Report on the Deliberation Results

May 20, 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	March 5, 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 May 20, 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 product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The vaccine product and its active substance are both classified as powerful drugs.

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.

4. The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. After the market launch, the applicant is required to continue to collect quality information and take necessary measures.
5. 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.
6. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 8 months after the approval. If new data, etc., submitted in accordance with the above, necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

Report on Special Approval for Emergency

May 17, 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	March 5, 2021
Dosage Form/Strength	Suspension for injection: Each vial contains 1.0 mg of CX-024414.
Application Classification	Prescription drug, (1) Drug with a new active ingredient
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.
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety in view of its benefits (see Attachment).

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)

Dosage and Administration

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

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 1
   The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. After the market launch, the applicant is required to continue to collect information on the quality aspects of the product and take necessary measures.
   (2) 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.
   (3) 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.
   (4) 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 product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. After the market launch, the

applicant is required to continue to collect information on the quality aspects of the product and take necessary measures.

(5) 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.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 8 months after the approval. If new data, etc., submitted in accordance with the above, necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

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)

May 10, 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	March 5, 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)

Proposed Dosage and Administration

For individuals 18 years of age and older, COVID-19 Vaccine Moderna is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

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List of Abbreviations

See Appendix.

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

Coronavirus is a positive-sense single-stranded RNA virus belonging to the family *Coronaviridae* and the order *Nidovirales*. Four types of human coronavirus (HCoV), HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, have been known to routinely infect humans causing common cold. In recent years, two types of zoonotic coronavirus causing severe pneumonia have been identified: Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) identified in 2003 and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) in 2012.

On December 31, 2019, the World Health Organization (WHO) received a report of the outbreak of pneumonia of unknown cause in Wuhan City, Hubei Province of China. On January 12, 2020, WHO announced that the pneumonia was caused by a novel coronavirus.[1)] On January 30, 2020, WHO declared that the outbreak of novel coronavirus-related pneumonia in Wuhan City, Hubei Province of China fulfills the criteria for a Public Health Emergency of International Concern.[2)3)] On February 11, 2020, WHO named the novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by SARS-CoV-2 as coronavirus disease (COVID-19).[4)] As of April 18, 2021, a total of 140,332,386 people have been infected globally, with a total death toll of 3,004,088. Cumulative COVID-19 cases and deaths by WHO region are as follows: the Region of the Americas accounts for 42% and 48% of the global cumulative cases and deaths, respectively, the European Region accounts for 35% and 34%, respectively, the South-East Asia Region accounts for 13% and 8%, respectively, the Eastern Mediterranean Region accounts for 6% and 6%, respectively, the African Region accounts for 2% and 3%, respectively, and the Western Pacific Region accounts for 2% and 1%, respectively.[5)]

In Japan, the first patient with SARS-CoV-2-related pneumonia was identified on January 15, 2020. On February 1, 2020, COVID-19[6)] was classified as a Designated Infectious Disease[7)] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Act No. 114 of 1998) (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease[8)] pursuant to the Quarantine Act (Act No. 201 of 1951). On April 7, 2020, the Japanese government declared its first state of emergency[9)] pursuant to the amended Act on Special Measures for Pandemic Influenza and New Infectious Diseases

1) https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/ (last accessed on April 22, 2021)
2) The term Public Health Emergency of International Concern is defined in the International Health Regulations (IHR) of WHO as:
(a) An extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease
(b) An extraordinary event which is determined to potentially require a coordinated international response
3) https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding- the-outbreak-of-novel-coronavirus-(2019-ncov) (last accessed on April 22, 2021)
4) https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (last accessed on April 22, 2021)
5) https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---20-april-2021 (last accessed on April 21, 2021)
6) Limited to the disease caused by the novel coronavirus of genus *Betacoronavirus* that was reported as transmissible to humans to WHO from the People's Republic of China in January 2020.
7) The term Designated Infectious Disease means already known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, and Novel Influenza Infection, etc.) specified by Cabinet Order as a disease which would be likely to seriously affect the health of the public in the event of its spread if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).
8) The term Quarantinable Infectious Disease means diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).
9) Initially, the state of emergency was limited to Saitama, Chiba, Tokyo, Kanagawa, Osaka, Hyogo, and Fukuoka prefectures, but temporarily expanded to cover the whole Japan.

Preparedness and Response (Act No. 31 of 2012) and, on January 7, 2021, its second state of emergency.[10] The former was lifted on May 25, 2020 and the latter on March 21, 2021. On April 25, 2021, the third state of emergency[11] was declared.

As of April 26, 2021, a total of 564,211 people have been infected in Japan, with a death toll of 9,969. In addition to these figures, 2,637 people tested positive at the airport/seaport quarantine, with 3 cases of death after testing positive, and 15 people tested positive after returning to Japan by international charter flights.[12]

The early symptoms of COVID-19 resemble influenza and common cold; this makes it difficult to differentiate the former from the latter during the early phase of the onset of the disease. The incubation period from the exposure to SARS-CoV-2 to symptom onset ranges from 1 day through 14 days, usually around 5 days.[13] Patients with COVID-19 become infectious before symptom onset and especially highly infectious early after the onset. Further, some patients are asymptomatic. This is considered to be the cause of community transmission, making it difficult to control the transmission. Many patients present with symptoms including fever, cough, malaise, dyspnea, taste disorder, and dysosmia. Approximately 80% of patients have mild symptoms and recover within approximately 1 week, approximately 20% of patients experience aggravated pneumonia symptoms, approximately 5% of patients progress to acute respiratory distress syndrome or multi-organ failure that requires ventilator support, and approximately 2% to 3% of patients die (*JAMA*. 2020; 323: 1239-42). The emergence of variants with altered infectivity/transmissibility and altered antigenicity has also been pointed out.[14] As of April 23, 2021, therapeutic agents approved in Japan are Veklury for Intravenous Injection 100 mg (Solution) and Veklury for Intravenous Injection 100 mg (Lyophilized powder) for the treatment of disease caused by SARS-CoV-2 infection (COVID-19) and Olumiant tablets 2 mg and 4 mg for the treatment of pneumonia caused by SARS-CoV-2 infection (COVID-19) (patients requiring oxygen inhalation only). Dexamethasone can be used within the approved indications. However, despite treatment with these drugs, the numbers of infected people, patients with severe COVID-19, and fatal cases keep rising in Japan, putting the nation's medical system under severe strain. In order to control the spread of the infection, COVID-19 prevention by SARS-CoV-2 vaccine is eagerly awaited. Vaccine development is thus an urgent need.

As of April 2021, Comirnaty Intramuscular Injection (Pfizer Japan Inc.) has been approved as a vaccine indicated for the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in Japan. The rapid supply of multiple types of vaccines is needed due to the prevalence of SARS-CoV-2 infection, the persistent and rapid spread of the infection, the tremendous impact of the pandemic on the healthcare system and society and economy, and the issues of the balance of supply and demand and stable supply associated with worldwide vaccination.

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[10] The state of emergency covered Tochigi, Saitama, Chiba, Tokyo, Kanagawa, Gifu, Aichi, Kyoto, Osaka, Hyogo, and Fukuoka prefectures.
[11] As of April 25, 2021, the state of emergency covered Tokyo, Osaka, Kyoto, and Hyogo prefectures.
[12] https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html#h2_1 (last accessed on April 26, 2021)
[13] https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations (last accessed on April 22, 2021)
[14] https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2484-idsc/10280-covid19-41.html (last accessed on April 26, 2021)

Moderna TX, Inc. has so far undertaken the development of messenger RNA (mRNA) vaccines against human cytomegalovirus (*Vaccine*. 2018; 36: 1689-99), influenza virus (*Front. Immunol*. 2017; 8: 1539), Zika virus (*Cell*. 2017; 168: 1114-25), etc., and has created its platform for these vaccines. The mRNA vaccine platform is based on the following principle: Lipid nanoparticles (LNP) enable the mRNA encoding the viral protein to be delivered into host cells, and the cells *in vivo* can take up the mRNA, translate it, and express the viral protein antigen at their surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, but causes temporary expression of the protein (*Med Sci Monit.* 2020; 26: e924700), and is degraded by ribonuclease *in vivo*. COVID-19 Vaccine Moderna (also referred to as mRNA-1273) is an LNP-encapsulated mRNA-based vaccine, and its active substance is the mRNA encoding the spike protein (S protein) of SARS-CoV-2. The base sequence of the mRNA is optimized for efficient translation. In January 2020, Moderna TX, Inc. started the rapid development of COVID-19 Vaccine Moderna based on the mRNA vaccine platform, for the prevention of disease caused by SARS-CoV-2 infection (COVID-19). A foreign phase I clinical study (Study 20-0003), a foreign phase IIa clinical study (Study mRNA-1273-P201), and a foreign phase III clinical study (Study mRNA-1273-P301) began in March, May, and July in 2020, respectively, and a Japanese clinical study (Study TAK-919-1501) began in January 2021. All those studies are still ongoing at the end of April 2021.

Based on the efficacy (vaccine efficacy to prevent COVID-19) and safety data from Foreign Study mRNA-1273-P301 at the interim analysis, an Emergency Use Authorization was granted in the US on December 18, 2020, and a conditional marketing authorization was granted in Europe as of January 6, 2021, for COVID-19 Vaccine Moderna for the prevention of COVID-19.

The vaccine was authorized for emergency use by the US Food and Drugs Administration (FDA), the conditional marketing authorization was granted in Europe, and Japanese Study TAK-919-1501 to evaluate the immunogenicity and safety of the vaccine is ongoing in Japan. Because of these and other reasons, Takeda Pharmaceutical Company Limited submitted a marketing application for COVID-19 Vaccine Moderna in Japan on March 5, 2021. Some of the results of Japanese Study TAK-919-1501 were submitted during the regulatory review of the present application.

This report contains the results of review conducted based on the data submitted by the applicant, in accordance with the "Handling of Drugs Submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification No. 0401-2 dated April 1, 2021).

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

COVID-19 Vaccine Moderna (mRNA-1273 formulation) contains the mRNA encoding the S protein of SARS-CoV-2 (CX-024414) encapsulated in LNP (Lipid Mixture). The active substance CX-024414, Lipid Mixture composed of 4 lipids (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate [SM-102], cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC], 1,2-dimyristoyl-rac-glycero-3-

methoxypolyethylene glycol-2000 [PEG2000-DMG]), and their complex, mRNA-1273 LNP, have been registered in the Master File (MF) (MF Registration Number, 303MF10038) by Lonza AG.

