Report on the Deliberation Results

December 15, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	COVID-19 Vaccine Moderna Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 10, 2021

Results of Deliberation

Under the current pandemic of disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on December 15, 2021, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product is the remainder of the re-examination period for the initial approval of the product (until May 20, 2029).

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
3. Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

4. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and who have provided written informed consent through the vaccine screening questionnaire in advance.

Report on Special Approval for Emergency

December 9, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	COVID-19 Vaccine Moderna Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 10, 2021
Dosage Form/Strength	Suspension for injection: Each vial contains 1.0 mg of CX-024414.
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act ("Handling of Drugs Submitted for Special Approval for Emergency (Request)" [PSEHB/PED No. 1125-15 dated on November 25, 2021])
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the booster dose of the product has a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety with no significant safety concerns.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

(No change)

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Dosage and Administration

Primary series:

COVID-19 Vaccine Moderna is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

Booster dose:

A single booster dose (0.25 mL) of COVID-19 Vaccine Moderna is administered intramuscularly.

(Underlines denote additions.)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.

(1) Matters related to Item 2

When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.

(2) Matters related to Item 3

The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(3) Matters related to Item 4

The applicant is required to report the quantity sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

(1) The applicant is required to develop and appropriately implement a risk management plan.

(2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.

(3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

(4) The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have

been provided with the most updated efficacy and safety information of the product in written form, and who have provided written informed consent through the vaccine screening questionnaire in advance.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to any Item of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

Attachment

Report on Special Approval for Emergency (1)

December 2, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	COVID-19 Vaccine Moderna Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 10, 2021
Dosage Form/Strength	Suspension for injection: Each vial contains 1.0 mg of CX-024414.

Proposed Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

(No change)

Proposed Dosage and Administration

Primary series:

COVID-19 Vaccine Moderna is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

Booster dose:

A single booster dose (0.25 mL) of COVID-19 Vaccine Moderna is administered intramuscularly at a recommended interval of at least 6 months after the second dose of the primary series.

(Underlines denote additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

COVID-19 Vaccine Moderna (also referred to as mRNA-1273) is a vaccine containing the mRNA encoding the spike protein of SARS-CoV-2 as the active substance. In Japan, COVID-19 Vaccine Moderna was approved in May 2021 for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)," and vaccinations with Moderna's vaccine started. As of November 26, 2021, more than 75% of the population in Japan has completed 2 doses of SARS-CoV-2 vaccines, including COVID-19 Vaccine Moderna (https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html [last accessed on November 26, 2021]).

Amid the global SARS-CoV-2 vaccine rollout, SARS-CoV-2 infections started to resurge in different parts of the world in the summer of 2021 (https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-october-2021 [last accessed on November 26, 2021]). The COVID-19 resurgence was inferred to be caused by the following factors: (i) the relaxation of restrictions on social activities, such as lifting of COVID-19 containment measures; and (ii) the emergence of the highly infectious and transmissible Delta variant that quickly became the dominant strain (https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10623-covid19-57.html [last accessed on November 26, 2021]). In addition, other concerns include the waning vaccine efficacy of SARS-CoV-2 vaccines which is evident by breakthrough infections in some fully vaccinated individuals (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html [last accessed on November 30, 2021]).

Under the circumstances, some countries and regions have begun to roll out booster vaccinations in individuals who have completed their primary series of vaccination against SARS-CoV-2, as public health measures to lower the risk of the COVID-19 resurgence. For example, Israel, ahead of other countries, started the rollout of booster dose shots in July 2021 for elderly people who completed their primary series of vaccination at least 5 months before, subsequently expanding vaccine eligibility to include individuals aged 12 years or older.

Study mRNA-1273-P201, a study evaluating the immunogenicity and safety of COVID-19 Vaccine Moderna as primary series, was initiated in May 2020. The applicant amended the original protocol of the then ongoing study and started an additional study in January 2021 to evaluate a booster dose of COVID-19 Vaccine Moderna in participants who completed the second dose of the primary series at least 6 months earlier. Based on data including the results of this study, an Emergency Use Authorization was granted to COVID-19 Vaccine Moderna in the US in October 2021, which allows administration of a booster dose to older people; individuals aged 18 years or older at an increased risk of severe COVID-19, such as those with underlying medical conditions; and individuals aged 18 years or older at high risk of exposure to SARS-CoV-2. In November 2021, vaccine eligibility was expanded to include all individuals aged 18 years or older. In Europe, an extension of the conditional marketing authorization concerning the booster dose in individuals aged 18 years or older was approved in October 2021. The approved SARS-CoV-2 vaccines in Japan include Comirnaty Intramuscular Injection (Pfizer Japan Inc.) and Vaxzevria Intramuscular Injection (AstraZeneca K.K.), in addition to COVID-19 Vaccine Moderna. For Comirnaty Intramuscular Injection, a partial change application was filed to add the booster dosing regimen and was approved in November 2021. For administration of a third dose as part of the primary series of COVID-19 Vaccine Moderna to immunocompromised people at least 28 days after the second

dose, an Emergency Use Authorization was granted in the US in August 2021 and a marketing authorization in Europe in October 2021. These authorizations were granted based on data from published literature (e.g., *N Engl J Med.* 2021;385:1244-6, *N Engl J Med.* 2021;385:661-2). No application has been filed in Japan for this dosing regimen.

Recently, a partial change application has been filed in Japan by Takeda Pharmaceutical Company Limited to add a booster dosing regimen, based mainly on data from Study mRNA-1273-P201 conducted by Moderna TX, Inc.

In this report, the 2 doses administered as primary series to individuals who have not previously received SARS-CoV-2 vaccine are referred to as the "first dose" and "second dose," and the third dose administered approximately 6 months after the second dose is referred to as the "booster dose."

This review was performed based on the data submitted by the applicant in accordance with the "Handling of Drugs Submitted for Special Approval for Emergency (Request)" (PSEHB/PED No. 1125-15 dated on November 25, 2021).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application is intended for the addition of a new dosage. The applicant submitted the results from a study evaluating the number of doses (0.25 mL each for booster doses) that can be extracted from a vial of the vaccine product.

2.R.1 Number of extractable doses per vial

COVID-19 Vaccine Moderna (mRNA-1273 formulation) is presented as suspension for injection in a multiple-dose vial (0.5 mL each for primary series doses or 0.25 mL each for booster doses). Each vial contains 1.0 mg/5.0 mL of the active substance (CX-024414).

The applicant's explanation about the extractable doses per vial:
The number of extractable doses (0.25 mL each) per vial was investigated by examining different dead volumes in several syringe/needle combinations through a simulation analysis and in a verification study. The results verified that ≥20 doses were extractable with a low dead-volume syringe/needle combination. The sealing capacity of the container/closure system and the fragmentation of the rubber stopper were evaluated after the vial stopper was punctured with the needle 20 times. The results indicated that 20 punctures would not affect the function of the container/closure system.

Based on the above, the maximum number of extractable doses (0.25 mL each) per vial is 20. The information on the maximum number of extractable doses per vial for the booster dose (0.25 mL) will be communicated appropriately to healthcare professionals.

PMDA accepted the applicant's explanation.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

No new data were submitted for the present application.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

No new data were submitted for the present application.

5. Toxicity and Outline of the Review Conducted by PMDA

No new data were submitted for the present application.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Neutralizing antibodies against SARS-CoV-2 in serum were measured by the neutralization assay using pseudoviruses. SARS-CoV-2 spike protein-specific binding antibodies were measured by enzyme-linked immunosorbent assay (ELISA).

6.2 Clinical pharmacology

No clinical pharmacology studies were conducted for the present application.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety data, in the form of evaluation data from 2 studies, and reference data from 1 study (Table 1). The evaluation data consisted of results from Part B of Study mRNA-1273-P201, which evaluated the booster dose after primary series, and results from Study mRNA-1273-P301 for primary series, which were used for comparison with those from Part B of Study mRNA-1273-P201. The results from both studies for primary series have already been evaluated during the review for the initial approval (“Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection” dated on May 17, 2021).

Table 1. Overview of clinical studies

Data category	Country	Study ID	Phase	Study population	Number of participants	Dosing regimen	Study objective
Evaluation	US	mRNA-1273-P201 Part B	IIa	Healthy adults aged ≥18 years who received 2 injections of mRNA-1273 as primary series in Part A	344	50 μg mRNA-1273 1 intramuscular (IM) injection	Safety Immunogenicity
Evaluation		mRNA-1273-P301[a)]	III	Healthy adults[b)] aged ≥18 years who have had no history of SARS-CoV-2 infection	15,184	100 μg mRNA-1273 2 IM injections, 28 days apart	Efficacy Safety Immunogenicity
Reference		DMID21-0012[c)]	I/II	Healthy adults aged ≥18 years who have completed SARS-CoV-2 vaccine authorized in the US under Emergency Use Authorization at least 12 weeks before	154	100 μg mRNA-1273 1 IM injection	Safety Immunogenicity

a) This study was initiated as a randomized, observer-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 for primary series (target sample size, 30,000 participants [15,000 each in the mRNA-1273 and placebo groups]). Only the results of the mRNA-1273 group were submitted as reference data from Part B of Study mRNA-1273-P201.
b) Individuals who had previously received SARS-CoV-2 vaccine were excluded.
c) The study consisted of several SARS-CoV-2 vaccine groups in addition to the mRNA 1273 group. Only data from the mRNA-1273 group were submitted.

7.1 Foreign phase IIa study (CTD 5.3.5.1-1, Study mRNA-1273-P201, ongoing since May 2020 [database lock date of June 10, 2021])

Study mRNA-1273-P201 was initiated as a randomized, observer-blind, placebo-controlled, parallel-group study to evaluate the safety and immunogenicity of COVID-19 Vaccine Moderna for primary series in healthy adults aged ≥18 years. Table 2 summarizes the study design for the primary series.

Table 2. Study mRNA-1273-P201: Summary of study design for primary series (previously evaluated)

Country	Phase	Study population	Number of participants enrolled	Dosing regimen	Study objective
US	IIa	Healthy adults aged ≥18 years	mRNA-1273 50 μg and 100 μg groups: 200 participants/group Placebo group: 200 participants	mRNA-1273 50 μg, 100 μg, or placebo 2 IM injections, 28 days apart	Safety Immunogenicity

7.1.1 Part B of Study mRNA-1273-P201

Study mRNA-1273-P201 (hereinafter referred to as "Study P201") was initiated as a study of the primary series (Part A), and included a follow-up period of 12 months after the second dose of the study vaccine. However, the study design was amended during the follow-up period to add Part B to the study,[1)] so as to evaluate the booster dose at least 6 months after the second dose (Protocol Amendment [redacted]).

Of the participants aged ≥18 years who had received 2 doses of 50 μg or 100 μg mRNA-1273 as the primary series in Part A, 345 participants who consented to receiving a booster dose entered in Part B (174 in the group of participants who had received 50 μg mRNA-1273 as primary series [hereinafter referred to as the "50 μg primary series group"] and 171 in the group of participants who had received 100 μg mRNA-1273 as primary series [hereinafter referred to as the "100 μg primary series group"]). The study was conducted in 8 study centers in the US in an unblinded manner to evaluate the safety and immunogenicity of mRNA-1273 as a booster dose administered at least 6 months after the second dose.

1) Part B was designed to evaluate not only the booster dose of 50 μg mRNA-1273 but also 2 doses of 100 μg mRNA-1273 in participants who had received placebo in Part A. However, the data submitted for the present application did not include the results from participants who were on placebo in Part A.

Participants were to receive a single IM injection of 50 μg mRNA-1273.

Of the 345 participants who consented to receiving a booster dose, 344 participants received a booster dose of mRNA-1273 (173 in the 50 μg primary series group and 171 in the 100 μg primary series group) and were included in the Safety Set, of which 330 participants (163 in the 50 μg primary series group and 167 in the 100 μg primary series group) were included in the Solicited Safety Set because their solicited adverse event data were available from the participant diary. Of the 306 participants who received a booster dose of mRNA-1273 and were assessed for immunogenicity at baseline (pre-booster) and 28 days post-booster, 11 participants were excluded from analysis (due to SARS-CoV-2 infection at baseline [10 participants] and serious protocol deviation [1 participant]), and the remaining 295 participants (146 in the 50 μg primary series group and 149 in the 100 μg primary series group) were included in the Per-protocol set (PP set), which was used as the immunogenicity analysis population.

The median interval between the second dose and the booster dose in the Safety Set was 218.0 days (range, 177-269).

The primary immunogenicity endpoints were assessed by SARS-CoV-2 spike protein-specific binding antibody response. The geometric mean titer (GMT) [two-sided 95% confidence interval (CI)] of the immune response at 28 days after the booster dose was 1,068.84 [991.58, 1,152.12] in the 50 μg primary series group, 1,080.35 [1,015.47, 1,149.39] in the 100 μg primary series group, and 1,074.68 [1,024.10, 1,127.76] for the total of the groups. The geometric mean fold rise (GMFR) [two-sided 95% CI] from pre-booster to 28 days after the booster dose was 12.36 [11.11, 13.73] in the 50 μg primary series group, 9.87 [8.78, 11.10] in the 100 μg primary series group, and 11.03 [10.18, 11.94] for the total of the groups.

The safety follow-up periods are shown below. The severity of adverse events was evaluated according to the Food and Drug Administration (FDA) guidance: “Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (September 2007).[2)]

- The following solicited adverse events: through 7 days after the booster dose
  - Local (injection site): pain, erythema/redness, swelling/induration, and lymphadenopathy[3)]
  - Systemic: headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, fever, and rash
- Unsolicited adverse events (excluding solicited adverse events occurring through 7 days after the study vaccine): through 28 days after the booster dose
- Serious adverse events: through 6 months after the booster dose

Table 3 shows solicited adverse events occurring through 7 days after the booster dose of mRNA-1273.

2) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (last accessed on November 26, 2021)
3) Reported in the participant diary as axillary swelling or tenderness ipsilateral to the side of injection.

Table 3. Solicited adverse events through 7 days after the booster dose (Study P201 Part B, Solicited Safety Set)

	Primary series 50 μg + booster dose 50 μg N = 163		Primary series 100 μg + booster dose 50 μg N = 167		Booster dose 50 μg Total N = 330	
	N1	n (%)	N1	n (%)	N1	n (%)
Local (injection site) (Any)	162	144 (88.9)	167	143 (85.6)	329	287 (87.2)
Pain	162	144 (88.9)	167	140 (83.8)	329	284 (86.3)
Erythema/redness	162	10 (6.2)	167	8 (4.8)	329	18 (5.5)
Swelling/induration	162	12 (7.4)	167	9 (5.4)	329	21 (6.4)
Lymphadenopathy[a)]	162	35 (21.6)	167	34 (20.4)	329	69 (21.0)
Systemic (Any)	163	127 (77.9)	167	126 (75.4)	330	253 (76.7)
Headache	162	97 (59.9)	167	92 (55.1)	329	189 (57.4)
Fatigue	162	103 (63.6)	167	98 (58.7)	329	201 (61.1)
Myalgia	162	86 (53.1)	167	82 (49.1)	329	168 (51.1)
Arthralgia	162	66 (40.7)	167	69 (41.3)	329	135 (41.0)
Nausea/vomiting	162	29 (17.9)	167	19 (11.4)	329	48 (14.6)
Chills	162	62 (38.3)	167	59 (35.3)	329	121 (36.8)
Fever[b)]	162	13 (8.0)	166	11 (6.6)	328	24 (7.3)
Rash	162	6 (3.7)	167	3 (1.8)	329	9 (2.7)

N = Number of participants analyzed, N1 = Number of participants reporting event data, n = Number of participants with the specified adverse event

a) Axillary swelling or tenderness ipsilateral to the side of injection

b) ≥38°C (oral temperature)

Unsolicited adverse events and adverse reactions (i.e., adverse events for which a causal relationship to the study vaccine could not be ruled out) reported through 28 days after the injection of the study vaccine were analyzed. In the 50 μg primary series group, unsolicited adverse events occurred in 17 of 173 participants (9.8%) and adverse reactions occurred in 6 of 173 participants (3.5%); and in the 100 μg primary series group, unsolicited adverse events occurred in 22 of 171 participants (12.9%) and adverse reactions in 7 of 171 participants (4.1%). In the combined 50 μg and 100 μg primary series recipients, unsolicited adverse events occurred in 39 of 344 participants (11.3%) and adverse reactions in 13 of 344 participants (3.8%).

