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

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27073 (Amendment 482)
Sponsor	ModernaTX, Inc.
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Signatory Authority	Peter Marks, M.D., Ph.D., Director, CBER, and Acting Director, CBER/OVRR
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Review Completion Date	August 31, 2022
Established Name/Names Used During Development	Moderna COVID-19 Vaccine, Bivalent/mRNA-1273.222
Dosage Forms/Strengths and Route of Administration	0.5 mL suspension for intramuscular injection
Intended Use for EUA	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 2 months after completion of primary vaccination or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine.
Intended Population	Individuals 18 years of age and older

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1 Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to be an ongoing global health challenge, and as of August 26, 2022, has led to over 599 million cases of coronavirus disease 2019 (COVID-19), including 6.4 million deaths worldwide.[1] The Moderna COVID-19 Vaccine (also known as mRNA-1273) is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the full-length spike (S) protein of the original (ancestral) Wuhan-Hu-1 SARS-CoV-2 strain. The Moderna COVID-19 Vaccine, also referred to as mRNA-1273, was authorized under Emergency Use Authorization (EUA) on December 18, 2020, and approved under the trade name Spikevax on January 31, 2022, as a 2-dose primary series for active immunization to prevent COVID-19 due to SARS-CoV-2 in individuals 18 years of age and older. Since the initial authorization in December 2020, the EUA has been amended to extend the age indication for the primary series down to 6 months of age and to include use of Moderna COVID-19 Vaccine as a first booster dose in adults 18 years of age and older and as a second booster dose in certain populations.

Multiple variants of SARS-CoV-2 have emerged since the beginning of the pandemic. After the emergence and rapid global spread of the Omicron variant (B.1.1.529, also referred to as the BA.1 sublineage) and more recent predominance of the Omicron BA.4 and BA.5 sublineages (hereafter referred to as BA.4/BA.5 due to the shared structure of their spike glycoproteins), along with clinical trial and real-world data indicating waning protection following primary series and booster doses of available COVID-19 vaccines, and reduced effectiveness of currently available monovalent (original) COVID-19 vaccines against Omicron BA.4/BA.5, a June 28, 2022 meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was held to discuss potential changes to COVID-19 vaccine strain composition for use in future vaccination campaigns. Following this VRBPAC meeting and discussions with the World Health Organization (WHO) and other global regulatory authorities, FDA recommended that manufacturers develop bivalent COVID-19 vaccines that include a component based on the original strain and a component based on Omicron BA.4/BA.5 for use as a booster dose potentially beginning in fall 2022.

On August 15, 2022, Moderna submitted a request to amend the EUA to include the use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in adults 18 years of age and older as a single booster dose after either completion of the primary vaccination or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. Each 50 µg booster dose of Moderna COVID-19, Bivalent (Original and Omicron BA.4/BA.5), also referred to as mRNA-1273.222, contains 25 µg mRNA encoding the S-protein of the original strain and 25 µg mRNA encoding the S-protein of Omicron BA.4/BA.5.

In consideration of this EUA request, the totality of data evaluated by the FDA to support the safety and effectiveness of mRNA-1273.222 include:

- clinical safety and immunogenicity data from a study which evaluated a second booster dose of another bivalent vaccine, mRNA-1273.214, which contains original and Omicron BA.1 mRNA components and is manufactured by the same process as mRNA-1273 and mRNA-1273.222,
- safety and effectiveness data from clinical trials and observational studies which evaluated primary and booster (homologous and heterologous) vaccination with the original Moderna COVID-19 Vaccine (previously reviewed by FDA),

- post-marketing safety surveillance data with primary series and booster doses of the original Moderna COVID-19 Vaccine, and
- supportive non-clinical immunogenicity data from a study with mRNA-1273.222.

While clinical data for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine, mRNA-1273.222, are not yet available, FDA determined that for purposes of this EUA it is reasonable to assess the effectiveness and the known and potential benefits and risks of this bivalent vaccine based primarily on extrapolation of data from another bivalent vaccine, mRNA-1273.214, manufactured by the same process and containing original and Omicron BA.1 components, and extensive experience to date with the original Moderna COVID-19 Vaccine. This extensive experience with the original vaccine also provides a basis for extrapolation to assess known and potential benefits and risks of mRNA-1273.222 as a booster dose administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose of any authorized or approved COVID-19 vaccine, even though clinical evaluation of mRNA-1273.214 was limited to use as a second booster dose administered at an interval range of 88 to 408 days since the previous COVID-19 vaccination.

Clinical data submitted to this EUA amendment consist of safety and immunogenicity data from an ongoing open-label Phase 2/3 study (P205), in which 437 participants 18 years of age and older received a 50 µg booster dose of the mRNA-1273.214 bivalent (Original and Omicron BA.1) vaccine. In a separate part of Study P205, 377 participants 18 years of age and older received a 50 µg booster dose of mRNA-1273 (original monovalent vaccine) as a second booster dose. The mRNA-1273 recipients served as the comparator group for the safety and immunogenicity assessments with the mRNA-1273.214 recipients. For both mRNA-1273.214 and mRNA-1273 recipients, the study vaccines were administered as a second booster dose at least 3 months after receipt of a first booster dose of the original Moderna COVID-19 Vaccine, which followed completion of a 2-dose primary series of the original Moderna COVID-19 Vaccine.

Effectiveness of mRNA-1273.222 is extrapolated and inferred, in part, from the immunogenicity of mRNA-1273.214, based on neutralizing antibody geometric mean titers (GMTs) against a pseudovirus expressing the SARS-CoV-2 S-protein from Omicron BA.1 and a pseudovirus expressing the S-protein from USA_WA1/2020 isolate carrying the D614G mutation (ancestral strain, hereafter referred to as D614G). Primary analyses evaluated the GMTs and seroresponse rates (SRRs) at 1 month following a second booster dose with mRNA-1273.214 compared to those after a second booster dose with mRNA-1273. The pre-specified statistical success criteria were met for superiority of GMT ratio (mRNA-1273.214 / mRNA-1273) against Omicron BA.1 and non-inferiority of GMT ratio against D614G. The statistical success criteria were also met for non-inferiority of difference in SRRs (mRNA-1273.214 minus mRNA-1273) against Omicron BA.1, based on protocol definition for seroresponse of pre-Dose 1 of primary series to 1 month following second booster. Post hoc analyses evaluated SRRs against Omicron BA.1 and D614G based on a definition for seroresponse of pre-second booster to 1 month following second booster. In these analyses, SRRs against both Omicron BA.1 and D614G were statistically superior for mRNA-1273.214 compared to mRNA-1273. Descriptive analyses of GMTs against Omicron BA.4/BA.5, using a non-validated assay, demonstrated higher responses among mRNA-1273.214 recipients compared to mRNA-1273 recipients.

Solicited and unsolicited safety data from mRNA-1273.214 recipients (N=437, median follow-up 43 days) were compared to those from mRNA-1273 recipients (N=377, median follow-up 57 days). Solicited local and systemic adverse reactions (ARs) were mostly mild to moderate in severity, generally of short duration, and reported with similar frequency among mRNA-

1273.214 and mRNA-1273 recipients. The solicited adverse reactions following mRNA-1273.214 as a second booster dose were injection site pain (77.3%), fatigue (54.9%), headache (43.9%), myalgia (39.6%) arthralgia (31.1%), chills (23.8%), axillary swelling/tenderness (17.4%), nausea/vomiting (10.3%), erythema at the injection site (6.9%), swelling at the injection site (6.9%), and fever (4.4%). Overall, solicited local and systemic ARs were reported less frequently in participants in the ≥65 years age cohort compared to the 18-64 years cohort. There were no substantial differences in the frequencies or severities of solicited local or systemic ARs based on participant pre-booster SARS-CoV-2 status (i.e., evidence of prior SARS-CoV-2 infection or no evidence of prior SARS-CoV-2 infection). The frequencies of unsolicited adverse events within 28 days after vaccination were generally similar between mRNA-1273.214 recipients and mRNA-1273 recipients, and no safety concerns were identified. As of the data cutoff, there were no reported cases of myocarditis or pericarditis among study participants and no serious adverse events that were assessed as related to the study vaccine.

The post-marketing safety data for the original Moderna COVID-19 Vaccine are relevant to the safety evaluation of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) because the vaccines are manufactured using the same process. Over 227 million doses of Moderna COVID-19 Vaccine have been administered in the US as of August 5, 2022. In recipients of any age, the most frequently reported AEs in the Vaccine Adverse Event Reporting System (VAERS) were headache, pyrexia, fatigue, pain, chills, pain in extremity, nausea, dizziness, injection site pain, and injection site erythema. For important risks identified in the pharmacovigilance plan for Moderna COVID-19 Vaccine, there were a total of 1037 US VAERS reports of anaphylactic/anaphylactoid reactions in recipients of any age (as of August 5, 2022) and 1321 reports of myocarditis/pericarditis in adults 18 years of age and older (as of May 26, 2022, using the CDC myocarditis case definition). Most myocarditis reports were in younger males (n=960, median age 28 years) and symptoms in most individuals resolved with conservative management. The Sponsor is conducting additional post-authorization/ post-marketing studies for the monovalent vaccine, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor will also conduct planned post-authorization studies to evaluate the association between the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs in the general US population.

Non-clinical studies demonstrated that a booster dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in mice that previously received two primary series doses of the Original Moderna COVID-19 Vaccine (mRNA-1273) given three weeks apart elicited a high level of neutralizing antibodies against Omicron BA.5 virus and offered protection from viral replication induced by a challenge with Omicron BA.5 virus.

The totality of scientific evidence available at this time supports the conclusion that a booster dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 18 years of age and older, when administered at least 2 months after either completion of a primary series or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine, may be effective and that the potential benefits outweigh the potential risks. Therefore, the review team recommends authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use in individuals 18 years of age and older as a single booster dose administered at least 2 months after either completion of a primary series or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. The review team also recommends a revision to the existing EUA for Moderna COVID-19 Vaccine to remove the use of the monovalent vaccine as a first or second booster dose.

2 Background

2.1 SARS-CoV-2 Virus and COVID-19

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with variable respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease while some others, especially those older than 65 years and those with certain co-morbid conditions[2], may develop severe respiratory tract disease including pneumonia and acute severe respiratory distress syndrome (ARDS), leading to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks, but symptoms may persist for months in some individuals.[3]

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of August 26, 2022, has led to over 599 million cases of COVID-19 and 6.4 million deaths worldwide.[1] In the US, more than 91 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[4] Over 82% of cases occurred in adults greater than 18 years of age and individuals 50 years of age and older accounted for 93.2% of deaths.[5]

Since the start of the pandemic caused by the Wuhan-Hu-1 strain of SARS-CoV-2 (also referred to as the original or ancestral strain), surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. Recent surges, both globally and in the US, have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron (B.1.1.529). The Omicron variant became the predominant variant circulating in the US in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the US have declined since the peak of the Omicron surge in January 2022, the Omicron variant continues to evolve into sublineages, including most recently BA.4 and BA.5 which account for nearly all reported COVID-19 cases in the US currently, and have been associated with recent increases in COVID-19 case rates.[6] In addition, population-level evidence suggests an increased reinfection risk associated with the Omicron variant and its sublineages compared to earlier SARS-CoV-2 variants.[7] Additionally, available evidence demonstrates waning of immunity elicited by COVID-19 primary vaccination and booster doses and reduced effectiveness of currently available vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the currently dominant Omicron variant sublineages (see Section 3.1 below). Consequently, a booster vaccine that is able to elicit improved protection against the Omicron BA.4/BA.5 sublineages is an important public health need.

Throughout this document, the term “sublineage” indicates the SARS CoV-2 Omicron variant BA.1, BA.4, and/or BA.5 lineage, as specified.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

2.2.1 Spikevax and Moderna COVID-19 Vaccine

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. Spikevax contains

nucleoside-modified mRNA that encodes for the full-length spike (S) protein of the original strain encapsulated in lipid particles. The primary immunization series consists of 2 intramuscular doses administered 1 month apart, with each 0.5 mL dose of the approved formulation containing 100 µg mRNA. During clinical development, the vaccine was called mRNA-1273.

Under EUA, the vaccine is called the Moderna COVID-19 Vaccine and is authorized for use as: a 2-dose primary series for individuals 6 months of age and older; a third primary series dose for individuals 6 months of age and older with certain immunocompromising conditions; a homologous or heterologous first booster dose after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a homologous or heterologous second booster dose administered at least 4 months after a first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions. Each of the authorized and approved primary series doses are administered according to the age group: 25 µg in 0.25 mL for 6 months through 5 years of age, 50 µg in 0.5 mL for 6 through 11 years of age, and 100 µg in 0.5 mL for 12 years old and older. When used as a first or second booster dose, the vaccine is administered as a dose of 50 µg in 0.5 mL or 0.25 mL. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.2 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older. Comirnaty contains a nucleoside-modified mRNA encoding the S protein of original SARS-CoV-2 strain that is formulated in lipid particles.

Under EUA, the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as a: three-dose primary series for individuals 6 months through 4 years of age, a two-dose primary series for individuals 5 years of age and older, a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. The Pfizer-BioNTech COVID-19 Vaccine is also authorized as: a first booster dose in individuals 5-17 years of age and older to be administered at least 5 months after completion of a primary series, a first booster dose in individuals 18 years of age and older after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination), and a second booster dose at least four months after a first booster dose of any authorized or approved COVID-19 vaccine in individuals 50 years of age and older and individuals 12-49 years of age with certain types of immunocompromise. Each of the authorized and approved primary series and booster doses are administered according to the age group: 3 µg in 0.2 mL (primary series only) for 6 months through 4 years of age, 10 µg in 0.2 mL for 5 through 11 years of age, and 30 µg in 0.3 mL for 12 years old and older. The Pfizer-BioNTech COVID-19 Vaccine safety and effectiveness data supporting approval of Comirnaty and authorization of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine, a non-replicating adenovirus type 26-vectored vaccine encoding the S protein of SARS-CoV-2 original strain, is authorized for active immunization to

prevent COVID-19 in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). The safety and effectiveness data supporting authorization of the Janssen COVID-19 Vaccine and limitations on its use are detailed in the decision memoranda available on the FDA website.

2.2.4 Novavax COVID-19 Vaccine

The Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for emergency use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older. The safety and effectiveness data supporting authorization of the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

2.2.5 Therapies for COVID-19

The antiviral Veklury (remdesivir) is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19.

The immune modulator Olumiant (baricitinib) is approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Other pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19 that have received emergency use authorization are as follows:

Antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Bebtelovimab is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Tixagevimab co-packaged with cilgavimab is authorized under EUA as pre-exposure prophylaxis for prevention

of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

Immune modulators: Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Tocilizumab is authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high antibody titer is authorized for emergency use as a treatment for patients with COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

3 Rationale for Bivalent Booster Doses

3.1 Post-Authorization Effectiveness Data Against Clinically Relevant Variants (e.g., Omicron)

While the currently authorized and approved COVID-19 vaccines in the US are based on the original strain, recently and currently circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Nonetheless, currently available vaccines have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease.[8,9,10,11,12,13,14,15,16,17,18]

Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the original strain) and waning effectiveness over time.[8,9,10,] Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,[8,9,10,11] observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization[8,12,13,14] and lower effectiveness among the immunocompromised.[15] In Israeli experience with a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine in adults 60 years of age and older,[16,18] a second booster dose improved VE overall (including a reduction in mortality), although effectiveness against mild disease decreased during a 10-week follow-up period.