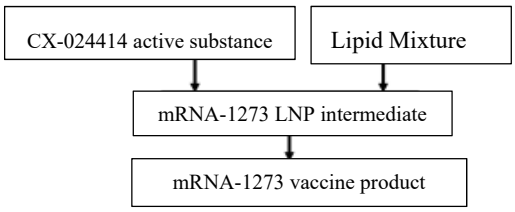

Figure 1. Overview of manufacturing process for mRNA-1273 vaccine product

mRNA-1273 LNP had been initially defined as the active substance at the time of regulatory submission, but CX-024414 was re-defined as the active substance during the regulatory review [see Section 2.R.1].

2.1 Active substance (CX-024414)

The active substance CX-024414 is the mRNA encoding the full-length S protein of SARS-CoV-2 (derived from the Wuhan-Hu-1 strain). The S protein is stabilized in the pre-fusion conformation by 2 amino acid substitutions (K986P and V987P). The CX-024414 mRNA sequence includes a 5' Cap 1 structure, the 5' untranslated region (UTR), the Open Reading Frame (ORF) encoding the pre-fusion stabilized S protein of SARS-CoV-2, the 3' UTR, and the 3' polyA tail. N^1-methylpseudouridine triphosphate (N1-Me-ΨTP) instead of uridine triphosphate (UTP) is used to avoid activation of Toll-like receptors (TLRs) and to dampen innate immune response.

2.1.1 Characterization of active substance

The active substance was subjected to characterization shown in Table 1.

Table 1. Characterization attributes

Attribute		Test method
Primary/structure	RNA sequence	Sanger sequencing, Oligonucleotide mapping ([redacted]), Identification of N1-Me-ΨTP ([redacted]), Next-generation sequencing
	5'-Cap1 structure	RP-HPLC/ESI MS after RNase H digestion
	PolyA tail length and dispersity	[redacted]
Higher order structure	Tertiary structure	Circular dichroism
	Higher order structure	Differential scanning calorimetry
Physicochemical properties	Extinction coefficient	UV
Biological properties	*In vitro* translation	SDS-PAGE, Western blotting

The biological properties of the active substance were evaluated using an *in vitro* translation assay, in which the mRNA (CX-024414) was translated into a protein in a cell-free system, and the molecular weight of the protein was confirmed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). A band of the same molecular weight as the desired product was identified as the S protein of SARS-CoV-2 by Western blotting.

Short mRNA species, high-molecular-weight mRNA, Cap variants, polyA tail variants, double-stranded RNA, variants with a point mutation, and variants with insertions/deletions were considered product-related impurities. Short mRNA species, high-molecular-weight mRNA, Cap variants, and polyA tail variants are controlled by the active substance specifications.

Residual DNA template, residual proteins (Process-related Impurity A, Process-related Impurity B, Process-related Impurity C, Process-related Impurity D, Process-related Impurity E, etc.), small molecular impurities (Process-related Impurity F, Process-related Impurity G, Process-related Impurity H, Process-related Impurity I, Process-related Impurity J, etc.), residual solvents (Process-related Impurity K and Process-related Impurity L), and residual [redacted] were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed in the manufacturing process. Residual proteins are controlled by in-process control testing, and residual DNA template is controlled by the active substance specifications.

2.1.2 Manufacturing process for active substance

See Supplement.

2.1.3 Control of active substance

The proposed specifications for the active substance consist of content, appearance, identity (the base sequence), pH, purity [mRNA purity and product-related impurities (reversed phase-high performance liquid chromatography [RP-HPLC]), % 5' Capped (RP-HPLC), % PolyA tailed RNA and [redacted] (RP-HPLC), residual DNA template (quantitative polymerase chain reaction [qPCR])], bacterial endotoxins, microbial limits, and assay (ultraviolet [UV]).

2.1.4 Stability of active substance

The primary stability studies on the active substance are shown in Table 2. In the long-term testing, the active substance was stable, whereas a decrease in mRNA purity and increases in product-related impurities were observed at [redacted] months under the accelerated conditions. The photostability data showed that the active substance is sensitive to light.

Table 2. Stability studies on active substance

Study	Primary batches [a)]	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	−20 ± 5°C	Ambient	[redacted] bag	6 months[b)]
Accelerated	3 pilot-scale batches	5 ± 3°C	Ambient		6 months

a) Although the primary batches were manufactured by a different process at a different scale at a different site, etc. from batches for use in the manufacture of the proposed commercial vaccine product in Japan, comparable quality between pre-change and post-change active substances has been demonstrated.
b) The testing will be continued for up to 24 months.

Based on the above, a shelf life of 6 months has been proposed for the active substance when stored in [redacted] bag at −20 ± 5°C.

2.2 Vaccine product (mRNA-1273 formulation)

2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is presented as a multiple-dose suspension for injection (doses of 0.5 mL). Each vial (13.5 mL) contains 1.0 mg/5 mL of the active substance (CX-024414) and the following excipients: SM-102, cholesterol, DSPC, PEG2000-DMG, glacial acetic acid, sodium acetate trihydrate, trometamol, tromethamol hydrochloride, sucrose, and water for injection. Lipid Mixture composed of 4 lipids (SM-102, cholesterol, DSPC, PEG2000-DMG) has been designed to optimize uptake into the target cells, deliver the encapsulated mRNA into the cell's cytosol, and block the access of nucleases.

2.2.2 Manufacturing process for vaccine product

See Supplement for the manufacturing process for Lipid Mixture and mRNA-1273 LNP.

The vaccine product manufacturing process after the manufacture of mRNA-1273 LNP consists of dilution of mRNA-1273 LNP, clarification, sterile filtration, filling, freezing/storage, and testing.

Quality by design (QbD) approaches were utilized to identify critical quality attributes (CQAs) (Table 3).

Table 3. Overview of vaccine product control strategy

CQA	Method of control
Appearance	Specification
mRNA identity	Specification
Lipid identity	Specification
mRNA content	Specification
mRNA purity	Specification
mRNA impurities	Specification
Lipid content	Specification
Lipid impurities	Specification
% RNA encapsulation	Specification
In vitro translation	Specification
pH	Specification
Osmolality	Specification
Mean particle size	Specification
Polydispersity index	Specification
Insoluble particulate matter	Specification
Extractable volume	Specification
Bacterial endotoxins	Specification
Sterility	Specification

[redacted] of mRNA-1273 LNP has been defined as the critical step.

2.2.3 Control of vaccine product

2.2.3.1 Control of Lipid Mixture

The proposed specifications for Lipid Mixture consist of [redacted].

2.2.3.2 Control of mRNA-1273 LNP

The following attributes have been included in the specification for mRNA-1273 LNP: content, appearance, identity [mRNA (the base sequence), SM-102, cholesterol, DSPC, and PEG2000-DMG (RP-HPLC/charged aerosol detection [CAD])], purity [mRNA purity and product-related impurities (RP-HPLC), lipid impurities (RP-HPLC/CAD)], % RNA encapsulation, pH, osmolality, mean particle size and polydispersity index, bacterial endotoxins, microbial limits, lipid content [SM-102, cholesterol, DSPC, and PEG2000-DMG (RP-HPLC/CAD)], and assay [anion exchange chromatography-high performance liquid chromatography (AEX-HPLC)].

2.2.3.3 Control of vaccine product (mRNA-1273 formulation)

The proposed specifications for the vaccine product consist of content, appearance, identity [mRNA (the base sequence), SM-102, cholesterol, DSPC, and PEG2000-DMG (RP-HPLC/CAD)], purity [mRNA purity and product-related impurities (RP-HPLC), lipid impurities (RP-HPLC/CAD)], % RNA encapsulation, *in vitro* translation (SDS-PAGE), pH, osmolality, mean particle size and polydispersity index (dynamic light scattering), foreign insoluble matter, insoluble particulate matter, extractable volume, bacterial endotoxins, sterility, lipid content [SM-102, cholesterol, DSPC, and PEG2000-DMG (RP-HPLC/CAD)], and assay [AEX-HPLC].

2.2.4 Stability of vaccine product

The primary stability studies on the vaccine product (mRNA-1273 formulation) are shown in Table 4, and the study results showed that the vaccine product is stable. Photostability data showed that the vaccine product is sensitive to light.

Table 4. Stability studies on vaccine product

Study	Primary batches [a)]	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	−20 ± 5°C	Ambient	Chlorobutyl rubber stopper and glass vial	6 months[b, c)]

a) Although the primary batches were manufactured by a different process at a different scale at a different site, etc. from the proposed commercial batches in Japan, comparable quality between pre-change and post-change vaccine products has been demonstrated.
b) Including 30 days at 2°C to 8°C and 12 hours at 8°C to 25°C. Because the vaccine product includes no preservatives, vials should be discarded 6 hours after first puncture.
c) The testing will be continued for up to 24 months.

Based on the above, a shelf life of 6 months has been proposed for the vaccine product when stored in a glass vial with a chlorobutyl rubber stopper packaged in a carton to protect from light at −20 ± 5°C.

The proposed storage periods for Lipid Mixture and mRNA-1273 LNP are 3 months when stored at −75 ± 15°C, based on the results of their respective long-term stability studies (3 pilot-scale batches).

2.R Outline of the review conducted by PMDA

Due to the very short time frame of product development and other reasons, the data presented at the time of regulatory submission and during the regulatory review and the explanation thereof were limited. However, considering the urgent need for this product, PMDA conducted its review based on the submitted data.

Based on the submitted data and the following considerations, PMDA concluded that the quality of the active substance and the vaccine product is adequately controlled. PMDA also took into account that batch analysis results were consistent across batches of the foreign commercial vaccine product and that the data demonstrated that the quality of the foreign commercial vaccine product is comparable with that of the proposed commercial vaccine product in Japan, which was manufactured at a different scale at a different site. The MF data for this product were submitted by the MF registrant separately. See Supplement for the results of the review of MF by PMDA.

2.R.1 Definition of active substance

At the time of regulatory submission for COVID-19 Vaccine Moderna and at the time of MF registration for mRNA-1273 LNP, mRNA-1273 LNP had been defined as the active substance. However, given that mRNA is used as a template for antigen protein synthesis and that LNP has been reported to play an important role in the kinetics of the active substance and the entry of mRNA into the cell and to the cytoplasm (*Pharm Res*. 2021; 38:473-8, *Front Mol Biosci*. 2021; 8:635245), mRNA (CX-024414) is considered to be the active substance of COVID-19 Vaccine Moderna (mRNA-1273). Thus, PMDA asked the applicant to change the definition of the active substance.

