalized patients[b] receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
COVID-19 Convalescent Plasma	Reissued March 9, 2021	Treatment of hospitalized patients with COVID-19

a Indicated for adults and pediatric patients 12 years of age and older weighing at least 40 kg
b Indicated for adults and pediatric patients 2 years and older
ECMO extracorporeal membrane oxygenation, EUA emergency use authorization
Source: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs Accessed August 2, 2021.

2.3 Moderna COVID-19 Vaccine

On December 18, 2020, FDA issued an Emergency Use Authorization for the Moderna COVID-19 Vaccine (also known as mRNA-1273), for active immunization to prevent COVID-19 due to SARS-CoV-2 in individuals 18 years of age and older. The vaccine is based on the SARS-CoV-2 spike glycoprotein antigen encoded by modified mRNA and formulated in lipid particles. The authorized regimen is a 2-dose primary vaccination series administered 1 month apart, with each dose containing 100 µg mRNA. Issuance of the EUA was based on a finding of vaccine efficacy (VE) of 94.1% compared to placebo against confirmed COVID-19 at least 14 days after completion of the 2-dose vaccination regimen and a favorable benefit/risk balance based on review of the safety data, in a study (P301) of approximately 30,000 participants with a median follow-up of 2 months after completion of the vaccination regimen.

Moderna COVID-19 Vaccine is provided as a white to off-white suspension for intramuscular injection. Each 0.5 mL dose of Moderna COVID-19 Vaccine contains 100 µg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of

SARS-CoV-2 virus. Each dose of the Moderna COVID-19 Vaccine contains the following ingredients: a total lipid content of 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and 43.5 mg sucrose. Moderna COVID-19 Vaccine does not contain a preservative.

2.3.1 Efficacy of a 2-Dose Primary Series of Moderna COVID-19 Vaccine From Clinical Trials

Efficacy of Moderna COVID-19 Vaccine for the prevention of COVID-19 occurring at least 14 days after the second dose of vaccine was evaluated in an ongoing Phase 3 study (P301) in approximately 30,351 participants (without evidence of SARS-CoV-2 infection prior to vaccination) randomized 1:1 to receive two doses of either mRNA-1273 or placebo, 28 days apart. Participants were enrolled with stratification by age and health risk into one of three groups: 18 to <65 years of age and not at risk of progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. The population for the primary vaccine efficacy analysis that supported authorization of Moderna COVID-19 Vaccine included participants 18 years of age and older who had been enrolled from July 27, 2020, and who were followed for the development of COVID-19 through a data cutoff date of November 21, 2020, with median follow-up of 9 weeks after dose 2 in the blinded, placebo-controlled follow-up period.

The primary efficacy analysis demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ≥65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group, with one severe case in the vaccine group confirmed after this analysis.

2.3.2 Safety of 2-Dose Primary Series of Moderna COVID-19 Vaccine From Clinical Trials

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo in study P301 with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. These safety data were the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other SAEs, and rates and types of solicited and unsolicited AEs, and unsolicited AEs of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ≥65 years of age as compared to younger participants. Among unsolicited AEs of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff,

lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Axillary swelling or tenderness of the vaccination arm (indicating presence of lymphadenopathy) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity AEs across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relationship to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The frequency of SAEs was 1.0% in the mRNA-1273 arm and 1.0% in the placebo arm. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

2.3.3 Post-EUA Surveillance

As of October 2, 2021, more than 150 million doses of the Moderna COVID-19 Vaccine have been administered in the U.S. Post-authorization surveillance has identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[1] Reported breakthrough cases of COVID-19 among vaccine recipients have been uncommon and have not raised a concern about vaccine-enhanced disease.[2]

Post-EUA safety surveillance reports received by FDA and CDC identified increased risks of myocarditis and pericarditis, particularly within 7 days following administration of the second dose of the 2-dose mRNA-1273 primary series. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS (Vaccine Adverse Event Reporting System) have been higher among males under 40 years of age than among females and older males and have been highest in males 18 through 24 years of age (~38 cases per million doses administered as per CDC presentation to the ACIP on August 30, 2021). In analyses with four FDA Biologics Effectiveness and SafeTy (BEST) administrative claims databases, the number of cases per million males 18-25 years of age fully vaccinated with the Moderna COVID-19 vaccine, estimated over a 7 day post-vaccination risk interval, varied from 72.4 (95% CI 23.2-228.1) to 283.7 (95% CI 145.2-573.5). Although some cases of vaccine-associated myocarditis/pericarditis have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes

in affected individuals, or whether the vaccine might be associated with initially subclinical myocarditis (and if it is what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

3. Rationale For COVID-19 Vaccine Booster Doses

Concerns have been raised that declining neutralizing antibody titers or reduced effectiveness against symptomatic disease may herald significant declines in effectiveness against severe disease. The recent emergence of the highly transmissible Delta variant of SARS-CoV-2 resulted in a new wave of COVID-19 cases in many parts of the world and has led to considerations for administration of booster doses to individuals who received primary series of vaccines in an effort to enhance immunity, and thus sustain protection from COVID-19.

The expected benefit of booster vaccination will depend on the impact that booster vaccination has in reducing disease relative to the primary series. If the primary series of Moderna COVID-19 Vaccine is still effective in preventing important COVID-19-related outcomes, then the benefit of booster vaccination is likely to be more limited than if effectiveness following the primary series has waned substantially. Factors supporting authorization of a booster dose should consider the effectiveness of primary vaccination with Moderna COVID-19 Vaccine over time and against circulating variants, the effectiveness (and its duration) of booster vaccination in preventing important COVID-19-related outcomes (including death, hospitalization, and infection with SARS-CoV-2 followed by long COVID-19) in individuals who have already received a primary vaccination series, the dynamics of the pandemic in the United States, and the risks of booster vaccination in the general population or in certain subpopulations.

Some real-world effectiveness studies have suggested declining efficacy of Moderna COVID-19 Vaccine over time against symptomatic infection or against the Delta variant, while others have not. However, overall, data indicate that currently US-licensed or authorized COVID-19 vaccines still afford protection against severe COVID-19 disease and death in the United States. There are many potentially relevant studies, but FDA has not independently reviewed or verified the underlying data or their conclusions.

3.1 EUA Amendment Request for the Moderna COVID-19 Vaccine

On September 3, 2021, Moderna submitted a request to amend this EUA for the purpose of including the use of a 50 µg booster dose of mRNA-1273 given at least 6 months after completion of a 2-dose mRNA-1273 primary series of 100 µg of mRNA-1273 in individuals 12 years and older. Following authorization of a booster dose of the Pfizer-BioNTech COVID-19 vaccine, and because the Moderna COVID-19 vaccine is not authorized at this time for use in adolescents 12 to <18 years of age, Moderna revised the requested authorization for a booster dose to use in individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. The request is accompanied by clinical trial data evaluating the safety and effectiveness of a booster vaccination given at least 6 months after a 2-dose 100 µg mRNA-1273 primary series to P201B participants ≥18 years of age (N=171) with ≥3 months of follow-up after the booster vaccination (median follow-up: 5.7 months; range 3.1 to 6.4 months. Additional safety data were provided for assessment of SAEs and other AEs of interest (e.g., myocarditis, pericarditis, hypersensitivity, neurologic, neuroinflammatory and thrombotic events*)* among participants in study P201B who received a 50 µg booster dose after 2 doses of a 50 µg mRNA-1273 primary series (a dose that had been investigated for the primary series, but not authorized) (N=173). Vaccine effectiveness of a booster dose is being inferred by immunobridging based on a comparison of immunogenicity

endpoints between P201B booster dose recipients and a random subset of P301 primary series recipients after the second primary series dose.

3.2 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[3]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in preventing, diagnosing, or treating such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can authorize unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that the known and potential benefits of a booster dose outweigh the known and potential risks (see Sections 3.3 through 3.5 below).

In the event an EUA is issued for a booster dose of this vaccine, it would be considered unapproved and further investigation (under an Investigational New Drug Application) would continue.

3.3 FDA Guidance for Industry Related to COVID-19 Vaccines

To facilitate the manufacturing, clinical development, and licensure of COVID-19 vaccines, FDA published the guidance for industry entitled Development and Licensure of Vaccines to Prevent COVID-19 (June 2020) describing FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19.[4] This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines. The guidance notes that the efficacy of COVID-19 vaccines should be demonstrated in adequate and well controlled clinical trials that directly evaluate the ability of the vaccine to protect humans from SARS-CoV-2 infection and/or disease. The guidance notes further that safety evaluations including the size of the database required to support licensure should be no different than for other preventive vaccines for infectious diseases. Of note, this guidance does not address immunogenicity studies to infer effectiveness of booster doses for COVID-19 vaccines. However, the guidance for industry document Emergency Use Authorization for Vaccines to Prevent COVID-19 (May 2021, February 2021, originally issued October 2020) describes data needed to support the

effectiveness of a modified COVID-19 vaccine against variants of concern (VOCs).[5] FDA has applied these concepts to effectiveness evaluations of booster doses afforded by the prototype vaccine (refer to Section 3.5 below).

3.4 Regulatory Considerations for a Booster Dose of COVID-19 Vaccines

The benefit of a booster dose must be weighed against potential risk. Available data should support the effectiveness of the booster dose, particularly against currently circulating SARS-CoV-2 variants, and benefit should be considered relative to the benefit provided by completion of the primary series. Safety data should be available to identify the most frequently reported adverse reactions associated with the booster dose. Pre-authorization clinical trials may not be adequately powered to characterize uncommon but potentially serious adverse reactions, such as myocarditis/pericarditis (see Section 2.3.3). It is currently not known if there will be an increased risk of myocarditis/pericarditis or other adverse reactions after a booster dose of the Moderna COVID-19 Vaccine. These risks and associated uncertainties have to be considered when assessing benefit and risk.

3.5 Data to Support an EUA Amendment for a Booster Dose of COVID-19 Vaccines

As noted above, the Guidance for Industry Emergency Use Authorization for Vaccines to Prevent COVID-19 (May 2021) describes data that could support the effectiveness of modified COVID-19 vaccines directed against a variant of concern (VOC). While the current EUA amendment is not for a booster dose targeted to a VOC, the intended use in the current pandemic situation is analogous, and corresponding recommendations have been conveyed to product sponsors seeking discussions on booster dosing with the prototype vaccine, as summarized below.

Safety

Safety assessments, including solicited and local and systemic adverse reactions assessed daily for at least 7 days after each study vaccination as well as serious and other unsolicited AEs assessed during the immunogenicity evaluation period, may be sufficient to support emergency use authorization of a booster dose. Evaluation in a larger safety database than initially planned for immunogenicity analysis may be warranted if safety signals that can be reasonably evaluated in pre-licensure/pre-authorization studies arise during clinical evaluation of the booster dose. Post-licensure/post-authorization studies should be conducted to assess longer-term safety for serious and other medically important adverse events.

Effectiveness

Effectiveness of a booster dose with a COVID-19 vaccine can be evaluated based on the efficacy of the manufacturer's authorized prototype vaccine made by the same manufacturing process and for which a clinical disease endpoint efficacy study has been conducted that met FDA's pre-specified success criteria. A determination of effectiveness of a booster dose should be supported by conducting clinical immunogenicity studies. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of a booster dose of COVID-19 vaccines. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (geometric least squares mean titer and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by a booster dose vs. after completion of the primary series.

Clinical immunobridging studies should be conducted in which the prototype COVID-19 vaccine is administered to persons who previously received the prototype COVID-19 vaccine according to the authorized or licensed dose and dose regimen. The immune response induced by the booster dose should be compared to the immune response induced by the primary series, as assessed by neutralizing antibody seroresponse rates and GMTs against the original virus (reference strain) upon which the prototype vaccine was based. It is expected that the booster would induce an immune response against the reference strain and clinically relevant variants of concern at levels that meet or exceed those elicited by the primary series against the reference strain. The study should be adequately powered for primary immunogenicity analyses to demonstrate statistical immunobridging of seroresponse rate and GMT elicited by the booster dose compared to the primary series using immunobridging margins of -10% for seroresponse rates and 1.5-fold for GMTs, respectively.

Conducting immunobridging analyses and evaluating neutralization against clinically relevant variant viruses will require development of the appropriate neutralization assays specific for the purpose. These assays would need to be sufficiently characterized (e.g., sensitivity, specificity) as part of the qualification/validation process to understand and account for differences in behavior of the different input viruses (e.g., as a result of expressing different spike protein antigens) that could confound the ability to compare measured neutralization titers.

Risk/Benefit Assessment

A favorable benefit-risk assessment to support authorization or approval of a booster dose would depend on evidence (e.g., longer term efficacy data and or data from post-authorization effectiveness studies) that a booster dose is needed and evidence (i.e., immunogenicity data) that the booster dose would be effective not only against the original reference or prototype SARS-CoV-2 strain but also against circulating variants. Furthermore, it is expected that justification for the interval chosen for the booster dose is provided taking into account both safety and effectiveness considerations.

4. FDA Review of Clinical Safety and Effectiveness Data

4.1 Overview of Clinical Studies

This EUA amendment request includes data from an ongoing clinical study, summarized in Table 3 below. Study mRNA-1273-P201B (hereafter referred as P201B or P201 Part B) is the second part of an ongoing Phase 2 study evaluating the safety and immunogenicity of a 50 µg booster dose of mRNA-1273 when administered at least 6 months after completion of a 2-dose mRNA-1273 primary series (50 µg or 100 µg primary series).

The focus of this EUA review is the safety and immunogenicity data following a 50 µg booster dose of mRNA-1273 administered to adults previously immunized with an authorized 2-dose primary series of 100 µg of mRNA-1273 in study mRNA-1273-P201A (hereafter referred as P201A or P201 Part A). P201 Part B participants who received a 50 µg mRNA-1273 booster dose after an unauthorized 2-dose 50 µg mRNA-1273 primary series contributed only to the evaluation of SAEs and AEs of interest (e.g., myocarditis, pericarditis, neurologic, neuroinflammatory and thrombotic events). As described in Sections 2.3.1 and 2.3.2, above, the comparator group for immunogenicity and some of the safety analyses was study P301 participants who received a 2-dose primary series.

Additional supportive safety data were provided from an ongoing Phase 1/2 open-label trial (study 20-0012; NCT04889209) conducted by the Division of Microbiology and Infectious

Diseases (DMID), National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Table 3. Booster Dose Regimens Evaluated During the Open-Label Portion (Part B) of the Phase 2 Safety and Immunogenicity Study P201 (NCT04405076)

2-Dose Primary Series	Booster Dose Test Product	Interval Between Booster Dose and Completion of Primary Series	Participants Vaccinated (N)	Study Status
100 µg mRNA-1273	50 µg mRNA-1273	≥6 months	171	Ongoing
50 µg mRNA-1273	50 µg mRNA-1273	≥6 months	173	Ongoing

Data are available from study P201B through 28 days (study Day 29) post-booster vaccination (June 10, 2021 database lock date); additional data subject to additional cleaning were provided through August 16, 2021.