3.2 June 28th VRBPAC and Subsequent Regulatory Discussions

On June 28th 2022, the 175th meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified (see FDA website for background materials). The committee heard presentations on the current epidemiology of the COVID-19 Pandemic and SARS-CoV-2 variants in the United States and COVID-19 vaccine effectiveness (CDC) and future COVID-19 Pandemic epidemiology modeling (J. Lessler, University of North Carolina). In addition, available clinical data on modified COVID-19 vaccines were presented by COVID-19 vaccine manufacturers (Pfizer Inc., ModernaTX, and Novavax Inc.) and considerations for vaccine strain composition from the WHO Technical Advisory Group on

COVID-19 Vaccine Composition (K. Subbarao, WHO). FDA perspective on considerations for strain composition for modifications of COVID-19 vaccines was also provided. After these presentations and committee discussions, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the US. Although there was no vote on a more specific strain composition, there was general preference among committee members for a bivalent vaccine with an ancestral strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. Several members stressed the need to continue to accumulate additional data on this complex issue.

Following the VRBPAC meeting, FDA and other global regulatory authorities met to discuss preliminary data on adapted vaccines addressing emerging variants and discuss alignment on the criteria for strain selection and regulatory approaches to address new waves of COVID-19 (see ICMR website for additional details). Based on emerging clinical data, there was a preference for a bivalent vaccine that incorporated a component based on the original strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron, as it is currently unknown which strains will be circulating in the future.

On June 30, 2022, FDA notified COVID-19 vaccine manufacturers of a recommendation to develop a bivalent booster vaccine (Original and Omicron BA.4/BA.5) to improve protection during a potential fall 2022 booster vaccination campaign. FDA requested that sponsors expeditiously begin clinical trials to generate safety and immunogenicity data evaluating a bivalent (Original and Omicron BA.4/BA.5) vaccine in relevant populations. FDA recognized that data in trial participants who would receive the bivalent (Original and Omicron BA.4/BA.5) vaccine would potentially not be available prior to the optimal timeframe for deployment of the vaccine in a potential fall 2022 booster vaccination campaign. Consequently, to address the urgent public health need for COVID-19 vaccine booster doses more closely matched to circulating variants, FDA considered that it may be appropriate to issue an Emergency Use Authorization of a bivalent (Original and Omicron BA.4/BA.5) vaccine based primarily on relevant safety and effectiveness data from participants who received an earlier bivalent vaccine (Original and Omicron BA.1), plus supportive non-clinical animal data for the recommended bivalent vaccine (prototype + BA.4/BA.5), as well as data from use of already-authorized vaccines. Section 4 of this memo provides FDA considerations for this approach.

4 Regulatory Considerations for an Omicron Booster EUA

4.1 US Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of the US Department 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 US citizens living abroad, FDA may issue an EUA after determining certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).

- The chemical, biological, radiological, or nuclear 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 to prevent, diagnose, or treat such serious or life-threatening disease or

condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition 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 allow 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 a vaccine's known and potential benefits outweigh its known and potential risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

4.2 FDA Guidance for Industry Related to COVID-19 Vaccines, Including Modified COVID-19 Vaccines

Appendix 2 of the FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (March 2022, originally issued October 2020)[19] discusses an approach to CMC, nonclinical and clinical data to support the safety and effectiveness of a modified vaccine to address emerging SARS-CoV-2 variants. Although the approach outlined in Appendix 2 does not specifically address considerations for multivalent modified vaccines, the approach and associated immunogenicity endpoints and analyses for supporting vaccine effectiveness are relevant to bivalent modified vaccines. In discussions with COVID-19 vaccine manufacturers, FDA has advised that effectiveness of a bivalent (original and Omicron variant) vaccine should be supported by immunobridging analyses demonstrating: 1) statistically superior neutralizing antibody GMTs against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original (monovalent) vaccine; 2) statistically non-inferior neutralizing antibody seroresponse rates against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original (monovalent) vaccine; 3) statistically non-inferior neutralizing antibody GMTs against the original strain elicited by the bivalent vaccine as compared to the previously authorized original (monovalent) vaccine; and 4) statistically non-inferior neutralizing antibody seroresponse rates against the original strain elicited by the bivalent vaccine as compared to the previously authorized original (monovalent) vaccine. FDA also advised vaccine manufacturers that, as discussed in the guidance document for monovalent modified vaccines, safety data to support EUA of a modified bivalent vaccine should include analyses of adverse events collected during the immunogenicity evaluation period. While the guidance encouraged clinical evaluation of modified vaccines across different age groups, the guidance also indicates that extrapolation of data accrued in one age group to support EUA of a modified vaccine in other age groups could be considered.

5 EUA Amendment Request for the Bivalent Moderna COVID-19 Vaccine for Use in Adults 18 Years of Age and Older

5.1 Summary of the EUA Request Submission

On August 15, 2022, the Sponsor submitted a request to amend the EUA to include the use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in adults 18

years of age and older as a single booster dose after either completion of primary vaccination or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. Each 50 µg booster dose of Moderna COVID-19, Bivalent, also referred to as mRNA-1273.222, contains 25 µg nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized S protein of the SARS-CoV-2 original strain and 25 µg mRNA encoding the pre-fusion stabilized S-protein of the SARS-CoV-2 Omicron variant sublineages BA.4 and BA.5 (Omicron BA.4/BA.5). The SARS-CoV-2 Omicron variant sublineages BA.4 and BA.5 have the same S-protein.

The EUA amendment submission included data from a clinical trial (P205) that enrolled participants 18 years of age and older. In this study, 437 participants 18 years of age and older received mRNA-1273.214 (a bivalent vaccine containing 25 µg mRNA encoding the S protein from the Omicron BA.1 sublineage and 25 µg mRNA encoding the S protein from the original strain) as a second booster dose following the 2-dose primary series of 100 µg Moderna COVID-19 Vaccine (mRNA-1273) and a first booster dose of 50 µg mRNA-1273. The median duration of safety follow-up was 43 days. The submission also included data from the same study from 377 participants 18 years of age and older who received 50 µg mRNA-1273 as a second booster dose following the 2-dose primary series of 100 µg mRNA-1273 and a first booster dose of 50 µg mRNA-1273 (authorized/approved monovalent vaccine based on the original strain). The median duration of safety follow-up in this group was 57 days. The submission includes immunobridging analyses comparing neutralizing antibody responses between mRNA-1273.214 second booster dose recipients and mRNA-1273 second booster dose recipients. Additionally, the EUA amendment submission included supportive non-clinical studies evaluating the immunogenicity of mRNA-1273.222.

5.2 FDA Approach to Extrapolation from Available Clinical Data

Due to the rapid evolution of SARS-CoV-2 virus variants, including the currently predominant circulating Omicron sublineages, improved protection for the upcoming winter season could be achieved with expedient authorization and deployment of modified COVID-19 vaccines, for use as booster doses, that are more closely antigenically matched to currently circulating SARS-CoV-2 variants than the currently authorized COVID-19 vaccines. This approach is supported by evidence, as summarized below and reviewed in detail in Section 6, indicating that an improved booster dose antibody response to SARS-CoV-2 Omicron sublineages and therefore the potential for improved vaccine effectiveness, results from inclusion of an Omicron component in the vaccine together with the original (ancestral) component, as a bivalent formulation.

Authorization of the mRNA1272.222 bivalent (Original and Omicron BA.4/BA.5) vaccine is being considered primarily based on extrapolation of available immunogenicity and safety data from the mRNA-1273.214 bivalent (Original and Omicron BA.1) vaccine formulation to meet the urgent public health need due to the currently circulating Omicron sublineages. This extrapolation is being considered in the context of the totality of available evidence, which includes:

- Extensive knowledge of the safety and efficacy of the mRNA COVID-19 vaccine platform;
- Safety, immunogenicity, efficacy, and observational effectiveness data from the original (monovalent) Moderna COVID-19 Vaccine (mRNA-1273); and
- Immunogenicity data from two other bivalent vaccine candidates manufactured using the same process as mRNA-1273 (containing Original and Beta mRNA components and

Beta and Delta mRNA components, respectively), which are not reviewed in detail in this memorandum but which, as reported by the Sponsor and as similar to the data for the bivalent (Original and Omicron BA.1) vaccine reviewed in this memorandum, showed statistically significant increases in neutralizing antibody GMTs, as compared to the original mRNA-1273 vaccine, to the variant components included in the bivalent vaccines.

Together, these data inform FDA's assessment of the effectiveness and the known and potential benefits and risks of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

As described in Section 6.1.4, neutralizing antibody responses against both Omicron BA.1 and the ancestral strain (D614G) elicited by mRNA-1273.214 were statistically superior to those elicited by mRNA-1273. Additionally, in exploratory analyses using a non-validated pseudovirus assay, booster vaccination with mRNA-1273.214 elicited neutralizing antibody GMTs against Omicron BA.4/BA.5 that were 1.7-fold higher compared to vaccination with mRNA-1273. Analysis of similarities and differences between Omicron BA.1 and BA.4/BA.5 Spike protein sequences reveal that Omicron BA.4/BA.5 shares 21 of the 30 mutations and 2 of the amino acid deletions; there are 10 additional amino acid changes in BA.4/BA.5. Looking only at the receptor binding domain (RBD) region, BA.1 has 15 amino acid changes relative to the original strain. BA.4/BA.5 shares 12 of these 15 amino acid changes and has an additional 7 changes in the RBD region, one of which is a reversion to the original strain sequence, for a total of 10 amino acid changes relative to BA.1. These data suggest that similar to mRNA-1273.214, mRNA-1273.222 would be expected to provide improved neutralizing antibody responses against BA.4/BA.5 as compared to mRNA-1273. Because mRNA1273.222 includes an Omicron BA.4/BA.5 component, booster dose neutralizing antibody responses against BA.4/BA.5 are expected to be further improved as compared to those elicited by mRNA1273.214.

Based upon the accumulated experience with primary series, first booster doses, and second booster doses (homologous and heterologous) of the Moderna COVID-19 Vaccine, as further detailed in Section 8, it is reasonable to extrapolate the available safety, efficacy, immunogenicity, and real-world evidence supporting a favorable benefit-risk balance for first and second booster doses of monovalent (ancestral) mRNA COVID-19 vaccines to conclude a favorable benefit-risk balance for use of mRNA-1273.222 as a single booster dose (including for individuals who previously received primary vaccination and two booster doses) at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. While the available clinical safety and immunogenicity data with the mRNA-1273.214 booster dose reflect a median interval of 136 days (range 88 to 408 days) after the previous COVID-19 vaccine dose, authorization of a minimum interval of 2 months for booster vaccination with mRNA-1273.222 is based on extrapolation of data from a published study with mRNA-1273 boosters evaluating shorter intervals between the primary series and booster doses, along with clinical experience in immunocompromised individuals who received third primary series doses within one to two months of the second primary series dose.[20,21]

Finally, it is reasonable to extrapolate the totality of clinical experience with administration of heterologous booster doses to support authorization of a bivalent mRNA COVID-19 vaccine booster dose following primary vaccination with the Novavax COVID-19 Vaccine, Adjuvanted. Published literature and data submitted to the agency by the respective sponsors regarding the safety and immunogenicity of the heterologous boosting with various COVID-19 vaccines[20] indicate: 1) heterologous primary series or booster doses provide similar vaccine effectiveness

to homologous regimens; 2) heterologous schedules with mRNA and vectored vaccines show similar or more robust immunogenicity compared with homologous schedules; and 3) limited safety data for heterologous schedules have generally shown similar to transiently increased reactogenicity compared with homologous regimens.[21]

5.3 Basis for EUA Revision to Remove Authorization of The Original Moderna COVID-19 Vaccine as a Booster Dose

FDA may revise or revoke an EUA if the circumstances justifying its issuance (under section 564(b)(1) of the FD&C Act) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety (see section 564(g)(2) of the FD&C Act).

Currently, circumstances exist that make it appropriate to revise the Moderna COVID-19 Vaccine EUA to protect the public health. As outlined in Section 2.2, the monovalent Moderna COVID-19 Vaccine (mRNA-1273) is currently authorized for use as a primary series, as a homologous or heterologous booster dose in adults 18 years of age and older, and as a homologous or heterologous second booster dose in certain populations. Authorization of mRNA-1273.222 for use as a booster dose following completion of primary vaccination or most recent booster dose with any authorized or approved monovalent COVID-19 vaccine is being considered for the express purpose of improving protection conferred by COVID-19 booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance for mRNA-1273.222 as compared to mRNA-1273. Consequently, at this time, revising the Moderna COVID-19 Vaccine EUA to remove the authorization of mRNA-1273 as booster doses is appropriate to protect the public health.

Accordingly, authorization of the bivalent vaccine (mRNA-1273.222) for use as a booster dose in adults 18 years and older, would be accompanied by revision of the authorization for the monovalent Moderna COVID-19 Vaccine (mRNA-1273) such that the monovalent vaccine would no longer be authorized for use as a first or second booster dose.

6 FDA Review of Clinical Safety and Effectiveness Data

6.1 Overview of Study P205

As discussed in Section 5, safety and effectiveness of mRNA-1273.222 (Original and Omicron BA.4/BA.5) is inferred based on clinical data from mRNA-1273.214 (Original and Omicron BA.1) when administered as a second booster dose to adults 18 years of age and older enrolled in Study P205. Available post-authorization safety surveillance data for mRNA-1273 when administered as booster doses in the general population also provide additional assurance of the expected safety profile for mRNA-1273.222 when administered as a booster dose (Section 6.2).

Study P205 is an ongoing, open-label, multi-part Phase 2/3 study evaluating the safety and immunogenicity of various modified mRNA-1273 vaccines when administered as single booster doses to adult participants 18 years of age and older who had previously completed at least a two-dose primary series of mRNA-1273. The vaccines evaluated in Study P205 use the same proprietary mRNA-1273 platform but have been modified to encode spike proteins representing SARS-CoV-2 variants of concern (VOCs). Table 1 lists each modified variant vaccine included in Study P205 (by study part) and describes the valency (monovalent vs bivalent) and strain

composition of each vaccine, and whether the vaccine was evaluated as a first or second booster dose.

Table 1. Modified Variant Vaccines Evaluated in Study P205

P205 Part	Vaccine	Valency (Strain Composition)	1st or 2nd Booster Dose (following a 2-dose mRNA-1273 primary series)
A.1	mRNA-1273.211	Bivalent (Original and Beta B1.351)	1st booster dose
A.2	mRNA-1273.214	Bivalent (Original and Omicron BA.1)	2nd booster dose following a 1st booster dose of mRNA-1273.211
B	mRNA-1273	Monovalent (Original)	1st booster dose
C	mRNA-1273.617.2	Monovalent (Delta B1.617.2)	1st booster dose
D	mRNA-1273.213	Bivalent (Delta B.1.617.2 and Beta B.1.351)	1st booster dose
F Cohort 1	mRNA-1273.529	Monovalent (Omicron BA.1)	1st booster dose
F Cohort 2	mRNA-1273 or mRNA-1273.529	see above	2nd booster dose following a 1st booster dose of mRNA-1273
G	mRNA-1273.214	Bivalent (Original and Omicron BA.1)	2nd booster dose following a 1st booster of mRNA-1273

Source: Reviewer-generated table adapted from Study protocol P205 Amendment 7, Section 3

6.1.1 Study Design: P205 Part G versus Part F Cohort 2

In the context of this EUA submission, two parts of Study P205 will be presented: Part G (mRNA-1273.214) and Part F Cohort 2 (mRNA-1273), both of which enrolled adult participants 18 years of age and older who received 50 µg dose levels of the respective second booster vaccines. Safety and immunogenicity data from mRNA-1273.214 second booster dose recipients were compared to data from mRNA-1273 second booster dose recipients. All participants had previously received 2-dose primary series of mRNA-1273 (100 µg dose) at least 6 months prior and a first booster dose mRNA-1273 (50 µg dose) at least 3 months prior. Study participants had received prior 1st booster or primary series vaccination doses as either participants in Study P301 or under Emergency Use Authorization (EUA).