The applicant's explanation:

Naked mRNA is inefficiently internalized into the target cell. Because naked extracellular mRNA undergoes degradation by enzymes, it is unable to exert its protective activity. Meanwhile, LNP is designed to form lipid bilayers to prevent the enzymatic degradation of mRNA and thereby to optimize mRNA uptake into the target cell. Studies showed that even a small change in the [redacted] of LNP could fully inhibit the activity of mRNA. Therefore, mRNA needs to be delivered with the LNP to maximize the biological activity of mRNA-1273. Taking into account the significant impact of the combination of [redacted] on the biological activity of mRNA, mRNA-1273 LNP should be defined as the active substance.

PMDA's view:

The active ingredient of the mRNA-1273 vaccine formulation should be mRNA (CX-024414), and not mRNA-1273 LNP. This is because: (1) the function of LNP described by the applicant, complies with the excipient's intended use specified in the General Rules for Preparations of the Japanese Pharmacopoeia (JP); and (2) according to the reflection papers on the development of nanotechnology-based drug products,[15)] if RNA or other nucleic acid substances as an active ingredient is delivered with nanocarriers via encapsulation or covalent-binding, then it is defined as a drug product. Accordingly, PMDA asked the applicant to define the active substance appropriately.

The applicant stated that the mRNA (CX-024414) is defined as the active substance of COVID-19 Vaccine Moderna.

15) Release of Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products (PFSB/ELD No. 0110-1 dated on January 10, 2014), and Reflection paper on nucleic acids (siRNA)-loaded nanotechnology-based drug products (Administrative Notice dated March 28, 2016)

PMDA accepted the applicant's response. Although the submitted data on Lipid Mixture and mRNA-1273 LNP were placed in CTD3.2.S instead of CTD3.2.P, PMDA did not request the amendment of CTD Module 3 structure during the regulatory review, considering an urgent need for COVID-19 Vaccine Moderna (mRNA-1273).

2.R.2 Control of active substance impurities

The applicant's explanation about the types of impurities eluting before and after the main peak (active ingredient) and the impact of the impurities on the test for mRNA purity, which are associated with the purity test of the active substance (mRNA purity and product-related impurities [RP-HPLC]):

In this purity test, different ion-pairing reagents are added to the mobile phase for gradient elution, which can separate full-length mRNAs from product-related impurities that are nucleotide fragments of different length. It has been confirmed that a peak fraction eluting immediately before the main peak corresponds to [redacted] and a peak fraction eluting immediately after the main peak corresponds to [redacted]. Because these impurities were detected as [redacted], the calculation of [redacted] can minimize the impact of the detected impurity peaks on the main peak.

PMDA considers it desirable to control impurities by adequately separating the impurity peaks and the main peak; at least the degree of removal of impurities should be consistent. PMDA asked the applicant to consider whether [redacted], etc. should be specified to ensure the consistency. The applicant agreed to do so in future.

Furthermore, the applicant provided the following explanation about the necessity of controlling RNA polymer by size exclusion chromatography (SEC):

RNA polymer is [redacted]. A study on [redacted] showed RNA polymer exhibits [redacted], as with the case of the active substance. There were no significant differences in [redacted] between monomer and dimer, and therefore the presence of mRNA polymer is unlikely to affect translation. For this reason, there is no need to control RNA polymer as [redacted]. It is appropriate to control RNA polymer as part of [redacted] by measuring [redacted] from RNA polymer in the tests for [redacted] included in the specifications for the active substance.

PMDA requested the applicant to tighten the specification limits for mRNA purity and product-related impurities, % 5'-Capped, % PolyA tailed RNA, and [redacted], on the basis of prior manufacturing experience. The applicant was also requested to tighten the specification limit for residual DNA based on the impurity removal capacity in the manufacturing process as well as prior manufacturing experience.

The applicant's explanation:
It is difficult to change the specification limits at present, because (1) the submission of marketing application for COVID-19 Vaccine Moderna is ongoing in several countries/regions around the world and (2) commercial-scale manufacturing experience is limited. However, the applicant plans to specify the final specification limits after further manufacturing experience is gained (around June 2021).

PMDA accepted the applicant's explanation. The control of double-stranded RNA (dsRNA) is described in the Supplement.

2.R.3 Control of biological activity

PMDA asked the applicant to explain whether the specifications for the vaccine product should include a test for quantitatively controlling the activity of the vaccine product to induce antigen protein expression (biological activity), so as to evaluate the potency of the vaccine product.

The applicant's explanation:
The *in vitro* translation assay for the vaccine product verifies the presence of the molecular mass band corresponding to the target protein encoded by mRNA (CX-024414) and the batch-to-batch consistency of the band pattern, in order to confirm the comparability of the translated antigen protein. In addition to the assay, tests for RNA content, mRNA purity, and LNP biophysical attributes are sufficient to demonstrate the comparability of the commercial scale batches and the clinical batches. Thus, the applicant considers that a test for the quantitative control of antigen protein expression is unnecessary. Protein expression testing in cells is conducted as a characterization study to assess the comparability of [redacted] before and after manufacturing process changes.

PMDA's view:
The *in vitro* translation assay included in the vaccine product specifications is a qualitative test and is unable to quantitatively assess the potency of mRNA-1273. According to the applicant, mRNA needs to be delivered with LNP into cells to allow mRNA-1273 to exhibit its biological activity; the [redacted] of LNP significantly regulates the protein expression level, immunogenicity, and biological activity of the vaccine; and tests showed that even a small change in [redacted] fully inhibited the biological activity of mRNA. Given the applicant's explanation above, the *in vitro* translation assay for the vaccine product and tests for RNA content, mRNA purity, LNP attributes, etc., appear to be unable to control the biological activity or potency of mRNA-1273. Because tests that can assess the biological activity of mRNA and the effects of LNP (e.g., efficient cellular uptake) should be established, the applicant was requested to consider including tests suitable for potency testing, such as protein expression testing in cells conducted for characterization of [redacted], in the vaccine product specifications.

The applicant's explanation:
In the protein expression testing in cells conducted for [redacted], [redacted] cells are cultured in the presence of [redacted], and the level of antigen proteins expressing on the [redacted] after uptake of mRNA (CX-024414) into cells is measured by [redacted]. The protein expression testing has been validated for its reasonable analytical capabilities (trueness, precision, linearity, and specificity). This test is included in the process controls of the vaccine product to quantitatively control biological activity. The applicant will collect data from batches of the vaccine product to continuously assess the analytical capabilities of the test method. In addition, when further manufacturing experience is gained, the appropriateness of specification limits will be reviewed. The applicant will also continue to consider the following: Using this test to evaluate the stability of the vaccine product within its shelf life; and if the shelf life of the vaccine product is extended in future, preparing sufficient stability data containing the results of this test and including the test in the vaccine product specifications.

PMDA accepted the applicant's explanation.

2.R.4 Control of product-related impurities

The applicant's explanation about the appropriateness of purity specification limits for the vaccine product (mRNA purity and product-related impurities [RP-HPLC]):
The purity of mRNA ([redacted]) at the time of vaccination in a foreign Phase-III clinical study was chosen as the mRNA purity specification limit for the vaccine product because the study demonstrated the efficacy of the vaccine product. Although a decrease in mRNA purity may have an impact on vaccine efficacy, the safety profile of the vaccine product is unlikely to be affected by an increase in impurities or variation in the types of impurities because mRNA degradation products are composed of natural nucleotides and metabolized in the same route as that of endogenous RNA. The purity of mRNA at release for [redacted] foreign commercial batches was consistent among batches, and the mean and standard deviation of mRNA purity were [redacted]% and [redacted]%, respectively. There were no variations in the amount or types of individual impurities.

There were no changes over time in mRNA purity in the long-term study (storage of 6 months). For this and other reasons, in addition to currently available manufacturing data, PMDA asked the applicant to tighten specification limits for mRNA purity and product-related impurities (RP-HPLC).

The applicant's explanation:
In Europe, a tighter release specification has been established, taking into account the loss of purity of mRNA during storage. In Japan, the applicant will [redacted] the control of mRNA purity at release, and will review the specification limits for mRNA purity and individual product-related impurities on the basis of commercial scale manufacturing experience and other data (scheduled for June 2021).

PMDA also asked the applicant to consider tightening specification limits for % RNA encapsulation and lipid impurities on the basis of manufacturing experience. The applicant agreed to do so in future.

PMDA's view:
The lower specification limit for mRNA purity is low compared with currently available manufacturing data, and it could be tightened further. However, given that batch analysis data from foreign commercial scale batches of the vaccine product indicated batch-to-batch consistency and that the release specification was [redacted], the ex post review of specification limits is inevitable due to the current COVID-19 pandemic situation and the public's need for COVID-19 Vaccine Moderna.

2.R.5 Novel excipients

The vaccine product contains SM-102, PEG2000-DMG, DSPC, cholesterol, and tromethamol hydrochloride as excipients. SM-102 and PEG2000-DMG are excipients that have not been previously used in an approved drug product. DSPC is permitted only for use in specific drug products, in accordance with "Handling of excipients that are permitted only for use in specific drug products or under specific conditions" (Administrative Notice dated June 23, 2009). Cholesterol is employed for a higher level of use than in existing intramuscular formulations, and tromethamol hydrochloride is used in a new route of administration (intramuscular).

SM-102 is used for [redacted], PEG2000-DMG for [redacted], DSPC for [redacted], and cholesterol for [redacted].

2.R.5.1 Specifications and stability

For the specifications for SM-102, PEG2000-DMG, DSPC, and cholesterol, PMDA asked the applicant to explain the critical quality attributes of the individual lipids for achieving their intended use and to prove that the quality attributes are adequately controlled.

The applicant's explanation:
SM-102 is [redacted] lipid, and [redacted] that are important to exert such properties are identified as the critical material attributes (CMA). [redacted] of SM-102 are also identified as the CMA because they may [redacted]. In contrast, PEG2000-DMG [redacted] is also identified as the CMA of PEG2000-DMG. Furthermore, [redacted] are identified as the CMA of PEG2000-DMG, DSPC, and cholesterol. The purity of the individual lipids is controlled by the release testing (lipid impurities) of mRNA-1273 LNP for manufacturing of mRNA-1273. [redacted] is controlled.

PMDA asked the applicant to consider whether more tests should be added to the specifications for each lipid, for the following reasons: (1) [redacted] of SM-102 interact with the mRNA, resulting in the formation of lipid-RNA species, (2) no [redacted] are included in the specification for PEG2000-DMG [redacted], and (3) it is unclear whether [redacted] of cholesterol can be controlled [redacted].