4.2 Study P201B

4.2.1 Design

In the context of this EUA submission, two parts (A, B) of ongoing Phase 2 study mRNA-1273-P201 pertain to the safety and immunogenicity of mRNA-1273 vaccine administered to adults 18 years of age and older. The study took place at 10 sites in the United States and its territories.

In Part A, the observer-blinded, randomized, placebo-controlled phase of the study, 600 participants were stratified into two age groups (18 to <55 years and ≥55 years) and randomized according to a 1:1:1 ratio to receive two doses of mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo 28 days apart.

Part B, the open-label interventional phase of the study and focus of this review, evaluated the safety and immunogenicity of a single 50 µg booster dose of mRNA-1273. Part A participants who were randomized to receive the 50 µg or 100 µg mRNA-1273 vaccine were offered a single booster dose of mRNA-1273 (50 µg) at least 6 months after planned completion of the primary series. After booster dose administration in Part B (N=344), sera were to be collected on Days 1, 29, and 57 and Month 6-7 to assess SARS-COV-2 neutralizing antibody titers. Neutralizing antibody titers were measured with an ID50 assay using a pseudovirus expressing the SARS-CoV-2 spike protein (USA_WA1/2020 isolate carrying the D614G mutation) [D614G strain]; the pseudovirus neutralizing antibody assay for the D614G strain has been validated. Sera collected from all participants on Days 1 and 29 were also to be analyzed using a pseudovirus neutralizing antibody ID50 assay for measuring antibodies against the SARS-CoV-2 B.1.617.2 variant virus (Delta variant). A pre-planned analysis for the booster dose at Day 29 was conducted (database lock date June 10, 2021).

Vaccine effectiveness was to be inferred from an immunobridging evaluation comparing immune responses (neutralizing antibody titers and seroresponse rates) against the D614G strain and against the B.1.617.2 variant virus 28 days after a single 50 µg booster dose in study P201B to the corresponding immune responses 28 days after the second 100 µg primary series dose (Day 57) in a random subset of participants from the efficacy study P301 (the reference study population in whom vaccine efficacy was demonstrated). Immunobridging analyses evaluated geometric mean of serum neutralizing antibody titers and seroresponse rate. Subgroup analyses were performed to assess immune responses among adults ≥18 years and <65 years of age and adults ≥65 years of age.

Reference study mRNA-1273-P301 is a randomized, observer-blind, placebo-controlled study evaluating the safety, efficacy, and immunogenicity of a 2-dose primary series of 100 µg of mRNA-1273 in over 30,000 participants ≥18 years of age (described in Sections 2.3.1 and 2.3.2, above). In this submission, safety data from all study P301 participants through March 26, 2021 were used as a comparator group for overall safety (solicited reactions and unsolicited AEs among all age groups combined); immunogenicity data from a random subset of P301 participants were used as the reference group for immunobridging analyses to infer vaccine effectiveness of the booster dose. Data from study P301 supported the EUA for the 2-dose primary series of the 100 µg dose of mRNA-1273 (EUA 27073.0, December 18, 2020).

Booster Dose Co-Primary Immunogenicity Endpoints Against the D614G Strain

The co-primary immunogenicity endpoints for D614G strain in study mRNA-1273-P201B, as measured by a pseudovirus neutralizing antibody ID50 assay (Duke University Medical Center assay), were as follows:

Co-primary endpoint 1: Geometric mean of the neutralizing antibody titers against the D614G strain SARS-CoV-2 D614G strain measured 28 days after a single 50 µg booster dose of mRNA-1273 in study P201B versus the corresponding responses measured 28 days after receipt of the second dose of the 100 µg mRNA-1273 2-dose primary series in study P301. The pre-specified immunobridging success criteria required both a lower limit of the 95% confidence interval for the GMT ratio (P201B/P301) ≥0.67 (1.5-fold immunobridging margin) and a GMT ratio point estimate ≥1.0.

Co-primary endpoint 2: Seroresponse rate against the SARS-CoV-2 D614G strain 28 days after a single 50 µg booster dose of mRNA-1273 in study P201B versus the corresponding responses 28 days after the second dose of the 100 µg mRNA-1273 2-dose primary series in study P301. The pre-specified immunobridging criterion required a lower limit of the 95% confidence interval for the difference in seroresponse rates (P201B-P301) ≥-10%. Seroresponse was defined as ≥4-fold rise in neutralizing antibody titers from baseline (pre-booster dose in study P201B and pre-dose 1 in study P301), where baseline titers <LLOQ are set to LLOQ for the analysis.

Immune responses to a single booster dose of 50 µg mRNA-1273 would be considered successfully bridged to that of the 2-dose primary series of 100 µg of mRNA-1273 if each of the immunobridging criteria above were met.

Reviewer Comments:

- *Immunogenicity analyses supporting authorization of the intended 50 µg mRNA-1273 booster dose are based on data from the subgroup of P201B booster dose participants previously immunized with an authorized 2-dose series of 100 µg mRNA-1273.*
- *Given the lack of randomization in study P201B, the statistical analysis plan pre-specified an analysis of covariance (ANCOVA) model for estimating the geometric mean titer (GMT) that adjusts for differences in age groups (<65 years, ≥65 years); the model provides a geometric least squares mean (GLSM) estimate of the geometric mean titer.*

Booster Dose Co-Primary Immunogenicity Endpoints Against the Variant Strain B.1.617.2

The co-primary immunogenicity endpoints for the B.1.617.2 variant in study mRNA-1273-P201B were as follows:

Co-primary endpoint 1: Neutralizing antibody GMTs against the B.1.617.2 variant measured 28 days after a single 50 µg booster dose of mRNA-1273 in study P201B versus the GMTs against the D614G strain measured 28 days after receipt of the second dose of the 100 µg mRNA-1273 2-dose primary series in study P301. The pre-specified immunobridging criteria required both a lower limit of the 95% confidence interval for the GMT ratio (P201B/P301 adjusted for age group, <64 years and ≥65 years, via an analysis of covariance model) ≥0.67 (1.5-fold immunobridging margin) and a GMT ratio point estimate ≥1.0.

Co-primary endpoint 2: Seroresponse rate against the SARS-CoV-2 B.1.617.2 variant induced by a 50 µg booster dose of mRNA-1273 in study P201B versus the responses induced by a 2-dose primary series of 100 µg mRNA-1273 against the D614G strain in study P301. The pre-specified immunobridging criterion required a lower limit of the 95% confidence interval for the difference in seroresponse rates (P201B-P301) ≥-10%. Seroresponse was defined as ≥4-fold rise of neutralizing antibody titers from baseline (pre-booster dose in study P201B and pre-dose 1 in study P301), where baseline titers <LLOQ are set to LLOQ for the analysis.

Immune responses against the D614G strain and variant were based on the Duke assay against the D614G strain and variant, respectively.

> ***Reviewer Comment:*** *Moderna plans to submit Day 1 and Day 29 neutralizing antibody titers against the B.1.617.2 variant virus, as measured with a validated pseudovirus neutralizing antibody ID50 assay, in a future EUA amendment. These data were not yet available at the time of this EUA submission, because the assay for the B.1.617.2 variant virus has not yet been validated. Exploratory descriptive neutralizing antibody titers against the B.1.617.2 variant using a non-validated pseudovirus neutralizing antibody ID50 assay, which were submitted on September 20, 2021 (EUA 27073.261) and October 7, 2021 (EUA 27073.272) as supportive data, are included in this memo.*

Evaluation of Safety

The primary safety objective in study P201B was to describe the safety of a single 50 µg booster dose of mRNA-1273. Participants recorded local reactions, systemic events, and antipyretic/pain medication usage during the 7 days after booster vaccination. Unsolicited adverse events (AEs) were collected through 28 days after the booster vaccination. Medically attended AEs (MAAEs) and serious AEs (SAEs) are being collected through 6 months after booster vaccination. Additional safety parameters include vital sign measurement, physical examination findings, and assessments for SARS-CoV-2 infection from Day 1 through study completion.

The table below shows the Phase 2 safety analyses populations that were used to determine the proportions of study participants who experienced AEs, including solicited adverse reactions after each dose, unsolicited AEs, medically attended adverse events, and SAEs.

Table 4. Safety Analysis Populations

Population	Description
Solicited Safety Set[a]	All participants who are randomized in Part A, received any study injection in Part B, and contribute any solicited adverse reaction data in Part B.
Safety Set[a]	All participants who are randomized and who receive any study injection.

a. Participants will be included in the treatment group corresponding to the study injection they actually received.

Immunogenicity Analysis

Neutralizing antibodies against the D614G strain were measured on all P201B participant serum samples collected on study Days 1 and 29 using a validated pseudovirus neutralization assay. Validation for the neutralization antibody assay for the B.1.617.2 (Delta) variant is ongoing.

For the purposes of immunogenicity analysis, the following populations were defined:

Table 5. Immunogenicity Analysis Populations

Population	Description
Full Analysis Set[a]	All randomized participants who received any study injection, have baseline data available for those analyses that require baseline data, and have at least 1 post-injection assessment for the analysis endpoint.
Per-Protocol Set[a]	All participants in the FAS who complied with the injection schedule, complied with timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective, did not have SARS-CoV-2 infection (positive RT-PCR result or positive Elecsys result) at baseline, and had no major protocol deviation that impacted immune response during the period corresponding to the immunogenicity analysis objective.

a. Participants will be included in the treatment group to which they were randomly assigned.

The per-protocol population served as the primary population for the analysis of immunogenicity data.

4.2.2 Participant Disposition and Inclusion in Analysis Populations

The safety and immunogenicity populations analyzed in studies P201A, P201B, and P301 are presented below in Table 6.

A total of 149 participants from the open-label phase of study P201B and 1,055 participants from a random sub-cohort of study P301 were included in the per-protocol immunogenicity subset for the primary immunogenicity analyses. Reasons for exclusion from the P201B per-protocol population included a major protocol violation involving incorrect dosing at the booster dose visit (receipt of a 100 µg booster dose instead of a 50 µg booster dose) and SARS-CoV-2 infection at baseline (which was an exclusion criterion for participation in study P301); reasons for exclusion from the P301 per protocol population included HIV infection (an exclusion criterion for participation in study P201) and error in the administration of the second primary series dose (not applicable to study P201B). Of note, one 100 µg-primed booster dose participant who did not receive dose 2 of the primary series was included in the per protocol population; participants were not required to receive both primary series doses to be included in the booster dose per protocol set. This participant received dose 1 on June 4, 2020 and a 50 µg dose on February 19, 2021 (~8 months after dose 1).

Table 6. Immunogenicity Analysis Populations, Participants ≥18 Years of Age, Studies P301 (Primary Series) and P201 Part B (Booster Dose, Open-Label Phase)

Population	Study P301 100 µg Primary Series N[a]=15,184 n (%)	Study P201B 50 µg Booster After 100 µg Primary Series N[b]=171 n (%)
Full Analysis Set (FAS)[c]	NA	156 (91.2)
Subjects excluded from FAS	NA	15 (8.8)
Reason for exclusion from FAS		
No baseline immunogenicity data	NA	12 (7.0)
No post-baseline immunogenicity data	NA	3 (1.8)
Subjects Selected for Random Subcohort (Baseline SARS-CoV-2 Negative)	1,080	NA
Per-Protocol Set (PPS)[d]	1,055 (97.7)	149 (95.5)
Subjects excluded from PPS	25 (2.3)	7 (4.5)
Reason for exclusion from PPS		
SARS-CoV-2 infection at baseline	0 (0.0)	6 (3.8)
Had other major protocol deviation	1 (<0.1)	1 (0.6)[e]
Human Immunodeficiency Virus Infection	18 (1.7)	0 (0.0)
Received dose 2 out of window for PPS	5 (0.5)	NA
Did not receive dose 2 per schedule	1 (<0.1)	NA

The FAS is not applicable to Study P301. A subset of P301 subjects were selected for immunogenicity sample testing.
a. N=number of subjects that received any dose of mRNA-1273 in P301 are included.
b. N=number of subjects vaccinated. Only subjects who received the booster injection in Part B of study P201 are included and summarized under the vaccination groups which they actually received in Part A.
c. All subjects who received any booster injection in Part B and had immunogenicity data available at both baseline (Part B Day 1) and at least 1 post-booster visit.
d. All subjects in the Full Analysis Set who did not have SARS-CoV-2 infection (positive reverse transcription polymerase chain reaction [RT-PCR] result or positive Elecsys result) at baseline (Part B Day 1), did not have a major protocol deviation that impacted immune response, had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for booster injection and Day 57 for Study P301). Denominator is the number of subjects in Full Analysis Set for P201 Part B and the number of subjects in the Random Subcohort with a negative baseline SARS-CoV-2 status in P301.
e. One participant was incorrectly dosed at the booster dose visit (a 100 µg mRNA-1273 booster dose was administered instead of a 50 µg mRNA booster dose). One participant in this same group received only the first primary series dose and missed the Day 29 primary series dose; this participant was included in the per-protocol population for the booster dose analysis.
Source: EUA 27073.263 Module 1.11.3 and 27073.250, Module 5, Reasons for Exclusion from Per-Protocol Set, Tables 14.1.2.4.1 and 14.1.2.5.3.

The disposition of P201A and P301 participants who received a 2-dose primary series of mRNA-1273 is presented below in Table 7 (safety population), and the disposition of P201B participants who received a mRNA-1273 booster dose is presented in Table 8 (safety population). There were no notable differences between the disposition of participants in studies P201A and P301 or between the disposition of participants in each study group within P201B.

Table 7. Disposition of Participants ≥18 Years of Age in Study P201 Part A (by Primary Series Dose) and Study P301, Safety Populations

Disposition	Study P201A 50 µg Primary Series N=200 n (%)	Study P201A 100 µg Primary Series N=200 n (%)	Study P301 100 µg Primary Series N=15209 n (%)
Number of subjects randomized	200 (100)	200 (100)	15209 (100)
Received first injection	200 (100)	200 (100)	15180 (99.8)
Received second injection	195 (97.5)	198 (99.0)	14727 (96.8)
Discontinued study vaccine	5 (2.5)	2 (1.0)	453 (3.0)
Reason for study vaccine discontinuation (in Part A for Study P201 and/or P301)			
P201 AE (COVID-19 infection)	1 (0.5)	0 (0.0)	NA
P201 AE (other)	1 (0.5)	1 (0.5)	NA
P301 AE	NA	NA	47 (0.3)
P301 SAE	NA	NA	12 (<0.1)
Death	0 (0.0)	0 (0.0)	2 (<0.1)
Lost to follow up	2 (1.0)	0 (0.0)	76 (0.5)
Physician decision	0 (0.0)	0 (0.0)	21 (0.1)
Pregnancy	0 (0.0)	0 (0.0)	3 (<0.1)
Protocol deviation	0 (0.0)	0 (0.0)	37 (0.2)
P201 withdrawal of consent (COVID-19 non-infection related)	1 (0.5)	0 (0.0)	NA
P301 withdrawal of consent	NA	NA	78 (0.5)
P301 due to SARS-CoV-2	NA	NA	81 (0.5)
Other	0	1 (0.5)	94 (0.6)
Discontinued participation in study	12 (6.0)	15 (7.5)	440 (2.9)
Reason for discontinuation of study participation			
P301 adverse AE	NA	NA	4 (<0.1)
P301 SAE	NA	NA	5 (<0.1)
Death	0 (0.0)	0 (0.0)	16 (0.1)
Lost to follow-up	6 (3.0)	6 (3.0)	160 (1.1)
Physician decision	1 (0.5)	2 (1.0)	13 (<0.1)
Protocol deviation	3 (1.5)	3 (1.5)	46 (0.3)
P201 withdrawal of consent (COVID-19 non-infection related)	1 (0.5)	0 (0.0)	NA
P201 withdrawal of consent (other)	1 (0.5)	4 (2.0)	NA
P301 withdrawal of consent	NA	NA	155 (1.0)
Other	0 (0.0)	0 (0.0)	41 (0.3)
Completed Part A	188 (94.0)	185 (92.5)	NA

Abbreviations: AE= Adverse event; SAE=Serious adverse event; COVID-19 = coronavirus disease 2019; NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Percentages are based on the number of safety subjects in Part A. Only subjects who received mRNA-1273 in Part A are included and are summarized under the vaccination groups which they actually received in Part A.
Safety Set in Part A included all randomized participants who received any mRNA-1273 primary series during Part A.
Source: EUA 27073.263 Module 1.11.3 27073.250. Module 2, Clinical Overview, Table 3; P301 CSR Table 14.1.1.1.1.2.2.