Evaluation of immunogenicity

The co-primary immunogenicity objectives were to demonstrate the non-inferiority and superiority of nAb GMTs against Omicron BA.1, the non-inferiority of SRRs against Omicron BA.1, and the non-inferiority of GMTs against the ancestral strain (D614G) in mRNA-1273.214 recipients (Part G) as compared to mRNA-1273 recipients (Part F), at 28 days after the second booster dose. The co-primary endpoint of superiority of GMT ratio (mRNA-1273.214 to mRNA-1273) against Omicron BA.1 would only be assessed after the success criterion for non-inferiority of GMT ratio against Omicron BA.1 was met. The protocol-specified success criteria for the co-primary endpoints were:

Co-primary endpoint 1: GMT

The ratio of GMTs (mRNA-1273.214 /mRNA-1273) against Omicron BA.1 at 29 days post-vaccination is non-inferior if the lower bound (LB) of the 97.5% confidence interval (CI) ≥ 0.67.

Co-primary endpoint 2: SRR
The difference in the SRRs (mRNA-1273.214 – mRNA-1273) against Omicron BA.1 at 29 days post-vaccination is non-inferior if the LB of the 97.5% CI > -10%.

For the protocol-defined analysis for the co-primary endpoints evaluating SRR at Day 29, seroresponse after the second booster dose was defined based on each participant's nAb titer level at pre-Dose 1 of the primary series relative to the lower limit of quantitation (LLOQ) for the assay as follows:

- Seroresponse for participants with pre-Dose 1 < LLOQ is defined as ⩾4 x LLOQ
- Seroresponse for participants with pre-Dose 1 ≥ LLOQ is defined as ≥4-fold increase in titers compared to pre-Dose 1 titer

For participants who did not have pre-dose 1 nAb titer information, a titer of <LLOQ was imputed. For participants whose pre-dose 1 SARS-CoV-2 status was unknown, the status at pre-2nd booster was imputed.

Post hoc analyses were conducted based on a more clinically meaningful seroresponse definition. For these descriptive analyses, seroresponse after the second booster dose was defined based on each participant's nAb titer level at pre-second booster dose relative to the LLOQ for the assay as follows:

- Seroresponse for participants with pre-2nd booster < LLOQ is defined as ≥4 x LLOQ
- Seroresponse for participants with pre-2nd booster ≥ LLOQ is defined as ≥4-fold increase in titers compared to pre-2nd booster titer

Co-primary endpoint 3: GMT
The ratio of GMTs (mRNA-1273.214 /mRNA-1273) against Omicron BA.1 at 29 days post-vaccination is superior if the LB of the 97.5% CI > 1.

Co-primary endpoint 4: GMT
The ratio of GMTs (mRNA-1273.214 /mRNA-1273) against the ancestral strain (D614G) at 29 days post-vaccination is non-inferior if the LB of the 97.5% CI ≥ 0.67.

A key secondary objective in the study was to demonstrate non-inferiority of mRNA-1273.214 based on SRR against the ancestral strain. Additional secondary objectives in the study included evaluation of the immunogenicity of mRNA-1273.214 compared to mRNA-1273 against other variants of concern (i.e., Omicron BA.4/BA.5).

Key secondary endpoint: SRR
The difference in SRRs (mRNA-1273.214 – mRNA-1273) against the ancestral strain (D614G) at 29 days post-vaccination is non-inferior if the LB of the 97.5% CI > -10%. The same seroresponse definitions as outlined above were used for this analysis.

Additional secondary endpoints: GMTs and SRRs (Omicron BA.4/BA.5)
The immune responses, as measured by nAb GMTs and SRRs, against relevant circulating variants of concern (i.e., Omicron BA.4/BA.5) in the two groups were evaluated.

The protocol specified analyses sets for immunogenicity are listed in Table 2 below. The Per Protocol Set for Immunogenicity – SARS-CoV-2 Negative (PPSI-Neg) was used for the analyses of co-primary immunogenicity endpoints.

Table 2. Immunogenicity Analysis Populations

Population	Description
Full Analysis Set[a] (FAS)	The FAS consisted of all participants who received investigational product (IP)
Per Protocol Set for Immunogenicity (PPSI)	The PPSI consisted of all participants in the FAS who received the planned dose of study vaccination and had no major protocol deviations that impacted key or critical data.
Per Protocol Set for Immunogenicity – SARS-CoV-2 Negative (PPSI-Neg)	Those participants in the PPSI who had no serologic or virologic evidence of SARS-CoV-2 infection prior to the second booster, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on binding antibodies specific to SARS-CoV-2 nucleocapsid.

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

Assays used for evaluation of immunogenicity

Primary and key secondary immunogenicity endpoints were evaluated using validated pseudotype virus neutralization assays against Omicron BA.1 and the ancestral strain. Additional secondary endpoints were evaluated using a non-validated pseudotype virus neutralization assay against Omicron BA.4/BA.5. Details regarding these assays are provided in Section 7.2.

Evaluation of efficacy

Study P205 Parts F and G did not include formal assessments of vaccine efficacy. However, as exploratory endpoints, participants were followed for potential cases of COVID-19, including symptomatic COVID-19, SARS-CoV-2 infection (regardless of symptoms), and asymptomatic SARS-CoV-2 infection. Participants were monitored with biweekly safety calls and scheduled laboratory testing, that included nasal swab for SARS-CoV-2 RT-PCR and blood draw for anti-nucleocapsid serology. Testing for SARS-CoV-2 was also performed as needed if participants developed symptoms suggestive of COVID-19. Data collected through a cutoff date of April 27, 2022, were included in the analyses for this EUA submission. Efficacy against COVID-19 was assessed as descriptive analyses.

The protocol specified analysis set for efficacy is described in Table 3 below.

Table 3. Efficacy Analysis Population

Population	Description
Per Protocol Set for Efficacy (PPSE)	The PPSE consisted of all participants in the FAS who received the planned dose of study vaccination, who were SARS-CoV-2 negative prior to the second booster dose (i.e., had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid at baseline), and had no major protocol deviations that impact key or critical data

Evaluation of safety

All participants in P205 Parts F and G recorded solicited local and systemic ARs, antipyretic/analgesic medication use in an e-diary through 7 days (day of injection and 6 subsequent days) after each dose. Unsolicited adverse events (AEs) were also collected through 28 days after each dose, while medically attended adverse events (MAAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs), including any suspected cases of myocarditis and/or pericarditis, will be collected through the entire study period of up to 12 months after the study dose. The primary safety objective for P205 Part G was to describe the safety of a single dose of mRNA-1273.214 (50 µg) when administered as a second booster dose. Safety data from Part G participants were compared to the safety data collected from Part F Cohort 2 participants who received mRNA-1273 (50 µg) as second booster dose.

An independent Cardiac Event Adjudication Committee (CEAC), consisting of pediatric and adult cardiologists, evaluated suspected cases of myocarditis, pericarditis, or myopericarditis based on the CDC working case definition. Safety data collected through a cutoff date of April 27, 2022, were included in the analyses for this EUA submission.

The protocol specified analyses sets for safety are listed in Table 4.

Table 4. Safety Analysis Populations

Population	Description
Safety Set[a]	All participants who are randomized and who receive the study product
Solicited Safety Set[a]	The Solicited Safety Set consists of all participants who receive the study product and contributed any solicited AR data.

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

6.1.2 Participant Enrollment and Disposition in P205 Part F & Part G

Table 5 below provides an overview of the number of participants enrolled in Parts F or G, enrollment dates (start, end), and median follow-up duration. As shown in the table, longer follow-up duration was reported for mRNA-1273 recipients in Part F compared to mRNA-1273.214 recipients in Part G due to the earlier start date for enrollment in Part F compared to Part G. The data cutoff date was April 27, 2022.

Table 5. Enrollment in Study P205 Parts F Cohort 2 & Part G

P205 Part	Total Enrolled N[a]	Enrollment Start[b]	Enrollment End[c]	Median Follow-up Duration[d] in Days (Min, Max)
F Cohort 2 (mRNA-1273)	379	February 18, 2022	March 8, 2022	57 days (51, 66)
G (mRNA-1273.214)	440	March 8, 2022	March 23, 2022	43 days (22, 51)

Source: Response to IR dated August 5, 2022
a. All participants enrolled regardless of inclusion in the Full Analysis Set
b. Enrollment start is the date of enrollment of the first study participant in the indicated study part
c. Enrollment end is the date of enrollment of the last study participant in the indicated study part
d. Follow-up duration from enrollment of participant through study cutoff date

Participant disposition for Part G and Part F Cohort 2 are presented in Table 6 below. Discontinuation from the study occurred in only 2 participants in Part G. Based on information provided, these two participants withdrew consent to participate due to reasons that were not related to vaccine safety or tolerability (i.e., conflict with work schedule and blood draw aversion, respectively). Overall, the proportions of study participants in each study part who contributed to the populations used for safety and immunogenicity analyses were comparable.

Table 6. Participant Disposition in Study P205, Part F Cohort 2 & Part G, All Enrolled

Disposition	Part G mRNA-1273.214 N=440 n (%)	Part F mRNA-1273 N=379 n (%)
Full Analysis Set[a]	437 (99.3)	377 (99.5)
Discontinued from study[b]	2 (0.5)	0
Per Protocol Immunogenicity Set[a,c]	428 (97.3)	367 (96.8)
Reason for exclusion from PP Immunogenicity Set[d]	--	--
No Baseline Immunogenicity Data	1 (0.2)	0
Missing Immunogenicity Data at D29	8 (1.8)	5 (1.3)
Immunogenicity Data at D29 Out of Window	0	2 (0.5)
Major Protocol Deviation	0	2 (0.5)
History of HIV Infection	0	1 (0.3)
Per Protocol Immunogenicity SARS-CoV-2 Negative Set[a,e]	334 (75.9)	260 (68.6)
Per Protocol Efficacy Set[a,f]	339 (77.0)	266 (70.2)
Safety Set	N=437	N=377
Solicited Safety Set[g]	437 (100.0)	351 (93.1)

Source: P205 Tables 14.1.2.8, 14.1.1.1.8, 14.1.2.2.8,
a. Numbers are based on planned treatment group and percentages are based on the number of participants enrolled.
b. Both participants discontinued due to withdrawal of consent by participant
c. The Per-protocol Immunogenicity Set consists of participants with no major protocol deviation and for whom Omicron antibody data was available regardless of evidence of prior SARS-CoV-2 infection
d. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest. Percentages are based on the number of participants in the Full Analysis Set.
e. The Per-protocol Immunogenicity SARS-CoV-2 Negative Set consists of all participants who had no evidence of prior SARS CoV-2 infection at baseline, without major protocol deviation and for whom Omicron antibody data (pre-booster and Day 29) was available. This population was used to determine the primary immunogenicity endpoints
f. All participants in the Full Analysis Set who received the planned dose of study vaccination, who were SARS-CoV-2 negative pre-booster (ie, have a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid pre-booster), and had no major protocol deviations
g. All participants who received study vaccine and contr buted any solicited AR data. Numbers are based on planned treatment group and percentages are based on the total participants included in the Safety Set.

6.1.3 Demographics and Other Baseline Characteristics

The PPSI-Neg Set, the population used to assess primary immunogenicity endpoints, consisted of 334 participants vaccinated with mRNA-1273.214 (P205 Part G) and 260 participants vaccinated with mRNA-1273 (P205 Part F, Cohort 2). The demographic and other baseline characteristics for the PPSI-Neg Set were similar for participants in each study part and included generally comparable proportions of participants 65 years of age or older (42% to 46%) (Table 7). In addition, participants in each part had similar time intervals between prior mRNA-1273 vaccination doses. The median interval between primary series Dose 2 and the first booster was ~8 months and between the first booster and the second booster was ~4 months. The demographic characteristics of the Per Protocol Set for Immunogenicity (PPSI) were similar to those for the PPSI-Neg Set.

Table 7. Demographics and Other Baseline Characteristics, Study P205, Part F Cohort 2 & Part G, PP Immunogenicity SARS-CoV-2 Negative Set

Characteristic	Part G mRNA-1273.214 N=334	Part F mRNA-1273 N=260	Total N=594
Sex, n (%)	--	--	--
Female	189 (56.6)	134 (51.5)	323 (54.4)
Male	145 (43.4)	126 (48.5)	271 (45.6)
Age (years), n (%)	--	--	--
18 to <65	195 (58.4)	140 (53.8)	335 (56.4)
≥65	139 (41.6)	120 (46.2)	259 (43.6)
Median (min, max)	61 (20,88)	63 (21,96)	62 (20,96)
Race, n (%)	--	--	--
White	291 (87.1)	234 (90.0)	525 (88.4)
Black or African American	24 (7.2)	11 (4.2)	35 (5.9)
Asian	11 (3.3)	11 (4.2)	22 (3.7)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Multiracial	6 (1.8)	0	6 (1.0)
Other	2 (0.6)	1 (0.4)	3 (0.5)
Not reported	0	2 (0.8)	2 (0.3)
Unknown	0	1 (0.4)	1 (0.2)
Ethnicity, n (%)	--	--	--
Hispanic or Latino	24 (7.2)	22 (8.5)	46 (7.7)
Not Hispanic or Latino	309 (92.5)	238 (91.5)	547 (92.1)
Not reported	1 (0.3)	0	1 (0.2)
Unknown	0	0	0
Obesity, n (%)	--	--	--
Obese (BMI>30 kg/m^2)	148 (44.3)	119 (45.8)	267 (44.9)
Non-obese	186 (55.7)	141 (54.2)	327 (55.1)
Time Interval: Primary Series Dose #2 to 1st Booster Dose (days)	--	--	--
Median	247.5	242	244
Min, Max	143, 457	172, 435	143, 457
Time Interval: 1st Booster Dose to 2nd Booster Dose (days)	--	--	--
Median	136	133	134
Min, Max	88, 408	90, 310	88, 408

Source: P205 Table 14.1.3.6.8, IR Response received August 19, 2022, Table 2

The demographic characteristics for the Safety Set for Part G and Part F are shown in Table 8 and were generally similar. The proportion of mRNA-1273.214 recipients with evidence of prior SARS-CoV-2 infection before receipt of the second booster dose was slightly lower (22%) compared to mRNA-1273 recipients (27%).