The applicant's explanation:
Since tests for [redacted] of SM-102 differ from [redacted] in terms of test conditions etc., the tests will be immediately included in the specifications. After gaining more manufacturing experience, the applicant will consider whether specification limits need to be established. The applicant will consider the inclusion of tests to control [redacted] of PEG2000-DMG in [redacted]. Cholesterol has been confirmed to comply with [redacted] as well as [redacted]. Since the conformity is thought to allow for the control of [redacted] which are the CMA, the tests will be added to the specifications.

PMDA accepted the applicant's explanation. Submission of validation reports of analytical methods for SM-102 and PEG2000-DMG [redacted] is scheduled for May 2021. The submitted data on the stability of individual lipids and the specification for and the stability of tromethamol hydrochloride showed no problems.

2.R.5.2 Safety

The applicant's explanation:
Regarding the single-dose toxicity, repeated-dose toxicity, genotoxicity, and reproductive and developmental toxicity of SM-102, PEG2000-DMG, cholesterol, and tromethamol hydrochloride, there are no safety concerns based on the submitted toxicity study data (CTD 4.2.3.2-1 to 4.2.3.2-6, 4.2.3.3.1-1 to 4.2.3.3.1-4, 4.2.3.3.2-1, 4.2.3.5.3-1, 4.2.3.7.7) and other data.

PMDA's view:
All of the novel excipients are necessary to assure the formulation attributes of COVID-19 Vaccine Moderna. Other mRNA-LNP products containing these excipients were administered to rats in repeated intramuscular dose toxicity studies (CTD 4.2.3.2-1 to 4.2.3.2-4, 4.2.3.2-6). In the studies, single cell necrosis and vacuolation of hepatocytes and single cell necrosis of seminal vesicle epithelium were observed, but all of the changes were considered of little toxicological significance [see Section 5.R.1]. For this reason, the use of these excipients in COVID-19 Vaccine Moderna is acceptable. However, SM-102 and PEG2000-DMG are excipients that have not been previously used in an approved drug product, and long-term safety was not evaluated in rat repeated intramuscular dose toxicity studies with other mRNA-LNP products (CTD 4.2.3.2-1 to 4.2.3.2-6). The use of

these excipients should be limited to the dosage regimen of COVID-19 Vaccine Moderna, and should not be deemed as a precedent.

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

The applicant submitted non-clinical pharmacology data on mRNA-1273, in the form of the results from primary pharmacodynamic studies. The doses of mRNA-1273 or SARS-CoV-2 S-2P mRNA are expressed as the mRNA.

3.1 Primary pharmacodynamics

An overview of the studies submitted (evaluation data) is shown in Table 5.

Table 5. Overview of primary pharmacodynamic studies (Evaluation data)

Cells or animal species Male or Female	Number of animals	Dose or immunization schedule Route of administration: IM in all studies	Main endpoints (Location in this Report)	Attached document CTD
HEK293T cells	–	· SARS-CoV-2 S-2P mRNA: 0.003125, 0.00625, 0.0125, 0.025, 0.05, 0.1, or 0.2 μg	*In vitro* antigen expression[a)] (3.1.1.1)	4.2.1.1.9 MOD-4112.1273
BALB/c mice F	mRNA 1273 groups: 6/group PBS group: 4	· mRNA 1273: 2 or 10 μg · PBS Single injection	*In vivo* antigen expression[b)] (3.1.1.2)	
BALB/c mice Young F	10 μg mRNA 1273 group and SARS-CoV-2 S protein + adjuvant group: 8/group 1 μg mRNA 1273 group: 7 PBS group: 3	· mRNA 1273: 1 or 10 μg · SARS-CoV-2 S protein 10 μg + adjuvant[c)] · PBS prime/boost (14-day interval)	Antibody production[d)] (3.1.2.1) T cell response[e)] (3.1.2.2)	4.2.1.1.2 MOD3937
BALB/c mice Young F	MOD-3938 0.08 μg mRNA 1273 group and PBS group: 4/group Other mRNA 1273 groups: 8/group MOD-3940 mRNA 1273 groups: 8/group PBS group: 8	· mRNA 1273: 0.0025, 0.005, 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.63, 1.25, 2.5, 5, 10, or 20 μg · PBS prime/boost (21-day interval)	Antibody production[f)] (3.1.2.1) T cell response[g)] (3.1.2.2)	4.2.1.1.3 MOD3938/ MOD3940
BALB/cJ mice Young F	30/group	· mRNA 1273: 0.1 or 1 μg · 0.2 or 1 μg double-inactivated SARS-CoV + adjuvant[c)] · 0.2 or 1 μg conformationally disrupted SARS-CoV-2 S protein + adjuvant[c)] · PBS prime/boost (21-day interval)	Antibody production[g)] (3.1.2.1) T cell response[h)] (3.1.2.2) Protection from infection/disease (3.1.3)	4.2.1.1.4 VRC05
BALB/c mice Aged (approximately 1-year-old) F	10/group	· mRNA 1273: 0.1 or 1 μg · 0.1 μg double-inactivated SARS-CoV + adjuvant[c)] · PBS prime/boost (21-day interval)	Antibody production[i)] (3.1.2.1) T cell response[j)] (3.1.2.2) Protection from infection/disease (3.1.3)	4.2.1.1.5 VRC02
Syrian hamsters F	15/group	· mRNA 1273: 1, 5, or 25 μg, prime/boost (21-day interval) · mRNA 1273: 25 μg or PBS, prime only	Antibody production[k)] (3.1.2.1) Protection from infection/disease (3.1.3)	4.2.1.1.6 UTMB01
Rhesus monkeys M and F	8/group	· mRNA 1273: 10 or 100 μg · PBS prime/boost (4-week interval)	Antibody production[l)] (3.1.2.1) T cell response[m)] (3.1.2.2) Protection from infection/disease (3.1.3)	4.2.1.1.7 VRC04
Rhesus monkeys M and F	6/group	· mRNA 1273: 2.5 or 30 μg · PBS · Noncoding mRNA: 100 μg prime/boost (4-week interval) · mRNA 1273: 100 μg, prime only	Antibody production[n)] (3.1.2.1) T cell response[o)] (3.1.2.2) Protection from infection/disease (3.1.3)	4.2.1.1.8 VRC07

a) Sample collection: 24, 48, and 72 hours after transfection
b) Sample collection: 24, 48, and 72 hours after injection
c) aluminum hydroxide
d) Sample collection: 13 days post-boost
e) Sample collection: 18 days post-boost
f) Sample collection: 1 day pre-boost and 14 days post-boost
g) Sample collection: 14 days post-boost
h) Sample collection: 14 days and 17 days post-boost
i) Sample collection: 14 days post-prime and 14 days post-boost
j) Sample collection: 2 days and 4 days post-challenge
k) Sample collection: 1 day pre-boost and 20 days post-boost
l) Sample collection: Week −1, Week 0, Week 2, Week 4, Week 6, Week 8, and Days 0, 7 and 14 post-challenge
m) Sample collection: Week 8, and Days 2 and 4 post-challenge
n) Sample collection: Week −1, Week 0, Week 2, Week 4, Week 6, Week 7, and Days 2, 4, and 7 post-challenge
o) Sample collection: Week 6

3.1.1 Antigen expression (CTD 4.2.1.1.9)

3.1.1.1 *In vitro*

HEK293T cells were transiently transfected with mRNA encoding SARS-CoV-2 S protein[16)] using a transfection reagent, and the expression of the S protein antigen was evaluated by flow cytometry. Cell-surface antigen expression was detected up to 72 hours after transfection.

3.1.1.2 *In vivo*

BALB/c mice received a single injection of mRNA-1273, and the expression of the S protein antigen was evaluated by flow cytometry. The expression of the antigen on plasmacytoid and conventional dendritic cells isolated from the spleen and lymph node was detected. There were no differences in the expression level of the antigen between plasmacytoid and conventional dendritic cells.

3.1.2 Immunogenicity

3.1.2.1 Antibody production (CTD 4.2.1.1.2 to 4.2.1.1.8)

Following immunization with mRNA-1273, S protein-specific binding and neutralizing antibody titers in sera or inhibition of binding to the angiotensin-converting enzyme 2 (ACE2) receptor were determined. The results of assays for different antigen-specific antibodies (enzyme-linked immunosorbent assay [ELISA]) and neutralizing antibodies (luciferase reporter assay using a pseudovirus[17)] or SARS-CoV-2, or plaque reduction assay using SARS-CoV-2), or the results of ACE2 binding inhibition assay (electrochemiluminescence) are described below.

In studies in mice, S protein-specific binding and neutralizing antibodies (luciferase reporter assay using a pseudovirus) elicited by mRNA-1273 were detected at each time point. mRNA-1273 induced S protein-specific antibodies, S1-specific antibodies, receptor binding domain (RBD)-specific antibodies or N-terminal domain (NTD)-specific antibodies, and neutralizing antibodies in a dose-dependent manner (CTD 4.2.1.1.3).

In a study in hamsters, S protein/RBD-specific antibodies and neutralizing antibodies (plaque reduction assay using SARS-CoV-2) were detected at each time point after administration of mRNA-1273, and the post-boost binding and neutralizing antibody titers were higher than the post-prime titers at all dose levels. The neutralizing antibody titers induced by the mRNA-1273 prime-boost schedule were higher than the neutralizing antibody titer in convalescent-phase serum[18)] at all dose levels, but the neutralizing antibody titer was lower in the 25 μg mRNA-1273 prime-only group than in convalescent-phase serum.

In studies in monkeys, S protein-specific antibodies, RBD-specific or S1 NTD-specific antibody titers, ACE2-specific antibody titers, and neutralizing antibodies (luciferase reporter assay using a pseudovirus or SARS-

16) The full-length SARS-CoV-2 S protein modified with 2 proline substitutions within the heptad repeat 1 domain to stabilize the S protein into a prefusion conformation

17) SARS-CoV-2 (Whuhan-1 strain) S protein-pseudotyped lentivirus carrying a luciferase reporter gene

18) Convalescent-phase serum specimens obtained from 6 donors between 18 and 55 years of age who recovered from COVID-19. The donors had a history of laboratory-confirmed SARS-CoV-2 infection 1 to 2 months before they provided specimens.

CoV-2) induced by mRNA-1273 were detected at each time point. S protein-specific antibodies, neutralizing antibody titers, and ACE2 binding inhibition were all highest in the 30 μg prime-boost group followed by the 100 μg prime-only group, and then the 2.5 μg prime-boost group, and these were higher in the 30 μg prime-boost group than in convalescent-phase serum[19] (CTD 4.2.1.1.8).