Table 8. Disposition of Participants ≥18 Years of Age in Study P201 Part B (by Primary Series Dose), Safety Populations

Disposition	Study P201B 50 µg Booster After 50 µg Primary Series N=200 n (%)	Study P201B 50 µg Booster After 100 µg Primary Series N=200 n (%)	Total N=400 n (%)
Completed Study P201 Part A	188 (94.0)	185 (92.5)	373 (93.3)
Consented to Study P201 Part B	188 (94.0)	185 (92.5)	373 (93.3)
Received Booster Injection[a]	173 (86.5)	171 (85.5)	344 (86.0)
Discontinued from Study in Part B	9 (4.5)	6 (3.0)	15 (3.8)
Reason for Discontinuation of Study in Part B			
Lost to follow up	3 (1.5)	2 (1.0)	5 (1.3)
Withdrawal of Consent (Other)	5 (2.5)	3 (1.5)	8 (2.0)
Other	1 (0.5)	1 (0.5)	2 (0.5)
Completed Study P201 Part B[b]	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on the number of safety subjects in Part A. Only subjects who received mRNA-1273 in Part A are included and are summarized under the vaccination groups which they actually received in Part A.
a. Includes one participant in the 100 µg-primed group that only received the 1st primary series dose and one participant in the 100 µg-primed group who received a third 100 µg dose instead of a 50 µg booster.
b. Study completion defined as a subject who completed 6 months of follow-up after the last injection received in Part B (Open-Label Phase).
Source: EUA 27073.250. Module 2, Clinical Overview, Table 3.

4.2.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics of the safety population for studies P201 (Parts A and B) and P301 and the per-protocol immunogenicity subsets for P201B and P301 are shown in Tables 9 and 10, respectively. Compared to study P301, participants in study P201A and P201B were less racially and ethnically diverse. Study P201A and P201B participants also had a lower median BMI, a lower rate of obesity (BMI ≥30 kg/m^2), and a lower percentage of males compared to study P301 participants. Studies P201A, P201B and P301 had a similar median participant age and a similar proportion of participants ≥65 years of age**.** The noted differences in demographic characteristics between study P201B and P301 participants are considered unlikely to impact the clinical results from the safety and primary immunobridging analyses. The subgroup analyses of mRNA-1273 vaccine's safety and efficacy by sex, race, and ethnicity in study P301 supported consistency in vaccine efficacy estimates across subgroups (see Moderna COVID-19 Vaccine Review Memorandum, EUA 27073).

In study P201, individuals with a history of chronic cardiovascular disease, chronic pulmonary disease, positive serology for human immunodeficiency virus (type 1 or 2), diabetes, and history of hypertension were excluded from participating in study P201 parts A and B. In study P301 however, 22.1% of participants in the safety set were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection).

Reviewer Comments:

- *The noted differences in demographic characteristics between the participants in study P201B and study P301 are considered unlikely to impact the conclusions from the primary immunobridging analyses. The subgroup analyses of mRNA-1273 vaccine's efficacy by sex, race, and ethnicity in study P301 supported*

consistency in vaccine efficacy estimates in these subgroups (see Moderna COVID-19 Vaccine EUA Review Memorandum, EUA 27073).

- *The noted differences in pre-existing medical conditions between study P201 and study P301 populations are considered unlikely to impact the conclusions of the primary analyses. Based on P301 subgroup efficacy analyses conducted under the original Moderna COVID-19 Vaccine EUA, there were no clear differences in vaccine efficacy estimates between P301 participants with a pre-existing condition (i.e., chronic lung disease, significant cardiac disease, severe obesity (BMI ≥40 kg/m^2), diabetes, liver disease and HIV infection) and the overall P301 per protocol population.*

Table 9. Demographic and Baseline Characteristics, Study P201 Part B (Booster; by Primary Series Dose) and Comparator Groups (Primary Series Only), Safety Population

Characteristic	Study P301 100 µg Primary Series N=15,184	Study P201A Primary Series[a] Total N=200	Study P201B 50 µg Booster After 50 µg Primary Series N=173	Study P201B 50 µg Booster After 100 µg Primary Series N=171
Age[b] (Years)				
Median (Min, Max)	53.0 (18, 95)	54.5 (18, 87)	56.0 (18, 87)	55.0 (18, 87)
Age Group, n (%)				
≥18 and <65 years old	11415 (75.2)	157 (78.5)	127 (73.4)	133 (77.8)
≥65 years old	3769 (24.8)	43 (21.5)	46 (26.6)	38 (22.2)
Sex, n (%)				
Female	7266 (47.9)	124 (62.0)	124 (71.7)	104 (60.8)
Male	7918 (52.1)	76 (38.0)	49 (28.3)	67 (39.2)
Race, n (%)				
White	12034 (79.3)	188 (94.0)	164 (94.8)	164 (95.9)
Black or African American	1567 (10.3)	8 (4.0)	3 (1.7)	5 (2.9)
Asian	656 (4.3)	2 (1.0)	2 (1.2)	1 (0.6)
American Indian or Alaska Native	113 (0.7)	1 (0.5)	1 (0.6)	1 (0.6)
Native Hawaiian or Other Pacific Islander	36 (0.2)	0	1 (0.6)	0
Multiple	320 (2.1)	0	1 (0.6)	0
Other	299 (2.0)	1 (0.5)	1 (0.6)	0
Not Reported	97 (0.6)	0	0	0
Unknown	62 (0.4)	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	3122 (20.6)	16 (8.0)	10 (5.8)	10 (5.8)
Not Hispanic or Latino	11920 (78.5)	184 (92.0)	162 (93.6)	161 (94.2)
Not Reported	105 (0.7)	0	1 (0.6)	0
Unknown	37 (0.2)	0	0	0
Body Mass Index (kg/m^2)				
Median	28.13	25.24	26.12	25.59

Characteristic	Study P301 100 µg Primary Series N=15,184	Study P201A Primary Series[a] Total N=200	Study P201B 50 µg Booster After 50 µg Primary Series N=173	Study P201B 50 µg Booster After 100 µg Primary Series N=171
Positive Baseline SARS-CoV-2 Status[c]	347 (2.3)	0	4 (2.3)	6 (3.5)
Comorbidities				
Obesity (≥30.0 kg/m^2)	5820 (38.3)	1 (0.5)[d]	17 (9.8)	17 (9.8)

a. Combined total of 50 µg mRNA-1273 primary series participants and 100 µg mRNA-1273 primary series participants.
b. For Study P201, age is defined at the time of screening for P201 Part A.
c. Participants who had immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 in Study P201 Part B or Day 1 in Study P301.
d. The difference in rates of obesity in study P201A vs P201B are explained by 14 subjects whose BMI changed from <30 kg/m^2 (i.e., 27.5 - 29.9) to ≥30 kg/m^2 (i.e., 30.1 - 32.3) during the time period between Part A and Part B of Study P201 and 2 subjects who appear to have an implausible weight or height recorded at P201B, leading to a BMI above 30 kg/m^2, but this could not be verified.
Source: EUA 27073.263 Module 1.11.3. EUA 27073.270 Module 1.11.3. EUA 27073.250/251. Module 2, Clinical overview, Table 5; Table 14.1.3.1 (P201A); Table 14.1.3.2.3 (P301A). BLA 125752. P301 CSR, Table 14.1.3.2.1 (p616) and Table 14.1.3.4.2 (p 733).

Table 10. Demographic and Baseline Characteristics, mRNA-1273 Booster Dose Recipients in Study P201 Part B (by Primary Series Dose) and Study P301 Comparator Group (Primary Series Only), Per-Protocol Immunogenicity Subset

Characteristic	Study P301 100 µg Primary Series N=1055	Study P201B 50 µg Booster After 50 µg Primary Series N=146	Study P201B 50 µg Booster After 100 µg Primary Series N=149
Age (Years)			
n	1055	146	149
Mean (SD)	54.51 (15.329)	52.85 (15.334)	52.69 (15.058)
Median	57	57.00	56.00
Min, Max	18.0, 87.0	19.0, 87.0	18.0, 82.0
Age Group			
≥18 and <65 years old	700 (66.4)	107 (73.3)	112 (75.2)
≥65 years old	355 (33.6)	39 (26.7)	37 (24.8)
Sex, n (%)			
Male	560 (53.1)	44 (30.1)	59 (39.6)
Female	495 (46.9)	102 (69.9)	90 (60.4)
Race, n (%)			
White	767 (72.7)	139 (95.2)	142 (95.3)
Black or African American	188 (17.8)	2 (1.4)	5 (3.4)
Asian	26 (2.5)	2 (1.4)	1 (0.7)
American Indian or Alaska Native	17 (1.6)	1 (0.7)	1 (0.7)
Native Hawaiian or Other Pacific Islander	5 (0.5)	1 (0.7)	0
Multiple	15 (1.4)	1 (0.7)	0
Other	27 (2.6)	0	0
Not Reported	5 (0.5)	0	0
Unknown	5 (0.5)	0	0
Ethnicity, n (%)			
Hispanic or Latino	334 (31.7)	10 (6.8)	10 (6.7)
Not Hispanic or Latino	717 (68.0)	135 (92.5)	139 (93.3)
Not Reported	2 (0.2)	1 (0.7)	0
Unknown	2 (0.2)	0	0

Characteristic	Study P301 100 µg Primary Series N=1055	Study P201B 50 µg Booster After 50 µg Primary Series N=146	Study P201B 50 µg Booster After 100 µg Primary Series N=149
Body Mass Index (kg/m^2)			
n	1050	143	147
Mean (SD)	30.96 (7.758)	25.84 (3.253)	25.47 (3.168)
Median	29.62	26.17	25.74
Min, Max	14.0, 79.2	18.3, 34.9	18.0, 32.7
Comorbidities			
Obesity (≥30.0 kg/m^2)	500 (47.2)	16 (11)	14 (9.4)

Percentages are based on the number of Per-Protocol Immunogenicity Subset subjects.
For Study P201, age is defined at the time of screening for P201 Part A.
Source: : EUA 27073.263 Module 1.11.3. EUA 27073.250/251. Module 2. Clinical Overview, Table 6 and Module 5.3.5.1 P301 PDF document t1401030501, Table 14.1.3.5.1 .

4.2.4 Timing of mRNA-1273 Booster Administration and Duration of Safety Follow-Up

The median interval between completion of the 100 µg mRNA-1273 primary series and the booster dose was 7.2 months (range: 5.8 to 8.5 months). Following the booster dose (N=171), the median duration of safety follow-up after the booster dose was 5.7 months (range: 3.1 to 6.4 months).

4.2.5 Vaccine Effectiveness

Primary Immunogenicity

Vaccine effectiveness of the 50 µg mRNA-1273 booster dose when given at least 6 months after a 2-dose primary series of 100 µg mRNA-1273 to adults ≥18 years of age in study P201B is being inferred based on immunobridging comparisons of the immune response induced by the booster dose in P201B to the immune response induced by a 2-dose primary series of 100 µg mRNA-1273 in P301, as assessed by neutralizing antibody GMTs and seroresponse rates (co-primary study endpoints).

SARS-CoV-2 Neutralizing Geometric Mean Titers to the D614G Strain

SARS-CoV-2 neutralizing GMTs measured 28 days after the booster dose in study P201B and 28 days after completion of the 2-dose primary series in study P301 are displayed in Table 11, below. The GMT ratio (P201B/P301, adjusted for age group) was 1.8 (95% CI 1.5, 1.9), which met the pre-specified success criteria of a lower limit (LL) of the 95% CI ≥0.67 and a point estimate of ≥1.0.

Table 11. SARS-CoV-2 Neutralizing GMTs (ID50)[a] at 28 Days After a 50 µg mRNA-1273 Booster Dose in Study P201B Versus 28 Days After the mRNA-1273 Primary Series in Study P301, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set

Study P301 100 µg Primary Series[b] GMT[c] (95% CI) N[d]=1053	Study P201B 50 µg Booster After 100 µg Primary Series[b] GMT[c] (95% CI) N[d]=149	GMT Ratio (P201B/P301)	Met Immunobridging Success Criteria (Yes/No)
1027 (968, 1089)	1802 (1548, 2099)	1.8 (1.5, 2.1)	LL of 95% CI ≥0.67 Criterion: Yes Point Estimate ≥1.0 Criterion: Yes

a. Pseudovirus neutralization antibody ID50 assay; neutralizing GMT against a pseudovirus expressing the SARS-Cov-V-2 spike protein (USA_WA1/2020 isolate carrying the D614G mutation).

b. Day 57 is 28 days after completion of the 2-dose primary series in study P301. Day 29 is 28 days after the booster dose in study P201B.
c. Given the lack of randomization in study P201B, the statistical analysis plan pre-specified an analysis of covariance (ANCOVA) model for estimating the geometric mean titer (GMT) that adjusts for differences in age groups (<65 years, ≥65 years); the model provides a geometric least squares mean (GLSM) estimate of the geometric mean titer.
d. Number of subjects with non-missing data at the corresponding timepoint.
Note: Antibody values < the lower limit of quantitation (LLOQ) are replaced by 0.5 × LLOQ. Values > the upper limit of quantitation (ULOQ) are replaced by the ULOQ if actual values are not available.
Source: EUA 27073.250. Module 2.5 Clinical Overview, Table 10 and Module 5.3.5.1 P201B Booster Immunogenicity Tables, Table 5.1, page 39.

Seroresponse Rates to the D614G Strain

Seroresponse rates are displayed in Table 12 below. The difference in the seroresponse rates between the 50 µg booster dose recipients in study P201B and the 100 µg primary series recipients in study P301 (P201B minus P301) was -10.5% (95% CI -16.7, -6.1), which was outside the pre-specified immunobridging success criterion of the LL of the 95% CI for the difference ≥-10%.