Table 8. Demographics and Other Baseline Characteristics, Study P205, Part F Cohort 2 & Part G, Safety Set

Characteristic	Part G mRNA-1273.214 N=437	Part F mRNA-1273 N=377	Total N=814
Sex, n (%)	--	--	--
Female	258 (59.0)	191 (50.7)	449 (55.2)
Male	179 (41.0)	186 (49.3)	365 (44.8)
Age (years), n (%)	--	--	--
18 to <65	263 (60.2)	227 (60.2)	490 (60.2)
≥65	174 (39.8)	150 (39.8)	324 (39.8)
Median age (min, max)	60 (20, 88)	60 (20, 96)	70 (65, 96)
Race, n (%)	--	--	--
White	381 (87.2)	322 (85.4)	703 (86.4)
Black or African American	31 (7.1)	29 (7.7)	60 (7.4)
Asian	14 (3.2)	16 (4.2)	30 (3.7)
American Indian or Alaska Native	0	1 (0.3)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	1 (0.1)
Multiracial	7 (1.6)	2 (0.5)	9 (1.1)
Other	3 (0.7)	2 (0.5)	5 (0.6)
Not reported	1 (0.2)	3 (0.8)	4 (0.5)
Unknown	0	1 (0.3)	1 (0.1)
Ethnicity, n (%)	--	--	--
Hispanic or Latino	46 (10.5)	37 (9.8)	83 (10.2)
Not Hispanic or Latino	390 (89.2)	340 (90.2)	730 (89.7)
Not reported	1 (0.2)	0	1 (0.1)
Obesity, n (%)	--	--	
Obese (BMI>30 kg/m^2)	201 (46.0)	176 (46.7)	377 (46.3)
Non-obese	236 (54.0)	201 (53.3)	437 (53.7)
Pre-booster SARS-CoV-2 Status, n (%)	--	--	--
Positive[a]	96 (22.0)	101 (26.8)	197 (24.2)
Negative[b]	340 (77.8)	267 (70.8)	607 (74.6)
Missing	1 (0.2)	9 (2.4)	10 (1.2)
Time Between Dose 2 of Primary Series to 1st Booster Dose (Days)	--	--	--
Median	245	242	244
Min, Max	143, 457	170, 438	143, 457
Time Between the 1st Booster Dose to the 2nd Booster Dose (Days)	--	--	--
Median	136	134	135
Min, Max	88, 408	90, 310	88, 408

Source: P205, Table 14.1.3.1.1.8, IR Response received August 19, 2022, Table 1
a. Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 (pre-booster).
b. Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1 (pre-booster).

The overall demographic characteristics for the PP Efficacy Set were similar to those for the Safety Set and were comparable for participants in each study part.

6.1.4 Vaccine Effectiveness Results

Primary immunogenicity analyses
Vaccine effectiveness was inferred based on the evaluation of the nAb GMT and the SRR against Omicron (BA.1) and the ancestral strain (D614G) elicited by mRNA-1273.214 as compared to mRNA-1273, 28 days following a second booster. Co-primary endpoints, described in Section 4.2, were evaluated in participants without evidence of prior SARS-CoV-2 infection pre-second booster (PPIS-Neg Set).

The primary analyses evaluating GMT ratios against Omicron BA.1 and the ancestral strain are shown in Table 9. The study met the pre-specified success criterion for superiority of mRNA-1273.214 compared to mRNA-1273 against Omicron BA.1 based on the LB of the 97.5% CI of the GMT ratio of 1.5 (>1 to demonstrate superiority). The study also met the pre-specified success criterion for non-inferiority of mRNA-1273.214 compared to mRNA-1273 against the ancestral strain. Though formal hypothesis testing for superiority of mRNA-1273.214 compared to mRNA-1273 against the ancestral strain was not pre-specified in the protocol, the LB of the 95% CI of the GMT ratio was >1.

Table 9. Geometric Mean SARS-CoV-2 Neutralizing Titers (GMTs) as Measured by Pseudovirus nAb Assay (ID50) against Omicron (BA. 1) and Ancestral Strain (D614G) at Day 29, Study P205 Part F Cohort 2 and Part G, PPSI-Neg

Variant	Part G mRNA-1273.214 GMT (95% CI)[a] N=334	Part F mRNA-1273 GMT (95% CI) [a] N=260	GMT Ratio mRNA-1273.214/mRNA-1273 (97.5% CI) [a]	Success Criterion Met
Omicron (BA. 1)	2479.9 (2264.5, 2715.8)	1421.2 (1283.0, 1574.4)	1.7 (1.5[d], 2.0)	Yes [b]
Ancestral (D614G)	6422.3 (5990.1, 6885.7)	5286.6 (4887.1, 5718.9)	1.2 (1.1, 1.4)	Yes [c]

Source: P205 Tables 14.2.2.1.1.8
Omicron (BA. 1): LLOQ: 19.85, ULOQ: 15502.7
Ancestral (D614G): LLOQ: 18.5, ULOQ: 45118
N = number of participants with non-missing data at the corresponding timepoint
a. Based on ANCOVA modeling, includes adjustment for treatment group, pre-booster ant body titers, and age
b. Non-inferiority: LB of 97.5% CI ≥ 0.67; Superiority: LB of 97.5% CI > 1
c. Non-inferiority: LB of 97.5% CI ≥ 0.67
d. Rounded from 1.493

For the primary analyses, seroresponse after the second booster dose was defined based on each participant's nAb titer level at pre-Dose 1 of the primary series relative to the LLOQ for the assay as follows:

- Seroresponse for participants with pre-Dose 1 < LLOQ is defined as ⩾4 x LLOQ
- Seroresponse for participants with pre-Dose 1 ≥ LLOQ is defined as 4-fold increase in titers compared to pre-Dose 1 titer

For participants without pre-primary series baseline antibody titer data available, a titer of <LLOQ was imputed. For participants without SARS-CoV-2 status information pre-primary series, the SARS-CoV-2 status reported pre-second booster dose was imputed.

The pre-specified primary analyses evaluating the seroresponse rates against Omicron BA.1 after a second booster dose estimated seroresponse rates of 100% for mRNA-1273.214 recipients and 99.2% for mRNA-1273 recipients, with SRR difference of 1.5% (97.5% CI: -1.1, 4.0), thus demonstrating non-inferiority based on the LB >-10%. The assessment of the key secondary endpoint of non-inferiority of mRNA-1273.214 compared to mRNA-1273 with regard

to seroresponse rates against the ancestral strain could not be performed as the rates were 100% for mRNA-1273.214 recipients and 100% for mRNA-1273 recipients.

As described above, for the primary analyses, seroresponse following the second booster dose was defined based on nAb titer levels prior to the 1st dose of the primary series. Therefore, nAb titer levels after the second booster dose are likely influenced by the prior three mRNA-1273 doses (two primary series doses and the first booster dose) and cannot solely be attributed to vaccination with the second booster dose. Additionally, to estimate seroresponse rates, the majority of study participants had baseline (pre-Dose 1) values imputed for nAb titers and SARS-CoV-2 status. Therefore, the primary analyses evaluating seroresponse rates have several limitations that make their interpretability difficult. As a result, FDA requested that Moderna conduct post hoc analyses using a revised seroresponse definition that assessed the increase in nAb titer levels from pre-second booster dose, a more clinically relevant time point than pre-first dose of the primary series. For these descriptive analyses, seroresponse following the second booster dose were defined as follows:

- Seroresponse for participants with pre-2nd booster < LLOQ is defined as ⩾4 x LLOQ
- Seroresponse for participants with pre-2nd booster ≥ LLOQ is defined as ≥4-fold increase in titers compared to pre-2nd booster titer

The post hoc descriptive analysis evaluating the revised seroresponse rates are shown in Table 10. With the revised seroresponse definition, the LB of the 97.5% CI of the difference in SRRs (mRNA-1273.214 minus mRNA-1273) against Omicron BA.1 was 12.9% and against the ancestral strain was 2.1%.

FDA guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19", (updated March 2022), recommends that studies be adequately powered to demonstrate non-inferiority of the SRR elicited by a modified booster vaccine compared to prototype vaccine using a non-inferiority margin of >-5%, or that 'simple' or 'super' superiority be demonstrated using a margin of >0% or >10%, respectively. Based on these statistical margins, if the post hoc SRR analyses using the revised definition had been pre-specified with formal hypothesis testing, then mRNA-1273.214 would have demonstrated super-superiority against Omicron BA.1 and simple superiority against the ancestral strain as compared to mRNA-1273.

Table 10. Post-hoc Analyses of Seroresponse Rates (SRR) as Measured by Pseudovirus nAb Assay (ID50) against Omicron (BA.1) and the Ancestral Strain (D614G) at Day 29, Study P205 Part F Cohort 2 and Part G, PPSI-Neg

Variant	Part G mRNA-1273.214 Seroresponders[a] n/N (%) (95% CI)[b]	Part F mRNA-1273 Seroresponders[a] n/N (%) (95% CI)[b]	Difference in SRR (mRNA-1273.214 – mRNA-1273) (97.5% CI)[c]
Omicron (BA.1)	250/334 (74.9) (69.8, 79.4)	138/260 (53.1) (46.8, 59.3)	21.6% (12.9, 30.3)
Ancestral (D614G)	180/334 (53.9) (48.4, 59.3)	111/260 (42.7) (36.6, 49.0)	11.2% (2.1, 20.3)

Source: IR response received August 19, 2022, Table 3
Omicron (BA.1): LLOQ: 19.85, ULOQ: 15502.7
Ancestral (D614G): LLOQ: 18.5, ULOQ: 45118
N = number of participants with non-missing data at the corresponding timepoint

a. Seroresponse from pre- to post-2nd booster at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ if subject pre-2nd booster baseline is below the LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ.
b. 95% CI is calculated using the Clopper-Pearson method.
c. 97.5% CI is calculated using the stratified Miettinen-Nurminen method adjusted by age group. When both groups have response rate equal to 100%, common risk difference and 97.5% CI cannot be calculated.

Subgroup analyses of primary and key secondary immunogenicity endpoints

Subgroup analyses of co-primary immunogenicity endpoints were performed in 2 age cohorts in the PPSI-Neg Set: 18 through 64 years and ≥65 years. Neutralizing antibody GMT results and SRR for each age cohort against Omicron (BA.1) and the ancestral strain (D614G) were generally consistent with the results observed in the overall primary immunogenicity analyses (Table 11 and Table 12). Subgroup analyses for SRRs against Omicron BA.1 and the ancestral strain are based on the revised seroresponse definition (described in the prior section) that is considered more clinically relevant.

Table 11. Geometric Mean SARS-CoV-2 Neutralizing Titers (GMTs) and Seroresponse Rates (SRR) as Measured by Pseudovirus nAb Assay (ID50) against Omicron (BA.1) at Day 29, Study P205 Part F Cohort 2 and Part G, PPSI-Neg, by Age Group

Age Group (Years)	Part G mRNA-1273.214	Part F mRNA-1273	mRNA-1273.214 (/or -) mRNA-1273
	GMT (95% CI)[a]	GMT (95% CI)[a]	GMT Ratio (95% CI)[a]
18-64	n=195 2264.7 (2019.6, 2539.6)	n=140 1207.2 (1054.5, 1381.9)	1.9 (1.6, 2.2)
≥65	n=139 2721.1 (2352.1, 3148.0)	n=120 1710.6 (1462.2, 2001.1)	1.5 (1.3, 2.0)
	Seroresponders[b] n1/N1 (%) (95% CI)[c]	Seroresponders[b] n1/N1 (%) (95% CI)[c]	Difference in SRR (97.5% CI)[d]
18-64	148/195 (75.9) (69.3, 81.7)	71/140 (50.7) (42.1, 59.3)	25.2% (13.3, 36.6)
≥65	102/139 (73.4) (65.2, 80.5)	67/120 (55.8) (46.5, 64.9)	17.6% (4.2, 30.5)

Source: P205 Tables Table 14.2.2.1.7.8, 14.2.2.1.8.8, IR response received August 19, 2022, Table 3
LLOQ: 19.85, ULOQ: 15502.7
n = number of participants with non-missing data at the corresponding timepoint
n1= number of partipants fulfilling seroresponse definition (see footnote C)
N1 = Number of participants with non-missing data pre- and post-2nd booster dose
a. Based on ANCOVA modeling, includes adjustment for treatment group, pre-booster ant body titers
b. Seroresponse from pre- to post-2nd booster at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ if subject pre-2nd booster baseline is below the LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. This was a post hoc analysis.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 97.5% CI is calculated by Miettinen-Nurminen method. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk difference.

Table 12. Geometric Mean SARS-CoV-2 Neutralizing Titers (GMTs) and Seroresponse Rates (SRR) as Measured by Pseudovirus nAb Assay (ID50) against the Ancestral Strain (D614G) at Day 29, Study P205 Part F Cohort 2 and Part G, PPSI-Neg, by Age Group

Age Group (Years)	Part G mRNA-1273.214	Part F mRNA-1273	mRNA-1273.214 (/or -) mRNA-1273
	GMT (95% CI)[a]	**GMT (95% CI)[a]**	**GMT Ratio (95% CI)[a]**
18-64	n=195 5444.6 (4979.8, 5952.7)	n=140 4212.6 (3791.3, 4680.7)	1.3 (1.1, 1.5)
≥65	n=139 7723.7 (6922.0, 8618.1)	n=120 6880.3 (6114.8, 7741.8)	1.1 (1.0[b], 1.3)
	Seroresponders[c] n (%) n1/N1 (%) (95% CI)[d]	**Seroresponders[c] n (%) n1/N1 (95% CI)[d]**	**Difference in SRR (97.5% CI)[e]**
18-64	104/195 (53.3) (46.1, 60.5)	55/140 (39.3) (31.1, 47.9)	14.1% (1.6, 26.0)
≥65	76/139 (54.7) (46.0, 63.1)	56/120 (46.7) (37.5, 56.0)	8.0% (-6.0, 21.7)

Source: P205 Table 14.2.2.1.7.8 and Response to IR received August 19, 2022, Table 3
LLOQ: 18.5, ULOQ: 45118
n = number of participants with non-missing data at the corresponding timepoint
n1= number of partipants fulfilling seroresponse definition (see footnote C)
N1 = Number of participants with non-missing data pre- and post-2nd booster dose
a. Based on ANCOVA modeling, includes adjustment for treatment group, pre-booster ant body titers
b. Rounded from 0.955
c. Seroresponse from pre- to post-2nd booster at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ if subject pre-2nd booster baseline is below the LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. This was a post hoc analysis.
d. 95% CI is calculated using the Clopper-Pearson method.
e. 97.5% CI is calculated by Miettinen-Nurminen method.. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk difference.

Most of the study participants in Part G and Part F were White and Non-Hispanic; therefore, subgroup analyses by race and ethnicity were not conducted, as the number of participants in most subgroups would be too small to allow for meaningful interpretation of the results.

Subgroup analyses of co-primary endpoints based on baseline SARS-CoV-2 status are shown in Table 13. GMT ratios for both Omicron (BA.1) and the ancestral strain were similar for all baseline groups. Neutralizing antibody GMTs against Omicron and the ancestral strains were notably higher after booster vaccinations in participants who were SARS-CoV-2 positive at baseline compared to those who were negative at baseline.