3.1.2.2 T cell response (CTD 4.2.1.1.2 to 4.2.1.1.5, 4.2.1.1.7 to 4.2.1.1.8)

Splenocytes collected from mice immunized with mRNA-1273 or peripheral blood mononuclear cells collected from monkeys immunized with mRNA-1273 were stimulated with the S1 and S2 peptide pools, and then cytokine responses (multiplex assay in mice; flow cytometry/intracellular immunostaining in mice and monkeys) were evaluated. The results are described below.

In the splenocytes from mice immunized with mRNA-1273, CD4+ and CD8+ T cell responses were observed, and T-helper 1 (Th1) cytokine levels (IFN-γ, TNF-α, IL-2) were higher than Th2 cytokine levels (IL-4, IL-5, IL-13).

In the peripheral blood mononuclear cells from monkeys immunized with mRNA-1273, CD4+ T cell responses and low CD8+ T cell responses were observed, and Th1 cytokines (IFN-γ, TNF-α, IL-2) were increased with low-to-undetectable Th2 cytokines (IL-4, IL-5, IL-13). Following stimulation with the S protein, CD40L+ CD4+ T cells and IL-21-producing CD4+ T cells were induced.

3.1.3 Challenge-protection studies (protection from infection/disease) (CTD 4.2.1.1.4 to 4.2.1.1.8)

The results of SARS-CoV-2 challenge-protection studies in mRNA-1273-vaccinated mice, hamsters, and monkeys are shown in Table 6. The applicant explained that these results demonstrated the protective efficacy of mRNA-1273 against SARS-CoV-2.

[19] Convalescent-phase serum specimens obtained from 42 donors between 18 and 84 years of age who recovered from COVID-19. The donors had a history of laboratory-confirmed SARS-CoV-2 infection 1 to 2 months before they provided specimens.

Table 6. Overview of challenge studies [a)]

<table>
<tr><th>Animal species (Number of animals/group)</th><th>Dose and immunization schedule for m-RNA-1273, Method of virus challenge</th><th>Overview of main results</th><th>Attached document CTD</th></tr>
<tr><td>BALB/cJ mice
Young
(20F)</td><td>mRNA-1273 0.1 or 1 μg administered intramuscularly on a prime-boost schedule (21-day interval)
Four weeks post-boost, mice were challenged intranasally with mouse-adapted SARS-CoV-2[b)] (1×10^4 PFU/body)</td><td>Viral RNA (lungs and nasal turbinates):
In the 0.1 μg group, virus was detected in both the lungs and nasal turbinates on Days 2 and 4 post-challenge, but the viral titers were lower on Day 4. In the 1 μg group, nasal turbinate viral titers were low on Day 2 post-challenge, but virus was below the detection limit at all other time points and in all other samples.

Lung hemorrhage (Day 7 post-challenge):
In the negative control group, lung hemorrhage was observed in all but 1 animal. In the 0.1 μg and 1 μg groups (except for 1 animal), lung hemorrhage was not observed.

Lung histopathological analysis (Necropsy on Day 4 post-challenge):
In the negative control group, moderate to severe inflammation was seen, and pneumocytes positive for viral antigen were diffused.
Mild to moderate inflammation was observed in the 0.1 μg group and minimal to mild inflammation in the 1 μg group. No eosinophil-dominant inflammatory response was observed, and viral antigen-positive pneumocytes were reduced or absent.</td><td>4.2.1.1.4
VRC05</td></tr>
<tr><td>BALB/c mice
Aged
(10F)</td><td>mRNA-1273 0.1 or 1 μg administered intramuscularly on a prime-boost schedule (21 day-interval)
Four weeks post-boost, mice were challenged intranasally with mouse-adapted SARS-CoV-2 [b)] (1×10^3 PFU/body).</td><td>Viral RNA (lungs and nasal turbinates):
In the 0.1 μg group, virus was detected in both the lungs and nasal turbinates on Days 2 and 4 post-challenge, but lung viral titers were lower on Day 4. In the 1 μg group, virus was detected in several animals on Day 2, but was below the detection limit on Day 4 in all but 1 animal with low lung viral titer.

Lung hemorrhage (Day 4 post-challenge):
In the negative control group and the 0.1 μg group (except for 1 animal), lung hemorrhage was observed (the area of lung hemorrhage was smaller in the 0.1 μg group than in the negative control group). In the 1 μg group, lung hemorrhage was not observed.

Lung histopathological analysis (Necropsy on Day 4 post-challenge):
In the negative control group, moderate to severe inflammation was seen, and pneumocytes positive for viral antigen were diffused.
In the 0.1 μg group, inflammation was observed, but viral antigen-positive pneumocytes were reduced compared to the negative control group.
Inflammation was observed also in the 1 μg group, but viral antigen-positive pneumocytes were absent.</td><td>4.2.1.1.5
VRC02</td></tr>
<tr><td>Syrian hamsters
(15F)</td><td>· mRNA-1273 25 μg administered intramuscularly on a prime only schedule
· mRNA-1273 1, 5, or 25 μg administered intramuscularly on a prime-boost schedule (21-day interval)

Twenty-one days post-boost (42 days post-prime in the prime-only group), hamsters were challenged intranasally with USA-WA1/2020 strain (1×10^5 PFU/body).</td><td>Viral RNA (lung and nasal turbinates):
On Day 4 post-challenge, viral RNA was below the detection limit at all dose levels in the prime-boost groups. Subgenomic RNA (sgRNA) as an indicator of viral replication was below the detection limit in the lungs in all but 1 animal in the 1 μg group. sgRNA in the nasal turbinates was reduced compared with the negative control group. In the prime-only group, viral RNA was below the detection limit in all but 1 animal, but sgRNA was detected in both the lungs and nasal turbinates.

Lung histopathological analysis (Necropsy on Days 2, 4, and 14 post-challenge):
In the negative control group, moderate inflammation appeared on Day 4 post-challenge and persisted until Day 14 post-challenge.
Inflammation was milder in the mRNA-1273 prime-boost groups than in the negative control group. On Day 4 post-challenge, viral antigen was not detected or slightly present.
In the prime-only group, localized diffuse inflammation or multifocal inflammation was observed, and the change was mild compared to the negative control group.</td><td>4.2.1.1.6
UTMB01</td></tr>
<tr><td>Rhesus monkeys
(8/sex)</td><td>mRNA-1273 10 or 100 μg administered intramuscularly on a prime-boost schedule (4-week interval)
Four weeks post-boost, monkeys were challenged intranasally and intratracheally with USA-WA1/2020 strain (7.6×10^5 PFU/body).</td><td>Viral RNA (8/group):
At both dose levels of mRNA-1273, the number of viral RNA (sgRNA) copies and the number of animals with detectable viral RNA were reduced compared to the negative control group.
Table. Number of animals with detectable viral RNA
<table>
<tr><th>Treatment group</th><th>Specimen</th><th>Day 1</th><th>Day 2</th><th>Day 4</th><th>Day 7</th></tr>
<tr><td rowspan="2">mRNA-1273 10 μg</td><td>BAL</td><td>—</td><td>1</td><td>1</td><td>0</td></tr>
<tr><td>Nasal swab</td><td>4</td><td>5</td><td>2</td><td>0</td></tr>
<tr><td rowspan="2">mRNA-1273 100 μg</td><td>BAL</td><td>—</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Nasal swab</td><td>3</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td rowspan="2">Negative control (PBS)</td><td>BAL</td><td>—</td><td>8</td><td>4</td><td>1</td></tr>
<tr><td>Nasal swab</td><td>6</td><td>6</td><td>4</td><td>0</td></tr>
</table>
Lung histopathological analysis (4/group, Necropsy at Day 7 or 8 post-challenge)
In the negative control group, moderate to severe inflammation that involved the airways and alveoli and inflammatory cell infiltrates in the lung were observed.
In the 10 μg group, mild inflammation in the airways and alveoli was seen, and viral antigen was detected in 1 animal.
In the 100 μg group, no substantial inflammation or viral antigen was observed.</td><td>4.2.1.1.7
VRC04</td></tr>
</table>

<table>
<tr><th>Animal species (Number of animals/group)</th><th>Dose and immunization schedule for m-RNA-1273, Method of virus challenge</th><th>Overview of main results</th><th>Attached document CTD</th></tr>
<tr><td>Rhesus monkeys (6/sex)</td><td>· mRNA-1273 2.5 or 30 μg administered intramuscularly on a prime-boost schedule (4-week interval)
· mRNA-1273 100 μg administered intramuscularly on a prime-only schedule

Four weeks post-boost, (8 weeks post-prime in the prime-only group), monkeys were challenged intranasally and intratracheally with USA-WA1/2020 strain (7.6 × 10^5 PFU/body)</td><td>Viral RNA (6/group):
At all dose levels of mRNA-1273, the number of viral RNA (sgRNA) copies and the number of animals with detectable viral RNA were reduced compared to the negative control group.
Table. Number of animals with detectable viral RNA
<table>
<tr><th>Treatment group</th><th>Specimen</th><th>Day 1</th><th>Day 2</th><th>Day 4</th><th>Day 7</th></tr>
<tr><td rowspan="2">mRNA-1273 2.5 μg</td><td>BAL</td><td>—</td><td>3</td><td>0</td><td>0</td></tr>
<tr><td>Nasal swab</td><td>2</td><td>4</td><td>1</td><td>0</td></tr>
<tr><td rowspan="2">mRNA-1273 30 μg</td><td>BAL</td><td>—</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Nasal swab</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td rowspan="2">mRNA-1273 100 μg (prime-only)</td><td>BAL</td><td>—</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Nasal swab</td><td>0</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td rowspan="2">Negative control (PBS)</td><td>BAL</td><td>—</td><td>6</td><td>1</td><td>0</td></tr>
<tr><td>Nasal swab</td><td>3</td><td>4</td><td>2</td><td>1</td></tr>
</table>
Lung histopathological analysis (6/group, Necropsy on Days 7 to 9 post-challenge)
In the negative control group, moderate to severe inflammation was observed, and viral antigen was detected in all animals.
In the 2.5 μg group, inflammation was absent or mild, and viral antigen was detected in 3 animals.
In the 30 μg group, inflammation was absent or mild, and no viral antigen was detected.
In the 100 μg prime-only group, inflammation was absent or mild, and viral antigen was detected in 2 animals.</td><td>4.2.1.1.8 VRC07</td></tr>
</table>

a) S protein-specific antibodies and neutralizing antibodies were induced by mRNA-1273 in all studies [see Section 3.1.2.1].
b) Since wild-type SARS-CoV-2 does not infect mice, a mouse-adapted strain of SARS-CoV-2 was used in the studies. Infection with this strain in young adult mice is associated with mild disease, and the strain causes more severe disease in aged mice (*Nature*. 2020; 586: 560-6).