In post-hoc analyses, participants with lower pre-booster neutralizing antibody titers were more likely to achieve a ≥4-fold rise in neutralizing antibody titers after booster vaccination compared to participants with higher pre-booster neutralizing antibody titers. Study P201B participants who met the ≥4-fold increase in titer post-booster dose had a baseline GMT of 109 (range of individual titers 9, 4393); whereas P201B participants who did not meet the ≥4-fold increase in titers post-booster had a baseline GMT of 492 (range of individual titers 162, 2239). Seroresponse rates and baseline GMTs by age groups are consistent with this as shown in Table 14 below. P201B participants 18 to <65 years of age had higher baseline GMTs compared to participants ≥65 years of age, and this age group achieved a lower seroresponse rate compared to the ≥65 year age group (Tables 14 and 16).

Table 12. Seroresponse Rates[a,b] at 28 Days After a 50 µg mRNA-1273 Booster Dose (Day 29) in Study P201B Versus 28 Days After the mRNA-1273 Primary Series (Day 57) in Study P301, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set

Study P301 100 µg Primary Series[c] Seroresponse n (%) (95% CI)[d] N[e]=1050	Study P201B 50 µg Booster After 100 µg Primary Series[c] Seroresponse n (%) (95% CI)[d] N[e]=149	Difference in Seroresponse Rate (P201B-P301) % (95% CI)[f]	Met Immunobridging Success Criterion (Yes/No)
1033 (98.4) (97.4, 99.1)	131 (87.9) (81.6, 92.7)	-10.5 (-16.7, -6.1)	LL of 95% CI ≥-10% Criterion: No

a. Pseudovirus neutralization antibody ID50 assay; SRR against a pseudovirus expressing the SARS-Cov-V-2 spike protein (USA_WA1/2020 isolate carrying the D614G mutation).
b. Seroresponse defined as ≥4-fold rise of pseudovirus neutralizing antibody titers from baseline (pre-booster dose in study P201B and pre-dose 1 in study P301), where baseline titers < LLOQ are set to LLOQ for the analysis.
c. Day 57 is 28 days after completion of the 2-dose primary series in study P301. Day 29 is 28 days after the booster dose in study P201B.
d. 95% CI is calculated using the Clopper-Pearson method.
e. Number of subjects with non-missing data at both baseline and the post-baseline timepoint of interest.
f. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
Source: EUA 27073.250. Module 5.3.5.1 P201B Booster Immunogenicity Tables, Table 6.1, page 47.

Reviewer Comment: *Seroresponse rates were not adjusted for differences in age. Because seroresponse rates were similar across age groups (18-64 and ⩾65 years), the lack of adjustment for age is not likely to have an impact on study conclusions.*

Reviewer Comment: *In a sensitivity analysis of the co-primary endpoints, participants with known Day 15 immune responses were excluded from the Day 29*

primary analysis. The results of this sensitivity analysis were consistent with the results from the primary analyses presented above [Data not shown, Table 2.1.1 (p17) and Table 4.1.2 (p31) in mRNA-1273-P201 Booster Immunogenicity Tables submitted to Module 5.3.5.1 in EUA 27073.250]. Similarly, the sensitivity analysis of the co-primary endpoints within the 100 µg primed booster dose group were consistent with the original analysis [Data not shown, Table 5.1.1 (p41) and Table 6.1.1 (p49) in mRNA-1273-P201 Booster Immunogenicity Tables submitted to Module 5.3.5.1 in EUA 27073.250].

Reviewer Comment: *The CBER statistician performed a sensitivity analysis of the co-primary endpoints excluding the one 100 µg-primed booster dose participant who did not receive dose 2 of the primary series. Results from this sensitivity analysis were consistent with the primary analysis and did not change study results. Exclusion of this participant, resulted in an increase in the GLSM ratio from 1.76 (95% CI 1.50, 2.06) to 1.77 (95% CI 1.51, 2.08) and a decrease in the difference in seroresponse rate from -10.5% (95% CI -16.7, -6.1) to -10.5% (95% CI -16.8%, -6.1%).*

Post-hoc analyses of rates of neutralizing antibody seroresponse to the D614G strain Moderna conducted an additional post-hoc analysis of seroresponse rates using baseline neutralizing antibody titers prior to dose 1 of the primary series. As shown in Table 13 below, the booster dose seoresponse rate, with seroresponse defined as at least a 4-fold rise relative to the *pre-dose 1* titer, was 100.0%. The difference in seroresponse rates in this post hoc analysis was 1.6% (95% CI -0.9, 2.6).

Table 13. Post hoc Analysis of Seroresponse Rates[a,b] at 28 Days After a 50 µg mRNA-1273 Booster Dose (Day 29) in Study P201B Versus 28 Days After the mRNA-1273 Primary Series (Day 57) in Study P301, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set

Study P301 100 µg Primary Series[c] Seroresponse n (%) (95% CI)[d] N[e]=1050	Study P201B 50 µg Booster After 100 µg Primary Series[c] Seroresponse n (%) (95% CI)[d] N[e]=148	Difference in Seroresponse Rate (P201B-P301) % (95% CI)[f]
1033 (98.4) (97.4, 99.1)	148 (100) (97.5, 100)	1.6 (-0.9, 2.6)

a. Pseudovirus neutralization antibody ID50 assay; SRR against a pseudovirus expressing the SARS-Cov-V-2 spike protein (USA_WA1/2020 isolate carrying the D614G mutation).
b. Seroresponse defined as ≥4-fold rise of pseudovirus neutralizing antibody titers from baseline (pre-dose 1 in study P201B and study P301), where baseline titers < LLOQ are set to LLOQ for the analysis.
c. Day 57 is 28 days after completion of the 2-dose primary series in study P301. Day 29 is 28 days after the booster dose in study P201B.
d. 95% CI is calculated using the Clopper-Pearson method.
e. Number of subjects with non-missing data at both baseline and the post-baseline timepoint of interest.
f. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
Source: EUA 27073.279. Module 1.11.1, Response to October 16, 2021 FDA Comments on Fact Sheets.

Baseline SARS-CoV-2 Neutralizing GMTs to the D614G Strain

Baseline neutralizing antibody GMTs prior to the booster dose at approximately 6 months after completion of the mRNA-1273 primary series, was lower among P201A participants ≥65 years of age compared to participants 18 to <65 years of age (Table 14).

Table 14. Baseline[a] SARS-CoV-2 Neutralizing GMTs (ID50)[b] at 6 Months After 100 µg mRNA-1273 Primary Series, by Age, Per Protocol Immunogenicity Subset

	18 to <65 Years of Age Study 201B N=112	≥65 Years of Age Study P201B N=37	All Ages Study P201B N=149
GMT (95% CI)	177 (146, 216)	91 (63, 131)	150 (126, 179)

a. Prior to the booster dose.
b. Pseudovirus neutralization antibody ID50 assay; neutralizing GMT against a pseudovirus expressing the SARS-Cov-V-2 spike protein (USA_WA1/2020 isolate carrying the D614G mutation).
Note: Antibody values reported as < LLOQ are replaced by 0.5 × Lower Limit of Quantification (LLOQ). Values > Upper Limit of Quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
Source: EUA 27073.250. Module 2. Clinical Overview, Table 8 and amendment 267.

Exploratory Analyses Against the Delta Variant

Moderna submitted exploratory descriptive analyses of neutralizing GMTs against the B.1.617.2 (delta) variant from study P201B 100 µg-primed booster participants and study P301 mRNA-1273 participants. These data are summarized in Table 15 below. These data are limited by the use of a non-validated pseudovirus neutralization antibody (ID50) assay against the Delta variant.

Table 15. SARS-CoV-2 Neutralizing GMTs (ID50)[a] Against Delta Strain at 28 Days After Booster Dose in Study P201B 100 µg-Primed Participants and 28 days After the mRNA-1273 Primary Series Dose 2 in Study P301, by Age, Per Protocol Immunogenicity Subset

	≥18 to <65 Years Study P201B Booster Dose N=112	≥65 Years Study P201B Booster Dose N=37	≥18 to <65 Years Study P301 Dose 2 N=434	≥65 Years Study P301 Dose 2 N=146
Pre-Vaccination				
GMT (95% CI)	54.8 (44.0, 68.3)	31.8 (22.6, 44.7)	NA	NA
1 month post-vaccination				
GMT[b] (95% CI)	872 (730, 1043)	706 (524, 951)	427 (390, 468)	277 (238, 322)
Seroresponse[d] % (95% CI)	n[c]=98 87.5 (79.9, 93.0)	n[c]=35 94.6 (81.8, 99.3)	NA	NA

NA: not available
a. Unvalidated pseudovirus neutralization ant body ID50 assay neutralizing GMT against a pseudovirus expressing the SARS-Cov-V-2 spike protein (B.1.617.2 (Delta) variant).
b. GMT estimated using an analysis of covariance (ANCOVA) model that adjusts for differences in age groups.
c. n= number of subjects with non-missing data at the post-baseline timepoint of interest and baseline.
d. Seroresponse defined as ≥4-fold rise of pseudovirus neutralizing antibody titers from baseline (pre-booster dose), where baseline titers < LLOQ are set to LLOQ for the analysis.
Source: EUA 27073.272 Module 5.3.5.3 Booster new variant tables 20210924 part 2 (P201B.617 vs P301.617)-100 Prime Group.pdf.

Subgroup Analyses

Due to the predominantly White, Non-Hispanic/Non-Latino population, exploratory subgroup analyses were limited to age, sex, and body mass index (Table 16). The GMT ratio bridging criterion was met in each subgroup category (GMT ratio point estimate ≥1.0, and lower limit (LL) of 95% CI was >0.67). The SRR bridging criterion was not met in any subgroup category (LL of 95% CI was <-10%).

Table 16. SARS-CoV-2 Neutralizing GMTs and Seroresponse Rates by Age, Sex and Body Mass Index, at 28 Days Post-Booster Dose (Day 29)[a] in Study P201B 100 µg-Primed Booster Participants and 28 Days After mRNA-1273 Primary Series (Day 57)[a] in Study P301

Characteristic	Study P201B 50 µg Booster n, GMT[b] (95% CI)	Study P301 Primary Series n, BMT[b] (95% CI)	GMT[b] Ratio (95% CI) P201B vs. P301	Study P201B 50 µg Booster SRR[c] n/N (%) (95% CI)	Study P301 Primary Series SRR[c] n/N (%) (95% CI)	Difference in SRR (95% CI) (P201B - P301)
Age						
≥18 to <65 Years	112 2070 (1752, 2445)	698 1207 (1129, 1290)	1.715 (1.433, 2.053)	98/112 87.5 (79.9, 93.0)	686/697 98.4 (97.2, 99.2)	-10.9 (-18.4, -5.9)
≥65 Years	37 1634 (1196, 2233)	355 871 (788, 964)	1.876 (1.351, 2.604)	33/37 89.2 (74.6, 97.0)	347/353 98.3 (96.3, 99.4)	-9.1 (-23.1, -2.4)
Sex						
Male	59 1937 (1504, 2495)	559 997 (917, 1084)	1.943 (1.497, 2.522)	50/59 84.7 (73.0, 92.8)	547/559 97.9 (96.3, 98.9)	-13.1 (-24.4, -5.9)
Female	90 1739 (1447, 2091)	494 1076 (992, 1168)	1.616 (1.325, 1.971)	81/90 90.0 (81.9, 95.3)	486/491 99.0 (97.6, 99.7)	-9.0 (-17.0, -4.2)
BMI						
<25 kg/m^2	58 1511 (1218, 1875)	245 933 (840, 1037)	1.619 (1.279, 2.051)	53/58 91.4 (81.0, 97.1)	241/245 98.4 (95.9, 99.6)	-7.0 (-17.1, -1.6)
≥25 kg/m^2	89 2056 (1681, 2515)	803 1067 (995, 1144)	1.927 (1.563, 2.377)	76/89 85.4 (76.3, 92.0)	787/800 98.4 (97.2, 99.1)	-13.0 (-21.8, -7.0)

Pseudovirus neutralization antibody ID50 assay; neutralizing GMT and SRR against a pseudovirus expressing the SARS-Cov-V-2 spike protein (USA_WA1/2020 isolate carrying the D614G mutation).

SRR: Seroresponse rate; LLOQ= lower limit of quantification; ULOQ= upper limit of quantification.

n=number of participants with non-missing data at the corresponding time point; N=number of participants with non-missing data at both post-baseline time point of interest and baseline.

Note: For Study P201, age is defined at the time of screening for P201 Part A. Participants with missing BMI are not included in this summary. Percentages are based on N. The upper limit of quantification for selected Study P301 participants tested previously was different.

a. Day 29 is 28 days after the booster dose in study P201B. Day 57 is 28 days after completion of the 2-dose primary series in study P301.

b. Given the lack of randomization in study P201B, the statistical analysis plan pre-specified an analysis of covariance (ANCOVA) model for estimating the geometric mean titer (GMT) that adjusts for differences in group variables [the group variable (P201 Part B and P301) as fixed effect]; the model provides a geometric least squares mean (GLSM) estimate of the geometric mean titer. Antibody values < LLOQ are replaced by 0.5 × LLOQ. Values > ULOQ are replaced by the ULOQ if actual values are not available.

c. Seroresponse at participant level is defined as a change of titer from below the LLOQ to equal to or above 4 × LLOQ, or a 4-times or higher ratio in participants with titers above LLOQ. For subjects who received primary series, seroresponse was defined based on the fold-rise from baseline titer prior to the first primary series vaccination. For subjects who received booster vaccination, seroresponse was defined based on the fold-rise from pre-booster titer.

d. 95% CI is calculated using the Clopper-Pearson method.

e. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Source: EUA 27073.267 Module 1.11.3.

SARS-CoV-2 Infection, Regardless of Symptoms

Assessment of the incidence of SARS-CoV-2 infection in study P201B was an exploratory endpoint. Case definitions of COVID-19 were not provided to study sites nor used in the analysis. In addition, information related to potential COVID-19 cases was not collected systematically (i.e., data collection relied on a combination of information collected from medical histories obtained during clinic visits, from e-diaries, and from telephone contacts outside of clinic visits during safety follow up).

SARS-CoV-2 infection was measured by RT-PCR (by Viracor lab), the Roche Elecsys Anti-SARS-CoV-2 N assay or a COVID-19 local diagnostic test. Nasal swabs for SARS-CoV-2 RT-PCR were collected per protocol at baseline (prior to booster vaccination on Day 1), on Day 29, on Day 57, and at unscheduled clinic visits for potential COVID-19 exposure and/or symptoms.

Through the August 16, 2021 cutoff date, a total of 18 participants in the 100 µg-primed booster group tested positive for SARS-CoV-2 infection; all positive tests were obtained at pre-planned study visits. Of the 18 participants who tested positive, two tested positive prior to when the maximum antibody response would have been anticipated after the booster dose (both testing positive on study Day 8). The remaining 16 participants were identified on day 29 or later. Only one of the 18 participants who tested positive for SARS-CoV-2 was symptomatic (a 50-year-old female with cough, sore throat and myalgia identified at an unscheduled visit approximately 2 weeks after testing positive). No SARS-CoV-2 infections were reported as severe.