Table 13. Geometric Mean SARS-CoV-2 Neutralizing Titers (GMTs) as Measured by Pseudovirus nAb Assay (ID50) against Omicron (BA.1) and Ancestral Strain (D614G) at Day 29, Study P205 Part F Cohort 2 and Part G, PPSI, by Baseline SARS-CoV-2 Status

Variant	Baseline SARS-CoV-2 Status	Part G mRNA-1273.214 GMT (95% CI)[a]	Part F mRNA-1273 GMT (95% CI) [a]	GMT Ratio mRNA-1273.214 /mRNA-1273 (95% CI) [a]
Omicron (BA.1)	Any	n=428 3232.5 (2951.8, 3539.9)	n=367 1815.1 (1650.0, 1996.7)	1.8 (1.6, 2.0)
Omicron (BA.1)	Positive	n=94 7669.2 (6470.7, 9089.6)	n=98 4041.5 (3375.1, 4839.5)	1.9 (1.5 [b], 2.4)
Ancestral (D614G)	Any	n=428 6555.7 (6122.3, 7019.7)	n=367 5301.4 (4931.8, 5698.7)	1.2 (1.1, 1.4)
Ancestral (D614G)	Positive	n=94 9891.5 (8732.2, 11204.8)	n=98 7776.5 (6813.0, 8876.3)	1.3 (1.1, 1.5)

Source: P205 Table 14.2.2.1.9.8, 14.2.2.1.3.8
Omicron (BA.1): LLOQ: 19.85, ULOQ: 15502.7
Ancestral (D614G): LLOQ: 18.5, ULOQ: 45118
n = number of participants with non-missing data at the corresponding timepoint
a. The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years) and pre-booster antibody titer level (in log 10 scale). The treatment variable corresponds to the each individual study arm dose. The resulted LS means, difference of LS means, and confidence intervals are back transformed to the original scale for presentation.
b. Rounded from 1.499

Secondary Immunogenicity Analyses: Omicron BA.4/BA.5

As descriptive analyses, nAb titers generated against Omicron BA.4/BA.5 subvariants in mRNA1273.214 (P205 Part G) recipients and mRNA-1273 (P205 Part F Cohort 2) recipients were evaluated with a non-validated pseudovirus nAb assay. Results of these analyses are shown in Table 14. The nAb GMTs against BA.4/BA.5 were higher in mRNA-1273.214 recipients compared to mRNA-1273 recipients, with a GMT ratio of 1.7 (95% CI of 1.5 to 1.8). Formal hypothesis testing were not prespecified for this endpoint; however, the observed results met the superiority (margin of >1-fold for GMT ratio) and super-superiority criteria (margin of >1.5-fold for GMT ratio) recommended in the FDA Guidance for Industry, "Emergency Use Authorization for Vaccines to Prevent COVID-19" (updated March 2022), with regard to clinical data to support effectiveness of modified COVID-19 vaccines. Since the pre-booster GMT was higher in the mRNA-1273 group, the ratio of geometric mean fold-rises (mRNA-1273.214 / mRNA-1273) is expected to be even higher than the post-booster GMT ratio.

Table 14. Geometric Mean SARS-CoV-2 Neutralizing Titers (GMTs) as Measured by Pseudovirus nAb Assay (ID50) against Omicron (BA.4/BA.5) at Pre- and Post-Second Booster (Day 29), Study P205 Part G and Part F Cohort 2, PPSI, Any Baseline SARS-CoV-2 Status

Time Point	Part G mRNA-1273.214 GMT (95% CI)	Part F mRNA-1273 GMT (95% CI)	GMT Ratio mRNA-1273.214/mRNA-1273 (95% CI)
Pre-**Second** Booster[a]	N1 = 428 172.7 (147.5, 202.3)	N1=367 209.3 (179.5, 244.1)	N/A
Post-**Second** Booster[b]	N1=427 985.4 (914.8, 1061.4)	N1= 367 588.4 (544.1, 636.2)	1.7 (1.5 [c], 1.8)

Source: P205, Table 5 and Table 10 from tables-mrna-p205-ba4-5-id50-id80-titers.pdf

CI = confidence interval, GMT = geometric mean titer
N1 = Number of subjects with non-missing data at the corresponding timepoint.
Antibody values reported as below the lower limit of detection (LOD) are replaced by 0.5 x LOD.
a. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value then back transformed to the original scale for presentation.
b.The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years), baseline SARS-CoV-2 status, and pre-booster antibody titer level (in log 10 scale). The treatment variable corresponds to each individual study arm dose.
c. Rounded from 1.521

Similar results as those presented above were observed when the analysis was restricted to participants with no evidence of prior SARS-CoV-2 infection or participants with evidence of prior infection pre-booster.

Clinical efficacy

The occurrences of COVID-19 and SARS-CoV-2 infection at least 14 days after vaccination were descriptively evaluated as exploratory endpoints in the study. As of the April 27, 2022, data cutoff, the mRNA-1273.214 group had a median follow-up for efficacy of 43 days, and the mRNA-1273 group had a median follow-up of 57 days. The study evaluated the first occurrence of symptomatic COVID-19 in participants without evidence of previous SARS-CoV-2 infection at baseline (pre-study vaccine) who received the planned dose of study vaccination and had no major protocol deviations. Two different case definitions of COVID-19 were used: the COVID-19 case definition used in study P301 (primary definition) and the CDC COVID-19 case definition (secondary definition). Both definitions, along with the case definitions for SARS-CoV-2 infection and asymptomatic SARS-CoV-2 infection, are further detailed in Appendix C.

In the mRNA-1273.214 (Part G) Per Protocol Set for Efficacy (PPSE, N=339), there were 4 cases of COVID-19 using the primary definition and 5 cases using the secondary definition. The exposure adjusted incidence rate per 1000 person-weeks (95% CI) was 1.9 (0.6, 5.0) using the primary case definition and 2.4 (0.8, 5.7) using the secondary case definition. In the mRNA-1273 (Part F, Cohort 2) PPSE (N=266), there was 1 COVID-19 case which met both case definitions, with an exposure adjusted incidence rate of 0.5 (0.0, 2.5) per 1000 person-weeks. There was an additional COVID-19 case (meeting both primary and secondary case definitions) reported in an mRNA-1273 recipient who was not in the PPSE due to missing baseline PCR, but who had negative serology for prior SARS-CoV-2 infection.

All reported cases of symptomatic COVID-19 were assessed as mild per the protocol-defined grading scale for severity of unsolicited AEs (i.e., mild was defined as events that did not interfere with the participant's daily activities).

Starting 14 days after study vaccination through data cutoff, in the PPSE for both study groups, SARS-CoV-2 infections, including symptomatic COVID-19 and asymptomatic infection, occurred in 11 mRNA-1273.214 recipients and 5 mRNA-1273 recipients. Of the 11 cases in the mRNA-1273.214 group, 9 were diagnosed based on RT-PCR results (the others based on nucleocapsid antibody testing), of which 5 had sequencing data available. All 5 were identified as Omicron BA.2, consistent with the prevailing SARS-CoV-2 epidemiology during the time period when COVID-19 cases accrued in the study. Among the 5 cases in the mRNA-1273 group, only 1 was diagnosed based on RT-PCR, and sequencing data was not available for this case.

Interpretation of the COVID-19 incidence rates in the two groups is limited by the small number of cases accrued during the short follow-up period, the open-label nature of the study, and evaluation of non-contemporaneous study groups in the setting of changing SARS-CoV-2 epidemiology. During the evaluation period for effectiveness, the predominant circulating SARS-

CoV-2 strain (Omicron BA.2) had already diverged from the strain sequence contained in the vaccine (Omicron BA.1). Although the incidence rate of COVID-19 in the mRNA-1273.214 group was higher compared to that in the mRNA-1273 group, confidence intervals were overlapping between the two groups. It is uncertain at this time what the relative effectiveness of a mRNA-1273.214 booster dose compared to a mRNA-1273 booster dose would be in the setting of Omicron BA.4/BA.5 predominance; however, the neutralizing antibody responses against Omicron BA.1, Omicron BA.4/5, and ancestral strain after mRNA-123.214 compared to after mRNA-1273 suggest that clinical effectiveness would be unlikely to be lower after boosting with mRNA-1273.214 compared with mRNA-1273.

6.1.5 Safety Results

Overview of adverse events

Primary safety analyses included safety data available through the cutoff date of April 27, 2022, with a median duration of safety follow-up of 43 days for the mRNA-1273.214 recipients in Part G and 57 days for the mRNA-1273 recipients in Part F Cohort 2. Table 15 summarizes ARs and AEs reported by the safety populations in each study part. Overall, the reported occurrences of ARs and unsolicited AEs within 28 days after vaccination were generally comparable for mRNA-1273.214 recipients compared to mRNA-1273 recipients, though MAAEs were more frequently reported in mRNA-1273 recipients, likely attributable to the longer follow-up duration. MAAEs reported within 28 days after vaccination were reported at a similar frequency in each study part, while SAEs were infrequently reported (3 SAEs mRNA-1273.214 vs 1 SAE mRNA-1273). There were no SAEs considered related to study vaccine and no deaths through data cutoff. There were no discontinuations due to AEs.

Table 15. Safety Overview, Study P205, Part F Cohort 2 and Part G, Safety Set, Solicited Safety Set

Event	Part G mRNA-1273.214	Part F mRNA-1273
Solicited ARs within 7 days of vaccination	n/N1 (%)	n/N1 (%)
Any solicited local AR	347/437 (79.4)	279/351 (79.5)
Grade 3 solicited local AR[a]	15/437 (3.4)	12/351 (3.4)
Any solicited systemic AR	307/437 (70.3)	232/351 (66.1)
Grade 3 solicited systemic AR[a]	24/437 (5.5)	16/351 (4.6)
--	--	--
Unsolicited AEs	n/N (%)	n/N (%)
Any TEAE through 28 days after vaccination	81/437 (18.5)	78/377 (20.7)
Any MAAE[b]	58/437 (13.3)	85/377 (22.5)
Related MAAE	2/437 (0.5)	3/377 (0.8)
SAE[b]	3/437 (0.7)	1/377 (0.3)
Related SAE	0	0
AESI[b,c]	0	1/377 (0.3)
Deaths[b]	0	0
AE leading to discontinuation[b]	0	0

Source: P205, Tables 14.3.1.1.1.8, 14.3.1.7.1.8, 14.3.1.7.2.8
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; MAAE=medically attended adverse events; SAE=serious adverse event; TEAE=Treatment Emergent Adverse Event
N = all participants included in the Safety Set
N1= all participants included in the Solicited Safety Set

a. There were no Grade 4 ARs reported in either group
b. Reported through data cutoff: April 27, 2022
c. Investigator assessed AESIs
Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline solicited safety assessment).

Solicited ARs

Solicited ARs were recorded by study participants using e-diaries through 7 days following vaccination. The rates were comparable for mRNA-1273.214 and mRNA.1273 recipients. Frequently reported solicited ARs in the mRNA-1273.214 recipients, in decreasing order of frequency, were injection site pain (77.3%), fatigue (54.9%), headache (43.9%), myalgia (39.6%), arthralgia (31.1%), chills (23.8%), axillary swelling/tenderness (17.4%), nausea/vomiting (10.3%), injection site swelling (6.9%), injection site erythema (6.9%), and fever (4.4%).

Solicited Local ARs

The occurrences and severities of solicited local ARs reported by study part and age cohort (18-64 years, ≥65 years) are shown in Table 16. There were no solicited local ARs with Grade 4 severity in either study part. Injection site erythema, including grade 3 erythema, was reported more frequently among mRNA-1273.214 recipients compared to mRNA-1273 recipients. The frequency of other reported local ARs was generally balanced across both sets of vaccine recipients. Overall, solicited local ARs were reported less frequently in participants in the ≥65 years age cohort compared to the 18-64 years cohort.

Among mRNA-1273.214 recipients, the median day of onset of local ARs was between 1 and 2 days post-vaccination and the median duration was 2 days (range 1 to 10 days). Among mRNA-1273 recipients, the median day of onset was also between 1 and 2 days post vaccination and the median duration was 2 days (range 1 to 22 days). There were no delayed (i.e., onset >7 days after vaccination) local ARs reported.

There were no substantial differences in the frequencies or severities of reported local solicited ARs based on participant pre-booster SARS-CoV-2 status (i.e., evidence of prior SARS-CoV-2 infection or no evidence of prior SARS-CoV-2 infection).

Table 16. Frequency of Solicited Local ARs Within 7 Days of Dose, by Age Cohort, Study P205 Part F Cohort 2 and Part G, Solicited Safety Set

Event	Part G mRNA-1273.214 18 – 64 years N=263 n (%)	Part F mRNA-1273 18 – 64 years N=211 n (%)	Part G mRNA-1273.214 ≥65 years N=174 n (%)	Part F mRNA-1273 ≥65 years N=140 n (%)
Solicited local AR				
Any	235 (89.4)	180 (85.3)	112 (64.4)	99 (70.7)
Grade 3	10 (3.8)	9 (4.3)	5 (2.9)	3 (2.1)
Pain				
Any	231 (87.8)	175 (82.9)	107 (61.5)	94 (67.1)
Grade 3[a]	2 (0.8)	4 (1.9)	2 (1.1)	0

Event	Part G mRNA-1273.214 18 – 64 years N=263 n (%)	Part F mRNA-1273 18 – 64 years N=211 n (%)	Part G mRNA-1273.214 ≥65 years N=174 n (%)	Part F mRNA-1273 ≥65 years N=140 n (%)
Axillary swelling/tenderness				
Any	56 (21.3)	39 (18.5)	20 (11.5)	15 (10.7)
Grade 3[a]	0	4 (1.9)	1 (0.6)	0
Swelling				
Any ≥25mm	22 (8.4)	15 (7.1)	8 (4.6)	8 (5.7)
Grade 3[b]	4 (1.5)	2 (0.9)	1 (0.6)	3 (2.1)
Erythema				
Any ≥25mm	20 (7.6)	10 (4.7)	10 (5.7)	3 (2.1)
Grade 3[b]	7 (2.7)	1 (0.5)	2 (1.1)	1 (0.7)

Source: P205, 14.3.1.1.2.8
N=number of exposed subjects who submitted any data for the event
No grade 4 solicited local ARs were reported.
a. Grade 3 pain and axillary swelling or tenderness: any use of prescription pain reliever/prevents daily activity
b. Grade 3 erythema (redness) and swelling (hardness): >100mm/>10cm
Notes: Any=Grade 1 or higher. The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline solicited safety assessment).

Solicited systemic adverse reactions

The frequencies and severities of solicited systemic ARs by study part and age cohort are shown in Table 17. Rates of systemic ARs were generally comparable between mRNA-1273.214 and mRNA-1273 recipients, with the exception of a higher frequency of fever and chills in the ≥65 years age cohort after mRNA-1273.214 (5.2% [n=9] and 23.0% [n=40], respectively) compared to after mRNA-1273 (1.4% [n=2] and 14.4% [n=20], respectively), although these were based on a small number of cases. There were no solicited systemic ARs with Grade 4 severity in either study part. Overall, solicited systemic ARs were reported less frequently in participants in the ≥65 years age cohort compared to the 18-64 years cohort.

Among mRNA-1273.214 recipients, the median day of onset of systemic ARs was between 1 and 2 days post vaccination and the median duration was 2 days (range 1 to 21 days). Among mRNA-1273 recipients, the median day of onset was also between 1 and 2 days post vaccination and the median duration was 2 days (range 1 to 13 days). There were no delayed (i.e., onset >7 days after vaccination) systemic ARs reported.

There were no substantial differences in the frequencies or severities of solicited systemic ARs based on participant pre-booster SARS-CoV-2 status.