3.2 Safety pharmacology

Although no safety pharmacology studies with mRNA-1273 were conducted, the safety pharmacology of mRNA-1273 was evaluated by clinical observations etc. in repeated-dose toxicity studies (CTD 4.2.3.2) and a reproductive and developmental toxicity study (CTD 4.2.3.5.3) in rats. The applicant explained that there were no mRNA-1273-related effects on the physiological functions, such as the cardiovascular, respiratory, and central nervous systems.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of mRNA-1273

PMDA asked the applicant to explain the mechanism of action of mRNA-1273.

The applicant's explanation:

Following intramuscular injection of mRNA-1273 in mice, the expression of the S protein antigen on dendritic cells from the spleen and lymph node was detected [see Section 3.1.1.2]. In addition, mRNA-1273 elicited SARS-CoV-2-specific antibodies and CD8+ and CD4+ T-cell responses in different animal models, and this demonstrated a certain level of protective efficacy of mRNA-1273 against SARS-CoV-2 challenge [see Sections 3.1.2 and 3.1.3].

Uptake of mRNA-1273 by antigen presenting cells leads to the activation of innate immune receptors. In the cytoplasm, the mRNA of mRNA-1273 is translated, and the S protein antigen is expressed. The S protein antigen stimulates the innate immune system for B and T cell activation. Antibodies produced by B cells

neutralize the virus in the airway and whole body, and antigen-specific CD8+ T cells target infected cells in the airway, thereby providing protection from infection.

PMDA accepted the applicant's explanation about the mechanism of action of mRNA-1273.

3.R.2 Disease enhancement risk

PMDA asked the applicant to explain whether the severity of disease caused by SARS-CoV-2 infection is potentially enhanced due to immune responses induced by mRNA-1273 vaccination compared with unvaccinated controls (disease enhancement risk).

The applicant's explanation:
Research points to vaccine-associated enhanced disease being triggered by 2 major mechanisms (*Front Microbiol*. 2018; 9: 2991, *Vaccine*. 2009; 27: 505-12). The first mechanism is when priming by the initial infection results in a Th2 biased immune response mediated more by myeloid lineage cells, including neutrophils and eosinophils with immune complex formation and complement activation. The Th2 biased immune response is characterized by high interleukin (IL) 4, 5, and 13 levels and localized tissue inflammation accompanied by neutrophil and eosinophil infiltration, immune complex deposition, and pulmonary inflammation and obstruction. The second mechanism is antibody-dependent enhancement (ADE), which is attributable to the generation of sub-neutralizing antibodies that bind the virus. These antibodies facilitate Fcγ-receptor mediated entry of viable virus into macrophages. This may result in an accelerated viremia and more severe disease.

In studies using multiple animal species, mRNA-1273 induced high neutralizing activity and the production of Th1 cytokines [see Section 3.1.2]. In mice, mRNA-1273 elicited Th1-biased IgG subclasses in contrast to the Th2-biased response seen when using the antigen with aluminum adjuvant, i.e., disease enhancement model. In challenge studies in mRNA-1273-vaccinated mice, hamsters, and monkeys, there were no observations of increased viral load. Lung histopathology assessments were performed to verify reduction of inflammation, immune complex deposition, and immune cell invasion in response to viral challenge in vaccinated animals versus negative control animals, and no significant neutrophil- or eosinophil-dominant inflammatory response was observed [see Section 3.1.3]. Based on the above results, the risk of mRNA-1273-associated enhanced disease is low from a non-clinical pharmacological perspective.

PMDA accepts the applicant's explanation from a pharmacological perspective, but continues to assess disease enhancement risk in humans in Section 7.R.3.4.

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

No non-clinical pharmacokinetic study with mRNA-1273 or CX-024414 was conducted.

mRNA-1647 contains 6 mRNAs that encode cytomegalovirus glycoproteins (gB, gH, gL, UL128, UL130,

UL131A) (The 6 mRNAs are formulated at a target mass ratio of 1:1:1:1:1:1) encapsulated in LNP having the same composition as the LNP of mRNA-1273. The applicant submitted the results from a biodistribution study with mRNA-1647.

A branched DNA hybridization assay was used for determination of mRNA in rat plasma and tissue (lower limit of quantification (LLOQ), 0.05 ng/mL for the gB mRNA and UL130 mRNA and 0.01 ng/mL for the gH, gL, UL128, and UL131A mRNAs).

Unless otherwise specified, PK parameters are expressed as the mean.

4.1 Distribution

4.1.1 Biodistribution in rats (CTD 4.2.2.3.1)

Following single intramuscular injection (the lateral thigh muscle) of 100 μg mRNA-1647 (the dose of total RNA) in rats (5 males/time point), mRNA concentrations in plasma and tissues (muscle [injection site], popliteal lymph node, axillary lymph node, brain, eye, bone marrow, heart, lung, kidney, liver, spleen, testis, stomach, jejunum) were determined at a total of 7 time points, i.e., at pre-dose and at other time points from 2 to 120 hours post-dose.

In plasma, peak concentrations of the 6 mRNAs, the components of mRNA-1647, were all reached at 2 hours post-dose. The gB, gL, UL128, UL130, and UL131A mRNAs were below the detection limit at 48 hours post-dose, and the gH mRNA was at or below the detection limit at 120 hours post-dose.

mRNA was detected in all tissues examined, except for the kidney. The mRNA concentration was highest in the muscle (injection site), followed by the popliteal lymph node, axillary lymph node, and spleen. mRNA was detectable in these tissues even at 120 hours post-dose. The tissue to plasma ratios of $AUC_{0\text{-}t}$ in the muscle, popliteal lymph node, axillary lymph node, and spleen were 939, 201, 62.8, and 13.4, respectively, and the elimination half lives (the average elimination half life of the 6 mRNAs) were 14.9, 34.8, 31.1, and 63.0 hours, respectively. mRNA was below the detection limit in other tissues at 24 to 72 hours post-dose.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there are no particular problems with the non-clinical pharmacokinetics of mRNA-1273.

4.R.1 Non-clinical pharmacokinetics of mRNA-1273

The applicant's explanation about the non-clinical pharmacokinetics of mRNA-1273:

mRNA-1647 was used as a test article in a non-clinical pharmacokinetic study submitted in the present application. mRNA-1647 is a vaccine product containing mRNA encapsulated in LNP. The manufacturing process and composition of the LNP are the same as those of the LNP of mRNA-1273. Generally, mRNA administered *in vivo* is rapidly metabolized, as with nucleic acids in *vivo*. mRNA encapsulated in LNP is not

metabolized but is taken up by host cells, which can express the protein in the cytoplasm. Thus, it is likely that the biodistribution of mRNA-based vaccines formulated in LNPs is not influenced by the mRNA itself but is dependent primarily on the composition and size of the LNP (*Mol Ther Nucleic Acids*. 2019; 15: 1-11, *Nanomedicine (Lond)*. 2016; 11: 673-92). Since the composition and size of the LNP of mRNA-1647 are the same as those of mRNA-1273, the results of a biodistribution study with mRNA-1647 can be extrapolated to mRNA-1273.

The biodistribution of intramuscularly administered mRNA-1647 was evaluated in rats [see Section 4.1]. mRNA was distributed mainly in the injection site and lymph nodes, suggesting distribution via the lymphatics, as with other intramuscular vaccines. mRNA was distributed also into other tissues, but the mRNA constructs fell below the LLOQ by 24 to 72 hours post-dose in tissues other than the injection site, lymph nodes, and spleen.

As mentioned above, the results of the biodistribution study with mRNA-1647 can be extrapolated to mRNA-1273. Thus, the biodistribution of mRNA-1273 is inferred to be similar to that of mRNA-1647.

PMDA accepted the applicant's explanation and concluded that the pharmacokinetic profile of mRNA-1273 can be understood to a certain extent, based on the submitted non-clinical pharmacokinetic study results.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted data including the results from the following studies for the toxicological assessment of mRNA-1273: repeated-dose toxicity and reproductive and developmental toxicity studies with mRNA-1273, and repeated-dose toxicity studies with other mRNA vaccine products (mRNAs encoding viral proteins different from that encoded by mRNA-1273) encapsulated in LNPs having the same composition as the LNP of mRNA-1273 (hereinafter referred to as other mRNA-LNP products).

5.1 Single-dose toxicity

No single-dose toxicity study with mRNA-1273 was conducted. The acute toxicity of a single dose of mRNA-1273 was assessed based on the findings obtained after the first dose in a repeated intramuscular dose toxicity study in rats (non-GLP compliant) (CTD 4.2.3.7.7). There were no treatment-related deaths, but injection site edema, emaciation, etc. were observed.

5.2 Repeated-dose toxicity

5.2.1 Studies with mRNA-1273

A repeated intramuscular dose toxicity study with mRNA-1273 in rats (GLP compliant) is ongoing as of April 26, 2021. Prior to this study, a repeated-dose immunogenicity and toxicity study with mRNA-1273 by intramuscular injection in rats (non-GLP compliant) was conducted (Table 7). The principal findings were inflammatory changes at the injection site.

Table 7. Repeated-dose toxicity study with mRNA-1273

Test system	Route of administration	Duration of dosing	Dose (μg RNA/body)	Principal findings	NOAEL (μg RNA/body)	Attached document CTD
Male and female rats (SD)	IM	22 days (2 doses[a]) + 13-day recovery period	0,[b] 30, 60, 100	Histopathological examination: Not performed ≥30 [c]: injection site edema, increases in neutrophils and eosinophils These findings were reversible.		Reference data 4.2.3.7.7

a) 200 μL/site was injected into the thigh muscle on Study Days 1 and 22.
b) An aqueous solution containing 20 mM Tris, 87 mg/mL sucrose, and 10.7 mM sodium acetate (pH 7.5)
c) S protein-specific antibodies were detected on Study Day 35.

5.2.2 Studies with other mRNA-LNP products

Repeated intramuscular dose toxicity studies with other mRNA-LNP products in rats (GLP compliant) were conducted (Table 8). The principal findings were inflammatory changes at the injection site.