Due to limitations of this analysis, including the lack of a control group and the exploratory nature of the analysis, these SARS-CoV-2 infection data do not allow any inference of vaccine efficacy.

Efficacy Summary

The clinical data to support emergency-authorized use of a booster dose are based on immunogenicity data from an ongoing Phase 2 study (P201) in individuals 18 years of age and older. The immunogenicity of the Moderna COVID-19 Vaccine 50 µg booster dose was assessed in 149 participants who received the 100 µg primary series approximately 6-8 months prior to the booster dose.

Effectiveness of the booster dose against the D614G strain is being inferred based on immunobridging to the 2-dose primary series, as assessed by SARS-CoV-2 neutralizing antibody titers elicited by the vaccine. Immunobridging analyses against the D614G strain met the pre-specified success criteria for the GMT ratio (P201B/P301). For the difference in seroresponse rates after the booster dose compared to after dose 2, the pre-specified success criterion was not met. The lower limit of the 95% confidence interval for the difference in seroresponse rate (P201B booster dose – P301 primary series) was <-10% (-16.7%). In post-hoc analyses, participants with lower pre-booster neutralizing antibody titers were more likely to achieve a 4-fold rise in neutralizing antibody titers after booster vaccination compared to participants with higher pre-booster neutralizing antibody titers. Moderna proposes to infer effectiveness of the booster dose against the Delta variant from exploratory descriptive analyses of neutralizing antibody titers against this variant evaluated among booster dose recipients from study P201 Part B.

4.2.6 Safety

The safety populations analyzed in studies P201A, P201B, and P301 are presented in Table 17, below. A total of 344 booster dose participants contributed to the P201B safety set. A total of 171 booster dose participants primed with the 100 µg-primary series contributed to the P201B solicited safety set.

Table 17. Safety Analysis Populations in Studies P201 Part B (Open-Label Phase), P201 Part A, and P301, Participants ≥18 Years of Age

Population	Study P301 100 µg Primary Series[b] N=15,184 n (%)	Study P201A 100 µg Primary Series N=200 n (%)	Study P201B 50 µg Booster After 50 µg Primary Series N[a]=173 n (%)	Study P201B 50 µg Booster After 100 µg Primary Series N[a]=171 n (%)	Study P201B Booster Total N[a]=344 n (%)
Safety Set[c]	15,184 (100.0)	200 (100.0)	173 (100.0)	171 (100.0)	344 (100.0)
Solicited Safety Set[d]	14,691 (96.8)	198 (99.0)	NA	167 (97.7)	NA

The solicited safety set is not applicable to 50 µg-primed booster dose participants in study P201B, because solicited safety comparisons were limited to study P201 Part A and 100 µg-primed Part B participants.
a. N=number of subjects vaccinated. Only subjects who received the booster injection in Part B of study P201 are included and summarized under the vaccination groups which they actually received in Part A.
b. N=number of subjects that received any dose of mRNA-1273 in P301 are included.
c. All P201 participants randomized in Part A and received any booster injection during Part B. All P301 participants randomized
d. All participants randomized in Part A and received any booster injection during Part B, and contribute any solicited adverse reaction data in Part B.
Source: EUA 27073.263, Module 1.11.3

Overview of Adverse Events

Safety analyses presented in this review are derived from a pre-planned analysis of booster dose safety data available through study Day 29 (database lock date of June 10, 2021) for study P201B and through a primary analysis cutoff date of November 5, 2020, for study P201A and March 26, 2021, for study P301. Additional safety data were provided from study P201B through August 16, 2021 (data subject to further cleaning). Participants in study P201A who completed a 100 µg primary series of mRNA-1273 were used as a comparator group; P301 participants who completed a primary series were included as an additional comparator group for overall solicited reactions and unsolicited AEs (i.e., all age groups combined) due to its larger sample size. Solicited and unsolicited safety analyses focused on participants in study P201B who received a 50 µg booster dose of mRNA-1273 following a 100 µg primary series of mRNA-1273 with respect to solicited adverse reactions through 7 days post-vaccination and unsolicited AEs through 28 days post-vaccination. SAEs, AEs of clinical interest, and deaths were reviewed for all participants in P201B, including recipients of a 50 µg mRNA-1273 primary series, to provide additional safety data.

Overall, immediate and solicited local and systemic reactions (Table 18) and unsolicited, medically attended AEs, and SAEs (Table 19) were reported by a similar proportion of participants across P201 and P301 studies.

Table 18. Solicited Adverse Reactions Through 7 Days After 50 µg mRNA-1273 Booster Dose in P201B and Through 7 Days After 100 µg mRNA-1273 Primary Series Dose 2 in P201A and P301, Participants ≥18 Years of Age, Solicited Safety Set

Event	Study P301 Dose 2 of 100 µg Primary Series	Study P201A Dose 2 of 100 µg Primary Series	Study P201B 50 µg Booster After 100µg Primary Series
Solicited adverse reactions	**n/N (%)**	**n/N (%)**	**n/N (%)**
Immediate[a] adverse reactions	1460/14691 (9.9)	10/198 (5.1)	22/167 (13.2)
Solicited injection site reaction within 7 days	13029/14688 (88.7)	170/198 (85.9)	143/167 (85.6)
Grade 3 or 4 solicited injection site reaction	1023/14688 (7.0)	7/198 (3.5)	8/167 (4.8)
Solicited systemic adverse reaction within 7 days	11678/14690 (79.5)	153/198 (77.3)	126/167 (75.4)
Grade 3 or 4 systemic adverse reaction	2350/14690 (16.0)	25/198 (12.6)	12/167 (7.2)

a. Immediate AR in P201B and P301 refers to an adverse reaction reported in the 30 minutes after vaccination (at study clinic). Immediate adverse reaction in 201A refers to an adverse reaction reported in the 1 hour after vaccination (at study clinic).
Source: EUA 27073.263 Module 1.11.3.

Table 19. Unsolicited Adverse Events After a 50 µg mRNA-1273 Booster Dose in Study P201B and After Any 100 µg mRNA-1273 Primary Series Injection in Studies P201A and P301, Participants ≥18 Years of Age, Safety Set

Event	Study P301A 100 µg Primary Series N=15184	Study P201A 100 µg Primary Series N=200	Study P201B 50 µg Booster After 50 µg Primary Series N=173	Study P201B 50 µg Booster After 100 µg Primary Series N=171
Unsolicited adverse events (AEs)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Unsolicited non-serious AEs up to 28 days after injection[a]	4716 (31.1)	56 (28.0)	16 (9.3)	20 (11.7)
Related non-serious unsolicited AEs	2062 (13.6)	28 (14.0)	6 (3.5)	7 (4.1)
Severe non-serious unsolicited AE	225 (1.5)	5 (2.5)	0 (0.0)	0 (0.0)
Related severe non-serious unsolicited AEs	82 (0.5)	2 (1.0)	0 (0.0)	0 (0.0)
Medically attended AEs[b]	3468 (22.8)	38 (19.0)	37 (21.4)	41 (24.0)
Related MAAEs[b]	213 (1.4)	5 (2.5)	0 (0.0)	2 (1.2)
Serious adverse events[b]	268 (1.8)	2 (1.0)	2 (1.2)	2 (1.2)
Related SAE[b]	12 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths[b]	17 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to study discontinuation[b]	26 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE=adverse event; MAAE=medically attended adverse event; NA=not applicable.
Note: The Safety Set consists of all randomized participants who received at least 1 dose of investigational product. Percentages of unsolicited AEs are based on the number of safety participants (N) who received any injection.
MedDRA (v23) coding dictionary applied.
a. Excludes adverse event reports of SARS-CoV-2 infections in study P201B which are described in Section 4.2.5.
b. Through the August 16, 2021 data snapshot for study P201B. Throughout the study for P201 Part A. Throughout the blinded phase for P301. The data presented in this table could not be verified at the time this memorandum was prepared.
Source: EUA 27073.263 Module 1.11.3 and amendment 267 Module 1.11.3.

Immediate AEs

Among the 171 booster participants in the 100 µg-primed group, a total of 22 reported any immediate adverse reaction. Of these reactions, one reaction was reported as severe (1 severe case of injection site pain). These immediate adverse reactions included the following:

- 17 participants (10.2%) who reported any immediate local reactions consisting of pain (n=16), erythema (n=1), and axillary swelling or tenderness of the vaccination arm (indicating presence of lymphadenopathy) (n=3); and

- 8 participants (4.8%) who reported immediate systemic reactions consisting of headache (n=5), fatigue (n=3), myalgia (n=1) arthralgia (n=3), and nausea/vomiting (n=1).

Solicited Adverse Reactions

Solicited local and systemic adverse reactions in addition to antipyretic/pain medication usage during the 7 days after booster vaccination were recorded daily by study participants using e-diaries. Solicited local injection site reactions included pain, erythema, swelling, and axillary swelling or tenderness of the vaccination arm indicating lymphadenopathy; systemic reactions included fever, headache, fatigue, myalgia, arthralgia, chills, nausea/vomiting, and rash.

Tables 19-22 show the frequencies of solicited local and systemic adverse reactions within 7 days of a 50 µg mRNA-1273 booster dose when given 6 months after a 100 µg mRNA-1273-primary series in study P201B participants 18 to <65 years of age (Tables 19 and 21) and P201B participants ≥65 years of age (Tables 20 and 22) with evaluable e-diary data. The tables also include post-dose 2 data from P201A participants within the respective age groups who received the 100 µg mRNA-1273 primary series as a comparison group.

P201A is the only comparator group in the solicited adverse reactions tables, because the age distribution of participants in P301 differed from the distribution of participants in P201. Enrollment in P301 was stratified by an age cutoff of 65 years, whereas enrollment in P201 was stratified by an age cutoff of 55 years.

Solicited Local Reactions

Among 100 µg-primed booster dose recipients aged 18 to <65 years and ≥65 years with evaluable e-diary data, injection site pain (86.0% and 76.3% respectively) was the most frequent local adverse reaction, followed by lymphadenopathy (24.8% and 5.3% respectively) (Table 20). Among participants 18 to <65 years of age, rates of lymphadenopathy, mostly mild in severity and transient, were higher after the booster dose (24.8%) compared to after the second primary series dose (11.6%). Among the participants who received both the second 100 µg primary series dose and the 50 µg booster dose, the estimated risk ratio was 2.3 (95% CI 1.7, 3.2), and the estimated risk difference was 13.8% (5.0%, 22.7%) when accounting for the correlation between doses for each participant. The rate of lymphadenopathy after the booster dose was, however, more similar to the frequency of lymphadenopathy following the second dose of the primary series (16.2%) among participants aged 18 to <65 years in the P301 efficacy trial (overall N=14,691).[6] The rate of lymphadenopathy after the booster dose was also numerically higher in participants 18 to <65 years of age compared to participants ≥65 years of age.

In participants ≥65 years of age, there were no notable differences or trends in the overall frequency of other solicited local reactions following the booster dose compared to after the second primary series dose (Table 21). Severe solicited local reactions after the booster dose

were uncommon (0%-5.3%) and were generally similar to rates after the second primary series dose in both age groups. No Grade 4 solicited local reaction was reported after the booster dose in either age group.

Among 100 µg-primed booster recipients ≥18 years of age, the median day of onset of local reactogenicity was generally between Day 1 and Day 3 and the median duration was 3 days (one participant reported mild erythema of 12 days duration), which were generally similar to corresponding values after dose 2 of the primary series.

> ***Reviewer Comment:*** *FDA conducted post hoc analyses of the rates of lymphadenopathy in study P201 participants by age subgroups to examine this trend described above. The highest rate of lymphadenopathy among booster dose participants was among those aged 18 through 39 years (40.4%). The highest rate after dose 2 was among participants aged 18-29 years (17.4%).*

Table 20. Frequency of Solicited Local Reactions, by Maximum Severity, Within 7 Days After a 50 µg mRNA-1273 Booster Dose in Study P201B 100 µg-Primed Participants Versus Within 7 Days After 100 µg mRNA-1273 Primary Series Dose 2 in Study P201A, Participants 18 to <65 Years of Age, Solicited Safety Set*

Event	Study P201A 100 µg Primary Series Dose 2 N[a]=155 n[b] (%)	Study P201B 50 µg Booster After 100µg Primary Series N[a]=129 n[b] (%)
Any Local Adverse Reaction	137 (88.4)	113 (87.6)
Pain at the injection site[c]		
Any	137 (88.4)	111 (86.0)
Mild	110 (71.0)	85 (65.9)
Moderate	26 (16.8)	22 (17.1)
Severe	1 (0.7)	4 (3.1)
Axillary swelling or tenderness ipsilateral to side of injection[c]		
Any	18 (11.6)	32 (24.8)
Mild	15 (9.7)	28 (21.7)
Moderate	3 (1.9)	3 (2.3)
Severe	0 (0.0)	1 (0.8)
Swelling[d]		
Any (>2.5 cm)	16 (10.3)	8 (6.2)
Mild	12 (7.7)	4 (3.1)
Moderate	4 (2.6)	4 (3.1)
Severe	0 (0.0)	0 (0.0)
Redness[d]		
Any (>2.5 cm)	12 (7.7)	7 (5.4)
Mild	7 (4.5)	4 (3.1)
Moderate	3 (1.9)	2 (1.6)
Severe	2 (1.3)	1 (0.8)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
* Participants who received any study injection in Part B and contributed any solicited adverse reaction data in Part B.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: interferes with activity or repeated use of over-the-counter pain reliever > 24 hours; Severe: prevents daily activity or any use of prescription pain reliever.
d. Mild: 2.5 to ≤5.0 cm; Moderate: 5.1 to ≤10.0 cm; Severe: >10.0 cm.
Source: EUA 27073.263 Module 1.11.3.

Table 21. Frequency of Solicited Local Reactions, by Maximum Severity, Within 7 Days After a 50 µg mRNA-1273 Booster Dose in Study P201B 100 µg-Primed Participants Versus Within 7 Days After 100 µg mRNA-1273 Primary Series Dose 2 in Study P201A, Participants ≥65 Years of Age, Solicited Safety Set*

Event	Study P201A 100 µg Primary Series Dose 2 N[a]=43 n[b] (%)	Study P201B 50 µg Booster After 100µg Primary Series N[a]=38 n[b] (%)
Any local adverse reaction	33 (76.7)	30 (78.9)
Pain at the injection site[c]		
Any	32 (74.4)	29 (76.3)
Mild	30 (69.8)	26 (68.4)
Moderate	2 (4.7)	1 (2.6)
Severe	0 (0.0)	2 (5.3)
Axillary swelling or tenderness ipsilateral to side of injection[c]		
Any	2 (4.7)	2 (5.3)
Mild	2 (4.7)	2 (5.3)
Moderate	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)
Swelling[c]		
Any (>2.5 cm)	5 (11.6)	1 (2.6)
Mild	2 (4.7)	0 (0.0)
Moderate	2 (4.7)	0 (0.0)
Severe	1 (2.3)	1 (2.6)
Redness[c]		
Any (>2.5 cm)	3 (7.0)	1 (2.6)
Mild	0 (0.0)	1 (2.6)
Moderate	0 (0.0)	0 (0.0)
Severe	3 (7.0)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
* Participants who received any study injection in Part B and contributed any solicited adverse reaction data in Part B.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: interferes with activity or repeated use of over-the-counter pain reliever > 24 hours; Severe: prevents daily activity or any use of prescription pain reliever.
Source: EUA 27073.263 Module 1.11.3.