Table 17. Frequency of Solicited Systemic ARs Within 7 Days of Dose, by Age Cohort, Study P205 Part F Cohort 2 and Part G, Solicited Safety Set

Event	Part G mRNA-1273.214 18 – 64 years N=262-263 n (%)	Part F mRNA-1273 18 – 64 years N=211 n (%)	Part G mRNA-1273.214 ≥65 years N=174 n (%)	Part F mRNA-1273 ≥65 years N=139-140 n (%)
Solicited Systemic AR	--	--	--	--
Any	197 (74.9)	149 (70.6)	110 (63.2)	83 (59.3)
Grade 3	17 (6.5)	9 (4.3)	7 (4.0)	7 (5.0)
Fever[a]	--	--	--	--
Any	10 (3.8)	10 (4.7)	9 (5.2)	2 (1.4)
Grade 3	1 (0.4)	0	0	0
Headache	--	--	--	--
Any	129 (49.0)	100 (47.4)	63 (36.2)	44 (31.7)
Grade 3[b]	4 (1.5)	1 (0.5)	1 (0.6)	1 (0.7)
Fatigue	--	--	--	--
Any	154 (58.6)	115 (54.5)	86 (49.4)	65 (46.8)
Grade 3[c]	10 (3.8)	7 (3.3)	5 (2.9)	4 (2.9)
Myalgia	--	--	--	--
Any	113 (43.0)	90 (42.7)	60 (34.5)	45 (32.4)
Grade 3[c]	9 (3.4)	8 (3.8)	1 (0.6)	5 (3.6)
Arthralgia	--	--	--	--
Any	87 (33.1)	69 (32.7)	49 (28.2)	42 (30.2)
Grade 3[c]	3 (1.1)	2 (0.9)	1 (0.6)	1 (0.7)
Nausea/vomiting	--	--	--	--
Any	35 (13.3)	27 (12.8)	10 (5.7)	8 (5.8)
Grade 3[d]	0	0	1 (0.6)	0
Chills	--	--	--	--
Any	64 (24.3)	54 (25.6)	40 (23.0)	20 (14.4)
Grade 3[e]	1 (0.4)	0	0	1 (0.7)
Use of antipyretic or pain medication	104 (39.5)	67 (31.8)	46 (26.4)	40 (28.6)

Source: P205, Table 14.3.1.1.2.8, 14.1.5.4.8
N=number of exposed subjects who submitted any data for the event
No grade 4 solicited systemic ARs were reported.
a. Fever is defined as: Any= ≥ 38°C; Grade 3 = 39 to 40°C
b. Grade 3 headache: significant, any use of prescription pain reliever or prevents daily activity
c. Grade 3 fatigue, myalgia, arthralgia: significant, prevents daily activity
d. Grade 3 nausea/vomiting: prevents daily activity, requires outpatient intravenous hydration
e. Grade 3 chills: prevents daily activity and requires medical intervention

Unsolicited adverse events

At least 28 days of follow-up after the study dose were available for 99.8% of mRNA-1273.214 recipients and 100% of mRNA-1273 recipients. Unsolicited AEs which occurred within 28 days of vaccination and at rates of ≥1% in any treatment group are shown in Table 18. Rates of unsolicited AEs were generally comparable across study groups. Unsolicited AEs were most frequently reported under the System Organ Class (SOC) *Infections and Infestations* (among 6.6% of mRNA-1273.214 recipients and 8.8% of mRNA-1273 recipients), of which *Upper respiratory tract infection* was the most commonly report Preferred Term (PT).

Severe unsolicited AEs were rare and were reported by 4 mRNA-1273.214 recipients (0.9%) in the 3 mRNA-1273 recipients (0.8%) within 28 days after vaccination.

Table 18. Unsolicited Adverse Events Occurring in ≥1% of Any Treatment Group Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Study P205, Safety Set

Adverse Event (AE)	Part G mRNA-1273.214 N=437 n (%)	Part F mRNA-1273 N=377 n (%)
Unsolicited AEs (Any)	81(18.5)	78 (20.7)
System Organ Class Preferred Term	--	--
Infections and infestations	29 (6.6)	33 (8.8)
Upper respiratory tract infection	5 (1.1)	9 (2.4)
Coronavirus infection	3 (0.7)	8 (2.1)
COVID-19	5 (1.1)	1 (0.3)
General disorders and administration site conditions	21 (4.8)	17 (4.5)
Fatigue	11 (2.5)	12 (3.2)
Musculoskeletal and connective tissue disorders	14 (3.2)	12 (3.2)
Arthralgia	7 (1.6)	7 (1.9)
Myalgia	5 (1.1)	6 (1.6)
Nervous system disorders	8 (1.8)	5 (1.3)
Headache	7 (1.6)	4 (1.1)
Respiratory, thoracic and mediastinal disorders	5 (1.1)	2 (0.5)
Skin and subcutaneous tissue disorders	4 (0.9)	7 (1.9)
Injury, poisoning and procedural complications	9 (2.1)	4 (1.1)

Source: P205, Table 14.3.1.8.1.8
COVID-19=coronavirus disease 2019; 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.

Unsolicited AEs that were considered related to the study vaccine were reported by 5.7% and 5.8% of the mRNA-1273.214 and mRNA-1273 recipients, respectively. The majority of these events were consistent with events assessed as solicited adverse reactions. By PT, *Fatigue* (2.1%), *Headache* (1.4%), and *Arthralgia* (1.4%) were the most commonly reported AEs considered related to study vaccine.

Adverse events of clinical interest
Participants are monitored in the study for AESIs based on a list of AEs developed by the Brighton Collaboration to be relevant to COVID-19 vaccines (Appendix A).

As of the data cutoff, there were no protocol-defined AESIs in mRNA-1273.214 Part G. There was one protocol-defined AESI in mRNA-1273 Part F reported by a 71-year-old male with a history of hypertension, hyperlipidemia, and type 2 diabetes who developed irregular heart rate on Day 17 post-vaccination. This event was considered by the investigator to be unrelated to the study vaccine. The FDA agrees with the investigator's assessment of the relatedness of this event based on the interval between vaccination and onset of the AESI and the participant's comorbid conditions.

FDA Standard MedDRA Queries
FDA conducted Standard MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited AEs with onset following study vaccination through the data cutoff date. SMQs were conducted on AE Preferred Terms (PTs) that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which resulted in an imbalance in events between Part

G and Part F and/or which captured events considered clinically relevant by the FDA, will be discussed.

Cardiac-related SMQs
To capture events potentially concerning for myocarditis and pericarditis, the safety data was queried using several cardiac-related SMQs (including *Cardiomyopathy*, *Cardiac arrhythmia*, *Cardiac failure, Ischemic heart disease, and Noninfectious myocarditis and pericarditis*). The search also included additional terms based on the CDC working case definition of myocarditis and pericarditis (Appendix C). Analysis of the data through the data cutoff identified one event in mRNA-1273.214 Part G and 3 events in mRNA-1273 Part F. All events were mild to moderate in severity. None of these events was clinically consistent with myocarditis or pericarditis, and FDA agrees with the investigator's assessment that none of these events was related to study vaccine.

The mRNA-1273.214 recipient who reported one event was a 53-year-old female participant with a history of obesity who developed tachycardia on Day 7 after vaccination, which resolved on the same day without treatment. Of note, this participant reported an AE of cough on Day 3 and symptomatic COVID-19 on Day 5.

The three events reported in mRNA-1273 Part F were:

- A 71-year-old male with irregular heart rate (discussed in AESI section above).
- A 78-year-old female with a history of cardiac catheterization, hyperlipidemia, and hypertension developed heart failure on Day 41 post-vaccination.
- A 73-year-old male with a history of hypertension and myocardial infarction developed peripheral edema of the left leg on Day 11 post-vaccination.

SMQ Hypersensitivity
Through the data cutoff, events under SMQ *Hypersensitivity* were reported by 0.9% of mRNA-1273.214 recipients and 1.9% of mRNA-1273 recipients. Within 28 days of vaccination, hypersensitivity events were reported by 0.9% of mRNA-1273.214 recipients (events of dermatitis, urticaria, contact dermatitis, and macular rash) and 1.3% of mRNA-1273 recipients (events of contact dermatitis [n=2], eczema, and urticaria [n=2]). None of the identified events were clinically consistent with anaphylaxis.

SMQ analyses by FDA did not identify any substantial imbalances in the reported types of AEs and no new safety concerns were identified.

Serious adverse events (SAEs)
From the study dose through data cutoff, SAEs were reported in 3 mRNA-1273.214 recipients (0.7%) and 1 mRNA-1273 recipient (0.3%).

The following SAEs occurred among mRNA-1273.214 recipients:

- A 75-year-old male participant was diagnosed with prostate cancer on Day 2 after vaccination. This participant had a history of elevated prostate specific antigen (PSA) and the diagnosis was based on results from prostate biopsy performed 2 days prior to study vaccination.
- A 67-year-old male participant developed kidney stones on Day 44 after vaccination requiring hospitalization.
- A 66-year-old female participant experienced traumatic pelvic fracture due to a motor vehicle accident on Day 13 after vaccination.

In mRNA-1273 Part F, a 67-year-old female participant with a history of spinal osteoarthritis had worsening osteoarthritis symptoms on Day 9 after vaccination requiring hospitalization and surgery for spinal fusion.

FDA agrees with the investigator's assessment that none of these events were related to study vaccine.

Deaths
There were no reported deaths among participants in either study group through the data cutoff.

Pregnancies
No pregnancies were reported through the data cutoff.

6.1.6 Summary of Findings from Study P205 Part G and Part F Cohort 2

The comparison of immune response post-booster between mRNA-1273.214 recipients and mRNA-1273 recipients against both the Omicron BA.1 strain and the ancestral strain (D614G) provided the primary evidence to support effectiveness of mRNA-1273.214 as a booster dose. The GMT ratio (mRNA-1273.214 to mRNA-1273) against Omicron BA.1 was 1.7 (95% CI 1.5, 2.0) which met the pre-specified success criterion for statistical superiority. Based on the protocol definition for seroresponse, which was defined as pre-primary series to post-second booster, the SRR against Omicron BA.1 after a second booster was 100% in the mRNA-1273.214 group and 99.2% in the mRNA-1273 group, with an SRR difference of 1.5% (97.5% CI -1.1, 4.0), which met the pre-specified success criteria of demonstration of non-inferiority against Omicron BA.1. In a post hoc analysis using a more clinically meaningful seroresponse definition comparing neutralizing antibody titers pre-second booster to post-second booster, the difference in SRRs (mRNA-1273.214 minus mRNA-1273) against Omicron BA.1 was 21.6% (95% CI 12.9, 30.3) which would have met the protocol pre-specified criterion for non-inferiority, as well as FDA-recommended criteria for statistical superiority and super-superiority. Statistical superiority was also demonstrated for the GMT ratio and difference in SRR against the ancestral strain. The primary immunogenicity endpoints were based on a population of participants without prior evidence of SARS-CoV-2 infection prior to the second booster dose. Similar GMT ratios against Omicron BA.1 and against the ancestral strain were noted when the endpoints were analyzed using a population of study participants with evidence of prior SARS-CoV-2 infection and in all participants, regardless of pre-booster SARS-CoV-2 status. Similar immune responses were observed across age subgroups (18-64 years and ≥65 years).

In an exploratory analysis, neutralizing antibody titers were evaluated against Omicron BA.4/BA.5 in participants from both study groups. Statistical success criteria were not prespecified for this endpoint; however, superiority (and super-superiority) of mRNA-1273.214 compared to mRNA-1273 was demonstrated, based on GMT ratio. The superior neutralizing antibody response elicited by mRNA-1273.214 compared to mRNA-1273 against the Omicron strain contained in the vaccine (BA.1), a divergent Omicron strain not contained in the vaccine (BA.4/BA.5), and the ancestral strain suggests an improved breadth of coverage provided by this bivalent vaccine compared to the original Moderna COVID-19 vaccine.

Participants were actively monitored for COVID-19 and SARS-CoV-2 infection throughout the study. As of the data cutoff, with a limited duration of follow-up (43 days in mRNA-1273.214 Part G and 57 days in mRNA-1273 Part F), there was a slightly higher incidence rate of COVID-19 observed in the mRNA-1273.214 recipients compared to the mRNA-1273 recipients, but confidence intervals were overlapping between the two groups. Sequencing data were available

from a limited number of cases and were all found to be Omicron BA.2. Interpretation of the COVID-19 incidence rates in the two groups is limited by the small number of cases and the open-label, non-contemporaneous comparison design of the study.

Solicited local and systemic ARs were mostly mild to moderate in severity, generally of short duration, and reported with similar frequency among mRNA-1273.214 and mRNA-1273 recipients. The most common solicited adverse reactions following mRNA-1273.214 as a second booster dose were injection site pain (77.3%), fatigue (54.9%), headache (43.9%), myalgia (39.6%) and arthralgia (31.1%). Overall, solicited local and systemic ARs were reported less frequently in participants in the ≥65 years age cohort compared to the 18-64 years cohort. There were no substantial differences in the frequencies or severities of solicited local or systemic ARs based on participant pre-booster SARS-CoV-2 status (i.e., evidence of prior SARS-CoV-2 infection or no evidence of prior SARS-CoV-2 infection).

The frequencies of reported unsolicited AEs within 28 days after vaccination were generally balanced across study groups. SMQ analyses, including for potential myocarditis or pericarditis related events, identified no substantial imbalances or safety concerns based on the types of reported AEs by the study groups. As of the data cutoff, there were no reported cases of myocarditis or pericarditis in either group. There were no SAEs that were assessed as related to the study vaccine.

6.2 FDA Review of Post-authorization Safety Data

As of August 5, 2022, more than 227 million doses of the original Moderna COVID-19 Vaccine have been administered in the US.[22] It is not known what proportions of these numbers represent unauthorized use of the vaccine. The Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) has not been previously authorized for use and as such, post-authorization safety data are not available. However, post-authorization data for the monovalent original Moderna COVID-19 Vaccine are relevant for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), as these vaccines are manufactured using the same process and both vaccines contain an original SARS-CoV-2 component.

The Vaccine Adverse Event Reporting System (VAERS) was queried for AE reports following administration of the original Moderna COVID-19 Vaccine, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported events were due to the vaccine. A 3rd, 4th, 5th, or 6th COVID-19 vaccine dose as recorded in VAERS might not represent a dose given as an authorized booster dose.

As of August 5, 2022, VAERS received 472,157 AE reports following vaccination with the original Moderna COVID-19 Vaccine, of which 392,530 were US reports, and there were 383,466 reports in adults at least 18 years of age. The top ten most frequently reported MedDRA PTs in US reports (all ages) were headache, pyrexia, fatigue, pain, chills, pain in extremity, nausea, dizziness, injection site pain, and injection site erythema. Note that a report may have one or more PTs.

An additional query of VAERS for US reports for adults ≥18 years of age by dose number retrieved the following: 178,534 reports after dose 1; 104,863 reports after dose 2; 37,460 reports after dose 3; 6,975 reports after dose 4; 146 reports after dose 5; and 21 reports after

dose 6 (data as of August 5, 2022). The most frequent PTs among persons ≥18 years of age receiving a booster dose were expired product administered, headache, pyrexia, fatigue, pain, COVID-19, chills, product storage error, SARS-COV-2 test positive, and pain in extremity.

Safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Anaphylaxis, myocarditis and pericarditis are existing safety concerns that have been added to the product Fact Sheets. Review of passive surveillance AE reports and the Sponsor's periodic safety reports does not indicate new safety concerns. Most AEs are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern.

Anaphylaxis
Post-authorization surveillance for the original Moderna COVID-19 Vaccine 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.[23] Anaphylaxis is an important identified risk in the pharmacovigilance plan (PVP) and included in the vaccine Fact Sheets and Prescribing Information (Section 4 Contraindications, Section 5 Warnings and Precautions, Section 5.1 Management of Acute Allergic Reactions, Section 6 Overall Safety Summary, Section 6.2 Post Authorization Experience).

As of August 5, 2022, there have been a total of 1,037 US reports of anaphylactic/anaphylactoid reaction following the original Moderna COVID-19 Vaccine among individuals of all ages (based on an automated search). PTs included in the automated VAERS query were as follows: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. The estimated crude reporting rate for anaphylaxis following the original Moderna COVID-19 Vaccine for all ages in the US is 4.6 cases per million doses administered which is similar to estimated rates for other vaccines.