No deaths, serious adverse events, or adverse events leading to study discontinuation were reported through the database lock date (June 10, 2021).

During the period until the August 16, 2021 (safety data snapshot date) after the database lock date, no deaths or adverse events leading to study discontinuation were reported. Serious adverse events occurred in 2 participants in the 50 μg primary series group (pulmonary embolism, deep vein thrombosis, and pericarditis in 1 participant each [a participant may have more than 1 event] and in 2 participants in the 100 μg primary series group (tendon rupture and abortion spontaneous in 1 participant each). A causal relationship to mRNA-1273 was ruled out for all these events.[4)]

7.1.2 Evaluation of immune responses in comparison with data from Study mRNA-1273-P301 as comparator (immunobridging analysis)

After the start of Study P201 Part B, an analysis was planned to evaluate the immunogenicity following a single booster dose of 50 μg mRNA-1273 in the participants of Study P201 Part B (database lock date of June 10, 2021) in comparison with the immunogenicity data (database lock date of May 4, 2021) following the primary

4) Based on data subject to further cleaning.

series of 100 μg mRNA-1273 in Study mRNA-1273-P301 (hereinafter referred to as “Study P301”) as the comparator (Statistical Analysis Plan for Immunobridging Analysis, Version [redacted], [redacted], 20[redacted]) [see Section 7.R.2].

The Per-Protocol (PP) Immunogenicity Subsets were used for this analysis. The PP Immunogenicity Subset for Study P201 Part B consisted of 295 participants (146 in the 50 μg primary series group and 149 in the 100 μg primary series group) included in the PP Set defined for immunogenicity analysis in Study P201. The PP Immunogenicity Subset for Study P301 consisted of 1,055 participants. Some participants were excluded from the immunogenicity PP random subcohort defined in Study P301 for reasons including the following: positive test result for SARS-CoV-2 at baseline, HIV infection, and the second dose administered outside the specified time window after the first dose (21-42 days post-first dose). The immunogenicity PP random subcohort in Study P301 was defined as participants who were selected by stratified random sampling (stratified by baseline SARS-CoV-2 status, age and at risk for severe COVID-19, and racial minority) from all participants in the mRNA-1273 group in Study P301. The participants also had to have completed 2 doses of study vaccine, of which the second dose was administered at 21 to 42 days after the first dose, with no major protocol deviations that might impact key study data.

The primary endpoints were the GMT of serum neutralizing antibody response against SARS-CoV-2 (prototype virus strain) (50% inhibitory dilution) and the proportion of participants achieving seroresponse (seroresponse rate). Both endpoints aimed to evaluate the non-inferiority of the immunogenicity data at 28 days after the booster dose of 50 μg mRNA-1273 to the immunogenicity data at 28 days after the second dose of primary series of 100 μg mRNA-1273. The non-inferiority of the immunogenicity of the 50 μg mRNA-1273 booster dose (28 days post-booster dose) to that of the 100 μg mRNA 1273 primary series (28 days post-second dose) is considered to be demonstrated if the prespecified non-inferiority criteria both in GMT and in seroresponse rate are met. The non-inferiority criteria were developed based on discussion with FDA and in accordance with the FDA’s “Guidance for Industry: Emergency Use Authorization for vaccines to Prevent COVID-19” (May 2021).[5)] The pre-booster titer (Study P201 Part B) and pre-vaccination titer of the first primary series dose (Study P301) were used as the baseline for seroresponse rate assessment. In the Statistical Analysis Plan for Immunobridging Analysis version 1, the definition of seroresponse used for the assessment of seroresponse rate was based on the description included in the General Chapter of the US Pharmacopeia (“critical fold difference” in <1033> Biological Assay Validation). Seroresponse was initially defined as “a change of titer from below the lower limit of quantification (LLOQ) to equal to or above the LLOQ, or at least a 3.3-fold rise if baseline is equal to or above the LLOQ.” Subsequently, FDA pointed out that a general definition for seroresponse should be used in the assessment of the primary endpoints for the following reasons: “a change of titer from below the LLOQ to equal to or above the LLOQ” may be caused simply by a variation of an assay, and “at least a 3.3-fold rise if baseline is equal to or above the LLOQ” would only exclude the difference derived from an assay variation; as a result, seroresponse rate using the assay-specific definition may not represent immunological response that is relevant to vaccination. The definition of seroresponse was

5) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19 (last accessed on November 26, 2021)

therefore amended per comments from the FDA to "a change of titer from below the LLOQ to equal to or above 4 × the LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ" (Statistical Analysis Plan for Immunobridging Analysis, Version [redacted], [redacted], 20[redacted]).

Table 4 shows serum neutralizing antibody titers against the prototype virus strain in Studies P201 Part B and P301.

Table 4. Serum neutralizing antibody titers against the prototype virus strain (50% inhibitory dilution) (PP Immunogenicity Subsets)

	P201 Part B[a)] Booster dose 50 μg N = 295	P301 Primary series 100 μg N = 1,055
Baseline		
n	294	1,052
GMT [two-sided 95% CI]	125.70 [111.01, 142.32]	9.62 [9.35, 9.90]
28 days post-booster dose (P201) or post-second primary series (P301)		
n	295	1,053
GMT [two-sided 95% CI]	1,892.71 [1,728.80, 2,072.16]	1,081.12 [1,019.80, 1,146.14]

N = Number of participants analyzed, n = Number of participants with non-missing data at the evaluation time point
Antibody titers reported as below the LLOQ are replaced by 0.5 × LLOQ. Antibody titers greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available (quantification range [LLOQ-ULOQ]: 18.5-45,118 (Study P201), 18.5-4,404 (Study P301)
a) Both mRNA-1273 primary series 50 μg and 100 μg recipient groups are combined

Table 5 shows serum neutralizing antibody titers against the prototype virus strain at 28 days after the booster dose (Study P201 Part B) compared with those at 28 days after the second dose (Study P301). The lower bound of the two-sided 95% CI of the ratio of geometric mean titers (GMR) exceeded the non-inferiority margin (0.67), with the point estimate ≥1.0, meeting the prespecified non-inferiority criterion for the GMR.

Table 5. Comparison of serum neutralizing antibody titers against SARS-CoV-2 (50% inhibitory dilution) (PP Immunogenicity Subsets)

P201 Part B[a)] Booster dose 50 μg N = 295		P301 Primary series 100 μg N = 1,055		GMR [two-sided 95% CI][b)] (P201 Part B post-booster dose /P301 post-primary series)
n	GLSM [two-sided 95% CI][b)]	n	GLSM [two-sided 95% CI][b)]	
295	1,767.94 [1,586.45, 1,970.19]	1,053	1,032.70 [974.21, 1,094.70]	1.71 [1.52, 1.93]

N = Number of participants analyzed, n = Number of participants with non-missing data at the evaluation time point
a) Both mRNA-1273 primary series 50 μg and 100 μg recipient groups are combined
b) An analysis of covariance (ANCOVA) with log-transformed antibody titer at 28 days post-booster dose (Study P201 Part B) and 28 days post-Dose 2 (Study P301) as the dependent variable, treatment group (P201 Part B 50 μg mRNA-1273 booster dose vs. P301 100 μg mRNA-1273 primary series) as the explanatory variable, and age (<65 years vs. ≥65 years) as the covariate.

Table 6 shows serum neutralizing antibody seroresponse rate to mRNA-1273 at 28 days after the booster dose in Study P201 Part B compared with that at 28 days after the primary series (second dose) in Study P301. The lower bound of the two-sided 95% CI of the difference in seroresponse rate is less than the non-inferiority margin (−10%), indicating that the prespecified criterion of non-inferiority in terms of seroresponse rate was not met.

Table 6. Comparison of seroresponse rates (serum neutralizing antibody against SARS-CoV-2) (50% inhibitory dilution) (PP Immunogenicity Subsets)

P201 Part B[a)] Booster dose 50 μg N = 295		P301 Primary series 100 μg N = 1,055		Difference in seroresponse rate [two-sided 95% CI][c)] (P201 Part B post-booster dose) − (P301 post-primary series)
n/N1	Seroresponse rate [two-sided 95% CI][b)]	n/N1	Seroresponse rate [two-sided 95% CI][b)]	
265/294	90.1 [86.1, 93.3]	1,033/1,050	98.4 [97.4, 99.1]	−8.2 [−12.2, −5.2]

N = Number of participants analyzed, N1 = Number of participants with non-missing data at both pre- and post-vaccination time points; n = Number of participants who met the seroresponse criteria (a change of titer from below the LLOQ to ≥4 × LLOQ, or ≥4-fold rise if baseline is equal to or above the LLOQ)

a) Both mRNA-1273 primary series 50 μg and 100 μg recipient groups are combined
b) Clopper-Pearson method
c) Miettinen-Nurminen method

7.R Outline of the review conducted by PMDA

7.R.1 Clinical significance of the booster dose

The applicant's explanation about the clinical significance of the booster dose of COVID-19 Vaccine Moderna: The efficacy data on the mRNA-1273 primary series that were obtained from clinical studies, overseas reports, and other sources after the initial approval are summarized below.

(a) Clinical study results and other data

The results of the final efficacy analysis in Study P301 (database lock date of May 4, 2021; CTD 5.3.5.1-2): In the PP Set,[6)] which serves as the primary population for the analysis of primary series efficacy (14,287 participants in the mRNA-1273 group and 14,164 participants in the placebo group), the vaccine efficacy (VE) for the prevention of symptomatic COVID-19[7)] starting 14 days after the second dose was 93.2% [two-sided 95% CI, 91.0%, 94.8%]. The median follow-up time after randomization was 5.3 months as of the final analysis. The VE values [two-sided 95% CIs] against symptomatic COVID-19 according to follow-up time after the second dose were as follows: 91.9% [78.0%, 97.9%] in ≥14 days and <28 days; 91.7% [85.9%, 95.5%] in ≥28 days and <56 days; 94.9% [91.0%, 97.4%] in ≥56 days and <84 days; 92.8% [88.0%, 96.0%] in ≥84 days and <112 days; and 91.8% [83.2%, 96.6%] in ≥112 days. The VE against severe COVID-19[8)] was 98.2% [two-sided 95% CI, 92.8%, 99.6%]. In the data evaluated for the initial approval, the VE against COVID-19 was 94.5% [two-sided 99.1% CI, 81.8%, 98.3%], while the VE against severe COVID-19 was 100% ("Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection" dated on May 17, 2021).

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6) Of the participants in the FAS, those who did not have SARS-CoV-2 infection at baseline were included in the mITT Set. Of the participants in the mITT Set, those who received the second dose of study vaccine within the pre-specified time window and had no major protocol deviation were included in the PP Set.

7) Symptomatic COVID-19 was defined as follows:
- The participant experienced at least 2 of the following systemic COVID-19 symptoms: fever ≥38°C, chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); OR
- The participant experienced at least one of the following respiratory signs/symptoms (cough, shortness of breath, or difficulty breathing), or clinical or radiographical evidence of pneumonia; AND
- The participant has at least one nasopharyngeal swab, nasal swab, saliva sample, or respiratory sample, positive for SARS-CoV-2 by nucleic acid amplification test.

8) Severe COVID-19 was defined as meeting at least one of the following criteria:
- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% or PaO_2/FiO_2 <300 mmHg)
- Respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- Evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurological dysfunction
- Admission to an intensive care unit
- Death

As part of the ongoing Study P301, a follow-up survey[9)] of breakthrough infections was conducted for an exploratory analysis of the incidence rate of symptomatic COVID-19 confirmed in the mITT Set between July 1, 2021 and August 27, 2021. The vast majority of symptomatic COVID-19 cases reported in the follow-up survey were attributed to the Delta variant. The incidence rate of breakthrough infections in participants who had been assigned to mRNA-1273 and had received their primary series (at least 1 dose) between July 27, 2020 and December 16, 2020 (median follow-up[10)] of 13 months) was 77.1 cases per 1,000 person-years, which was higher than that in participants who had been assigned to placebo and then had received their mRNA-1273 primary series after unblinding, between December 29, 2020 and April 30, 2021 (median follow-up[10)] of 7.9 months)―49.0 cases per 1,000 person-years. The data showed that protection against the Delta variant is higher in participants more recently vaccinated than in those more remotely vaccinated.

The change in neutralizing antibody titers over time was evaluated using sera from the Study P201 participants who had received 2 doses of mRNA-1273. Serum neutralizing antibody titers decreased over time. The neutralizing antibody titers were 6- to 7- fold lower against the prototype virus strain at 6 to 8 months after the second dose than at 1 months after the second dose, and approximately 40-fold lower against the Beta, Gamma, and Delta (*Nat Med.* 2021;27:2025-31).

(b) Overseas reports of epidemiological investigation and other studies on mRNA vaccines including mRNA-1273

A recent publication has suggested that the waning of immunity within 6 months after vaccination or natural infection may partly contribute to re-infection or breakthrough infection with SARS-CoV-2 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1005517/Technical_Briefing_19.pdf [last accessed on November 26, 2021]). There is a publication reporting that the efficacy of SARS-CoV-2 mRNA vaccines, including mRNA-1273, for prevention of SARS-CoV-2 infection and COVID-19 symptoms reduced over time (medRxiv[11)] preprint doi: https://doi.org/10.1101/2021.08.06.21261707, *MMWR Morb Mortal Wkly Rep.* 2021;70:1150-5).

Although the duration of efficacy of mRNA-1273 primary series for prevention of COVID-19 is not clear, as in the discussions in Subsections (a) and (b) above, the vaccine efficacy is likely to decline over time. On the other hand, while drugs for the treatment of COVID-19 are beneficial, they are not sufficient to control the global pandemic. The vaccination against SARS-CoV-2 is still essential for the prevention of COVID-19.