Table 8. Repeated-dose toxicity studies with other mRNA-LNP products

Test article	Test system	Route of administration	Duration of dosing	Dose (μg RNA/body)	Principal findings	NOAEL (μg RNA/body)	Attached document CTD
mRNA-1706 [a)]	Male and female rats (SD)	IM	4 weeks (3 doses[d)]) + 2-week recovery period	13,[f)] 65, 129, or PBS	≥13[j)]: swelling and inflammation at the injection site, increases in white blood cells, neutrophils, and eosinophils, increased fibrinogen, hepatocyte vacuolation 129: increases in IP-10 and MCP-1 [k)] These findings were reversible.	129	4.2.3.2-1
				10,[f)] 50, 100, or PBS	≥10[j)]: decreased body weight gain, swelling and inflammation at the injection site, increases in white blood cells, neutrophils, monocytes, eosinophils, and large unstained cells, increased APTT, increased fibrinogen, Kupffer cell hypertrophy ≥50: adrenal cortical hypertrophy 100: increases in IP-10, MIP-1α, and MCP-1,[k)] centrilobular necrosis/degeneration in the liver These findings were reversible.	100	4.2.3.2-2
mRNA-1653 [b)]				10,[g)] 50, 150, or PBS	≥10[j, l)]: swelling and inflammation at the injection site, increases in white blood cells, neutrophils, eosinophils, and large unstained cells, increased fibrinogen ≥50: decreased body weight gain, increased APTT 150: increases in IP-10, MIP-1α, and MCP-1,[k)] hepatocyte vacuolation These findings were reversible.	150	4.2.3.2-3
mRNA-1893 [a)]				10,[h)] 30, 96, or PBS	≥10[j, l)]: swelling and inflammation at the injection site, increases in neutrophils and eosinophils, increased fibrinogen, increased APPT, Kupffer cell hypertrophy ≥30: increases in monocytes and white blood cells, increases in α_1-acid glycoprotein, α_2-macroglobulin, IL-1β, and IP-10,[k)] hepatocyte vacuolation 96: single cell necrosis in the seminal vesicle epithelium	96	4.2.3.2-4
mRNA-1647 [c)]			6 weeks (4 doses[e)]) + 2-week recovery period	8.9,[i)] 27, 89, or PBS	≥8.9 [l, m)]: decreased body weight gain, swelling, inflammation, and edema at the injection site, increases in neutrophils, eosinophils, and large unstained cells, increases in α_1-acid glycoprotein and fibrinogen, increased APPT ≥27: increased α_2-macroglobulin 89: decreased platelet count, increases in IP-10 and MCP-1[k)]	89	4.2.3.2-5
mRNA-1443 [c)]				9.6,[i)] 29, 96, or PBS	≥9.6[l, m,)]: inflammation at the injection site, increased eosinophils, increased fibrinogen, hepatocyte vacuolation ≥29: swelling at the injection site, increased neutrophils, increases in α_1-acid glycoprotein and α_2-macroglobulin, increased APPT 96: increased white blood cells, decreased platelet count, increased IP-10[k)]	96	4.2.3.2-6

a) Zika virus vaccine
b) Human metapneumovirus and parainfluenza virus type 3 vaccine
c) Cytomegalovirus vaccine
d) 200 μL/site was injected into the thigh muscle on Study Days 1, 15, and 29
e) 200 μL/site was injected into the thigh muscle on Study Days 1, 15, 29, and 43
f) 20 mM Tris buffer and 8% sucrose (pH 7.4)
g) An aqueous solution containing 93 mM Tris, 7% propylene glycol, and 1 mM DTPA (pH 7.4)
h) An aqueous solution containing 100 mM Tris, 7% propylene glycol, and 1 mM DTPA (pH 7.5)
i) An aqueous solution containing 93 mM Tris, 7% propylene glycol, and 60 mM sodium chloride
j) Antibodies specific to the protein encoded by mRNA were detected on Study Days 30 and 43.
k) Measured only in the PBS and high dose groups.
l) Inflammation in the adjacent tissue of the injection site surrounding the sciatic nerve was observed. This finding was caused by an excessive dose volume administered per rat quadriceps femoris muscle and considered specific to this study using rats.
m) Antibodies specific to the protein encoded by mRNA were detected on Study Days 43 and 57.

5.3 Genotoxicity

Although no genotoxicity studies with mRNA-1273 were conducted, the genotoxicity of mRNA-1273 was assessed based on the results of an *in vivo* genotoxicity study with another mRNA-LNP product and *in vitro*

genotoxicity studies with novel excipients (SM-102 and PEG2000-DMG) (Table 9). In *in vivo* micronucleus test with mRNA-1706, weak increases in micronuclei were observed in males only with no clear dose response. The applicant explained that this finding is of little toxicological significance because this positive finding was observed at extremely high exposure levels after intravenous administration at high doses, given the dosing regimen used in the clinical setting. Furthermore, the mRNA contained in mRNA-1273 comprises natural nucleosides, and novel excipients (SM-102 and PEG2000-DMG) were negative in *in vitro* studies. Based on these findings, the applicant concluded that the genotoxicity potential to humans is low.

Table 9. Genotoxicity studies

Test article	Type of study		Test system	S9 (Treatment)	*In vivo*: Dose (mg/kg) *In vitro*: Concentration (μg/mL)	Test result	Attached document CTD
mRNA-1706[a)]	*In vivo*	Micronucleus test	Male and female rats (SD) bone marrow		Single intravenous injection Males: 0,[b)] 1.3,[c)] 2.6, 5.2[d)] Females: 0,[b)] 0.6, 1.3, 2.6[e)]	Positive	4.2.3.3.2-1
SM-102	*In vitro*	Bacterial reverse mutation test	*Salmonella typhimurium*: TA98, TA100 TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	+ (3 days)	0, 1.58, 5, 15.8, 50, 158, 500,[f)] 1581,[f)] 5000 [f)]	Negative	4.2.3.3.1-1
				– (3 days)	0, 1.58, 5, 15.8, 50, 158, 500, 1581,[f)] 5000 [f)]		
		Mammalian cell micronucleus test	Human peripheral blood lymphocytes	+ (4 hours)	0, 163, 286, 500	Negative	4.2.3.3.1-2
				– (4 or 24 hours)	0, 163, 286, 500 [f)]		
PEG2000-DMG	*In vitro*	Bacterial reverse mutation test	*Salmonella typhimurium*: TA98, TA100 TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	+ (3 days)	0, 50, 158, 500, 1581, 5000[f)]	Negative	4.2.3.3.1-3
				– (3 days)	0, 50, 158, 500, 1581, 5000		
		Mammalian cell micronucleus test	Human peripheral blood lymphocytes	+ (4 hours)	0, 163, 286, 500	Negative	4.2.3.3.1-4
				– (4 or 24 hours)	0, 53.3, 93.3, 163,[d)] 286,[g)] 500 [g)]		

a) Zika virus vaccine
b) PBS
c) 24 hours post-dose, $P \leq 0.001$
d) 24 hours post-dose, $P \leq 0.01$; 48 hours post-dose, $P \leq 0.001$
e) Statistically significant increases in micronuclei ($P \leq 0.05$) were observed at 48 hours post-dose, but were within the historical control range.
f) Test article precipitated.
g) Cytotoxic after 24-hour treatment, in the absence of S9.

5.4 Carcinogenicity

No carcinogenicity studies with mRNA-1273 were conducted because its intended clinical use is not for ≥6 months.

5.5 Reproductive and developmental toxicity

A reproductive and developmental toxicity study with mRNA-1273 was conducted in rats (Table 10). It was concluded that there are little safety concerns about the effects of mRNA-1273 on maternal animals and the offspring.

Table 10. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Duration of dosing	Dose (μg RNA/body)	Principal findings	NOAEL (μg RNA/body)	Attached document CTD
Fertility and early embryonic development to implantation, embryo-fetal development, prenatal and postnatal development, including maternal function	Female rats (SD)	IM	From 28 days prior to mating through gestation day 13 (4 doses[a])	0,[b] 100	Dams 100[c]: None Embryos/fetuses 100[c]: wavy ribs[d] F1 pups 100[c]: None	Maternal general toxicity and reproductive performance: 100 Embryos/fetuses: 100 F1 pups: 100	4.2.3.5.3-1

a) 200 μL/site was injected into the thigh muscle at 28 and 14 days prior to mating and on gestation days 1 and 13.
b) An aqueous solution containing 20 mM Tris, 8.7% sucrose, and 17.5 mM sodium acetate (pH 7.5)
c) S protein-specific antibodies were detected in dams on Study Day 15 (14 days prior to mating), gestation days 1, 13, and 21 (at caesarean sectioning), and lactation day 21. Maternal-to-fetal transfer of S protein-specific antibodies was observed on gestation day 21 (at caesarean sectioning), and maternal-to-F1 pup transfer of S protein-specific antibodies was observed on lactation day 21.
d) An increase in the incidence of wavy ribs in the F1 pups of the mRNA-1273 group was observed, but this finding was secondary to transient deteriorated condition of maternal animals and considered of little toxicological significance.

5.6 Local tolerance

The local tolerance of mRNA-1273 was evaluated in repeated intramuscular dose toxicity studies with other mRNA-LNP products (CTD 4.2.3.2.1 to 4.2.3.2.6). Reversible inflammatory changes were noted at the injection site.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there are no particular concerns about the toxicity of mRNA-1273 at present.

5.R.1 Repeated-dose toxicity

PMDA asked the applicant to explain the reasons for considering that the repeated-dose toxicity of mRNA-1273 can be evaluated based on the results from repeated intramuscular dose toxicity studies with other mRNA-LNP products (CTD 4.2.3.2-1 to 4.2.3.2-6) [see Section 5.2.2, Table 8].

The applicant's explanation:

The repeated-dose toxicity of mRNA-1273 can be evaluated based on the results from repeated intramuscular dose toxicity studies with other mRNA-LNP products (CTD 4.2.3.2-1 to 4.2.3.2-6), for the following reasons:

(a) The manufacturing principle, manufacturing process, manufacturing control, quality control, etc. of other mRNA-LNP products are the same as those of mRNA-1273.
(b) The biodistribution of mRNA encapsulated in LNP is considered to be influenced by the composition of LNP [see Section 4.R.1]; and the mRNAs contained in mRNA-1273 and other mRNA-LNP products are all considered to be translated into antigen proteins in the organs/tissues where they are distributed, and

to elicit similar immune responses.

(c) The quality test results of the test articles used in the repeated intramuscular dose toxicity studies indicate that mRNA-1273 is comparable to other mRNA-LNP products, except for the mRNA base sequence.

The ongoing repeated intramuscular dose toxicity study with mRNA-1273 (GLP compliant) has raised no safety concerns as of April 26, 2021. The study results will be reported to PMDA promptly upon completion of the study.