Myocarditis and pericarditis
As of May 26, 2022, CDC has verified 1,321 reports using the CDC case definition of myocarditis among people 18 years and older following primary series and first booster of mRNA COVID-19 vaccination. The median age of this group was 28 years (IQR ages 21-42 years), and median time to onset was 3 days (IQR: 2-5 days). The majority of reports were after dose 2 (n=962), followed by dose 1 (n=257), and first booster dose (n=102). Most cases occurred in males (male: n=960; female: n=361) (data per CDC presentation to the VRBPAC on July 19, 2022). Among reports from days 0-7 after vaccination, VAERS reporting rates of myocarditis after mRNA COVID-19 vaccination were highest among young males after dose 2 for ages 18-24, 25-29, and 30-39 (38.9, 15.2, and 7.5 per 1 million doses administered, respectively). Rates among males after the first booster dose were also elevated for ages 18-24 and 25-29 (9.9 and 4.8 per million, respectively) (data per CDC presentation to the ACIP on July 19, 2022).[24]

In summary, postmarketing data with the original Moderna COVID-19 Vaccine demonstrate increased risks of myocarditis and pericarditis, particularly within the period 0-7 days following the second dose of the Moderna COVID-19 Vaccine (monovalent) primary series and following a first booster dose. The observed risk is highest in males 18 through 24 years of age. Although some cases 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. Some, but not all, observational analyses of postmarketing data suggest that there may be an increased risk of

myocarditis and pericarditis in males under 40 years of age following the second dose of the original Moderna COVID-19 Vaccine primary series relative to other authorized or approved mRNA COVID-19 vaccines.

Myocarditis and pericarditis were added as important identified risks in the PVP and included in the vaccine Fact Sheets and Prescribing Information (Section 5 Warnings and Precautions, Section 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience). The Sponsor is conducting additional post-authorization/ postmarketing studies for the monovalent vaccine, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor will also conduct planned post-authorization studies to evaluate the association between the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs in the general US population. To help ensure appropriate monitoring of such risks and protect public health, the Sponsor and vaccination providers will be required, under the conditions of authorization, to report all cases of myocarditis and pericarditis (regardless of seriousness) to VAERS. Because some cases of myocarditis or pericarditis following vaccine administration are conservatively managed and may not meet the definition of serious adverse events, this will help ensure that all cases are reported by the Sponsor and vaccination providers.

7 FDA Review of Other Information Submitted in Support of the EUA

7.1 Summary of Non-clinical Data in Support of the Immunogenicity of mRNA-1273.222

A study in BALB/c mice was conducted to evaluate the immunogenicity elicited by a 2-dose primary vaccination series of monovalent vaccines encoding the S protein from the original strain or the Omicron BA.1 or BA.4/BA.5 sublineages, and bivalent vaccines encoding the original strain S protein and either the Omicron BA.1 or the BA.4/BA.5 S protein. Both binding and neutralizing antibodies were investigated. Binding antibodies were measured (after the first and second vaccine doses) by ELISA using S protein antigens derived from the various strains included in the vaccines under study. The results demonstrate that all vaccines, whether monovalent or bivalent, elicited robust and comparable levels of binding antibodies to the three S protein antigens from the original strain, Omicron BA.1, and Omicron BA.4/BA.5. The monovalent mRNA-1273.045 vaccine, which encodes the BA.4/BA.5 S protein, induced lower IgG titers against the non-matched BA.1 S protein antigen.

Neutralizing antibodies were also assessed after administration of two doses of the respective vaccines. Two single-cycle pseudotype virus systems were used to quantify neutralizing antibodies – the vesicular stomatitis virus system and the lentivirus system. Both systems gave concordant results. The original mRNA-1273 monovalent vaccine induced robust neutralizing antibodies against pseudotype viruses with the homologous S protein, but low activity against pseudotype viruses with the Omicron BA.4/BA.5 S protein. Vaccination with mRNA-1273.222 (bivalent vaccine that encodes S proteins from both the original strain and Omicron BA.4/BA.5) induced neutralizing antibodies against both pseudotype viruses with original strain S protein and those with Omicron BA.4/BA.5 S protein, with titers that exceeded or were similar to those induced by the monovalent vaccines.

A second study was conducted in K18-hACE2 mice to evaluate immunogenicity and protection from Omicron BA.5 challenge after a booster dose of the mRNA-1273.222 vaccine following a primary series vaccination with mRNA-1273. The primary series was administered to mice as a two-dose regimen given 3 weeks apart. Approximately 31 weeks after the second dose, the mice were boosted with either mRNA-1273, mRNA-1273.214, mRNA-1273.222 or with a

negative control. Serum was isolated from the mice at about four weeks after the boost and assessed for neutralizing activity against the original strain and against the Omicron BA.1 and BA.5 viruses. While boosting with mRNA-1273 enhanced the level of neutralizing antibodies against the original virus, it did not boost the neutralizing antibody levels against the BA.1 or BA.4/BA.5 viruses. In contrast, boosting with either mRNA-1273.214 or mRNA-1273.222 increased the levels of neutralizing antibodies against BA.1 or BA.4/BA.5 viruses. Importantly, these vaccines also increased the level of neutralizing antibodies against the original strain.

To monitor the level of protection afforded by boosting, these mice were challenged with Omicron BA.5, and viral load was measured in the upper and lower respiratory tract. In mice vaccinated with mRNA-1273 and boosted with mRNA-1273, mRNA-1273.214 or mRNA-1273.222 vaccine, viral load in lungs, nasal turbinates, and nasal wash was substantially lower than in mice boosted with negative controls. The amount of protection from infection as indicated by the viral load in the lungs was greatest with the mRNA-1273.222 vaccine, followed by the mRNA-1273.214 vaccine, and then the mRNA-1273 vaccine.

From the results of both the immune responses and the challenge studies, boosting with the mRNA-1273.214 or mRNA-1273.222 vaccine improved neutralizing antibody responses and reduced BA.5 viral load in the upper and lower respiratory tract.

7.2 Clinical Assay Information

A pseudovirus neutralization assay (PsVNA) was used for the assessment of neutralizing antibody endpoints in the Phase 2/3 (P205) study of mRNA-1273.214, bivalent vaccine containing mRNAs expressing the SARS-CoV-2 S protein of Omicron BA.1 and (Original) strain. Effectiveness of this vaccine was inferred based on neutralizing antibody responses against a pseudotype virus containing the SARS-CoV-2 S protein from the Omicron BA.1 sublineage and a pseudotype virus containing the spike S protein from the original strain. The PsVNA was developed and validated at the Neutralizing Antibody Core Laboratory at the Duke University Medical Center. The samples from the clinical study were also tested in this laboratory. The quantification of SARS-CoV-2 neutralizing antibodies uses lentivirus particles that incorporate the SARS-CoV-2 S protein on their surface and contain a firefly luciferase reporter gene for quantitative measurement of infection by relative luminescence units (RLU). The presence of neutralizing antibodies in the test samples reduces infection of cells and results in lower RLUs upon infection. In addition, a similar PsVNA, also developed and qualified at the Neutralizing Antibody Core Laboratory at the Duke University Medical Center, was used for a secondary immunogenicity endpoint in study P205 for the assessment of neutralizing antibody responses against the Omicron BA.4/BA.5 sublineage.

7.3 Chemistry, Manufacturing, and Controls (CMC) Information

Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) contains mRNA encoding the Spike protein (S protein) from original strain and mRNA encoding the S protein from the SARS-CoV-2 Omicron BA.4/BA.5 sublineage. A single 0.5 mL dose contains a total of 50 µg (25 µg each of Original and BA.4/BA.5) mRNA, total lipids of 1.01 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.25 mg tromethamine, 1.2 mg tromethamine hydrochloride, 0.021 mg acetic acid, 0.10 mg sodium acetate trihydrate, and 43.5 mg sucrose.

The Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) Drug product (DP) is supplied in multi-dose vials containing a target volume of 3.2 mL (2.5 mL nominal) for extraction of five 0.5 mL doses. Each vial contains an equal mass fraction of each, Original and Omicron BA.4/BA.5 mRNA, totaling (b) (4) mg mRNA and (b) (4) mg of SM-102 lipid nanoparticle (LNP) in a preservative-free buffer. The vaccine is stored frozen between -50º to -15ºC but can be stored refrigerated between 2° to 8°C for up to 30 days prior to first use.

The Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) DP is formulated with two drug substances (DS), each comprised of nucleoside-modified mRNA encoding the pre-fusion stabilized S protein and encapsulated in lipid nanoparticles (LNPs). mRNA-1273 LNP DS contains CX-024414 mRNA expressing the S protein of the original strain and the mRNA-1273.045 LNP-B DS contains CX-034476 mRNA expressing the S protein of the BA.4/BA.5 sublineage. The manufacturing and quality testing sites as well as all unit operations and process controls used to manufacture CX-034476 mRNA, mRNA-1273.045 LNP-B DS, and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) DP are consistent with the previously filed DS and DP processes and controls for the authorized 0.10 mg/mL original Moderna COVID-19 Vaccine. No changes other than the (b) (4) (b) (4) have been made to the CX-034476 mRNA manufacturing process. The DP manufacturing changes are related to the formulation of a bivalent rather than a monovalent vaccine. The lipid composition of the LNP is the same as used in the 0.10 mg/mL original Moderna COVID-19 Vaccine.

All quality tests and acceptance criteria for Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) intermediate, DS and DP are the same as for the original Moderna COVID-19 Vaccine, except for (b) (4) release testing methods. These include a new (b) (4) test performed using (b) (4) of the (b) (4) for release of DS and the mRNA identity and (b) (4) test by (b) (4) and (b) (4) for release of DP. Both tests have been successfully validated for their intended use.

The stability profiles of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5 are expected to remain unchanged compared to the prototype vaccine for all storage conditions.

The manufacture of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is performed at existing facilities that were previously authorized under EUA for the manufacture of the original Moderna COVID-19 Vaccine.

FDA's review of facilities in support of this amended EUA was limited to evaluating whether the facilities involved in the manufacture of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are adequate to support the use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

One manufacturing facility was not included as a facility authorized to manufacture Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), because we were not able to assess the facility's adequacy due to an ongoing FDA inspection. FDA may further consider the inclusion of that manufacturing facility following its review of the inspectional information and any other pertinent information.

FDA finds that all facilities authorized for the manufacture of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are adequate to support its use under an Emergency Use Authorization.

7.4 Inspection of Clinical Study Sites

The review team determined that Bioresearch Monitoring (BIMO) inspections are not needed to support the review of this EUA amendment, because clinical study sites participating in study P205 also participated in studies that supported previous authorizations, and FDA is not aware of any new issues that would raise concerns about clinical trial conduct.

7.5 Planned Pharmacovigilance Activities

Moderna is conducting safety-related post-authorization/post-marketing studies for the monovalent vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Moderna submitted a revised pharmacovigilance plan to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).
The plan includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.
- Missing Information: use in pregnancy and while breast-feeding, long-term safety, use in immunocompromised subjects, interaction with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), use in subjects with autoimmune or inflammatory disorders

Sponsor pharmacovigilance activities

The Sponsor will conduct passive and active surveillance to monitor the post-authorization safety for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); multisystem inflammatory syndrome (MIS); myocarditis; pericarditis; COVID-19 resulting in hospitalization or death.
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether or not associated with an AE; and newly identified safety concerns.
- Post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of adverse events of special interest (AESIs), including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The studies should be conducted in large scale databases with an active comparator. This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Moderna COVID-19 Vaccine, Bivalent in the following studies:
- Study mRNA-1273-P903: Post-Authorization Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity
    - Objective: To characterize the risk of myocarditis and pericarditis and other AESI following Spikevax and include the mRNA-1273.222 booster dose subgroup

analyses for myocarditis and pericarditis if cases following exposure accrue in the database.

- Study mRNA-1273-P911: Long-term Outcomes of Myocarditis Following Administration of Spikevax.
    - Objective: To characterize the long-term outcomes of myocarditis in a mRNA-1273.222 booster dose analysis as a potential risk factor, and pending feasibility, as a subgroup of exposure.

- The Sponsor will propose a new stand-alone post-authorization observational study to evaluate the association between the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs in the general US population for individuals ≥18 years of age who will receive a bivalent booster dose in the US; a study protocol will be submitted by 11/1/2022.

Other pharmacovigilance activities

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)
- Myocarditis
- Pericarditis
- Cases of multisystem inflammatory syndrome
- Cases of COVID-19 that result in hospitalization or death

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 parents/guardians (or the recipient) for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant AE.

7.6 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.

Updates to the Fact Sheet for Health Care Providers (HCP), not directly related to Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), include additional text regarding a case of probable myocarditis in a 14-year-old male Moderna COVID-19 Vaccine recipient in Study P203. Previously, this event had not met criteria for probable/confirmed myocarditis by the study's Cardiac Event Adjudication Committee (CEAC) during the review of the pediatric 6 months through 17 years EUA amendment. Subsequently, the CEAC updated their assessment for this event as probable myocarditis, warranting its inclusion in the Fact Sheet. This event is described in the HCP Fact Sheet under Section 6.1 Clinical Trial Experience; Moderna COVID-19 Vaccine Administered as a Two-Dose Primary Series; Adolescents 12 Years Through 17 Years of Age; Unsolicited Adverse Events.

8 Benefit-Risk Assessment in the Context of Proposed EUA for Moderna COVID-19 Vaccine, Bivalent in Adults 18 Years of Age and Older

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2 and the virus has been responsible for nearly 94 million cases of COVID-19 and over 1.04 million deaths in the US. Since the start of the pandemic, there has been a succession of COVID-19 variants including Beta, Delta, Omicron BA.1 and most recently Omicron BA.5. Current treatment options for COVID-19 include antiviral medications and monoclonal antibodies approved or authorized for the management of individuals with COVID-19. These interventions are generally most effective in disease of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2 they are usually not effective in severe disease. Additionally, such treatments may not prevent complications from COVID-19 including post-acute sequelae of COVID-19 (long COVID).

In addition to the currently authorized and approved treatments, FDA approved and authorized vaccines provide protection to individuals against COVID-19 and play an important role in controlling the pandemic and reducing the societal and economic interruption caused by the pandemic. There are currently 4 approved or authorized COVID-19 vaccines for disease prevention. These include two mRNA-based vaccines, one from Moderna and one from Pfizer-BioNTech, one non-replicating viral vectored vaccine from Janssen/Johnson & Johnson, and one protein-based adjuvanted vaccine from Novavax. These monovalent vaccines are based on the original (ancestral) strain of SARS-CoV-2 and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. A succession of viral variants and waning of individual immunity has led to a reduction in vaccine effectiveness over time. In the setting of the viral variants that have emerged, boosting with available vaccines (based on the ancestral strain) has been able to restore some degree of protection against serious and symptomatic disease, but it appears that effectiveness against transmission and symptomatic disease declines more rapidly than that against serious disease, as has been illustrated by studies conducted in the United States,[25,26] Israel,[17] Qatar,[14] Portugal,[27] and England.[9]

The immunogenicity and safety of mRNA booster vaccines developed against the Beta, Delta, and Omicron BA.1 variants have previously been evaluated by both Moderna and Pfizer-BioNTech. However, these booster vaccines were not deployed in the United States due to the rapid evolution of the SARS-CoV-2 variants. In addition to those clinical data, nonclinical studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response to current predominantly circulating BA.4 and BA.5 variants which is several-fold higher than the response provoked by the original (monovalent) vaccine.