Under the circumstances, Study P201 Part B was conducted to investigate the booster dose of mRNA-1273. The Part B evaluated the immunogenicity and safety of a booster dose in participants primed with mRNA-1273 6 to 8 months earlier. Administration of a booster dose increased neutralizing antibody titers against SARS-CoV-2 [see Sections 7.1 and 7.R.3]. Given the demonstrated efficacy of the primary series of mRNA-1273 and

9) In this analysis, a data snapshot was created because patients did not have a definitive diagnosis. The date of the onset of COVID-19 was defined as the date on which a positive RT-PCR test result was obtained or the date on which COVID-19 symptoms were reported, whichever occurred later.
10) The duration of follow-up after the first dose (1 month defined as 28 days)
11) medRxiv (The Preprint Server For Health Sciences): https://www.medrxiv.org/ (last accessed on November 26, 2021)

an increase in neutralizing antibody titers against the Delta and other variants following a booster dose, the booster dose of mRNA-1273 is expected to be effective [see Section 7.R.3]. The safety profile of the booster dose in Study P201 Part B is similar to the safety profile of mRNA-1273 observed in Study P301, which evaluated the efficacy of the primary series. No significant safety concerns were identified in Part B [see Section 7.R.4].

Based on the above, a booster dose of mRNA-1273 in individuals primed with mRNA-1273 at least 6 months earlier is expected to increase neutralizing antibody levels, thereby preventing COVID-19 after breakthrough infection, and maintaining effective protection against COVID-19 during the resurgence of infections due to the Delta and other variants. Therefore, administration of a booster dose of mRNA-1273 is of clinical significance.

PMDA's view:
In the Expert Discussion meeting held for the review of the initial application for COVID-19 Vaccine Moderna, it was pointed out that the need for a booster dose should be considered when the duration of efficacy has become clear from post-marketing data ("Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection" dated on May 17, 2021). Neutralizing antibody titers in Study P201 participants decreased at 6 to 8 months after the completion of mRNA-1273 primary series (*N Engl J Med.* 2021;384:2259-61). However, so far there are no specific indicators to determine the duration of the efficacy of mRNA-1273, or no established neutralizing antibody titer threshold conferring protection. Therefore, whether the neutralizing antibody titer at 6 to 8 months after the completion of primary series is sufficient to prevent COVID-19 is unknown. The duration of efficacy of primary series is not clear. However, in the follow-up survey of breakthrough infections performed as part of Study P301 during the Delta variant surge, though the analysis was retrospective, the incidence rate of COVID-19 was higher among participants more remotely vaccinated with mRNA-1273 at the time of survey than among those more recently vaccinated. A decline in neutralizing antibody titers over time may partly contribute to the higher incidence rate of COVID-19.

Some countries and regions have begun to roll out booster vaccinations in individuals who have completed their primary series of vaccination against SARS-CoV-2 as public health measures. In countries and regions where SARS-CoV-2 vaccination programs had been initiated ahead of other countries, booster doses have already given to primary series vaccine recipients. There is a publication reporting the early efficacy of a booster dose (*Lancet.* 2021 Oct 29; S0140-6736(21)02249-2. doi: 10.1016/S0140-6736(21)02249-2). In the US where the largest number of doses of mRNA-1273 have been used for vaccination, the Emergency Use Authorization was amended on October 20, 2021 for the use of a single booster dose of COVID-19 Vaccine Moderna (mRNA-1273) that may be administered at least 6 months after completion of the primary series of mRNA-1273 to individuals aged ≥65 years; individuals aged 18 through 64 years at high risk of severe COVID-19; and individuals aged 18 through 64 years with frequent institutional or occupational exposure to SARS CoV-2, who are at high risk of serious complications of COVID-19, including severe COVID-19. On November 19, 2021, the eligible population was expanded to all individuals aged ≥18 years. Furthermore, the use of mRNA-1273 as a booster dose is also allowed in individuals who have completed their primary series

vaccination with a different COVID-19 vaccine (i.e., Comirnaty Intramuscular Injection or Janssen's SARS-CoV-2 vaccine), according to the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html [last accessed on November 27, 2021]).

In Japan, the primary series vaccination campaign was rolled out quickly. After the rapid surge of COVID-19 cases in July and August 2021, a trend towards a decline in new cases has been continuing since September 2021 (https://www.mhlw.go.jp/content/10906000/000852320.pdf [last accessed on November 26, 2021]). However, in view of the resurgence of COVID-19 in countries where SARS-CoV-2 vaccination started earlier than in Japan, even after the majority of the citizens have completed their primary series, large-scale outbreaks of SARS-CoV-2 infection or a rapid surge in COVID-19 cases could occur, and this will overwhelm hospitals. Therefore, the evaluation of booster dose vaccination in Japan is necessary in preparation for a possible future resurgence of SARS-CoV-2 infections.

Based on the data, including clinical study results, submitted in support of the present application, the booster dose of mRNA-1273 is expected to have a certain level of efficacy [see Section 7.R.3], and has tolerable safety [see Section 7.R.4]. However, the benefit-risk balance of the booster dose varies depending on the status of COVID-19 outbreaks, circulating strains, and the presence of risk factors for severe COVID-19 in individuals, and is different from that for the primary series, for which all individuals aged ≥12 years are essentially eligible. With the current situations, such as the SARS-CoV-2 vaccination status and the number of COVID-19 cases in Japan, while urgent booster vaccination may not be necessary for all individuals primed with mRNA-1273, a booster dose has a certain level of clinical significance from the standpoint of preventing severe COVID-19 and serious outcomes caused by SARS-CoV-2 infection.

7.R.2 Review strategy

The applicant submitted the data from Study P201 Part B, a study which evaluated the immunogenicity and safety of a booster dose of 50 μg mRNA-1273, as the data to support the efficacy of a booster dose of mRNA-1273.

The applicant's explanation about the outline of protocol design for Study P201 Part B and the evaluation of immune response:
Based on the "Appendix 2: Evaluation of Vaccines to Address Emerging SARS-CoV-2 Variants" to the FDA Guidance[5)] regarding vaccine development in response to the emergence of variants, immunobridging was performed to evaluate the efficacy of a booster dose of mRNA-1273. Clinical efficacy was evaluated using clinical immunogenicity data.

When protocol design for a booster dose study began, some period of time had elapsed since the completion of the primary series of mRNA-1273. At that time, Study P201 was the only study that allowed for evaluation of a booster dose. For this reason, the protocol of Study P201 (Part A) was amended during the post-primary series follow-up period to include a study design for Part B.[1)] Under the amended protocol, among Part A

participants who received 50 μg or 100 μg mRNA-1273, those who would choose to receive a booster dose of mRNA-1273 were to be enrolled in Part B. The participants in Part B were to be assessed for immunogenicity and safety following a booster dose of 50 μg mRNA-1273 (Protocol Amendment [redacted], [redacted], 20[redacted]).

The immunogenicity data from Study P301, which evaluated the efficacy of the primary series, were to be used as reference data, to evaluate the immunogenicity of Study P201 Part B (Statistical Analysis Plan for Immunobridging Analysis, Version [redacted], [redacted], 20[redacted]). Because a new analysis was to be performed using data from a different study, a statistical analysis plan was developed separately from that for Study P201. To minimize the impact of comparing results from different studies on immunogenicity evaluation, analysis populations for both studies were defined as participants who tested negative for SARS-CoV-2 at baseline and who had no major protocol deviation that might affect results. Antibody titers for both studies were measured using the same test system in the same institution.

In the primary analysis of booster dose-related immunogenicity, Part A included 200 participants each in the 50 μg and 100 μg mRNA-1273 groups, but only approximately 170 participants per group were expected to give consent to receiving a booster dose; therefore, it was decided to use the combined data of both primary series dose groups in Study P201 (50 μg mRNA-1273 group and 100 μg mRNA-1273 [approved dosage] group). In addition, in view of the possibility that results would differ between the dose groups, data were to be analyzed also for each primary series dose. The results of analyses for each primary series dose in Part B showed that the immunogenicity data and safety profile were similar between the dose groups, indicating that the use of the combined data of both primary series dose groups is justified.

In the immunobridging analysis, the GMT of (prototype virus strain) neutralizing antibodies and the proportion of participants achieving seroresponse were selected as the primary endpoints. The non-inferiority of immunogenicity data of 50 μg mRNA-1273 at 28 days after the booster dose in Study P201 Part B to the immunogenicity data at 28 days after the second dose in Study P301 was to be evaluated. The non-inferiority success criterion and seroresponse criterion to be used for the assessment of seroresponse rate were specified in accordance with the FDA Guidance[5)] and discussion with FDA [see Section 7.1.2].

PMDA's view:
As it is becoming clear that the neutralizing antibody titer after SARS-CoV-2 vaccination correlates with vaccine efficacy for the prevention of COVID-19 (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11), immunobridging analyses based on naturalizing antibody titer have been increasingly used as an approach to the evaluation of vaccine efficacy in cases including expansion of eligible individuals for SARS-CoV-2 vaccines to include children, development of variant-specific versions of approved SARS-CoV-2 vaccines, and case where assessment of vaccines in clinical endpoint studies is no longer feasible (e.g., *ICMRA COVID-19 Vaccine development: Future steps Workshop.* 24 June 2021[12)]). In Japan, the method of evaluation of the efficacy of a variant-specific vaccine based on the comparison of the immunogenicity after the booster dose

12) http://www.icmra.info/drupal/en/covid-19/24june2021 (last accessed on November 27, 2021)

with that after the primary series with the parent vaccine is presented in the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of vaccines against variants" (Office of Vaccines and Blood Products, PMDA, dated on April 5, 2021). This approach is applicable to the evaluation of efficacy of a booster dose in individuals who completed the primary series with the same SARS-CoV-2 vaccine. Because the efficacy of mRNA-1273 primary series in preventing COVID-19 has been demonstrated in Study P301, the present application may be reviewed in line with the approach proposed by the applicant: immunogenicity is evaluated in Study P201 Part B, and the efficacy of the booster dose of mRNA-1273 is demonstrated by establishing the non-inferiority of post-booster immunogenicity results from Study P201 Part B in comparison to the immunogenicity data after the second dose of primary series in Study P301, in accordance with the analysis plan, which was agreed upon between FDA and Moderna TX, Inc.

Study P201 is the only study in which evaluation of a booster dose can be practically performed. Given the urgent need for development of the booster dose of mRNA-1273, there seems no alternative way to the approach proposed by the applicant, i.e., comparing data from different studies. Some of the demographics and baseline characteristics of the participants vary between the populations from the different studies, and the impact of the variation on evaluation requires further verification when data become available. However, given that there are no significant differences in the subgroup analyses of VE and neutralizing antibody titers after the primary series according to demographics and baseline characteristics [see Section 7.R.3] and that antibody titers for the studies were measured by the same assay methodology, comparison of the immunogenicity results from the two studies is considered acceptable.

On the basis of the evaluation results of post-booster dose, which did not differ between the different primary series dose levels, the applicant claimed the appropriateness of the use of combined data in Study P201 Part B obtained from recipients of the different primary series dose levels. However, the reason that the applicant decided to use the combined data at the time of planning, as well as the appropriateness of the decision have not been fully rationalized. The impacts of the difference in primary series dose levels on immune response after a booster dose are not clear. In addition, the GMT of pre-booster neutralizing antibody titer was 104.66 [two-sided 95% CI, 88.28, 124.07] in the 50 μg primary series group and 150.22 [two-sided 95% CI, 125.73, 179.50] in the 100 μg primary series group (Table 8). The data do not indicate that these groups are similar to each other; therefore, it cannot be determined that the study design of pooling data from different primary series dose groups is appropriate. For the present application, the submitted data are assessed based on the evaluation results of immunogenicity in Study P201 Part B, with a primary focus on the results of 100 μg primary series (approved dosage).

The safety of the booster dose of mRNA-1273 is evaluated mainly focusing on the results of Study P201 Part B. The results of Study DMID21-0012, which evaluated the safety and immunogenicity of a booster dose of 100 μg mRNA-1273, submitted as reference data, is also examined.

7.R.3 Efficacy

The applicant's explanation about the efficacy of a booster dose of mRNA-1273:

Both the study populations of Studies P201 and P301 were healthy adults aged ≥18 years (including adults with pre-existing medical conditions who were in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment). Study P301, however, enrolled more individuals who were at risk of severe COVID-19,[13)] compared to Study P201.

Table 7 shows the demographics and baseline characteristics of the PP Immunogenicity Subsets for Study P201 Part B and Study P301.

Table 7. Demographics and baseline characteristics of participants in Study P201 Part B and Study P301 (PP Immunogenicity Subset [a)])

Study	P201 Part B			P301
	50 μg primary series 50 μg booster N = 146	100 μg primary series 50 μg booster N = 149	Primary series (combined) 50 μg booster N = 295	100 μg primary series N = 1,055
Age				
Mean ± SD	52.8 ± 15.33	52.7 ± 15.06	52.77 ± 15.170	54.51 ± 15.329
Median (min, max)	57.0 (19, 87)	56.0 (18, 82)	56.00 (18.0, 87.0)	57.00 (18.0, 87.0)
Age group, n (%)				
≥18 and <65 years	107	112	219 (74.2)	700 (66.4)
≥65 years	39	37	76 (25.8)	355 (33.6)
Sex, n (%)				
Male	44 (30.1)	59 (39.6)	103 (34.9)	560 (53.1)
Female	102 (69.9)	90 (60.4)	192 (65.1)	495 (46.9)
Race, n (%)				
White	139 (95.2)	142 (95.3)	281 (95.3)	767 (72.7)
Black or African-American	2 (1.4)	5 (3.4)	7 (2.4)	188 (17.8)
Asian	2 (1.4)	1 (0.7)	3 (1.0)	26 (2.5)
Other[b)] or unknown	3 (2.5)	1 (0.7)	4 (1.4)	74 (7.0)
Ethnicity, n (%)				
Hispanic or Latino	10 (6.8)	10 (6.7)	20 (6.8)	334 (31.7)
Not Hispanic or Latino	135 (92.5)	139 (93.3)	274 (92.9)	717 (68.0)
Unknown	1 (0.7)	0	1 (0.3)	4 (0.4)
BMI (kg/m^2)				
n	143	147	290	1,050
Mean ± SD	25.84 ± 3.253	25.47 ± 3.168	25.65 ± 3.210	30.96 ± 7.758
Median (min, max)	26.17 (18.3, 34.9)	25.74 (18.0, 32.7)	26.05 (18.0, 34.9)	29.62 (14.0, 79.2)
Positive baseline SARS-CoV-2 status[c)], n	0	0	0	0

N = Number of participants analyzed, n = Number of applicable participants
a) Study P201 Part B, PP Set; Study P301, Immunogenicity PP random subcohort
b) Not white, black/African American, or Asian
c) Defined as positive if there is immunologic or virologic evidence of prior SARS-CoV-2 infection (positive reverse transcription polymerase chain reaction (RT-PCR) test or positive anti-SARS-CoV-2 antibody test result) on Day 1 of each study

There were differences in distribution of sex, race, and ethnicity between the subsets. However, the differences in demographics and baseline characteristics between the subsets of Studies P201 and P301 are unlikely to affect the results of analysis of neutralizing antibody responses. This is because (i) subgroup analyses by age, sex, race, ethnicity, underlying medical conditions, and obesity status (body mass index [BMI]) in Study P301 showed the consistency of VE estimates across subgroups ("Report on Special Approval for Emergency of

13) Defined as individuals with at least 1 of the risk factors for severe COVID-19 (chronic lung disease, moderate to severe asthma, significant cardiac disease, severe obesity [BMI ≥40 kg/m^2], diabetes, liver disease, or HIV infection).