Solicited Systemic ARs

Among 100 µg-primed booster dose recipients 18 to <65 years of age with evaluable e-diary data, fatigue (62.0%) was the most frequent systemic adverse reaction, followed by headache (58.9%), myalgia (49.6%), arthralgia (41.9%) and chills (40.3%) (Table 22). Severe reactions after the booster dose were uncommon (0%-3.1%) and generally reported by a numerically lower proportion of participants after the booster dose compared to after the second primary series dose. There were no notable differences or trends in the overall frequency of systemic reactions following the booster dose compared to after the second primary series dose in this age group (Table 23). No Grade 4 systemic reaction was reported after the booster dose in either age group.

Among 100 µg-primed booster recipients ≥18 years of age, the median day of onset and duration of systemic reactogenicity was Day 2 and 2 days, respectively, which were generally similar to systemic reactogenicity after dose 2 of the primary series.

Table 22. Frequency of Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After a 50 µg mRNA-1273 Booster Dose in Study P201B 100 µg-Primed Participants Versus Within 7 Days After 100 µg mRNA-1273 Primary Series Dose 2 in Study P201A, Participants 18 to <65 Years of Age, Solicited Safety Set*

Event	Study P201A 100 µg Primary Series Dose 2 N[a]=155 n[b] (%)	Study P201B 50 µg Booster After 100 µg Primary Series N[a]=129 n[b] (%)
Any systemic adverse reaction	125 (80.6)	101 (78.3)
Fatigue[c]		
Any	105 (67.7)	80 (62.0)
Mild	31 (20.0)	36 (27.9)
Moderate	58 (37.4)	40 (31.0)
Severe	16 (10.3)	4 (3.1)
Headache[d]		
Any	87 (56.1)	76 (58.9)
Mild	42 (27.1)	49 (38.0)
Moderate	37 (23.9)	26 (20.2)
Severe	8 (5.2)	1 (0.8)
Myalgia[c]		
Any	89 (57.4)	64 (49.6)
Mild	25 (16.1)	35 (27.1)
Moderate	49 (31.6)	25 (19.4)
Severe	15 (9.7)	4 (3.1)
Arthralgia[c]		
Any	66 (42.6)	54 (41.9)
Mild	22 (14.2)	32 (24.8)
Moderate	36 (23.2)	18 (14.0)
Severe	8 (5.2)	4 (3.1)
Chills[c]		
Any	71 (45.8)	52 (40.3)
Mild	28 (18.1)	31 (24.0)
Moderate	42 (27.1)	21 (16.3)
Severe	1 (0.6)	0 (0.0)
Nausea/Vomiting[e]		
Any	36 (23.2)	16 (12.4)
Mild	22 (14.2)	15 (11.6)
Moderate	14 (9.0)	1 (0.8)
Severe	0 (0.0)	0 (0.0)
Fever		
≥38.0°C	24 (15.5)	9 (7.0)
≥38.0°C to 38.4°C	18 (11.6)	5 (3.9)
>38.4°C to 38.9°C	3 (1.9)	2 (1.6)
>38.9°C to 40.0°C	3 (1.9)	2 (1.6)
>40.0°C	0 (0.0)	0 (0.0)
Rash		
Any[f]	5 (3.2)	3 (2.3)
Use of antipyretic or pain medication[f]	86 (55.5)	64 (49.6)

Note: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

* Participants who received any booster injection in Part B or the second primary series dose in P201A and contr buted any solicited adverse reaction data.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: does not interfere with activity; Moderate: interferes with activity or repeated use of over-the-counter pain reliever > 24 hours; Severe: prevents daily activity or any use of prescription pain reliever.
e. Mild: 1 to 2 times in 24 hours or no interference with activity; Moderate: >2 times in 24 hours or some interference with activity; Severe: requires outpatient intravenous hydration or prevents daily activity.
f. Severity was not collected for rash or for use of antipyretic or pain medication.
Source: EUA 27073.273 Module 1.11.3.

Among 100 µg-primed booster dose recipients ≥65 years of age with evaluable e-diary data, systemic reactions were generally reported by a lower proportion of participants compared to the 18 to <65 year age group. Fatigue (47.4%) and myalgia (47.4%) were the most frequent systemic adverse reactions after the booster dose, followed by headache (42.1%), arthralgia (39.5%) and chills (18.4%) among participants ≥65 years of age.

Rates of myalgia and arthralgia were numerically higher after the booster dose (47.4% and 39.5%, respectively) among participants ≥65 years of age compared to after the second primary series dose (34.9% and 25.6%, respectively). However, the rates after the booster dose were similar to the frequencies of myalgia and arthralgia following the second dose of the primary series (47.1%, and 35.0% respectively) among the corresponding age group in the larger P301 efficacy trial (overall N=14,691).[6] Severe reactions were reported by 0% to 7.9% of participants ≥65 years of age. Rates of severe reactions were numerically higher after the booster dose than the corresponding rates after the second primary series dose in study P201A for fatigue, myalgia, and arthralgia, but they were notably similar to the rates reported after the second primary dose in the larger P301 study.[6] There were no other notable differences in the frequency of systemic reactions in this age group.

Table 23. Frequency of Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After a 50 µg mRNA-1273 Booster Dose in Study P201B 100 µg-Primed Participants Versus Within 7 Days After 100 µg mRNA-1273 Primary Series Dose 2 in Study P201A, Participants ≥65 Years of Age, Solicited Safety Set*

Event	Study P201A 100 µg Primary Series Dose 2 N[a]=43 n[b] (%)	Study P201B 50 µg Booster After 100 µg Primary Series N[a]=38 n[b] (%)
Any systemic adverse reaction	28 (65.1)	23 (65.8)
Fatigue[c]		
Any	23 (53.5)	18 (47.4)
Mild	13 (30.2)	11 (28.9)
Moderate	8 (18.6)	4 (10.5)
Severe	2 (4.7)	3 (7.9)
Myalgia[c]		
Any	15 (34.9)	18 (47.4)
Mild	10 (23.3)	12 (31.6)
Moderate	5 (11.6)	5 (13.2)
Severe	0 (0.0)	1 (2.6)
Headache[d]		
Any	17 (39.5)	16 (42.1)
Mild	14 (32.6)	12 (31.6)
Moderate	2 (4.7)	3 (7.9)
Severe	1 (2.3)	1 (2.6)
Arthralgia[c]		
Any	11 (25.6)	15 (39.5)
Mild	10 (23.3)	11 (28.9)
Moderate	1 (2.3)	3 (7.9)
Severe	0 (0.0)	1 (2.6)

Event	Study P201A 100 µg Primary Series Dose 2 N[a]=43 n[b] (%)	Study P201B 50 µg Booster After 100 µg Primary Series N[a]=38 n[b] (%)
Chills[c]		
Any	7 (16.3)	7 (18.4)
Mild	2 (4.7)	5 (13.2)
Moderate	5 (11.6)	2 (5.3)
Severe	0 (0.0)	0 (0.0)
Nausea/Vomiting[e]		
Any	5 (11.6)	3 (7.9)
Mild	3 (7.0)	1 (2.6)
Moderate	2 (4.7)	2 (5.3)
Severe	0 (0.0)	0 (0.0)
Fever[f]		
≥38.0℃	2 (4.7)	2 (5.4)
≥38.0℃ to 38.4℃	1 (2.3)	1 (2.7)
>38.4℃ to 38.9℃	0 (0.0)	1 (2.7)
>38.9℃ to 40.0℃	1 (2.3)	0 (0.0)
>40.0℃	0 (0.0)	0 (0.0)
Rash		
Any[g]	1 (2.3)	0 (0.0)
Use of antipyretic or pain medication[g]	11 (25.6)	11 (28.9)

Note: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

* Participants who received any booster injection in Part B or the second primary series dose in P201A and contr buted any solicited adverse reaction data.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: does not interfere with activity; Moderate: interferes with activity or repeated use of over-the-counter pain reliever > 24 hours; Severe: prevents daily activity or any use of prescription pain reliever.
e. Mild: 1 to 2 times in 24 hours or no interference with activity; Moderate: >2 times in 24 hours or some interference with activity; Severe: requires outpatient intravenous hydration or prevents daily activity.
f. N=37 for fever for P201B.
g. Severity was not collected for rash or for use of antipyretic or pain medication.

Source: EUA 27073.263 Module 1.11.3.

Unsolicited AEs

Unsolicited Adverse Events

Table 24 presents the unsolicited AEs obtained from 171 100 µg-primed booster dose recipients in study P201B through 28 days post-booster vaccination. The most common unsolicited AEs were headache (n=4, 2.3%) and fatigue (n=4, 2.3%). No severe unsolicited AEs were reported, and no participants were withdrawn due to AEs. There were no unsolicited AEs not already captured by solicited local and systemic reactions that were considered causally related to Moderna COVID-19 Vaccine.

Other AEs of clinical interest identified from study P301 and post-authorization use include myocarditis/pericarditis, anaphylaxis, syncope, Bell's palsy, and hypersensitivity-related AEs. No cases of anaphylaxis or syncope were reported in study P201B booster dose recipients through the August 16, 2021 data cutoff date. One case of Bell's palsy, one case of pericarditis, and six cases of hypersensitivity are described in the section below.

Table 24. Unsolicited Adverse Events Occurring up to 28 Days After Booster Dose in Study P201B or Up to 28 Days After Any Injection in Studies P201A or P301, by MedDRA Primary System Organ Class and Preferred Term, Participants ≥18 Years of Age, Safety Set

Event	Study P201B 50 µg Booster After 100µg Primary Series N=171 n (%)
Number of subjects reporting unsolicited AEs	20 (11.7)
Headache	4 (2.3)
Fatigue	4 (2.3)
Abdominal pain	1 (0.6)
Allergy to arthropod bite	1 (0.6)
Anxiety	1 (0.6)
Arthralgia	1 (0.6)
Dizziness	1 (0.6)
Gastroesophageal reflux disease	1 (0.6)
Glycosylated hemoglobin increased	1 (0.6)
Humerus fracture	1 (0.6)
Influenza	1 (0.6)
Injection site erythema	1 (0.6)
Myalgia	1 (0.6)
Oropharyngeal pain	1 (0.6)
Rash	1 (0.6)
Urinary tract infection	1 (0.6)
Vitamin D deficiency	1 (0.6)
Wheezing	1 (0.6)

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities
Note: Percentages are based on the number of safety participants (N). The Safety Set consists of all randomized participants who received any study injection.
Source: EUA 27073.250, module 2.5, Clinical Overview, Table 20.

Adverse Events of Clinical Interest

FDA conducted Standardized MedDRA Queries (SMQs) to evaluate for constellations of unsolicited AEs with onset following the booster dose among 50 µg- or 100 µg-primed booster recipients ≥18 years of age in study P201B through the August 16, 2021 cutoff date. SMQs (narrow and broad in scope) were conducted on AE Preferred Terms (PTs) that could represent various conditions, including but not limited to angioedema, arthritis, cardiomyopathy, ischemic heart disease, cardiac arrhythmia, cardiac failure, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. For example, the cardiomyopathy SMQ includes PTs that may be related to myocarditis and pericarditis, such as chest pain, palpitations, dyspnea, syncope, troponin elevation, ECG with ST elevation or PR depression, pericardiac rub, or echocardiographic findings.

The SMQ analyses resulted in no identification of P201B participants with AEs of interest in the SMQs (narrow and broad in scope) of vasculitis, peripheral neuropathy, demyelination, convulsions, CNS vascular disorders, thrombophlebitis, hematopoietic cytopenias, cardiac failure, or cardiomyopathy.

Results for the angioedema, arthritis, angioedema, hypersensitivity, hearing and vestibular disorders, cardiac arrhythmias, and ischemic heart disease and embolic and thrombotic events

SMQs (broad search) through the August 16, 2021 cutoff in study P201B are listed below. No new unexpected adverse reactions were identified based on these SMQ results.

- Arthritis SMQ results: Six participants (1.7%) reported AEs of arthralgia, two (0.6%) of which were considered by the investigator as *related* to mRNA-1273 and which both resolved. One 48 year-old participant in the 50 µg-primed group reported moderate joint aches on several joints from Day 1 to Day 8 after the booster vaccination that was considered related, and one 66-year-old participant in the 100 µg-primed group reported moderate joint aches on Day 1 and 2 after booster vaccination that was considered related. Three additional participants reported arthralgias (starting on Day 7, Day 70, and Day 135 post-booster), that were considered unrelated to study vaccination. One 50 µg-primed participant reported spinal osteoarthritis (worsening of cervical spondylosis) from Day 50-72 post-booster dose that was considered unrelated to vaccination.

- Angioedema SMQ results: A 69-year-old female participant (0.3%) in the 100 µg-primed group with a history of seasonal allergy and drug hypersensitivity and taking hydrocodone (concomitant medication) reported an AE of mild left lower lobe wheezing on Day 1 after booster vaccination that was considered by the investigator to be unrelated to mRNA-1273.

- Hypersensitivity SMQ results: Six participants (1.7%) reported hypersensitivity events (3 in the 50 µg-primed group and 3 in the 100 µg-primed group), two of which (0.6%) were considered related to mRNA-1273. One 37-year-old male participant with a history of atopic dermatitis and seasonal allergy in the 50 µg-primed group reported mild pruritis on the left hand on the day after booster vaccination lasting 1 day; this was considered related to mRNA-1273. One 60-year-old female participant in the 100 µg-primed group with a history of seasonal allergy reported a mild rash on her trunk and bilateral arms on Day 2 to Day 30 after the booster vaccination, which was considered by the investigator to be *related* to mRNA-1273. Unrelated events included the following: a 50 µg-primed participant who reported mild exfoliative dermatitis of the face 12 days after booster vaccination and immediately after an exfoliative scrub spa treatment; a 50 µg-primed participant who reported contact dermatitis due to poison ivy 157 days after the booster dose; a 100 µg-primed participant who reported contact dermatitis on the bilateral forearms on Day 56 post-booster vaccination, and a 100 µg-primed participant with mild left lower lobe wheezing, as described above under the angioedema SMQ results.

- Hearing and vestibular disorders SMQ results: Four participants (1.2%), two in the 50 µg primed group and two in the 100 µg-primed group, reported events in this SMQ. None of these events were considered related to study vaccination. A 35-year-old female in the 50 µg-primed group reported mild vertigo on Days 1 to 8 after booster vaccination that was considered not related to vaccination. A 40-year-old female with no medical history in the 50 µg-primed group reported grade 2 “Bell’s palsy” facial paralysis 5 hours after the booster vaccination, which resolved 25 days after vaccination and was considered *unrelated*. This participant was taking cyclobenzaprine, naproxen and prednisone as concomitant medications at around the onset of the event. No additional information was provided. A 69-year-old female in the 100 µg-primed group reported moderate dizziness/ lightheadedness 5 days after the booster dose, which resolved on the same day and was considered by the investigator to be unrelated to mRNA-1273. A 38-year-old 100 µg-primed participant reported tinnitus 57 days after the booster vaccination and was considered unrelated.