Based on previous experience and available evidence, vaccination with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose is expected to provoke a stronger immune response to the currently circulating BA.4 and BA.5 variants. That noted, it is uncertain exactly how the magnitude of the increase in antibody response to the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose will translate into effectiveness against specific COVID-19 outcomes in humans, including symptomatic and serious disease with currently circulating variants, and this uncertainty is even greater for potential variants that may emerge in the future.

Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and booster doses given previously. The most notable uncommon side effect of the mRNA COVID-19 vaccines has been myocarditis. Based on the

data from BEST, within a week after second dose of mRNA-based COVID-19 vaccine primary series, the crude observed rate (without adjustment for delay of reporting and other factors) of myocarditis or pericarditis events was 2.1 per 100,000 doses for individuals aged 18–64 years (unpublished data), and 12.5 per 100,000 doses for males aged 18–25 years.[28] Within a week after a second dose of vaccine, the adjusted observed rate of myocarditis or pericarditis for individuals aged 18–64 years who received mRNA-based COVID-19 vaccines was 1.8 per 100,000 doses (unpublished data), and 13.0 per 100,000 doses for males aged 18–25 years.[28] The myocarditis associated with the administration of mRNA COVID-19 vaccines has been mild and transient in most cases (>95%). Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns in addition to those previously characterized. In addition, passive and active surveillance systems will be utilized to continuously monitor adverse reactions and any emerging safety concerns post EUA.

The totality of the available evidence indicates that Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster doses will likely increase the immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant. Administration of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster is appropriate for all individuals 18 years of age and older at least two months after previous primary or booster vaccination regardless of the number of prior COVID-19 vaccinations they have had, but is particularly important in those individuals who have never been previously boosted since protection against symptomatic and serious COVID-19 may have waned over time since administration of the primary series. Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns additional to the extensively characterized safety profile of originally authorized and approved mRNA COVID-19 vaccines, and post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess whether any new safety concerns emerge. Table 19 provides a summary of the benefit risk considerations in a standard FDA format.

Table 19. Summary of Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID caused by SARS-CoV-2 has been responsible for nearly 94 million cases and 1.04 million deaths in the US • There has been a succession of variants (Delta, Omicron BA.1 and most recently BA.5) that have led to a reduction in vaccine effectiveness • Although the available COVID-19 vaccines based on the original (ancestral) strain continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased	• COVID-19 is a serious disease associated with significant morbidity and mortality from initial infection and additional morbidity from post-acute sequelae of COVID-19 (long COVID) in a subset of those individuals • Certain available COVID-19 vaccines initially had high effectiveness (90-95%) against symptomatic disease; however, vaccine effectiveness has declined in the setting of the recent Omicron variant in combination with waning individual immunity; this effect is most clearly observed in older individuals

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Antiviral medications and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity • There are four approved or authorized COVID-19 vaccines (two mRNA-based, one non-replicating viral vector, and one protein-based, adjuvanted); these are all effective as primary series, and the mRNA-based and non-replicating viral vector vaccines are effective as boosters	• Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID) • Vaccines play an important role in pandemic control and provide important protection
Benefit	• The immunogenicity and safety of booster vaccines against Beta, Delta, and Omicron BA.1 variants were previously evaluated by both current mRNA vaccine manufacturers; however, these vaccines were not deployed in the US because of SARS-CoV-2 variant evolution • Non-clinical studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response against BA.4 and BA.5 that is many-fold higher than the Original booster • Uncertain how the magnitude of the increase in antibody response in humans will translate into effectiveness against COVID-19 outcomes, including symptomatic and serious disease	• The totality of the available evidence indicates that bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses will likely increase the broad immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant • Administration of bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses is appropriate for all previously vaccinated individuals 18 years and older, regardless of the number of prior COVID-19 vaccinations, but especially those who have never been previously boosted since protection against serious disease may have waned over time since administration of the primary series
Risk and Risk Management	• Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and prior booster doses • Within a week after a second dose of vaccine, the adjusted observed rate of myocarditis or pericarditis for individuals aged 18–64 years who received mRNA-based COVID-19 vaccines was 1.8 per 100,000 doses (unpublished data), and 13.0 per 100,000 doses for males aged 18–25 years.[28]	• Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns additional to the extensively characterized safety profile of original mRNA COVID-19 vaccines • Post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess whether any new safety concerns emerge

8.2 Conclusions Regarding Benefit-Risk

The known and potential benefits of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose outweigh the known and potential risks of the booster considering the totality of available evidence and the outstanding uncertainties. The benefit-risk profile of available mRNA COVID-19 vaccines is well understood following the

administration of over one billion doses. FDA's previous benefit-risk assessments based on real-world evidence clearly demonstrated that the benefits of available COVID-19 vaccines outweigh their risks. During the current wave of COVID-19 caused in large part by the BA.5 lineage, administration of a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose is expected to have a favorable benefit-risk profile, potentially not only restoring protection against serious outcomes from COVID-19, but also by reducing symptomatic disease that may be followed by debilitating post-acute COVID-19 syndrome. Broader protection against COVID-19 variants potentially elicited by the bivalent vaccine may also help protect against future emerging variants.

9 Overall Summary and Recommendation

Following review of information submitted in support of the EUA request, and VRBPAC recommendations from the June 28, 2022, meeting, the review team considered the following in its assessment of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5):

- 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.
- The scientific evidence available to support this EUA request was as follows:
    - clinical safety and immunogenicity data from a study which evaluated a second booster dose with bivalent vaccine (Original and Omicron BA.1) following a primary series and first booster dose with the original Moderna COVID-19 Vaccine,
    - clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the original Moderna COVID-19 Vaccine,
    - post-marketing safety surveillance data with primary series and booster doses of the original Moderna COVID-19 Vaccine, and
    - non-clinical immunogenicity data from a study of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

- Based on FDA's review of the available scientific evidence, it is reasonable to conclude that the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), when administered as a single booster dose to adults 18 years of age and older who have completed primary vaccination or a booster dose of an authorized or approved COVID-19 vaccine at least 2 months prior, may be effective in preventing serious or life-threatening disease or condition that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5. Vaccine effectiveness for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was inferred based on extrapolation of clinical immunogenicity data from a related bivalent COVID-19 vaccine (mRNA-1273.214) containing original and Omicron BA.1 sublineage mRNA components and manufactured using the same process as the original Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Effectiveness of the mRNA-1273.214 vaccine was based on a comparison of SARS-CoV-2 nAb GMTs and seroresponse rates at 1 month following a second booster dose of mRNA-1273.214 to those following a second booster dose of the original Moderna COVID-19 vaccine. Analyses of GMTs against Omicron BA.1 and Original strains met pre-specified statistical success criteria for superiority and non-inferiority, respectively. Post hoc analyses evaluated the seroresponse rates (proportion achieving a ≥4-fold rise in titers from pre-second booster) against both the Original strain and Omicron BA.1 and would

have met statistical criteria for superiority. In a descriptive analysis, nAb GMTs against Omicron BA.4/BA.5, evaluated with an unvalidated assay, were higher in bivalent vaccine (Original and Omicron BA.1) recipients compared to the original Moderna COVID-19 recipients.

- Based on FDA's review of the available scientific evidence, including the data summarized in Section 6 and assessment of benefits and risks in Section 8 of this review, the known and potential benefits of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) outweigh the known and potential risks of the vaccine when used as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to Omicron variant sublineages BA.4 and BA.5. Uncertainties related to benefits include that effectiveness of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to prevent COVID-19 is inferred and extrapolated from immunogenicity data with a different Omicron-containing bivalent vaccine (Original and Omicron BA.1) manufactured by the same process. It is also uncertain how any given magnitude of the increase in antibody response to a bivalent (Original and BA.4/BA.5) booster vaccine, relative to the original (monovalent) vaccine, will translate into effectiveness against COVID-19 outcomes, including symptomatic disease. However, this uncertainty is considered against available evidence demonstrating waning protection from COVID-19 vaccine primary series and booster doses, decreased effectiveness of currently available COVID-19 vaccines against Omicron BA.5 (the predominant SARS-CoV-2 sublineage in the US) compared to previous strains, and the time that would be needed to accrue clinical trial data with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to more directly assess effectiveness. Additional uncertainties include effectiveness against future SARS-CoV-2 variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, and effectiveness in certain high-risk populations such as severely immunocompromised individuals. Known potential risks include generally self-limited common local and systemic adverse reactions, notably injection site pain, fatigue, headache and myalgias, and rarely myocarditis/pericarditis and anaphylaxis based on experience with the original Moderna COVID-19 Vaccine. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

- The Moderna COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine are currently authorized for use under EUA as a first booster dose in individuals 18 years of age and older and individuals 5 years of age and older, respectively, and as a second booster dose in certain populations. The Janssen COVID-19 vaccine is also authorized for limited use under EUA as a first booster dose in individuals 18 years of age and older. These vaccines are monovalent vaccines based on the original (ancestral) SARS-CoV-2 strain. COVID-19 vaccines based on currently circulating variants of concern are not currently approved or available.

Based on the considerations outlined above, the review team recommends authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a booster dose in adults 18 years of age and older at least 2 months after either completion of a primary series or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. The review team also recommends a revision to the existing EUA for Moderna COVID-

19 Vaccine to remove the use of the monovalent vaccine as a first or second booster dose because the benefit/risk profile for booster dose use is expected to be inferior against the currently circulating Omicron variant compared to Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

10 Appendix A. Adverse Events of Special Interest

Table 20. Adverse Events of Special Interest

Medical Concept	Medical Concept Descriptions/Guidance
Anosmia, ageusia	New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
Subacute thyroiditis	Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) DOES NOT INCLUDE new onset of chronic thyroiditis
Acute pancreatitis	New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	Any event of appendicitis
Rhabdomyolysis	New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute respiratory distress syndrome (ARDS)	New onset of ARDS/respiratory failure due to acute inflammatory lung injury DOES NOT INCLUDE non-specific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
Coagulation disorders	New onset of thrombosis, thromboembolic event, or non-traumatic hemorrhage/bleeding disorder (e.g., stroke, DVT, pulmonary embolism, disseminated intravascular coagulation (DIC), etc.)
Acute cardiovascular injury	New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia, confirmed by ECG (e.g., atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute kidney injury	New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc. Increase in serum creatinine by ≥ 0.3 mg/dl (or ≥26.5 µmol/l) within 48 hours; OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days
Acute liver injury	New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc.: >3-fold elevation above the upper normal limit for ALT or AST; OR >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP

Medical Concept	Medical Concept Descriptions/Guidance
Dermatologic findings	Chilblain-like lesions Single organ cutaneous vasculitis; Erythema multiforme Bullous rash Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions
Systemic inflammatory syndromes	Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C) Kawasaki's disease Hemophagocytic lymphohistiocytosis (HLH)
Thrombocytopenia	Platelet count <150 x 10^9/L (thrombocytopenia) New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR. DOES NOT INCLUDE new onset of chronic arthritic conditions
New onset or worsening of neurological disease	Immune-mediated neurological disorders Guillain-Barre syndrome Acute disseminated encephalomyelitis (ADEM) Peripheral facial nerve palsy (Bell's palsy) Transverse myelitis Encephalitis/Encephalomyelitis Aseptic meningitis Seizures/convulsions/epilepsy Narcolepsy/hypersomnia
Anaphylaxis	Anaphylaxis associated with study drug administration
Other syndromes	Fibromyalgia Postural Orthostatic Tachycardia Syndrome Chronic Fatigue Syndrome Myalgic encephalomyelitis Post viral fatigue syndrome Myasthenia gravis

Source: Sponsor's Clinical Study Protocol, mRNA-1273-P205, Appendix 4

11 Appendix B. List of Preferred Terms Used in the Enhanced Analysis for Potential Cases of Myocarditis or Pericarditis, Based on CDC Case Definition

The following PTs were used in the enhanced analysis to identify potential cases of myocarditis or pericarditis based on the CDC case definition (for adults).

- acute chest syndrome
- angina pectoris
- autoimmune myocarditis
- autoimmune pericarditis
- cardiac dysfunction
- cardiac function test abnormal
- cardiomyopathy
- cardiovascular function test abnormal
- chest discomfort
- chest pain
- conduction disorder
- defect conduction intraventricular
- dyspnea
- dyspnea at rest
- dyspnea exertional
- ECG electrically inactive area
- ECG P wave inverted
- ECG signs of myocardial infarction
- ECG signs of myocardial ischemia
- ECG signs of ventricular hypertrophy
- electrocardiogram abnormal
- electrocardiogram ST segment
- electrocardiogram ST segment abnormal
- electrocardiogram ST segment depression
- electrocardiogram ST segment elevation
- electrocardiogram ST-T segment depression
- electrocardiogram ST-T segment abnormal
- electrocardiogram ST-T segment elevation
- eosinophilic myocarditis
- giant cell myocarditis
- hypersensitivity myocarditis
- immune-mediated myocarditis
- magnetic resonance imaging heart
- musculoskeletal chest pain
- myocardial edema
- myocarditis
- painful respiration
- palpitations
- pericardial effusion
- pericardial effusion malignant
- pericardial rub
- pericarditis
- pericarditis constructive
- pleuropericarditis
- syncope
- troponin
- troponin C
- troponin I
- troponin I increased
- troponin I normal
- troponin T increased

Table 21. CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

Condition	Probable Case Definition	Confirmed Case Definition
Acute myocarditis	Presence of ≥ 1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR,** infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥1 new finding of • troponin level above upper limit of normal (any type of troponin) • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[c] • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis[c] **AND** No other identifiable cause of the symptoms and findings	Presence of ≥ 1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR,** infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥1 new finding of • histopathologic confirmation of myocarditis[b] • cMRI findings consistent with myocarditis[c] in the presence of troponin level above upper limit of normal (any type of troponin) **AND** No other identifiable cause of the symptoms and findings
Acute pericarditis[d]	Presence of ≥ 2 new or worsening of the following clinical features: • acute chest pain • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

Source: Sponsor's Clinical Overview, mRNA-1273.214, Appendix 1
Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG/EKG = electrocardiogram.
Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
a Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
b Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
c To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects. Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).
d Adler et al 2015.
e Typically descr bed as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

12 Appendix C. COVID-19 Case Definitions

Table 22. COVID-19 and SARS-CoV-2 Infection Case Definitions in Study P205

Endpoint	Definition
COVID-19 based on P301 case definition	A positive RT-PCR test result by nasal swab, starting 14 days after study vaccination, together with eligible symptoms as follows: At least 2 systemic symptoms: Fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** At least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia
COVID-19 based on CDC case definition	A positive RT-PCR test result by nasal swab, starting 14 days after study vaccination, together with at least one of the following systemic symptoms: fever (temperature >38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours), cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea or vomiting
SARS-CoV-2 infection (regardless of symptoms)	A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline, starting 14 days after study vaccination: bAb levels against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by *Roche Elecsys*) post-study vaccination, **OR** Positive RT-PCR post-study vaccination
Asymptomatic SARS-CoV-2 infection	For participants with negative SARS-CoV-2 status at baseline, starting 14 days after study vaccination: Absence of COVID-19 symptoms **AND** bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 29 or later, **AND/OR** Positive RT-PCR test at scheduled or unscheduled/illness visits

Source: Study P205 protocol amendment 7, P205 Statistical Analysis Plan v3
Abbreviations: bAb=binding antibody; CDC=Centers for Disease Control and Prevention; IP=investigational product; RT-PCR=reverse-transcriptase polymerase chain reaction; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

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