COVID-19 Vaccine Moderna Intramuscular Injection" dated on May 17, 2021); and (ii) neutralizing antibody responses by sex and by BMI (<25 kg/m^2 vs. ≥25 kg/m^2) in Study P301 were similar across subgroups.

(a) Primary endpoints (evaluation for prototype virus strain)

The GMR (P201 Part B vs. P301, against the prototype virus strain) was 1.71 [two-sided 95% CI, 1.52, 1.93]. The lower bound of the two-sided 95% CI exceeded the prespecified non-inferiority margin. However, the difference in seroresponse rate between the 2 studies was −8.2% [two-sided 95% CI, −12.2%, −5.2%], and the prespecified criterion of non-inferiority margin were not met [see Section 7.1].

Table 8 shows the neutralizing antibody titers by primary series dose level. Post-booster dose GMT and seroresponse rate in the 100 μg primary series group did not differ from those in the overall population. Likewise, the GMR and seroresponse rate in the 100 μg primary series group did not differ from those in the overall population.

Table 8. Serum neutralizing antibody titers against the prototype virus strain by primary series dose level (50% inhibitory dilution) (PP Immunogenicity Subset)

	P201 Part B			P301
	50 μg primary series 50 μg booster N = 146	100 μg primary series 50 μg booster N = 149	Primary series (combined) 50 μg booster N = 295	100 μg primary series N = 1,055
Baseline				
n[a)]	145	149	294	1,052
GMT [two-sided 95% CI]	104.66 [88.28, 124.07]	150.22 [125.73, 179.50]	125.70 [111.01, 142.33]	9.62 [9.35, 9.90]
28 days post-booster dose (P201 Part B) or 28 days post-Dose 2 of primary series (P301)				
n[a)]	146	149	295	1,053
GMT [two-sided 95% CI]	1,834.31 [1,600.23, 2,102.62]	1,951.74 [1,729.61, 2,202.39]	1,892.71 [1,728.80, 2,072.16]	1,081.12 [1,019.80, 1,146.14]
GMR [two-sided 95% CI][b)]	1.663 [1.412, 1.958]	1.755 [1.496, 2.060]	1.712 [1.519, 1.929]	—
Seroresponse rate				
N1	145	149	294	1,050
n[c)]	134	131	265	1,033
Seroresponse rate (%) [two-sided 95% CI][d)]	92.4 [86.8, 96.2]	87.9 [81.6, 92.7]	90.1 [86.1, 93.3]	98.4 [97.4, 99.1]
Difference in seroresponse rate [two-sided 95% CI][e)]	−6.0 [−11.5, −2.5]	−10.5 [−16.7, −6.1]	−8.2 [−12.2, −5.2]	—

N = Number of participants analyzed, N1 = Number of participants with non-missing data at both pre- and post-vaccination time points; GMR = ratio of Study P201 Part B to Study P301; Difference in seroresponse rate = (Study P201 Part B) − (Study P301)
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Antibody values greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available (quantification range [LLOQ-ULOQ]: 18.5-45,118 (Study P201), 18.5-4,404 (Study P301)

a) Number of participants with non-missing data at the evaluation time point
b) An ANCOVA analysis with treatment group (P201 Part B 50 μg mRNA-1273 booster dose vs. P301 100 μg mRNA-1273 primary series) as the explanatory variable, and age (<65 years vs. ≥65 years) as the covariate
c) Number of participants who met the seroresponse criteria (a change of titer from below the LLOQ to ≥4 × LLOQ, or ≥4-fold rise if baseline is equal to or above the LLOQ)
d) Clopper-Pearson method
e) Miettinen-Nurminen method

Seroresponse rate may be affected by baseline neutralizing antibody titers because seroresponse reflects the fold rise from baseline. The baseline value used for assessment of seroresponse was the pre-first dose titer for the primary series (Study P301) and the pre-booster titer for the booster dose (Study P201). In Study P301 (100

μg primary series), the baseline neutralizing antibody titer (GMT [two-sided 95% CI] is 9.62 [9.35, 9.90]) indicated that the majority of participants were equal to or below the LLOQ. In contrast, the baseline neutralizing antibody titer GMT [two-sided 95% CI] was higher in Study P201 Part B than in Study P301: 125.70 [111.01, 142.33] (104.66 [88.28, 124.07] for 50 μg primary series, and 150.22 [125.73, 179.50] for 100 μg primary series) (Table 8). Participants who achieved a 4-fold rise in neutralizing antibody titer following the booster dose had a baseline GMT of 108.64 (range, 9.25-4393.49) while participants who failed to achieve a 4-fold rise had a baseline GMT of 492.28 (range, 162.43-2,238.93), indicating that a higher baseline GMT was observed in participants who failed to achieve the 4-fold rise in neutralizing antibody titer following the booster dose. The above findings suggest that this difference in the baseline neutralizing antibody titer precluded achievement of the non-inferiority criterion of the difference in seroresponse rate.

Nevertheless, participants who failed to achieve the 4-fold rise in neutralizing antibody titer following the booster dose had a post-booster GMT of 1,354 (range, 540.0-5,050.6), which was higher than the GMT at 28 days after the second dose in Study P301 (1,081.12). To eliminate the difference in baseline values, the post-booster seroresponse rate (Study P201 Part B) was calculated in a post-hoc analysis using the neutralizing antibody titers before the first dose of the primary series (Study P201 Part A) as the baseline value (GMT of 9.30 [9.35 in the 50 μg primary series group and 9.25 in the 100 μg primary series group]. The calculated post-booster seroresponse rate was 100% (294 of 294 participants [100% for both groups; 146 of 146 in the 50 μg primary series group and 148 of 148 in the 100 μg primary series group]), with the difference (P201 Part A vs. P301) being 1.6% [two-sided 95% CI, 0.3%, 2.6%] (1.6% [two-sided 95% CI, −1.0%, 2.6%] in the 50 μg primary series group and 1.6% [two-sided 95% CI, −0.9%, 2.6%] in the 100 μg primary series group).

Table 9 shows neutralizing antibody titers against the prototype virus strain by age group. Neutralizing antibody titers in the 100 μg primary series group and those in the combined data of the 2 dose groups increased after the booster dose regardless of age. GMR and the difference in seroresponse rate in the recipients of 100 μg primary series plus booster dose did not differ between the age groups.

The subgroup analyses by sex and by BMI (<25 kg/m^2 vs. ≥25 kg/m^2) showed no differences between the subgroups in terms of GMR or the difference in seroresponse rate.

Table 9. GMR and difference in seroresponse rate by age (50% inhibitory dilution) (PP Immunogenicity Subset)

	18-64 years			≥65 years		
	P201 Part B		P301	P201 Part B		P301
	100 μg primary series 50 μg booster N = 112	Primary series (combined) 50 μg booster N = 219	100 μg primary series N = 700	100 μg primary series 50 μg booster N = 37	Primary series (combined) 50 μg booster N = 76	100 μg primary series N = 355
Baseline						
n[a)]	112	218	699	37	76	353
GMT [two-sided 95% CI]	177.25 [145.54, 215.86]	145.57 [126.68, 167.27]	9.77 [9.37, 10.18]	91.05 [63.08, 131.42]	82.51 [64.25, 105.96]	9.35 [9.16, 9.54]
28 days post-booster dose (P201 Part B) or 28 days post-Dose 2 of primary series (P301)						
n[a)]	112	219	698	37	76	355
GMT [two-sided 95% CI]	2,069.62 [1,800.99, 2,378.33]	1,940.39 [1,749.49, 2,152.12]	1,206.59 [1,125.71, 1,293.28]	1,634.26 [1,277.13, 2,091.26]	1,761.77 [1,458.19, 2,128.56]	871.20 [785.48, 966.29]
GMR [two-sided 95% CI][b)]	1.715 [1.433, 2.053]	1.608 [1.403, 1.844]	—	1.876 [1.351, 2.604]	2.022 [1.591, 2.570]	—
Seroresponse rate						
N1	112	218	697	37	76	353
n[c)]	98	194	686	33	71	347
Seroresponse rate (%) [two-sided 95% CI][d)]	87.5 [79.9, 93.0]	89.0 [84.1, 92.8]	98.4 [97.2, 99.2]	89.2 [74.6, 97.0]	93.4 [85.3, 97.8]	98.3 [96.3, 99.4]
Difference in seroresponse rate [two-sided 95% CI][e)]	−10.9 [−18.4, −5.9]	−9.4 [−14.4, −5.8]	—	−9.1 [−23.1, −2.4]	−4.9 [−12.9, −0.7]	—

N = Number of participants analyzed, N1 = Number of participants with non-missing data at both pre- and post-vaccination time points,
GMR = ratio of Study P201 Part B to Study P301, Difference in seroresponse rate = (Study P201 Part B) − (Study P301)
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Antibody values greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available (quantification range [LLOQ-ULOQ]: 18.5-45,118 (Study P201), 18.5-4,404 (Study P301)

a) Number of participants with non-missing data at the evaluation time point
b) An ANCOVA analysis with treatment group (P201 Part B 50 μg mRNA-1273 booster dose vs. P301 100 μg mRNA-1273 primary series) as the explanatory variable, and age (<65 years vs ≥65 years) as the covariate
c) Number of participants who met the seroresponse criteria (a change of titer from below the LLOQ to ≥4 × LLOQ, or ≥4-fold rise if baseline is equal to or above the LLOQ)
d) Clopper-Pearson method
e) Miettinen-Nurminen method

(b) Evaluation of neutralizing antibody responses against various variants

Neutralizing antibody titers against the circulating Delta variant at 28 days post-booster dose were greater than those at 28 days post-second dose in Study P301 in both age groups (18-64 years and ≥65 years) (Table 10). The seroresponse rate in the combined dose groups was 90.4% [two-sided 95% CI, 85.7%, 93.9%] for participants aged 18 to 64 years and 97.3% [two-sided 95% CI, 90.7%, 99.7%] for participants aged ≥65 years.

Table 10. Neutralizing antibody titers against the Delta variant (50% inhibitory dilution) (PP Immunogenicity Subset)

	18-64 years			≥65 years		
	P201 Part B		P301	P201 Part B		P301
	100 μg primary series 50 μg booster N = 112	Primary series (combined) 50 μg booster N = 219	100 μg primary series N = 434	100 μg primary series 50 μg booster N = 37	Primary series (combined) 50 μg booster N = 76	100 μg primary series N = 146
Baseline						
n[a)]	112	218	—	37	75	—
GMT [two-sided 95% CI]	54.82 [43.98, 68.33]	47.20 [40.64, 54.81]	—	31.82 [22.64, 44.72]	30.67 [24.20, 38.88]	—
28 days post-booster dose (P201 Part B) or post-Dose 2 of primary series (P301)						
n[a)]	112	219	434	37	76	146
GMT [two-sided 95% CI]	872.39 [770.78, 987.41]	822.98 [743.49, 910.97]	427.33 [387.93, 470.73]	706.13 [538.55, 925.87]	749.94 [600.87, 935.99]	276.77 [237.25, 322.87]
GMR [two-sided 95% CI][b)]	2.041 [1.671, 2.494]	1.926 [1.651, 2.246]	—	2.551 [1.828, 3.560]	2.710 [2.078, 3.553]	—

N = Number of participants analyzed
GMR = ratio of Study P201 Part B to Study P301
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Antibody values greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available (quantification range [LLOQ-ULOQ]: 18.5-45,118)
a) Number of participants with non-missing data at the evaluation time point
b) An ANCOVA analysis with treatment group (P201 Part B 50 μg mRNA-1273 booster dose vs. P301 100 μg mRNA-1273 primary series) as the explanatory variable, and age (<65 years vs. ≥65 years) as the covariate

Exploratory analyses of neutralizing antibody responses against various variants were performed in randomly selected subsets of participants in Study P201 Part B, who had received 100 μg mRNA-1273 as primary series. The neutralizing antibody titers against the Beta, Delta, and Gamma variants at 15 days post-booster dose increased significantly compared with pre-booster titers (Table 11).

Table 11. Neutralizing antibody titers against various variants (50% inhibitory dilution) (Study P201 Part B; part of PP Set)

Pseudotyped viruses[a)] used for pseudovirus neutralization assay	GMT [two-sided 95% CI]			GMFR [two-sided 95% CI] (Post-booster / pre-booster)
	N	Pre-booster[b)]	Post-booster	
Prototype virus strain	20	198 [124, 314]	4,588 [3,244, 6,488]	23.2 [15, 36]
Beta variant	20	27 [16, 47]	864 [542, 1,379]	32.0 [20, 52]
Delta variant	11[c)]	30 [20, 40]	1,268 [983, 1,553]	42.3 [28, 69]
Gamma variant	20	30 [17, 53]	1,308 [829, 2,064]	43.6 [27, 72]

N = Number of participants assayed
a) Pseudovirus (vesicular stomatitis virus) expressing the spike protein of the prototype virus strain (D614G) and other variants.
b) The neutralizing antibody titers at 6 months post-vaccination in participants who received the 2-dose 100 μg mRNA-1273 primary series in Study P201 Part A.
c) Testing of only 11 samples on the plate was possible. Of 20 randomly selected samples, 11 samples with high titer (4 samples), moderate titer (4 samples), and low titer (3 samples) against the prototype virus strain were selected for assay.

As discussed above, data on the immunogenicity after completion of 100 μg mRNA-1273 primary series in Study P301 were used as the comparator to evaluate the immunogenicity after the booster dose of 50 μg mRNA-1273 in Study P201 Part B. Neutralizing antibody titers against the prototype virus strain increased, and the GMT at 28 days post-booster dose was higher than the GMT at 28 days post-second dose. In addition, neutralizing antibody titers against the Beta, Gamma, and Delta variants also increased significantly after the booster dose; therefore, the efficacy of 50 μg mRNA-1273 booster dose is promising.

The efficacy of 50 μg mRNA-1273 booster dose is being further evaluated in another sub-study. An open-label part was added to Study P301 to evaluate the efficacy, immunogenicity, and safety of the 50 μg mRNA-1273 booster dose in all of mRNA-1273 primary series recipients in Study P301 who choose to receive a booster

dose, and is ongoing (Protocol Amendment [redacted], [redacted], 20[redacted]). In addition, the protocol of Study P901 will be amended to conduct a follow-up survey for VE after booster dose. Study P901 is an ongoing prospective observational cohort study initiated by the applicant in collaboration with Kaiser Permanente Southern California to evaluate the efficacy of the mRNA-1273 primary series in preventing COVID-19 and severe COVID-19.