- Cardiac arrhythmias: A 71-year-old female 50 µg-primed booster recipient with no relevant medical history was reported to have ongoing (as of August 16, 2021) nonserious grade 2 premature ventricular contractions beginning 92 days after booster vaccination. This event was assessed by the investigator as *unrelated* to mRNA-1273.

- Ischemic heart disease: An 87-year-old female with a history of hypothyroidism, hypercholesterolemia, grade 1 diastolic dysfunction, and chronic bradycardia in the 50 µg-primed group reported a SAE of pericarditis that lasted 6 days along with an AE of moderate angina pectoris that lasted 1 day with onset 89 days after the booster vaccination. This participant developed worsening chronic bradycardia 44 days post-dose 2 in P201 Part A. Approximately 60 days post-dose 2 of the 50 µg primary series, the participant was hospitalized for pacemaker placement and was discharged in stable condition. This participant also reported grade 2 pericarditis from Day 122-127 after the booster vaccination. Both events of pericarditis were assessed by the investigator as unrelated to mRNA-1273.

- Embolic and thrombotic events: A 71-year-old male in the 50 µg-primed group with a history of hypertension experienced a deep vein thrombosis of the deep femoral vein and pulmonary embolism 79 days post-booster vaccination. This SAE was considered unrelated to study vaccination.

In addition to the cases described above resulting from FDA's SMQs, Moderna identified a 50 µg primed booster dose participant who reported an AE that mapped to relevant clinical symptoms for the evaluation of myocarditis or pericarditis. In addition to the cases described above resulting from FDA's SMQs, Moderna identified a 50 µg-primed booster dose participant who reported an AE that mapped to relevant clinical symptoms for the evaluation of myocarditis or pericarditis. This involved a 67-year-old female with no relevant medical history who reported nonserious moderate dyspnea on exertion 78 days after the booster vaccination; this participant's symptom resolved 112 days after booster vaccination and was considered *unrelated* to mRNA-1273.

The above SMQs did not identify any new (unexpected) adverse reactions. FDA agrees with the investigator's assessment that the following AEs are not likely to be related to mRNA-1273, because the timing of the events in relation to vaccination did not suggest a causal relationship (e.g., lack of consistency with risk period identified during post-authorization use of Moderna COVID-19) or a more likely alternative etiology was identified: Bell's palsy, pericarditis, angina, deep femoral vein thrombosis, and pulmonary embolism.

SAEs

There were no SAEs reported within 28 days after booster vaccination in P201 Part B.

In the review of cumulative SAEs following the data cutoff (as of the August 16, 2021 snapshot of Moderna's P201B live database), 5 SAEs were reported in 4 booster dose recipients (2 in each of the 50 µg and 100 µg primary series groups). None of the SAEs were considered related to the vaccine by the study investigator, Moderna, or FDA.

- A 23-year-old male in the 100 µg primary series group experienced a tendon rupture 93 days after booster vaccination.
- A 26-year-old female in the 100 µg primary series group experienced a spontaneous abortion 52 days after vaccination. This event was not considered by the study

investigator to be related to mRNA-1273 vaccination. Please see more information in the narrative below under 'Pregnancies.'

- A 71-year-old male in the 50 µg primary series group with a history of hypertension experienced a pulmonary embolism and deep vein thrombosis 79 days after booster vaccination.
- An 87-year-old female in the 50 µg primary series group with a serious event of pericarditis reported 89 days after booster vaccination and grade 2 pericarditis (not reported as serious) reported on Days 122-127 after the booster, as described above under the ischemic heart disease SMQ. Both events of pericarditis were considered not related to vaccination.

Deaths

There were no deaths reported in study P201 Part A or among P201 Part B booster participants.

AEs Leading to Study Withdrawal

There were no study discontinuations due to an AE in P201 Part B.

Medically Attended Adverse Events

Among a cumulative total of 110 MAAEs reported by P201B participants who received a booster dose as of the August 16, 2021 cutoff for the live clinical database, 2 (1.2%) P201B participants in the 100 µg prime group reported medically attended AEs that were considered related to mRNA-1273 (grade 2 headache and grade 1 rash on trunk and bilateral arms).

Pregnancies

There were no pregnancies reported within 28 days after vaccination through the P201B data cutoff.

In the review of cumulative data following the August 16, 2021 data cutoff of Moderna's P201B live database, a 26-year-old female in the 100 µg primary series group, and taking oral contraception for a year prior to booster vaccination, reported a pregnancy about one month after her booster vaccination based on a positive home pregnancy test. This participant had a negative pregnancy test on the day of booster vaccination; the first day of her last menstrual period was on the same day as booster vaccination. The subject reported continuation of her oral contraception after her pregnancy test. The estimated date of conception was two days after her booster vaccination. The subject experienced a spontaneous abortion 52 days after vaccination at an estimated 8 weeks gestation (10 months and 11 days after the first prime dose of 100 µg mRNA-1273 and 9 months and 12 days after the second prime dose of 100 µg mRNA-1273). This event was not considered by the investigator or Moderna to be related to study vaccination. This participant subsequently became pregnant again 115 days after the booster vaccination, and this second pregnancy was reported as ongoing.

> ***Reviewer Comment:*** *This reviewer agrees with the investigator's causality assessment regarding this adverse event of spontaneous abortion.*

Safety Summary

In adults 18 through 64 years of age, with the exception of axillary swelling or tenderness of the vaccination arm (indicating lymphadenopathy), solicited safety data do not show evidence of

increased frequency or severity of local or systemic reactions after the booster dose (N=129) relative to dose 2 of the primary series (N=155). The rate of lymphadenopathy was higher (24.8%) after the booster dose compared to after the second primary series dose (11.6%) in this age group. Among the participants who received both the second 100 µg primary series dose and the 50 µg booster dose, the estimated risk ratio was 2.3 (95% CI 1.7, 3.2), and the estimated risk difference was 13.8% (5.0%, 22.7%) when accounting for the correlation between doses for each participant. The rate of lymphadenopathy was also numerically higher among booster participants 18 to <65 years of age (24.8%) compared to booster participants ≥65 years of age (5.3%). Among participants ≥65 years of age, there were no notable differences in the frequency or severity of local and systemic adverse reactions following the booster dose compared to dose 2. Overall, the median duration of solicited local and systemic adverse reactions was generally no longer than 3 days in both age groups.

Some of the solicited local and systemic adverse reactions were reported in a lower proportion of participants 65 years of age and older than participants 18 through 64 years of age; there were no other notable differences in the overall safety profiles observed in participants 65 years of age and older and younger participants.

Among unsolicited AEs, fatigue (2.3%) and headache (2.3%) were the most commonly reported AEs. There were no unsolicited AEs not already captured by solicited local and systemic reactions that were considered causally related to Moderna COVID-19 Vaccine. Overall, the 344 study P201B participants the median duration of safety follow-up (from the time of the booster dose to the August 16, 2021 data cutoff date) was 5.7 months (range 3.1, 6.4), during which there were no deaths, vaccine-related serious AEs, or vaccine-related AEs of clinical interest (i.e., myocarditis, pericarditis, anaphylaxis, Bell's palsy, thrombotic or embolic events) reported.

4.3 COVID-19 Cases Among P301 Study Participants During the Delta Variant Surge

As described in Section 4.2.5, 38 cases of COVID-19 infection occurred after booster vaccination among the 171 booster dose participants in the 100 µg-primed group of study P201 through the data cutoff date for the EUA amendment submission. Due to limitations in study design (no control group, exploratory COVID-19 endpoint, lack of case definitions, lack of systematic collection of COVID-19 symptoms, and differences in transmission rates in Part A vs Part B of study P201), no inferences can be made based on these data from P201 Part B.

Responding to an FDA request, Moderna performed a post hoc analysis of protocol-specified COVID-19 cases in the ongoing efficacy study P301 accrued during the period between July 1, 2021 and August 27, 2021 (corresponding to the Delta variant surge) among participants 18 years of age and older who completed the 2-dose primary series. The analysis compared rates of COVID-19 among participants who completed the 2-dose primary series early in the study (i.e., those who were originally randomized to Moderna COVID-19 Vaccine) vs. those who completed the 2-dose primary series later in the study (i.e., those who were originally randomized to placebo and then crossed over to Moderna COVID-19 Vaccine). Study participants included in the analysis were those who remained at risk for first occurrence of COVID-19 following the Moderna COVID-19 Vaccine primary series (i.e., participants who previously reported COVID-19 or who received additional study vaccinations after the primary series were excluded).

Although not independently verified by FDA, the post hoc analysis appears to indicate that the incidence of SARS-CoV-2 during the analysis period among 15,209 study participants originally randomized to Moderna COVID-19 Vaccine (median of 13 months post-dose 2, range 7.8-13.3

months, at the beginning of the analysis period) was 77.1 cases per 1,000 person-years versus 49.0 cases per 1,000 person-years among 15,206 study participants originally randomized to placebo and crossed over to Moderna COVID-19 Vaccine (median 7.9 months post-dose 2, range 4.4-7.7 months, at the beginning of the analysis period). An additional analysis appears to indicate that incidence of COVID-19 generally increased in each group of study participants with increasing time post-dose 2 at the start of the analysis period. Nineteen severe COVID-19 cases were reported during the analysis period, 13 of which occurred among study participants who were originally randomized to Moderna COVID-19 Vaccine (6.2 per 1,000 person-years) and 6 of which occurred among study participants who were originally randomized to placebo (3.3 per 1,000 person-years). Overall, 15 of these 19 cases occurred among adults who were ≥65 years of age and/or had a risk factor for severe COVID-19 (i.e., chronic lung disease, significant cardiac disease, liver disease, severe obesity, diabetes). The three remaining cases occurred in participants aged 42, 59, 63 and 64 years who were not at risk of severe disease.

4.4 DMID Study 21-0012

This ongoing Phase 1/2, open-label study included participants who received 100 µg mRNA-1273 booster dose at least 12 weeks following Moderna mRNA-1273 primary series, which differs from the dose level (50 µg) and interval (at least 6 months) for use of a booster dose requested by the Sponsor. Therefore, of the safety data submitted from this study, only the SAE results are described here. One SAE was reported in a mRNA-1273 recipient 28 days post-vaccination involving acute renal failure due to rhabdomyolysis after a fall; this SAE was considered unlikely to be causally related to the study vaccination. No deaths, AEs leading to withdrawal, or pregnancies were reported through an August 16, 2021 data cutoff date.

5. FDA Review of Other Information Submitted

5.1 Data from Post-Authorization Safety Surveillance in Vaccine Participants 18 Years of Age and Older

VAERS was queried for reports that indicated receipt of a third dose of the Moderna COVID-19 Vaccine (query run on September 9, 2021). The query returned 1086 reports, including 36 (3.3%) serious reports (31 U.S. and 5 unknown) of which 8 (0.7%) were death reports. Among the 36 serious reports, 15 (41.6%) were female, 21 (58.4%) were male. The median age was 65 years (range 17-97 years); the median onset of symptoms post-vaccination based on VAERS dates was 0 days (range 0-398 days) post-vaccination. None of the serious reports indicated the individual was pregnant.

There was 1 serious report consistent with anaphylaxis (important identified risk according to the Pharmacovigilance Plan [PVP]) following a third dose of the Moderna COVID-19 vaccine:

- VAERS ID: 1657847: A female of unknown age with rheumatoid arthritis, scleritis, migraine headache, asthma, diaphragmatic hernia, antiphospholipid syndrome, hypertension, antinuclear antibody, Hashimoto's disease and history of anaphylaxis (reactions to Levaquin, sulfa, flu shot, latex gloves, pineapple, shrimp, lobster tail, raw tomatoes, most adhesives, and gadolinium contrast dye). On August 21, 2021, the patient received third dose of Moderna COVID-19 Vaccine and experienced an anaphylactic reaction feeling abnormal, vaccination site pruritus, vaccination site swelling, myalgia, pyrexia, and vaccination site pain on the day of vaccination. Recovery unknown.

There was 1 serious report of myocarditis (PVP important identified risk) following a third dose of the Moderna COVID-19 vaccine:

- VAERS ID: 1624055: 74-year-old male with hypertension, systemic lupus erythematosus, with dyspnea, new chronic heart failure, possible myocarditis 1 day post vaccination. Recovery unknown.

Reviewer Comment: *The above reports describe individuals who received a third dose (100 µg mRNA 1273) of the Moderna COVID-19 Vaccine after the second dose. In these reports, dates of vaccination are not known, and there is confounding due to the likely predominance of immunocompromised persons seeking a third dose, based on current recommendations. The proposed booster is for 50 µg, thus the third dose administered to these patients was at a higher dose level than the proposed booster dose. The risk of adverse events such as anaphylaxis and myocarditis associated with this higher 3rd dose versus the proposed lower booster dose is unknown.*

Death Reports:
All 8 death reports were from the U.S.; 6 (75.0%) were male and 2 (25.0%) female. The median age was 72 years (range 47-88 years) and median onset of symptoms post-vaccination based on VAERS dates was 1 day (range 0-11 days post-vaccination). Most patients reported multiple co-morbidities, including HIV, malignant neoplasm on chemotherapy, type 2 diabetes and osteomyelitis, congestive heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, and COVID-19 disease. Three death reports occurred in individuals with no significant past medical history, one of whom had a fall.

Reviewer Comment: *Most of the death reports following a third dose of the Moderna COVID-19 Vaccine occurred in older individuals with co-morbidities and/or concurrent conditions that could have contributed to their deaths. In addition, some reports did not contain sufficient detail to assess further. In all 8 reports, the dose interval between the second and third dose was not stated, and the dose was higher than the currently proposed booster dose. While the deaths were temporally associated with the third dose of vaccine, there were no patterns among the cases that suggest a causal association with vaccination. The role of a third dose of vaccine in the deaths is unclear.*

In general, VAERS data have limitations due to the passive and voluntary nature of VAERS reporting, including that reports may not contain sufficient information to assess the interval between vaccine doses or the indication for a third dose, and may lack relevant clinical information and/or details regarding AEs that occurred. However, review of VAERS data following a third dose of the Moderna COVID-19 Vaccine did not reveal patterns suggesting a new safety concern that needs to be addressed in the PVP.

5.2 Pharmacovigilance Activities

ModernaTX, Inc. submitted a revised Pharmacovigilance Plan to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine booster dose. The Sponsor includes anaphylaxis, myocarditis, and pericarditis as important identified risks, and vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and while breastfeeding, long term safety, use in immunocompromised subjects, interaction with other vaccines, use in frail subjects and unstable health conditions and comorbidities, and use in subjects with autoimmune or inflammatory disorders are areas the Sponsor identified as missing information.