PMDA's view on the efficacy of mRNA-1273:
The data on immunogenicity 28 days after the second dose of mRNA 1273 primary series in Study P301, a study which demonstrated the efficacy of the mRNA-1273 primary series in preventing COVID-19, were used as the comparator to evaluate the immune response 28 days after the booster dose of 50 μg mRNA-1273 in Study P201 Part B. This immunobridging analysis was not necessarily based on a thoroughly designed study. In Study P201, an amendment to the protocol was made after the database lock date to change the definition of seroresponse. Furthermore, the seroresponse rate [two-sided 95% CI] after the booster dose was 90.1% [86.1%, 93.3%] (92.4% [86.8%, 96.2%] for 50 μg primary series and 87.9% [81.6%, 92.7%] for 100 μg primary series), and only one of the 2 primary endpoints was achieved. While the prespecified non-inferiority criterion for the GMR for neutralizing antibody titer against the prototype virus strain was met, the criterion for the non-inferiority of seroresponse rate was not met. According to the applicant, the baseline titers were higher in the booster dose group than in the primary series group, which resulted in a lower seroresponse rate in the booster recipients than in the primary series second dose recipients. In principle, the endpoints and their definitions, criteria for the study population (including time elapsed from the primary series), and target sample size should be optimized based on the objective of booster vaccination, and then appropriate verification should be performed. However, given the development schedule for the mRNA-1273 booster dose and its urgency, there was no other choice but to take the current development policy. In addition, the mRNA-1273 primary series has already been demonstrated to have a high vaccine efficacy in preventing COVID-19. In the evaluation of booster dose in Study P201 Part B, neutralizing antibody titers increased after the booster dose even in participants who failed to achieve the criterion for seroresponse rate, and the titers were higher than the post-second dose titers in the P301 data used as the comparator. Taken together, based on the data from Study P201 Part B, it can be concluded that the booster dose of mRNA-1273 induces immune response that serves as evidence supporting its clinical efficacy.

The booster dose of mRNA-1273 is expected to have a certain level of efficacy, based on comprehensive consideration of the following information: (i) the results showing the increase in neutralizing antibody titer against variants after the booster dose of mRNA-1273; (ii) data on the booster dose of another mRNA vaccine, Comirnaty Intramuscular Injection ("Report on Special Approval for Emergency of Comirnaty Intramuscular Injection" dated on November 2, 2021); and (iii) an epidemiological report on outcomes after the booster dose (*N Engl J Med.* 2021;385:1393-400).

However, currently available post-booster dose data are limited to short-term immunogenicity. There are no data on change in neutralizing antibody titer over time or the duration of efficacy of a booster dose. Globally, countries and regions implementing programs for booster vaccination are gradually increasing, and more

reports on post-booster efficacy and other findings will become available. The applicant should therefore continuously gather data. When new findings become available, the applicant should consider the need for provision of information to healthcare professionals and other additional actions. When any new data on change in neutralizing antibody titer over time and the duration of efficacy of booster vaccination are obtained from evaluation of a booster dose in Study P301 and other studies, the applicant should take additional actions including provision of information to healthcare professionals. The applicant should continue to keep track of the emergence of SARS-CoV-2 variants as well as currently circulating strains, gather data on the efficacy and immunogenicity of mRNA-1273 against variants, and consider actions appropriately in response to the situations.

The timing of the booster dose and the appropriateness of the dosage regimen will be discussed in Section 7.R.5.

7.R.4 Safety

7.R.4.1 Safety profile

The applicant's explanation about the safety of the booster dose of mRNA-1273:

(a) Study P201 Part B

The incidence of local and systemic solicited adverse events occurring within 7 days after the booster dose in recipients of 100 μg mRNA-1273 primary series in Study P201 Part B was compared with that after the second dose of the primary series in recipients of 100 μg mRNA-1273 primary series in Study P201 Part A and Study P301. In Study P301, solicited local (injection site) adverse events (pain, erythema/redness, swelling/induration, and lymphadenopathy) and solicited systemic adverse events (headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever) were prespecified, and those occurring within 7 days after each dose of the study vaccine were recorded using participants' diaries for analysis. The details of the adverse events were the same as those of Study P201 Part B [see Section 7.1.1], except that rash was not recorded as a solicited local adverse event. Table 12 shows the incidence of solicited adverse events after the booster dose in the 100 μg primary series group in Study P201 Part B versus that after the second dose of the primary series in each study. In the 100 μg primary series group in Study P201 Part B, among solicited local adverse events, lymphadenopathy tended to be more common, while among solicited systemic adverse events, myalgia, chills, and fever tended to be less common. There were no Grade ≥3 events (including lymphadenopathy) that were clearly more common in Study P201 Part B than in other studies. The majority of solicited local adverse events (134 of 167 participants; 80.2 %) occurred within the first 1 to 2 days after vaccination with a median duration of 3 days. The majority of solicited systemic adverse events (118 of 167 participants; 70.7%) occurred within the first 1 to 2 days after vaccination with a median duration of 1 to 2 days. Solicited adverse events, both local and systemic, occurring after the booster dose did not differ significantly from those occurring after the primary series doses in terms of the trend in the incidence of adverse events.

The incidence of solicited local and systemic adverse events in participants receiving the 50 μg mRNA-1273 as a booster dose in Study P201 Part B is similar between the 50 μg primary series group and 100 μg primary

series group (Table 3). The applicant considers that the results of combined data of both primary series dose groups can also serve to support the safety of 50 μg mRNA-1273 as a booster dose. When the incidence of solicited adverse events in the combined data of both primary series dose groups was compared to that after the second dose of the primary series in each study, there were no clear differences in terms of the trend in the incidence of adverse events. The results were similar to that of the comparison between the 100 μg primary series groups.

Table 12. Incidence of solicited adverse events within 7 days post-mRNA-1273 vaccination by dose number (Solicited Safety Set; aged ≥18 years)

Study	P201				P301	
	Part A		Part B			
Dose number	100 μg primary series Dose 2 N = 198		100 μg primary series 50 μg booster N = 167		100 μg primary series Dose 2 N = 14,691	
Event	All grades n (%)	Gr ≥3[a)] n (%)	All grades n (%)	Gr ≥3[a)] n (%)	All grades n (%)	Gr ≥3[a)] n (%)
Local total	170 (85.9)	7 (3.5)	143 (85.6)	8 (4.8)	13,029 (88.7)[d)]	1,023 (7.0)[d)]
Pain	169 (85.4)	1 (0.5)	140 (83.8)	6 (3.6)	12,964 (88.3)[d)]	606 (4.1)[d)]
Erythema/ redness	15 (7.6)	5 (2.5)	8 (4.8)	1 (0.6)	1,274 (8.7)[e)]	287 (2.0)[e)]
Swelling/ induration	21 (10.6)	1 (0.5)	9 (5.4)	1 (0.6)	1,807 (12.3)[e)]	255 (1.7)[e)]
Lymphadenopathy	20 (10.1)	0	34 (20.4)	1 (0.6)	2,092 (14.2)[e)]	68 (0.5)[e)]
Systemic total	153 (77.3)	25 (12.6)	126 (75.4)	12 (7.2)	11,678 (79.5)[f)]	2,350 (16.0)[f)]
Headache	104 (52.5)	9 (4.5)	92 (55.1)	2 (1.2)	8,637 (58.8)[e)]	666 (4.5)[e)]
Fatigue	128 (64.6)	18 (9.1)	98 (58.7)	7 (4.2)	9,607 (65.4)[e)]	1,433 (9.8)[e)]
Myalgia	104 (52.5)	15 (7.6)	82 (49.1)	5 (3.0)	8,529 (58.1)[e)]	1,321 (9.0)[e)]
Arthralgia	77 (38.9)	8 (4.0)	69 (41.3)	5 (3.0)	6,303 (42.9)[e)]	775 (5.3)[e)]
Nausea/ vomiting	41 (20.7)	0	19 (11.4)	0	2,794 (19.0)[e)]	22 (0.1)[e)]
Chills	78 (39.4)	1 (0.5)	59 (35.3)	0	6,500 (44.3)[e)]	191 (1.3)[e)]
Fever[b)]	26 (13.1)	4 (2.0)	11 (6.6)[c)]	2 (1.2)[c)]	2,276 (15.5)[g)]	216 (1.5)[g)]
Rash	6 (3.0)	-	3 (1.8)	-	-	-

N = Number of participants analyzed, n = Number of participants with the specified event
a) Gr 3 = Grade 3
b) Grade 3, 39°C-40°C, Grade 4, >40°C
c) N = 166; d) N = 14,688; e) N = 14,687; f) N = 14,690; g) N = 14,682

The incidence of solicited adverse events within 7 days after a booster dose of mRNA-1273 in participants (aged ≥55 years) in Study P201 Part B who had received 100 μg primary series was compared with that after the second dose of 100 μg mRNA-1273 primary series in participants of Study P201 Part A and participants (aged ≥65 years) of Study P301 (Table 13). Although different age group classification systems employed by the studies preclude strict comparison of data from older participants, there were some differences between the former data and the latter data. An analysis for solicited local adverse events showed that the incidence of lymphadenopathy following the booster dose in the 100 μg mRNA-1273 primary series group in Study P201 Part B tended to be higher than that after the second dose of the primary series in either study. This trend is similar to that observed in all age groups combined. For solicited systemic adverse events, headache, myalgia, arthralgia, and chills tended to occur more frequently after the booster dose compared to after the second dose of the primary series in both studies.

Table 13. Incidence of solicited adverse events within 7 days after mRNA-1273 vaccination by dose number (Solicited Safety Set; elderly people)

Study	P201 (≥55 years)				P301 (≥65 years)	
	Part A		Part B			
Dose number	100 μg primary series Dose 2 N = 99		100 μg primary series 50 μg booster N = 88		100 μg primary series Dose 2 N = 3,691	
Event	All grades n (%)	Gr ≥3[a)] n (%)	All grades n (%)	Gr ≥3[a)] n (%)	All grades n (%)	Gr ≥3[a)] n (%)
Local total	81 (81.8)	5 (5.1)	74 (84.1)	4 (4.5)	3,093 (83.8)[d)]	220 (6.0)[d)]
Pain	80 (80.8)	0	72 (81.8)	3 (3.4)	3,071 (83.2)[d)]	100 (2.7)[d)]
Erythema/redness	7 (7.1)	4 (4.0)	3 (3.4)	0	285 (7.7)[d)]	77 (2.1)[d)]
Swelling/ induration	10 (10.1)	1 (1.0)	4 (4.5)	1 (1.1)	408 (11.1)[d)]	72 (2.0)[d)]
Lymphadenopathy	10 (10.1)	0	12 (13.6)	0	315 (8.5)[d)]	21 (0.6)[d)]
Systemic total	75 (75.8)	9 (9.1)	67 (76.1)	6 (6.8)	2,655 (71.9)	400 (10.8)
Headache	49 (49.5)	5 (5.1)	47 (53.4)	1 (1.1)	1,708 (46.3)[d)]	107 (2.9)[d)]
Fatigue	63 (63.6)	7 (7.1)	52 (59.1)	4 (4.5)	2,154 (58.4)[d)]	255 (6.9)[d)]
Myalgia	47 (47.5)	4 (4.0)	45 (51.1)	2 (2.3)	1,740 (47.2)[d)]	205 (5.6)[d)]
Arthralgia	38 (38.4)	2 (2.0)	35 (39.8)	3 (3.4)	1,293 (35.1)[d)]	125 (3.4)[d)]
Nausea/vomiting	13 (13.1)	0	7 (8.0)	0	439 (11.9)[d)]	11 (0.3)[d)]
Chills	31 (31.3)	0	29 (33.0)	0	1,143 (31.0)[d)]	27 (0.7)[d)]
Fever[b)]	11 (11.1)	1 (1.0)	5 (5.7)[c)]	1 (1.1)[c)]	367 (9.9)[d)]	19 (0.5)[d)]
Rash	2 (2.0)	-	2 (2.3)	-	-	-

N = Number of participants analyzed, n = Number of participants with the specified event
a) Gr 3, Grade 3
b) Grade 3, 39°C-40°C, Grade 4, >40°C
c) N = 87; d) N = 3,689

In Study P201 Part B (database lock date of June 10, 2021), the incidence of unsolicited adverse events (excluding solicited adverse events reported within 7 days after each dose of study vaccine) and the incidence of adverse reactions (both reported within 28 days after the booster dose of mRNA-1273) were 12.9% (22 of 171 participants) and 4.1% (7 of 171 participants), respectively, in the 100 μg primary series group; and 11.3% (39 of 344 participants) and 3.8% (13 of 344 participants), respectively, when both primary series dose groups are combined. These are lower than the incidence of unsolicited adverse events (28.0%, 56 of 200 participants) and the incidence of adverse reactions (13.5%, 27 of 200 participants) reported within 28 days after the second dose of 100 μg primary series in Study P201 Part A, and the incidence of unsolicited adverse events (31.3%, 4,752 of 15,184 participants) and the incidence of adverse reactions (13.6%, 2,067 of 15,184 participants) reported within 28 days after the second dose in Study P301. Unsolicited adverse events occurring in ≥1% of participants (≥4 participants) reported within 28 days after the booster dose of mRNA 1273 in Study P201 Part B were headache (5 participants [4 in the 100 μg primary series group]; the same applies hereinafter), COVID-19 (4 participants [3 participants]), and fatigue (4 participants [4 participants]). Headache and fatigue were solicited adverse events that persisted beyond 7 days after the booster dose. The adverse events classified as COVID-19 in 4 participants were asymptomatic COVID-19. The 4 participants had their nasal swab samples collected at a regular visit or when SARS-CoV-2 exposure was suspected, and tested positive for SARS-CoV-2. Adverse reactions occurring in ≥2 participants within 28 days after the booster dose of mRNA-1273 in Study P201 Part B were headache (4 participants), fatigue (3 participants), and lymphadenopathy (2 participants), and the outcome was reported as "resolved" for all participants except for fatigue in 1 participant ("unresolved"). No severe unsolicited adverse events were reported.

In participants aged ≥55 years in Study P201 Part B, the incidence of unsolicited adverse events and that of adverse reactions reported within 28 days after the booster dose of mRNA-1273 were 19.1% (17 of 89 participants) and 6.7% (6 of 89 participants), respectively, in the 100 μg primary series group; 13.2% (24 of 182 participants) and 3.8% (7 of 182 participants) in the combined data from both primary series dose groups. The results were similar to those of the overall population. Unsolicited adverse events occurring in ≥1% of participants (≥2 participants) were headache (3 participants), fatigue (3 participants), and oropharyngeal pain (2 participants). The results are similar to those of the overall population. The outcome was reported as "resolved" for all participants except for fatigue (1 participant).

No serious adverse events, deaths, or adverse events leading to study discontinuation occurred by the database lock date (June 10, 2021). After the database lock date through the date of safety data snapshot (August 16, 2021), no deaths or adverse events leading to study discontinuation occurred. Serious adverse events occurred in 4 participants (tendon rupture [1 participant], abortion spontaneous [1 participant], pulmonary embolism and deep vein thrombosis [1 participant], and pericarditis [1 participant]). A causal relationship to mRNA-1273 was ruled out for all these events, with reported outcome being "resolved" or "resolving with sequelae."

In a clinical study of 100 μg mRNA-1273 primary series, local reaction (delayed local reaction) occurred in ≥7 days after injection, while in Study P201 Part B, no delayed local reaction occurred after the booster dose of 50 μg mRNA-1273 as of the date of safety data snapshot.

(b) Study DMID21-0012 (CTD 5.3.5.1-3, ongoing since May 2021 [data snapshot date of July 8, 2021]
An open-label study, sponsored by the National Institutes of Health (NIH), is being conducted in healthy adults aged ≥18 years to evaluate the safety and immunogenicity of a booster dose of 100 μg mRNA-1273 or other SARS-CoV-2 vaccines (Janssen's SARS-CoV-2 vaccine or Comirnaty Intramuscular Injection) 12 to 20 weeks after the last dose of the primary series of a SARS-CoV-2 vaccine approved under the Emergency Use Authorization in the US (Janssen's SARS-CoV-2 vaccine, mRNA-1273, or Comirnaty Intramuscular Injection). For the present application, only data from the cohort in which mRNA-1273 was administered as a booster dose were submitted as reference data. Recipients of Janssen's SARS-CoV-2 vaccine, mRNA-1273, or Comirnaty Intramuscular Injection as the primary series were included in Groups 1E, 2E, and 3E, respectively. All of 154 participants who received mRNA-1273 (53 in Group 1E, 51 in Group 2E, and 50 in Group 3E) were included in the Safety Set.

Table 14 shows the safety results after a booster dose of 100 μg mRNA-1273.

Table 14. Solicited adverse events occurring within 7 days after a booster dose (Study DMID21-0012, Safety Set)

Group	1E	2E	3E	Total
Primary series[a)]	Janssen's SARS-CoV-2 vaccine	mRNA-1273	Comirnaty Intramuscular Injection	
Booster dose	100 μg mRNA-1273			
	N = 53	N = 51	N = 50	N = 154
	n (%)	n (%)	n (%)	n (%)
Solicited local adverse events				
Pain/tenderness	40 (75.5)	44 (86.3)	41 (82.0)[b)]	125 (81.2)
Erythema/redness	3 (5.7)	11 (21.6)	7 (14.0)	21 (13.6)
Induration/swelling	11 (20.8)	20 (39.2)	16 (32.0)	47 (30.5)
Solicited systemic adverse events				
Headache	16 (30.2)	33 (64.7)	33 (66.0)	82 (53.2)
Malaise/fatigue	36 (67.9)	40 (78.4)	37 (74.0)	113 (73.4)
Myalgia	20 (37.7)	38 (74.5)	36 (72.0)	94 (61.0)
Arthralgia	9 (17.0)	19 (37.3)	18 (36.0)	46 (29.9)
Nausea	9 (17.0)	11 (21.6)	11 (22.0)	31 (20.1)
Chills	10 (18.9)	21 (41.2)	22 (44.0)	53 (34.4)
Fever[c)]	7 (13.2)	8 (15.7)	9 (18.0)	24 (15.6)

N = Number of participants analyzed, n = Number of participants with the specified event
a) The dosage regimen for each vaccine is the dosage regimen approved in the US.
b) One of the 50 participants analyzed had no data.
c) ≥38°C (oral temperature)

Severe solicited adverse events occurring within 7 days after the booster dose were as follows: induration/swelling in 1 of 154 participants (0.6%; 1 in Group 2E); pain/tenderness in 1 of 154 participants (0.6%; 1 in Group 2E); malaise/fatigue in 7 of 154 participants (4.5%; 4 in Group 1E, 2 in Group 2E, 1 in Group 3E); myalgia in 3 of 154 participants (1.9%; 1 each in Groups 1E, 2E, and 3E); headache in 2 of 154 participants (1.3%; 1 each in Groups 1E and 2E); nausea in 1 of 154 participants (0.6%; 1 in Group 1E); chills in 5 of 154 participants (3.2%; 1 in Group 1E, 3 in Group 2E, 1 in Group 3E); arthralgia in 1 of 154 participants (0.6%; 1 in Group 2E); fever in 2 of 154 participants (1.3%; 1 each in Groups 1E and 2E).

The incidences of unsolicited adverse events and adverse reactions occurring within 28 days after the booster dose were 29.9% (46 of 154 participants) and 15.6% (24 of 154 participants), respectively. The incidences of unsolicited adverse events and adverse reactions in each group were 24.5% (13 of 53 participants) and 13.2% (7 of 53 participants), respectively, in Group 1E; 29.4% (15 of 51 participants) and 11.8% (6 of 51 participants), respectively, in Group 2E; and 36.0% (18 of 50 participants) and 22.0% (11 of 50 participants), respectively, in Group 3E.

No deaths, serious adverse events, or adverse events leading to study discontinuation occurred by the date of safety data snapshot (July 8, 2021).

(c) Foreign post-authorization or post-marketing safety information

Between December 18, 2020 (Emergency Use Authorization in the US) and October 31, 2021, a total of 5,077 cases of adverse events were spontaneously reported in 1,599 recipients after the third dose (including the third dose as part of the primary series administered to immunocompromised individuals). Among these, data from 1,005 recipients were medically confirmed, and 1,035 cases in 325 recipients (including 32 deaths) were classified as serious events. According to the results of causality assessment of deaths performed on a 5-point scale ("certainly related," "probably/likely related," "possibly related" "unlikely related," and "not related"), the fatal cases were shown to be "possibly related" (26 recipients) and "unlikely related" (6 recipients) to

vaccination, and many of the cases were confounded by underlying medical conditions. Adverse events were reported in 929 women (58.1%) and 599 men (37.5%), and the remaining 71 recipients (4.4%) were unknown. More women tended to be reported than men, a trend which is similar to that observed in the primary series. In many cases, events tended to occur within 7 days following the vaccination, with fever and headache being common events. The safety profile for a booster dose have so far indicated no specific concerns.

As shown above, solicited adverse events occurred in many participants after a booster dose of 50 μg mRNA-1273 in Study P201 Part B, but the majority of the events were mild or moderate, and subsided within several days after the onset of the symptom. The incidence of serious adverse events was low, and a causal relationship to mRNA-1273 was ruled out for all the events. The analysis by age group showed no differences between age groups for solicited or unsolicited adverse events. Adverse events occurring in participants who received a booster dose of 100 μg mRNA-1273 in Study DMID21-0012 did not differ significantly from those observed in Study P201. Post-marketing safety information obtained overseas has identified no new safety concerns. Therefore, there are no major concerns about the safety profile of mRNA-1273 in adults aged ≥18 years, and the tolerability of the booster dose of 50 μg mRNA-1273 has been demonstrated by the submitted data.

PMDA's view:
Based on the submitted safety information from the clinical studies, the safety profile of the booster dose of 50 μg mRNA-1273 is generally similar to that of the 100 μg mRNA-1273 primary series, with no major significant concerns about the booster dose.

However, due to the limited number of evaluable participants who received the booster dose of 50 μg mRNA-1273 in Study P201 Part B after completion of the 100 μg mRNA-1273 primary series, the applicant is required to continue to gather data including data from overseas, and then take appropriate actions based on the information obtained. As with the case of the primary series of mRNA-1273, healthcare professionals and vaccine recipients should be informed of systemic reactions that occurred in many participants and that may affect activities of daily living, as well as lymphadenopathy which were more common after the booster dose than after the primary series. Such information should include the time to onset of and duration of those events.

The safety in special populations and the details of specific events are summarized in the sections below.

7.R.4.2 Safety in individuals with underlying medical conditions

The applicant's explanation about safety in individuals with underlying medical conditions:
Unlike Study P301, Study P201 did not proactively include individuals with underlying medical conditions; therefore, currently, data on the safety of 50 μg mRNA-1273 as a booster dose in individuals with underlying medical conditions who are likely to be at an increased risk of severe COVID-19 and require vaccination against SARS-CoV-2 have not been evaluated. The applicant plans to gather data on the safety of 50 μg mRNA-1273 as a booster dose in the ongoing Study P301.

PMDA's view:

The review of the application for the primary series confirmed that the safety profile of the primary series in participants with underlying medical conditions enrolled in Study P301 was similar to that in the overall population of Study P301 ("Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection" dated on May 17, 2021). The safety profile of the booster dose was generally similar to that of the primary series [see Section 7.R.4.1]. Based on the above, safety information on the booster dose in individuals with underlying medical conditions is not currently available, but the safety profile of the booster dose in such individuals is expected to be similar to that in the overall study population. The applicant should continue to gather data including those from Study P301 and other clinical studies that will evaluate booster doses, and take appropriate actions including provision of information to healthcare professionals when new findings become available.

7.R.4.3 Details of safety specification

At the time of the initial approval of COVID-19 Vaccine Moderna, vaccine-associated enhanced disease (VAED)/vaccine-associated enhanced respiratory disease (VAERD) were specified as important potential risks in the risk management plan, and the safety of COVID-19 Vaccine Moderna in pregnant and breastfeeding women as important missing information. Subsequently, based on the post-marketing safety information, myocarditis/pericarditis were added to the important potential risks (Risk Management Plan, revised on November 11, 2021).

7.R.4.3.1 Details of safety specification for mRNA-1273 primary series

Based on the post-authorization or post-marketing spontaneous reports for mRNA-1273 (received between December 21, 2020 and October 31, 2021), the applicant reported the following information on VAED/VAERD and the safety of the vaccine in pregnant and breastfeeding women. No new safety signals were detected. The applicant plans to continue to gather data.

(a) VAED/VAERD

Based on the guidance Brighton Collaboration Case Definition of the term "Vaccine Associated Enhanced Disease" (*Vaccine.* 2021;39:3053-66), COVID-19 cases with documented time to onset of COVID-19 after vaccination with mRNA-1273 were assessed to collect reports on COVID-19 occurring at ≥14 days after the second dose and/or vaccine failure.

A total of 7,015 cases were reported as COVID-19 with documented time to onset of symptoms following the first or second dose of mRNA-1273 and/or vaccine failure. Of them, 3,274 cases were COVID-19 occurring at ≥14 days after the second dose and/or vaccine failure. None of the cases were clearly identifiable as VAED.

(b) Vaccination in pregnant/breastfeeding women

There were 10,870 cases of spontaneously reported events related to vaccination during pregnancy in 3,671 recipients. A total of 1,366 cases of serious pregnancy-related events were reported in 905 recipients. Among them, pregnancy-related events accompanying clinical symptoms reported for ≥50 cases were maternal

exposure to the vaccine during pregnancy (545 cases), spontaneous abortion (400 cases), and foetal death (51 cases).

There were 1,343 spontaneous reports regarding breastfeeding in 1,271 recipients. A total of 240 cases of serious breastfeeding-related events were reported in 317 recipients.[14)] Among them, an event accompanying clinical symptoms reported for ≥40 cases was mastitis (41 cases).

PMDA's view:
PMDA reviewed the post-marketing safety information concerning VAED/VAERD and vaccination in pregnant/breastfeeding women. The former was identified as important potential risks, and the latter as important missing information, at the time of the initial approval of mRNA-1273. There is no currently available information on factors that may have an impact on the benefit-risk balance of mRNA-1273. The applicant should continue to gather data on booster dose vaccination, including data from overseas, and take appropriate actions based on the information obtained.

At the time of the initial approval of COVID-19 Vaccine Moderna, only limited data were available regarding the use of the vaccine in humans. Based on post-marketing data collected overseas[15)] and overseas academic societies' recommendations[16)] on the administration of SARS-CoV-2 vaccines, the Japan Society of Obstetrics and Gynecology, the Japan Association of Obstetricians and Gynecologists, and the Japan Society for Infectious Diseases in Obstetrics and Gynecology released the following information on vaccines, thereby recommending that pregnant and breastfeeding women be vaccinated against SARS-CoV-2: "About COVID-19 vaccines (messenger RNA): second report" (in Japanese) (dated on August 14, 2021) (https://www.jsog.or.jp/news/pdf/20210814_COVID19_02.pdf [last accessed on November 27, 2021]); and "Latest information on the safety of COVID-19 vaccines" (dated on October 25, 2021) (in Japanese) (https://www.jsog.or.jp/news/pdf/20211025_COVID19.pdf [last accessed on November 27, 2021]).

7.R.4.3.2 Myocarditis/pericarditis

Data from post-marketing surveillance of mRNA-1273 and other data have identified the risks of myocarditis/pericarditis after administration of mRNA vaccines against SARS-CoV-2.

The applicant's explanation about myocarditis/pericarditis:
Myocarditis/pericarditis following administration of the mRNA-1273 primary series was evaluated as summarized below (Monthly Safety Report No.10 [issued on November 15, 2021, for the period of October 1-31, 2021]). According to the global safety database of Moderna TX, Inc., 317.68 million doses of COVID-19

14) Serious cases include non-breastfeeding-related events that were classified as serious events.
15) CDC: Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html [last accessed on November 27, 2021])
16) The American College of Obstetricians and Gynecologists: Statement of Strong Medical Consensus for Vaccination of Pregnant Individuals Against COVID-19 (https://www.acog.org/news/news-releases/2021/08/statement-of-strong-medical-consensus-for-vaccination-of-pregnant-individuals-against-covid-19 [last accessed on November 27, 2021]), COVID-19 Vaccines if You Are Pregnant or Breastfeeding (https://s3.amazonaws.com/cdn.smfm.org/media/3040/COVID_vaccine__Patients_JULY_29_2021_final.pdf [last accessed on November 27, 2021])

Vaccine Moderna was administered to 177.10 million people between December 18, 2020 and October 31, 2021. A total of 2,804 cases of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) myocarditis or pericarditis were reported in 2,630 recipients. The event was further classified into "myocarditis with or without pericarditis" (1,824 cases in 1,807 recipients), "pericarditis with or without myocarditis" (980 cases in 974 recipients), "pericarditis without myocarditis" (823 recipients), and "pericarditis with myocarditis" (151 recipients). Medically confirmed cases were myocarditis in 1,446 recipients (26 of whom died) and pericarditis in 774 recipients (3 of whom died). The causality assessment of the fatal cases included "not evaluable" (11 recipients), and the rest of the cases were evaluated on a 5-point scale ("certainly related," "probably/likely," "possibly" "unlikely," and "not related"). The cases were shown to be "possibly related" (12 recipients) and "unlikely related" (6 recipients) to vaccination.

The incidence of "myocarditis with or without pericarditis" was highest in men aged 18 to 24 years (Table 15). Of the 1,824 reported cases, 952 cases (52.2%) occurred after the second dose, and 1,068 cases (58.6%) occurred within 7 days of vaccination, regardless of the dose number. There were 4 reported cases of myocarditis after the administration of mRNA-1273 as the third dose or as the booster dose. The incidence rate (observed) of myocarditis among all mRNA-1273 recipients is 1.02 cases per 100,000 recipients, which is lower than the incidence rate (expected) based on the US Military Health System, 2.12 cases per 100,000 population. The observed/expected (O/E) ratio was higher in men than in women. The O/E ratio was highest in the 18 to 24 year-age group (Table 16).