Division of Epidemiology recommendations are as follows:

1. Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
   - SAEs (irrespective of attribution to vaccination)
   - Cases of MIS
   - Cases of COVID-19 that result in hospitalization or death

2. The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:
   - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and AESIs
   - A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval
   - Newly identified safety concerns in the interval
   - Actions taken since the last report because of adverse experiences (e.g., changes made to Fact Sheet for Vaccination Providers, changes made to studies, studies initiated)

3. The Sponsor will conduct one or more post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine and pre-specified list of AESIs, including myocarditis and pericarditis, along with deaths, hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Moderna COVID-19 Vaccine under EUA in the general U.S. population (18 years of age and older), individuals that receive a booster dose, and populations of interest such as pregnant women, immunocompromised individuals, and subpopulations with specific comorbidities. The studies should be conducted in large-scale databases with an active comparator.

   The above condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of a booster dose in the following planned and ongoing studies for which the Sponsor will provide protocols and status update reports to the agreed-upon study designs and milestone dates:

   - Study mRNA-1273-P903: Post Authorization Safety of Moderna mRNA-1273 Vaccine in the US:
     Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation study in Health Verity which aims to augment ongoing active and passive safety signal detection through signal refinement and, where warranted, evaluation of potential safety signals associated with exposure to the Moderna COVID-19 Vaccine and booster dose, including AESI and emerging validated safety signals. A sample of pediatric, adolescent and adult individuals enrolled in health plans contributing data to Health Verity will be used for calculation of background rates.

   - Study mRNA-1273-P904: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the Moderna mRNA-1273 Vaccine in the European Union (EU).
     Study to assess the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of the Moderna COVID-19 Vaccine and booster dose use in

pregnancy, concomitant administration observed with non-COVID vaccines, use in frail participants with unstable health conditions and co-morbidities, and use in participants with autoimmune or inflammatory disorders.

4. Mandatory reporting by vaccination providers to VAERS, and to the extent feasible, to the Sponsor, for the following events:
   - Vaccine administration errors whether or not associated with an AE
   - Serious AEs (irrespective of attribution to vaccination)
   - Cases of multisystem inflammatory syndrome
   - Cases of COVID-19 that result in hospitalization or death

5. Active surveillance of vaccine recipients via the v-safe program: v-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses where the participant received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate. v-safe may be modified to allow adolescents to self-register and report to v-safe, and a pathway created for a parent/guardian to report on behalf of younger children.

5.3 Clinical Assay Information

Immunogenicity Assays

Neutralizing Antibody Assay

The pseudotype virus neutralization assay used to assess the effectiveness of a booster dose was developed at the Vaccine Research Center (VRC), National Institutes of Health (NIH), Maryland and optimized and validated at Duke University, North Carolina. The assay measures neutralizing antibodies using a pseudotype lentivirus expressing SARS-CoV-2 Spike protein and 293T cells expressing high levels of ACE2 (293T/ACE2 cells) in a 96 well plate format. The pseudotype lentivirus particle expresses the SARS-CoV-2 Spike protein (D614G form of the USA-WA1/2020 Wuhan strain) and a firefly luciferase reporter gene. Infected cells express luciferase, and luciferase activity is quantified by relative light units (RLU) of luminescence. Neutralization is measured as the serum dilution at which RLU is reduced by 50% (ID50) and 80% (ID80) relative to mean RLU in virus-control wells. The assay was validated using both convalescent serum samples and clinical samples from individuals who received Moderna's mRNA-1273 vaccine. The assay-validation study evaluated Accuracy, Precision, Limit of Detection, Lower and Upper Limits of Quantification, Dilutional Linearity, Specificity and Robustness. The validation results met the pre-established acceptance criteria and support the suitability of the assay to accurately quantify neutralizing antibodies in human serum samples.

The pseudotype virus neutralization assay used to assess the effectiveness of a booster dose to the SARS CoV-2 Delta variant was developed in the same laboratory at Duke University leveraging the platform technology. This assay measures neutralizing antibodies using a pseudotype virus expressing Spike protein from the SARS CoV-2 Delta strain and 293T cells expressing high levels of ACE2 (293T/ACE2 cells) in a 96 well plate format. Neutralization is measured as the serum dilution at which RLU is reduced by 50% (ID50) and 80% (ID80) relative to mean RLU in virus-control wells. Assay validation is ongoing.

5.4 Inspection of Clinical Study Sites

The review team decided that BIMO inspections are not needed to support the review of this EUA amendment.

5.5 EUA Prescribing Information and Fact Sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

6. Benefit / Risk Assessment in the Contest of the Proposed Use Under EUA

6.1 Known and Potential Benefits

The Moderna COVID-19 Vaccine has been demonstrated to be highly efficacious against COVID-19 and severe COVID-19 (94.1% VE and 100% VE, respectively, in analyses from the ongoing Phase 3 clinical trial that supported Emergency Use Authorization). Clinical benefit of a booster dose administered at least 6 months after completion of the primary series would be related to restoration of high vaccine effectiveness (or more durable vaccine effectiveness) in individuals for whom protective immunity has waned. In considering the statutory criteria for EUA, the relevant clinical benefit would be related specifically to protection against potential serious outcomes of COVID-19. The evidence for benefit of a booster dose is therefore derived from: 1) data to support waning protection against serious outcomes of COVID-19 in those populations for which use of a booster dose under EUA is being considered; and 2) data to support effectiveness of a booster dose against currently circulating SARS-CoV-2 variants.

With regard to evidence to support waning protection against serious outcomes of COVID-19, data from observational studies (although not independently verified by FDA) indicate that COVID-19 vaccines continue to provide high protection against severe disease, hospitalization and death in most individuals, although some studies suggest a trend over time toward decreasing protection against hospitalization among vaccinated individuals 65 years of age and older. Evidence from observational studies and from post hoc analyses of COVID-19 cases among mRNA-1273 primary series recipients in the ongoing clinical trial P301 (although not independently verified by FDA) do indicate waning of protection against SARS-CoV-2 infection and symptomatic COVID-19 over time following the primary series. Considering this evidence, it is reasonable to conclude that in the setting of waning neutralizing antibody titers following primary vaccination, certain subgroups may be at higher risk of severe COVID-19 (e.g., due to underlying medical conditions) or at higher risk of serious complications of COVID-19 (e.g., long COVID) in the setting of frequent institutional or occupational exposure to SARS-CoV-2. Thus, despite a lack of data at this time directly demonstrating waning protection against serious COVID-19 outcomes in these subgroups, it is reasonable to conclude that in these subgroups a booster dose will potentially prevent serious COVID-19 outcomes as a result of improving protection against all symptomatic COVID-19.

With regard to evidence to support effectiveness of a booster dose against currently circulating SARS-CoV-2 variants, the successful booster dose immunobridging analysis based on neutralizing antibody (ID50) GMTs from Studies P201B and P301 and the robust seroresponse rate from study P201B support inference of effectiveness of the booster dose in individuals 18 years of age and older against the D614G reference strain. Additional exploratory descriptive immunogenicity analyses evaluating neutralization of the Delta variant, although limited by the

use of a non-validated assay, support the potential for the booster dose to provide additional protection against the currently circulating Delta variant.

6.2 Uncertain Benefits/Data Gaps

Effectiveness of booster dose against SARS-CoV-2 Variants of Concern
As summarized above, immunogenicity data to support effectiveness of the booster dose against the Delta variant are limited to exploratory analyses using non-validated assays. Additionally, data are lacking at this time to directly demonstrate efficacy of a booster dose against clinical disease outcomes from SARS-CoV-2 Delta variant infection. Furthermore, other variants against which the Moderna COVID-19 booster dose may be less effective could emerge in the future.

Booster Dose Durability of Protection
Immunogenicity analyses were conducted 1 month post-booster. Therefore, it is not possible to assess sustained effectiveness over a period of time longer than 1 month.

Effectiveness of booster dose against viral shedding and transmission
The effectiveness of a booster dose against transmission of SARS-CoV-2 from individuals who are infected despite vaccination has not yet been established. Observational studies are planned and ongoing to further evaluate this effect.

Effectiveness of booster dose against long term effects of COVID-19 disease
The effectiveness of a booster dose against long term effects of COVID-19 disease has not been established.

Future effectiveness of booster dose as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections
The evolution of the pandemic characteristics, such as increased attack rates, emergence of new variants, and/or the effect of coinfections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of booster dose effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

6.3 Known and Potential Risks

In study P201 Part B, reported frequencies and severities of solicited adverse reactions following the booster dose were generally similar to or lower than those following Dose 2 of the primary series, with the exceptions of: lymphadenopathy, mostly mild in severity and transient, reported approximately 2-fold more frequently following a booster dose than following Dose 2 among 18 through 64 years of age; and myalgia and arthralgia, mostly mild or moderate in severity and transient, reported more frequently after the booster dose compared to after Dose 2 among participants $\geqslant$65 years of age.

Anaphylaxis and myocarditis/pericarditis are known uncommon but serious risks associated with the Moderna COVID-19 vaccine primary series. There were no anaphylaxis, pericarditis or myocarditis reactions reported with close temporal relation to the vaccine through the data cutoff date (August 16, 2021) that were considered related to the study intervention by the investigator or this reviewer. However, the number of study participants exposed to a booster dose precludes a meaningful evaluation of these risks. With regard to anaphylaxis, individuals who experience a severe allergic reaction to a primary series dose would be contraindicated to receive a booster dose, and it is unlikely that an individual would experience an anaphylactic reaction to a booster dose in the absence of a prior severe allergic reaction to a primary series

dose. With regard to myocarditis/pericarditis, available data suggest that this risk is greatest in males under the age of 40 years following the second primary series dose. It is unknown whether this risk would be similar, increased, or decreased following a booster dose as compared to following the second primary series dose. While observational safety data from widespread use of a Pfizer-BioNTech COVID-19 Vaccine booster dose in Israel were presented at the VRBPAC meeting, these data have not been independently reviewed by FDA and are lacking for individuals under the age of 30 years.

6.4 Uncertain Risks/Data Gaps

Adverse reactions that are very uncommon or that require longer follow-up to be detected
In addition to uncertainty around the risk of myocarditis/pericarditis following a booster dose as described above, the duration of safety follow-up and the size of the available booster dose safety database limit the ability to detect the emergence of rare adverse reactions, which may only be identified with broader use and more prolonged safety follow up. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Safety of booster dose in certain subpopulations
No clinical safety data for a booster dose are available at this time for certain subpopulations, such as pediatric populations less than 18 years of age or pregnant or lactating individuals. For pregnant or lactating individuals, available safety data from use of the primary series do not raise specific safety concerns about extrapolating safety of a booster dose from data in non-pregnant, non-lactating individuals.

Vaccine-enhanced disease
Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

7. VRBPAC Summary

The Vaccines and Related Biological Products Advisory Committee convened on October 14, 2021 to discuss if the available data support the safety and effectiveness of Moderna COVID-19 Vaccine for use under EUA as a booster dose (50 mcg mRNA-1273) at least 6 months after completion of a primary series in the following populations:

- Individuals 65 years of age and older,
- Individuals 18 through 64 years of age at high risk of severe COVID-19, and
- Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2.

Please vote Yes or No.

The results of the vote were as follows: Yes=19, No=0.

The committee was then asked to discuss (without a vote) whether updated information on effectiveness of mRNA COVID-19 vaccines and experience with the Pfizer-BioNTech COVID-19 Vaccine booster dose in Israel would support use of a mRNA COVID-19 vaccine (Pfizer-

BioNTech or Moderna) booster dose administered at least 6 months after completion of the same mRNA COVID-19 vaccine primary series in the general population of adults in an age group less than 65 years. There was consensus among the committee that current data do not support widespread use of mRNA COVID-19 vaccine booster doses in the U.S. among the general population of adults 18 years of age and older. Concerns cited by committee members included differences in the COVID-19 epidemiologic curve in the U.S. currently versus in Israel when booster dose implementation decisions were made there, lack of data to support waning protection against serious COVID-19 outcomes among younger adults in the U.S. general population, and uncertainties regarding the risk of myocarditis following a booster dose among younger adults. However, as the discussion of this question continued over the 2-day VRBPAC meeting, some committee members expressed that as FDA might consider authorizing use of mRNA COVID-19 vaccine booster doses for use in a somewhat younger age group of the general population (e.g., 40 years and older) based on the lower risk of myocarditis following primary series doses in this age group and based on emerging vaccine effectiveness data.

8. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request, the review team concludes that:

- As summarized in Section 2 of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the immunogenicity data summarized in Section 4 of this review, a Moderna COVID-19 Vaccine booster dose, when administered at least 6 months after the primary series, may be effective in improving protection against serious outcomes of COVID-19 among individuals in whom primary series immunity has waned.

- Based on the data summarized in Section 4 of this review and assessment of benefits and risks in Section 6 of this review, the known and potential benefits of a booster dose of the vaccine outweigh the known and potential risks of the vaccine for certain subgroups who are at increased risk of waning protection against serious outcomes of COVID-19. These subgroups include individuals 65 years of age and older (based on data from observational studies), individuals 18 through 64 years of age at high risk for severe COVID-19 (e.g., due to underlying medical conditions), and individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. Considering the current uncertainties around waning protection against serious COVID-19 outcomes among younger primary series recipients without risk factors for severe COVID-19 or frequent and unavoidable exposure to SARS-CoV-2, and the current uncertainties around safety of a booster dose in younger adult age groups, available data at this time do not clearly support a favorable benefit/risk determination for use of a booster dose in the general population of adults 18 through 64 years of age.

- COMIRNATY is the only COVID-19 vaccine currently FDA-approved for active immunization for prevention of COVID-19 caused by SARS-CoV-2. It is licensed as a 2-dose primary series given 3 weeks apart. A third dose of the Pfizer-BioNTech COVID-19 Vaccine is authorized for use under EUA in immunocompromised individuals as part of the primary series, and a booster dose of the Pfizer-BioNTech COVID-19 Vaccine is authorized for use under EUA in certain adult populations, but neither the 3rd primary

series dose nor the booster dose are included in the approved dosing regimen for COMIRNATY. None of the currently-authorized COVID-19 vaccines is FDA-approved for use as a booster dose.

The review team therefore recommends authorization of the Moderna COVID-19 Vaccine under EUA for use as a booster dose administered at least 6 months after the primary series in the following populations:

- individuals 65 years of age and older,
- individuals 18 through 64 years of age at high risk of severe COVID-19, and
- individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2.

9. References

[1] CDC COVID-19 Response Team. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine - United States, December 21, 2020-January 10, 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(4):125-129.
[2] CDC. COVID-19 Breakthrough Case Investigations and Reporting. COVID-19 Breakthrough Case Investigations and Reporting | CDC. Accessed, September 21, 2021.
[3] Federal Food Drug and Cosmetic Act. 21 U.S.C. § 360bbb–3 and 360bbb-3b. (2011). 2011.
[4] FDA. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/media/139638/download
[5] FDA. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. February 2021. https://www.fda.gov/media/142749/download
[6] Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) Emergency Use Authorization (EUA) of the Moderna Covid-19 Vaccine to Prevent Coronavirus Disease 2019 (Covid-19). August 27, 2021. https://www.fda.gov/media/144637/download