Table 15. Incidence rate of myocarditis reported within 7 days post-mRNA-1273 vaccination in the US by age and sex (per 100,000) (December 18, 2020 to October 31, 2021)

Age	Overall population			Male			Female		
	Dose 1	Dose 2	Dose 3[a)]	Dose 1	Dose 2	Dose 3[a)]	Dose 1	Dose 2	Dose 3[a)]
<18 years	0.5	0.7	0.0	1.1	1.3	0.0	0.0	0.0	0.0
18-24 years	2.3	3.1	0.0	4.4	5.9	0.0	0.3	0.6	0.0
25-39 years	0.7	1.0	0.1	1.3	1.9	0.2	0.2	0.3	0.0
40-49 years	0.3	0.5	0.1	0.4	0.6	0.3	0.1	0.3	0.0
50-64 years	0.1	0.2	0.1	0.1	0.2	0.0	0.0	0.1	0.1
65-74 years	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0
≥75 years	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0

a) Including the third dose as part of the primary series in immunocompromised individuals

Table 16. The O/E ratio of myocarditis by age group (analyses based on the data from the US Military Health System) (December 18, 2020 to October 31, 2021)

	Number of vaccinees[a)]	Observed		Expected[b)]		O/E ratio [two-sided 95% CI]
		n	Incidence rate[c)]	n	Incidence rate[c)]	
Overall population aged:	177,096,375	1,807	1.02	3,754	2.12	0.48 [0.46, 0.51]
<18 years	5,312,891	51	0.96	89	1.67	0.57 [0.41, 0.81]
18-24 years	15,938,674	664	4.17	267	1.67	2.49 [2.16, 2.87]
25-39 years	38,961,202	628	1.61	652	1.67	0.96 [0.86, 1.08]
40-49 years	26,564,456	179	0.67	563	2.12	0.32 [0.27, 0.38]
50-64 years	46,045,057	136	0.30	976	2.12	0.14 [0.12, 0.17]
65-74 years	26,564,456	64	0.24	563	2.12	0.11 [0.09, 0.15]
≥75 years	17,709,637	31	0.18	375	2.12	0.08 [0.06, 0.12]
Males aged:	84,120,778	1,424	1.69	1,783	2.12	0.8 [0.74, 0.86]
<18 years	2,523,623	48	1.90	54	2.12	0.9 [0.61, 1.32]
18-24 years	7,570,870	590	7.79	161	2.12	3.68 [3.09, 4.38]
25-39 years	18,506,571	517	2.79	392	2.12	1.32 [1.16, 1.5]
40-49 years	12,618,117	118	0.94	268	2.12	0.44 [0.36, 0.55]
50-64 years	21,871,402	75	0.34	464	2.12	0.16 [0.13, 0.21]
65-74 years	12,618,117	34	0.27	268	2.12	0.13 [0.09, 0.18]
≥75 years	8,412,078	14	0.17	178	2.12	0.08 [0.05, 0.14]
Females aged:	92,975,597	355	0.38	1,615	1.74	0.22 [0.2, 0.25]
<18 years	2,789,268	3	0.11	34	1.23	0.09 [0.03, 0.29]
18-24 years	8,367,804	74	0.88	103	1.23	0.72 [0.54, 0.97]
25-39 years	20,454,631	107	0.52	251	1.23	0.43 [0.34, 0.54]
40-49 years	13,946,340	60	0.43	296	2.12	0.2 [0.15, 0.27]
50-64 years	24,173,655	59	0.24	512	2.12	0.12 [0.09, 0.15]
65-74 years	13,946,340	30	0.22	296	2.12	0.1 [0.07, 0.15]
≥75 years	9,297,560	17	0.18	197	2.12	0.09 [0.05, 0.14]

a) Estimated from the number of vaccinees of Dose 1 and that of Dose 2.
b) Expected values were calculated based on the data from the US Military Health System (*Vaccine.* 2021;39:3666-77). For females aged 12-39 years, expected value were calculated after making adjustments based on the information from CDC.
c) The incidence rate was calculated per 100,000 vaccinees.

On the other hand, 42.6% (417 of 980 cases) of reported "pericarditis with or without myocarditis" occurred after the second dose, and 39.6% (388 of 980 cases) occurred within 7 days of vaccination regardless of the dose number. Five cases of pericarditis were reported after the administration of mRNA-1273 as the third dose of the primary series or as the booster dose. The incidence rate (observed) of pericarditis in all mRNA-1273 recipients is 5.33 cases per 100,000 person-years, which is lower than the estimated incidence rate (observed) based on the data on hospitalized patients in the US (5.7 cases per 100,000 person-years).

The incidence rate (observed) of "pericarditis without myocarditis" in all mRNA-1273 recipients is 4.51 cases per 100,000 person-years, which is lower than the estimated incidence rate (observed) based on the data on hospitalized patients in the US, 5.7 cases per 100,000 person-years. The O/E ratio of "pericarditis without myocarditis" calculated based on the data on hospitalized patients in the US was higher in men than in women. The O/E ratio was highest in the 18 to 24 year-age group (Table 17).

Table 17. The O/E ratio of pericarditis without myocarditis by age (based on the data on hospitalized patients in the US) (December 18, 2020 to October 31, 2021)

	Person-years	Observed		Expected[a)]		O/E ratio [two-sided 95% CI]
		n	Incidence rate[b)]	n	Incidence rate[b)]	
Overall population aged:	18,264,867	974	5.33	986	5.40	0.99 [0.9, 1.08]
<18 years	547,946	7	1.28	20	3.70	0.35 [0.15, 0.82]
18-24 years	1,643,838	199	12.11	61	3.70	3.27 [2.46, 4.36]
25-39 years	4,018,271	277	6.89	149	3.70	1.86 [1.53, 2.27]
40-49 years	2,739,730	135	4.93	101	3.70	1.33 [1.03, 1.72]
50-64 years	4,748,865	187	3.94	323	6.80	0.58 [0.48, 0.69]
65-74 years	2,739,730	99	3.61	233	8.50	0.43 [0.34, 0.54]
≥75 years	1,826,487	42	2.30	159	8.70	0.26 [0.19, 0.37]
Males aged:	8,675,812	587	6.77	581	6.70	1.01 [0.9, 1.13]
<18 years	260,274	6	2.31	12	4.59	0.5 [0.19, 1.34]
18-24 years	780,823	154	19.72	36	4.59	4.3 [2.99, 6.18]
25-39 years	1,908,679	172	9.01	88	4.59	1.96 [1.52, 2.54]
40-49 years	1,301,372	74	5.69	60	4.59	1.24 [0.88, 1.74]
50-64 years	2,255,711	99	4.39	190	8.44	0.52 [0.41, 0.66]
65-74 years	1,301,372	51	3.92	137	10.55	0.37 [0.27, 0.51]
≥75 years	867,581	20	2.31	94	10.79	0.21 [0.13, 0.35]
Females aged:	9,589,055	369	3.85	393	4.10	0.94 [0.81, 1.08]
<18 years	287,672	1	0.35	8	2.81	0.12 [0.02, 0.99]
18-24 years	863,015	44	5.10	24	2.81	1.81 [1.1, 2.98]
25-39 years	2,109,592	102	4.84	59	2.81	1.72 [1.25, 2.37]
40-49 years	1,438,358	61	4.24	40	2.81	1.51 [1.01, 2.25]
50-64 years	2,493,154	85	3.41	129	5.16	0.66 [0.5, 0.87]
65-74 years	1,438,358	47	3.27	93	6.45	0.51 [0.36, 0.72]
≥75 years	958,905	22	2.29	63	6.61	0.35 [0.21, 0.56]

a) Expected values were calculated based on the data on hospitalized patients (aged ≥16 years) in the US (*Cardiology.* 2016;135:27-35).
b) The incidence rate was calculated per 100,000 person-years.

SARS-CoV-2 infection is considered to be associated with the development of myocarditis in young males. The risk of myocarditis associated with the first onset of COVID-19 in 12 to 17 year-old males is estimated to be 450 cases per 1 million, according to a study (medRxiv[11)] preprint doi: https://doi.org/10.1101/2021.07.23.21260998). On the other hand, according to the post-emergency authorization or post-marketing safety data between December 18, 2020 and September 30, 2021, of 716,547 men aged <18 years who were inferred to have received mRNA-1273, 16 recipients had myocarditis. This value is adjusted to 22.3 cases per 1 million vaccine recipients. According to CDC's modeling study, 9,600 COVID-19 cases, 300 hospitalizations, 60 ICU admissions, 3 deaths, and 22 to 27 cases of myocarditis can be prevented by 1 million doses of mRNA vaccine over 120 days in the population at the highest risk of myocarditis/pericarditis (males aged 18-29 years) (https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/05-COVID-Rosenblum-508.pdf [last accessed on November 27, 2021]).

In Study P201 Part B, no myocarditis or pericarditis occurred after vaccination with the booster dose of mRNA-1273 by the database lock date; however, 1 case of pericarditis was reported by the safety data snapshot date (August 16, 2021). This event occurred in a female aged 87 years in the 50 μg primary series group 89 days after the booster dose, and angina pectoris was observed concurrently. This participant had a medical history of Grade 1 diastolic dysfunction and chronic bradycardia. A causal relationship to the study vaccine was ruled

out for both events.

The applicant plans to evaluate the risk of myocarditis and pericarditis after the booster dose of mRNA-1273 based on overseas post-marketing surveillance or other data.

Based on the above findings, given the continued public health emergency due to SARS-CoV-2 and the burden of COVID-19 in adolescents, the known and potential benefits of vaccination with mRNA-1273 would outweigh potential myocarditis/pericarditis-related risks. The applicant plans to continue to gather data on myocarditis and pericarditis (including post-booster data) from post-marketing data, clinical studies, and research reports, and take appropriate actions as necessary.

PMDA reviewed the following information obtained in and outside Japan:
Myocarditis and pericarditis reported to Vaccine Adverse Event Reporting System (VAERS) in the US as of October 6, 2021 were analyzed by CDC by vaccine product, sex, dose number, and age (https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf [last accessed on November 27, 2021]). Table 18 shows the reporting rates of myocarditis/pericarditis per 1 million doses within 7 days after vaccination with mRNA-1273. Myocarditis/pericarditis were more frequently reported in young males, particularly after the second dose.

Table 18. Reporting rates of myocarditis/pericarditis within 7 days after mRNA-1273 vaccination (per 1 million doses administered; in the US)

	Males and females		Males		Females	
Age	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
12-15 years	0.0	Not calculated	0.0	Not calculated	0.0	0.0
16-17 years	0.0	Not calculated	0.0	Not calculated	0.0	0.0
18-24 years	3.1	20.7	6.1	38.5	0.6	5.3
25-29 years	1.8	11.2	3.4	17.2	0.4	5.7
30-39 years	1.4	3.6	2.3	6.7	0.5	0.4
40-49 years	0.2	2.1	0.2	2.9	0.2	1.4
50-64 years	0.5	0.5	0.5	0.6	0.5	0.4
≥65 years	0.0	0.3	0.1	0.3	0.0	0.3

Excerpt of the results of "Moderna" from Slides 7-9 at https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf (last accessed on November 27, 2021)

After the market launch in Japan, 152 cases of suspected myocarditis-related events were reported by the marketing authorization holder from May 22, 2021 (start of vaccination) through October 24, 2021, with a trend towards higher reporting rates in males in their teens and 20s (Table 19).

Table 19. Reporting rates of myocarditis/pericarditis after mRNA 1273 vaccination (per 1 million doses administered; in Japan)

	Males		Females	
Age	Dose 1 + Dose 2	Dose 2	Dose 1 + Dose 2	Dose 2
10-19 years	33.62	60.56	1.17	2.62
20-29 years	20.94	39.27	1.00	1.41
30-39 years	2.48	4.08	2.05	0.86
40-49 years	2.88	5.01	2.52	2.98
50-59 years	0.57	0.59	0.89	0.91
60-69 years	1.49	3.04	1.10	0.00
70-79 years	0.00	0.00	0.00	0.00
≥80 years	0.00	0.00	0.00	0.00

Material 2-6-1, Slide 47 for the joint meeting of the Adverse Reaction Working Group of the Subcommittee of the Immunization and Vaccines of the Health Sciences Council (the 72nd of meeting) and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (the 22nd meeting of FY 2021)
(https://www.mhlw.go.jp/stf/shingi2/0000208910_00034.html [last accessed on November 27, 2021])

PMDA's view on the risk of myocarditis/pericarditis following vaccination with mRNA-1273:
Myocarditis-related events after the primary series of mRNA vaccine against SARS-CoV-2, including mRNA-1273, were discussed on October 15, 2021 at the joint meeting of the Adverse Reaction Working Group of the Subcommittee of the Immunization and Vaccines of the Health Sciences Council (the 70th meeting) and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (the 19th meeting of FY 2021): https://www.mhlw.go.jp/stf/shingi2/0000208910_00032.html [last accessed on November 27, 2021]),. Although the differences in the attributes of vaccine recipients between Comirnaty Intramuscular Injection and mRNA-1273 require careful interpretation, the analysis of reporting rates of myocarditis-related events in Japan by age and sex showed that the reporting rate of myocarditis-related events in men in their teens and 20s was higher after mRNA-1273 than after Comirnaty Intramuscular Injection. However, the incidence rate of myocarditis-related events after mRNA-1273 vaccination is lower than that associated with COVID-19 reported in and outside Japan, and therefore the benefits of the vaccine outweigh the risks. The meeting concluded that vaccination with mRNA vaccines including mRNA-1273 can be continued individuals including younger males on the condition that precautionary statements and thorough information are provided in the package insert and other materials ("Information for males in their teens and 20s and their parents or guardians: On myocarditis and pericarditis after vaccination against the novel coronavirus" in Japanese [Ministry of Health, Labour and Welfare] https://www.mhlw.go.jp/content/000844011.pdf [last accessed on November 27, 2021]). Subsequently, a joint meeting of the Adverse Reaction Working Group of the Subcommittee of the Immunization and Vaccines of the Health Sciences Council (the 72nd meeting) and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs and Food Sanitation Council (the 22nd meeting of FY 2021) was held on November 12, 2021: https://www.mhlw.go.jp/stf/shingi2/0000208910_00034.html [last accessed on November 27, 2021]). The conclusion of the meeting is as follows: Among the fatal cases after the mRNA-1273 primary series reported between May 22, 2021 and October 24, 2021, 4 individuals died due to myocarditis-related events. The causal relationship between mRNA vaccines and death due to myocarditis-related events requires close monitoring.

The benefits of mRNA-1273 outweigh the risk of myocarditis/pericarditis following the mRNA-1273 primary series, as judged by the Adverse Reaction Working Group of the Subcommittee of the Immunization and Vaccines of the Health Sciences Council and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council. The applicant needs to take appropriate actions as necessary in response to safety data which will become available in and outside Japan. Although there is currently no evidence suggesting that the risk of myocarditis/pericarditis after the booster dose is higher than the risk of the event after the primary series, the incidence and severity of myocarditis/pericarditis reported after the booster dose and its risk according to the demographics and baseline characteristics have yet to be known due to limited number of recipients of the booster dose of mRNA-1273. Precautionary statements should be provided regarding the risk of myocarditis/pericarditis after the booster dose, in the same manner as it was performed for the primary series. The applicant should also continue to gather data on the incidence after the primary series and overseas data, and take appropriate actions based on the information obtained.

7.R.5 Dosage and administration

The proposed dosage regimen for the booster dose is "A single booster dose (0.25 mL) of COVID-19 Vaccine Moderna is administered intramuscularly at a recommended interval of at least 6 months after the second dose of the primary series."

The applicant also proposed a statement in the Precautions Concerning Dosage and Administration section of the package insert to the effect that the booster dose should be administered to adults aged ≥18 years, and in principle, at least 6 months after the second dose of the primary series.

Based on the discussions in Sections "7.R.1 Clinical significance of the booster dose," "7.R.3 Efficacy," "7.R.4 Safety," "7.R.5.1" through "7.R.5.3," as well as the dosage regimens of the approved SARS-CoV-2 vaccines and other vaccines to prevent infectious diseases, PMDA concluded that the dosage regimen for the booster dose should be "A single booster dose (0.25 mL) of COVID-19 Vaccine Moderna is administered intramuscularly," and that the timing of and eligible age for the booster dose should be specified in the Precautions Concerning Dosage and Administration section of the package insert.

Although the objective of the third dose of the mRNA-1273 is not necessarily the same as that of the booster dose of the approved vaccine, PMDA concluded that it is acceptable to use the proposed term "booster dose" to keep a consistency with the term used in the dosage regimen for the approved vaccine.

The Precautions Concerning Dosage and Administration section of the package insert should also include precautionary statements to the effect that the necessity of a booster dose should be determined based on the benefit-risk balance taking into account the status of COVID-19 outbreaks and the presence of risk factors for severe COVID-19 in individuals [see Section 7.R.1].

Additionally, the applicant should provide information in the package insert and other materials to the effect that there are no available data on 50 μg mRNA-1273 booster dose administered to recipients of other SARS-CoV-2 vaccines as primary series.

7.R.5.1 Dosage

The applicant's explanation about the selection of the dosage of the booster dose:

The dosage of the primary series of mRNA-1273 is 100 μg, which was used in Study P301, a study that demonstrated the efficacy of mRNA-1273. In Study P201 Part B, 50 μg was selected as the booster dose based on the results of evaluation of the dosage of the primary series in Study P201 Part A, in which sufficiently high neutralizing antibody titers were elicited both in the 50 μg and 100 μg groups, while the incidence of solicited local or systemic adverse events tended to be lower in the 50 μg group than in the 100 μg group ("Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection" dated on May 17, 2021). On the basis of the results from Study P201 Part B, the applicant considered that the booster dose of 50 μg mRNA-1273 is expected to be effective [see Section 7.R.3], and no significant safety concerns have been identified [see Section 7.R.4]; therefore, a dose of 50 μg (injection volume, 0.25 mL) was selected for the booster dose of mRNA-1273.

Based on the discussions in Sections "7.R.1," "7.R.2," and "7.R.4," PMDA concluded that 50 μg (injection volume, 0.25 mL) can be selected as the booster dose of mRNA-1273.

7.R.5.2 Interval for booster dose (interval between the second dose of the primary series and the booster dose)

The applicant's explanation about the interval between the second dose of the primary series and the booster dose:

Since Study P201 Part B started approximately 6 months after the second dose of the primary series in participants in Study P201 Part A, a period of "at least 6 months after the completion of the primary series" was selected as the timing of the booster dose in Study P201 Part B. The study evaluated a booster dose at the specified interval. The results of the study demonstrated the efficacy and favorable safety profile of the booster dose [see Sections 7.R.3 and 7.R.4]. The median interval between the second and booster doses of mRNA-1273 was 218.0 days (range, 177-269).

Based on the above findings, a period of "at least 6 months" was selected as the interval between the second dose of the primary series and the booster dose.

PMDA's view:

While no definite conclusion has been reached to date regarding the duration of efficacy after the primary series of the mRNA-1273, in Study P201 Part B which provides pivotal evidence in the present application, participants were allowed to receive a booster dose "at least 6 months after the completion of the primary series" in view of the feasibility. The evaluation of the immunogenicity data from Study P201 Part B showed that the non-inferiority criterion of seroresponse rate were not met. According to the applicant, this may have been

partly caused by relatively high antibody titer levels observed before the booster dose in some participants. The study included individuals who had completed their primary series ≥6 months before, but it is thus not clear whether the study design was most suitable to evaluate the efficacy of the booster dose of mRNA-1273. However, increased antibody responses after the booster dose were shown in individuals with relatively high pre-booster antibody titers who had not met the criterion for seroresponse rate. For the following reasons, PMDA concluded that "at least 6 months after the completion of the primary series" can be selected as the interval between the second dose of the primary series and the booster dose of mRNA-1273 in Japan: (1) the results of Study P201 Part B conducted in participants who were to receive their booster dose at least 6 months after the completion of their primary series demonstrated that the booster dose of mRNA-1273 was expected to have a certain level of efficacy [see Section 7.R.3]; and (2) in the US and Europe, a booster dose can be administered to individuals who received the second dose of mRNA-1273 at least 6 months before. Furthermore, taking into consideration that the booster dose of Comirnaty Intramuscular Injection can be administered at least 6 months after the second dose of the primary series in Japan, a booster dose of mRNA-1273 "at least 6 months after the completion of the primary series" is beneficial to the public also to avoid confusion in clinical practice.

No study data on the immunogenicity and safety of the booster dose of 50 μg mRNA-1273 at >8 months after the second dose are available. However, because of the absence of an established threshold for protection against COVID-19, it is not clear whether a recommended interval for the booster dose needs to be specified. The applicant should review clinical data on the booster dose of mRNA-1273 in Study P301, and various data including epidemiological data from the US and Europe where booster rollout of mRNA-1273 began earlier than in Japan.

7.R.5.3 Age indication

The applicant's explanation about the age indication for the booster dose of mRNA-1273:
In the US, adults aged ≥18 years were eligible for the primary series of mRNA-1273, and the indication for use in adolescents aged ≥12 years was under review. In Europe, individuals aged ≥12 years are eligible for the primary series. In the US and Europe, the application for the booster dose was filed for use in adults and adolescents aged ≥12 years based on data including results from Study P201 Part B conducted in healthy adults aged ≥18 years. In Europe, however, on October 25, 2021, the European Medicines Agency (EMA) issued a recommendation stating that a booster dose of 50 μg mRNA-1273 may be considered at least 6 months after the primary series for people aged ≥18 years because of no safety data on the booster dose in adolescents aged 12 to 17 years and other reasons. In the US, on October 20, 2021, the FDA granted an Emergency Use Authorization for administration of a booster dose of 50 μg mRNA-1273 at least 6 months after the completion of the primary series to individuals aged ≥65 years, individuals aged ≥18 years at an increased risk of severe COVID-19, and individuals with frequent institutional or occupational exposure.

Although individuals aged ≥12 years are eligible for the primary series of 100 μg mRNA-1273 in Japan, "individuals aged ≥18 years" were selected for the eligible population for the booster dose of mRNA-1273, consistently with the authorized or approved age in the US and Europe.

The applicant plans to amend the protocol of the ongoing Study mRNA-1273-P203, a study on the primary series in adolescents aged 12 to 17 years, to evaluate the booster dose of mRNA-1273 in the age group.

PMDA's view:
Based on the age of eligible participants (≥18 years) in Study P201 Part B, and recommendations in the US and Europe, the applicant's proposed age indication for the booster dose (≥18 years) is appropriate at this point.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance of COVID-19 Vaccine Moderna (mRNA-1273):
Although the safety profile of the booster dose of COVID-19 Vaccine Moderna does not differ greatly from that of the primary series, currently available data on the booster dose of COVID-19 Vaccine Moderna are all from overseas. Given this, it is meaningful to review the safety of the booster dose of COVID-19 Vaccine Moderna.

Data on the safety of the primary series of COVID-19 Vaccine Moderna up to 28 days after the second dose were collected by a government-initiated Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan (Research on Emerging and Re-emerging Infectious Diseases and Immunization funded by the Health, Labour and Welfare Policy Research Grant of FY 2020). When a similar government-initiated cohort survey is conducted to assess the safety of the booster dose of COVID-19 Vaccine Moderna, another survey, if planned by the applicant, would place an extra burden on healthcare professionals in clinical practice because such survey will be performed in the same participants for the same objective. Therefore, as soon as the plan for such government-initiated cohort survey is clarified, the scheme for the collection of safety data on the booster dose of COVID-19 Vaccine Moderna in clinical practice will be decided.

PMDA's view:
Because of the limited data on the booster dose of COVID-19 Vaccine Moderna and the absence of data on Japanese booster recipients, it is important to gather safety data on the booster dose of COVID-19 Vaccine Moderna in Japan, provide information on the incidence of adverse reactions in clinical settings promptly and appropriately, and provide precautionary statements based on the information obtained as necessary. The plan for post-marketing surveillance will be finalized taking into account the comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Report (2).

9. Overall Evaluation during Preparation of the Report on Special Approval for Emergency (1)

On the basis of the data submitted, PMDA has concluded that the booster dose of COVID-19 Vaccine Moderna has a certain level of efficacy in the prevention of the disease caused by SARS-CoV-2 infection (COVID-19), and that COVID-19 Vaccine Moderna has acceptable safety with no significant safety concerns.

PMDA has concluded that COVID-19 Vaccine Moderna may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

Report on Special Approval for Emergency (2)

December 9, 2021

Product Submitted for Approval

Brand Name	COVID-19 Vaccine Moderna Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 10, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Clinical significance, review strategy, and efficacy of the booster dose

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Sections "7.R.1 Clinical significance of the booster dose," "7.R.2 Review strategy," and "7.R.3 Efficacy" in the Report (1), and also made the following comments:

- It should be pointed out that data on the efficacy of the booster dose of mRNA-1273 are not sufficient. In the future, the circulating strain will be replaced by new variants, and this may raise concerns about the efficacy of the original vaccine. In that case, the introduction of a modified vaccine should be considered promptly.
- Any new data on the duration of efficacy of the booster dose and the efficacy of the vaccine against variants should be published immediately when they become available.

PMDA communicated the expert advisors' comments to the applicant. The applicant agreed to continue to gather data and take appropriate actions based on the findings.

1.2 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.4 Safety" in the Report (1), and made the comment that the applicant should gather data to assess the safety of the booster dose in Japanese vaccine recipients and the risk of myocarditis/pericarditis following booster vaccination.

PMDA communicated the comments above to the applicant. The applicant agreed to continue to gather data.

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.5 Dosage and Administration" in the Report (1), and made the comment that the reason for selecting the booster dosage of 50 μg rather than 100 μg (primary series dosage) should be explained more clearly.

Determination of dosage for the booster dose of mRNA-1273, and the PMDA's conclusion:
Study P201 Part B was planned to evaluate the booster dose of mRNA-1273. A 50 μg dose, a half of the approved dose for the primary series, was selected for the booster dose [see Section 7.R.5.1]. Study P201 Part A was submitted in the support of the application for mRNA-1273 as the primary series, and its results demonstrated that serum neutralizing antibody titers against SARS-CoV-2 increased in both 50 μg and 100 μg primary series groups, and that the incidence of solicited adverse events (local and systemic) was lower in the 50 μg primary series group than in the 100 μg primary series group ("Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection" dated on May 17, 2021). The applicant opts for a booster dose of 50 μg, a half of the primary series dose, if sufficient immune responses can be induced by the half-dose vaccination which is associated with a decreased incidence of adverse events. The applicant's strategy is acceptable.

Study P201 Part B was conducted using the thus-selected dose level. The immunogenicity of the 50 μg booster dose of mRNA-1273 and other data were evaluated in this study. The results of the study has demonstrated that the 50 μg booster dose of mRNA-1273 has a certain level of efficacy [see Section 7.R.3], and no significant safety concerns have been identified [see Section 7.R.4]; therefore, PMDA has concluded that a dose of 50 μg mRNA-1273 can be selected for the booster dose. In the US and Europe, 50 μg mRNA-1273 has been granted an Emergency Use Authorization or marketing authorization.

Results from Study DMID21-0012, submitted as reference data, include the outcomes of vaccination with a 100 μg mRNA-1273 booster dose. In the study, however, the booster dose was administered at an interval that was different from the proposed interval. This precluded comparison with the data of the 50 μg booster dose. In addition, the results of Study DMID21-0012 do not necessarily indicate that the efficacy can only be demonstrated with a 100 μg booster dose. For this reason, PMDA has concluded that there is no need to ask the applicant to evaluate the efficacy of a 100 μg booster dose.

At the Expert Discussion, the expert advisors made another comment: there is no objection to specifying the administration of the booster dose at least 6 months the second dose, but it is desirable to provide information on a recommended interval for a booster dose if it becomes available.

PMDA communicated the comments to the applicant. The applicant agreed to take appropriate actions when findings become available.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.6 Post-marketing investigations" in the Report (1), and also made the following comment: government-initiated observational epidemiological studies, including the ongoing government-initiated cohort survey to be extended, are expected to collect not only safety data, but also data on the duration of efficacy of the booster dose and its efficacy against variants.

PMDA has concluded that the risk management plan (draft) for COVID-19 Vaccine Moderna should include the safety specification presented in Table 20, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 21. "Myocarditis and pericarditis," which had been specified as important potential risks, were classified as important identified risks during the review process based on the post-marketing information obtained.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Myocarditis, pericarditis	• Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	• Safety of COVID-19 Vaccine Moderna in pregnant and breastfeeding women
Efficacy specification		
None		

Table 21. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (primary series) • General use-results survey (a follow-up of participants in the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan) • Post-marketing database survey: shock, anaphylaxis (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) • Post-marketing database survey: acute phase solicited adverse events (primary series) • Post-marketing database survey: non-acute phase hospitalization events (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) • Post-marketing clinical study (TAK-919-1501) (primary series) • Foreign phase III study (mRNA-1273-301) (primary series)	• Disseminate data gathered during early post-marketing phase vigilance (primary series) • Develop and distribute information materials for healthcare professionals (Proper use guide) • Develop and distribute information materials for vaccine recipients (For those who are receiving COVID-19 Vaccine Moderna Intramuscular Injection) • Publish information on reported adverse reactions periodically (primary series)

Underline denotes additions for the present application

The post-marketing surveillance plan explained by the applicant in Section "7.R.6 Post-marketing investigations" in the Report (1) remains undetermined, because the details of the plan for the government-initiated cohort survey for the booster dose have not been clarified. As soon as the details of the above plan become available, the applicant will review and determine the plan for their survey. PMDA accepted the applicant's plan.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the dosage and administration shown below, with the following conditions. Although the present application has been submitted for the approval of a new dosage, the re-examination period for the present application should be the remainder of the ongoing re-examination period (until May 20, 2029) because it has more than 4 years left.

Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

(No change)

Dosage and Administration

Primary series:

COVID-19 Vaccine Moderna is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

Booster dose:

A single booster dose (0.25 mL) of COVID-19 Vaccine Moderna is administered intramuscularly.

(Underline denotes additions.)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.

(1) Matters related to Item 2

When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.

(2) Matters related to Item 3

The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(3) Matters related to Item 4

The applicant is required to report the quantity sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

(1) The applicant is required to develop and appropriately implement a risk management plan.

(2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.

(3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

(4) The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and who have provided written informed consent through the vaccine screening questionnaire in advance.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to any Item of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

4. Other

The current brand name “COVID-19 Vaccine Moderna Intramuscular Injection” will be changed to “Spikevax Intramuscular Injection” after the approval of the present application. Since the Japanese non-proprietary name (Japanese Accepted Name [JAN]) for the active substance “CX-024414” has been established, the name of the active substance will also be changed to “Elasomeran.”

Appendix

List of Abbreviations

BMI	Body mass index
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of February 1, 1961)
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
COVID-19 Vaccine Moderna	COVID-19 Vaccine Moderna Intramuscular Injection (or mRNA-1273)
CX-024414	mRNA that encodes the S protein of SARS-CoV-2
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
GLSM	Geometric least squares mean
GMFR	Geometric mean fold rise
GMR	Ratio of Geometric mean titers
GMT	Geometric mean titer
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
mRNA	Messenger RNA
MSR	Monthly Safety Report
NIH	National Institutes of Health
O/E ratio	Observed/Expected ratio
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
PP Set	Per-protocol set
Prototype virus strain	Wuhan-Hu-1 strain (D614G)
Reports (1) / (2)	Reports on Special Approval for Emergency (1) / (2)
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard Deviation
ULOQ	Upper limit of quantification
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine Efficacy