Effects on the liver and seminal vesicle were observed in repeated intramuscular dose toxicity studies with other mRNA-LNP products (CTD 4.2.3.2-1 to 4.2.3.2-4, 4.2.3.2-6). PMDA asked the applicant to explain the safety of vaccination with mRNA-1273 in humans.

The applicant explained that none of the findings suggest risk in humans, based on the following:

(1) Effects on the liver

In a study with mRNA-1706 (CTD 4.2.3.2-2), single cell necrosis of hepatocytes (minimal to mild) was observed in a small number of animals. This finding was adjacent to inflammatory cells accumulating in the sinusoids following administration of the test article, and thus is considered to be induced by micro-environmental changes associated with accumulated inflammatory cells. In studies with mRNA-1706, mRNA-1653, mRNA-1893, or mRNA-1443 (CTD 4.2.3.2-1, 4.2.3.2-3 to 4.2.3.2-4, 4.2.3.2-6), an increased incidence of hepatocellular vacuolation was noted. As the both findings were reversible without corresponding changes in clinical chemistry parameters, these hepatic effects are considered of little toxicological significance. An analysis was made on the safety of vaccination with mRNA-1273 in humans in a foreign phase III study [Study mRNA-1273-P301, see Section 7.4]. The incidence of hepatobiliary adverse events was low (≤0.1%), and there were no clear differences between the vaccine and placebo groups in the study.

(2) Effects on the seminal vesicle

In a study with mRNA-1893 (CTD 4.2.3.2-4), single cell necrosis in the seminal vesicle epithelium (minimal to mild) was seen in the high dose group. This finding was reversible, and there were no test article-related effects on the weights of the reproductive organs other than the seminal vesicle (testis, prostate gland, epididymis) or histopathological findings. Based on these results, this finding is considered a stress response to test article administration (*Toxicol Pathol*. 2013; 41: 560-614), and considered of little toxicological significance.

PMDA's view:

The applicant's explanation is acceptable. Although the results of the repeated intramuscular dose toxicity study with mRNA-1273 (GLP compliant) need to be reviewed, evaluating the repeated-dose toxicity of mRNA-1273 based on the results from repeated intramuscular dose toxicity studies with other mRNA-LNP products (CTD 4.2.3.2-1 to 4.2.3.2-6) is acceptable at present. There are no particular concerns about the repeated-dose toxicity of mRNA-1273.

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

To assess the baseline SARS-CoV-2 status of study participants, viral RNA in serum was detected by reverse transcription polymerase chain reaction (RT-PCR), and anti-nucleoprotein antibodies in serum were measured by electrochemiluminescence immunoassay. For immunogenicity assessment, SARS-CoV-2 S protein-specific binding antibodies in the sera of participants were measured by an ELISA, and neutralizing antibodies were measured by microneutralization assay using a clinical isolate of SARS-CoV-2 (USA-WA1/2020 strain) (*in situ* ELISA) (Studies TAK-919-1501, mRNA-1273-P201, and mRNA-1273-P301) or by pseudovirus luciferase assay (Study 20-0003 [Study 101]). For assessment of cell mediated immunity, peripheral blood mononuclear cells were isolated from the blood of participants in Study 20-0003, and CD4+ and CD8+ T-cell responses were measured by intracellular cytokine straining.

6.2 Clinical pharmacology

In the present application, no clinical pharmacology studies were conducted.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 4 studies presented in Table 11.

Table 11. Overview of clinical studies (Evaluation data)

Geographical location (Country)	Study ID	Phase	Study population	Number of participants enrolled	Dosing regimen	Study objectives
Japan	TAK-919-1501	I/II	Healthy adults aged ≥20 years	mRNA-1273 group: 150 participants (20-64 years [n = 100], ≥65 years [n = 50]) Placebo group: 50 participants (20-64 years [n = 40], ≥65 years [n = 10])	100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart	Safety Immunogenicity
Overseas (the US)	20-0003 (101)	I	Healthy adults aged ≥18 years	mRNA-1273 25, 50, and 100 µg groups: 35 participants /group (18-55 years [n = 15], 56-70 years [n = 10], ≥71 years [n = 10]) mRNA-1273 250 µg group: 15 participants (18-55 years)	25, 50, 100, or 250 µg mRNA-1273 2 IM injections, 28 days apart	Safety Immunogenicity
	mRNA-1273-P201	IIa	Healthy adults aged ≥18 years	mRNA-1273 50 and 100 µg groups: 200 participants /group Placebo group: 200 participants (18-54 years [n = 100] and ≥55 years [n = 100] for all groups)	50 or 100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart	Safety Immunogenicity
	mRNA-1273-P301	III	≥18 years of age	mRNA-1273 group: 15,000 participants Placebo group: 15,000 participants	100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart	Efficacy Safety Immunogenicity

7.1 Japanese phase I/II study (CTD 5.3.5.1.4, Study TAK-919-1501, ongoing since January 2021, data cutoff date of March 31, 2021)

A randomized, observer-blind, placebo-controlled, parallel-group study was conducted at 2 sites in Japan to evaluate the safety and immunogenicity of mRNA-1273 (COVID-19 Vaccine Moderna) in Japanese healthy adults aged ≥20 years (target sample size, 200 participants [150 in the mRNA-1273 vaccine group, 50 in the placebo group]). Participants and the personnel for data collection and evaluation were blinded to study vaccine assignment.

Study vaccine (100 μg mRNA-1273 or placebo) was to be administered intramuscularly as a series of 2 doses 28 days apart (Days 1 and 29; The window for receiving the second dose was Days 29-32).

All of 200 randomized participants (150 in the vaccine group, 50 in the placebo group) received at least 1 dose of study vaccine and were included in the Full Analysis Set (FAS) and in the Safety Set. Among the FAS, 196 participants who received planned doses of study vaccine per schedule, had no major protocol deviations that may have an impact on immunogenicity assessment,[20] and had evaluable immunogenicity data from blood samples collected per schedule (147 in the vaccine group, 49 in the placebo group) were included in the Per-Protocol Set (PP Set) and in the Immunogenicity Subset.

The primary immunogenicity endpoints of geometric mean titer (GMT) of SARS-CoV-2 S protein-specific IgG antibody on Day 57 (28 days after the second dose of study vaccine), geometric mean fold rise (GMFR) in IgG titer from pre-first dose baseline to Day 57, and seroconversion rate[21] on Day 57 were 813.05 [759.31, 870.60], 1009.25 [865.11, 1177.40], and 100% [97.5, 100.0], respectively, in the vaccine group (147 participants with results available) and 0.60 [0.53, 0.68], 0.90 [0.83, 0.98], and 2.0% [0.1, 10.9], respectively, in the placebo group (49 participants). The titer of neutralizing antibody against SARS-CoV-2 (microneutralization assay using SARS-CoV-2) was a secondary endpoint.

The safety follow-up period is shown below. Severity grading of adverse events[22] took place according to the grading scales modified from the FDA guidance on the toxicity grading scale in preventive vaccine clinical trials (Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007).[23]

- The following solicited adverse events: through 7 days after each dose of study vaccine (Days 1-7 and Days 29-35)
  - Local (injection site): pain, erythema/redness, swelling, induration, and lymphadenopathy[24]
  - Systemic: headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever
- Unsolicited adverse events (excluding solicited adverse events occurring through 7 days after each dose of

[20] Use of prohibited medications specified in the protocol, SARS-CoV-2 infection confirmed before the first dose of study vaccine, and no blood sample collected for immunogenicity assessment on Day 57
[21] Percentage of participants with a change in binding antibody levels from below the LLOQ to equal to or above the LLOQ, or at least a 4-fold rise from baseline
[22] All adverse events were coded using MedDRA Version 24.0.
[23] https://www.fda.gov/media/73679/download (last accessed on April 23, 2021)
[24] Reported as localized axillary swelling or tenderness ipsilateral to the injected arm in the participant diary.

study vaccine): through 28 days after each dose of study vaccine (Days 1-28, Days 29-56)

- Serious adverse events: from the first dose of study vaccine through 12 months after the second dose (Days 1-394)

Solicited adverse events occurring through 7 days after each dose of study vaccine are shown in Table 12.

Table 12. Solicited adverse events through 7 days after each dose of study vaccine (Japanese Study 1501: Safety Set)

	Dose 1		Dose 2	
	Vaccine (N = 150) n (%)	Placebo (N = 50) n (%)	Vaccine (N = 147) n (%)	Placebo (N = 50) n (%)
Solicited local (injection site) adverse events				
Any	129 (86.0)	5 (10.0)	125 (85.0)	3 (6.0)
Pain	124 (82.7)	3 (6.0)	125 (85.0)	1 (2.0)
Erythema/Redness	3 (2.0)	0	26 (17.7)	0
Swelling	16 (10.7)	0	24 (16.3)	0
Induration	9 (6.0)	0	19 (12.9)	0
Lymphadenopathy[a)]	17 (11.3)	2 (4.0)	15 (10.2)	3 (6.0)
Solicited systemic adverse events				
Any	71 (47.3)	9 (18.0)	121 (82.3)	10 (20.0)
Headache	20 (13.3)	0	70 (47.6)	5 (10.0)
Fatigue	28 (18.7)	5 (10.0)	93 (63.3)	4 (8.0)
Myalgia	56 (37.3)	2 (4.0)	73 (49.7)	5 (10.0)
Arthralgia	12 (8.0)	0	47 (32.0)	0
Nausea/Vomiting	1 (0.7)	0	6 (4.1)	0
Chills	8 (5.3)	1 (2.0)	74 (50.3)	0
Fever[b)]	3 (2.0)	1 (2.0)	59 (40.1)	0

N = Number of participants analyzed, n = Number of participants with event
a) Localized axillary swelling or tenderness ipsilateral to the injected arm
b) ≥38°C (Oral temperature)

The incidences of unsolicited adverse events and adverse reactions through 28 days after any injection of study vaccine were 30.0% (45 of 150 participants) and 18.0% (27 of 150 participants), respectively, in the vaccine group and 22.0% (11 of 50 participants) and 2.0% (1 of 50 participants), respectively, in the placebo group. Unsolicited adverse events reported by ≥2 participants in the vaccine group were injection site pruritus (9 participants), nasopharyngitis (4 participants), headache (4 participants), diarrhoea (3 participants), vertigo (2 participants), dental caries (2 participants), chest discomfort (2 participants), fatigue (2 participants), injection site rash (2 participants), injection site warmth (2 participants), dizziness (2 participants), pollakiuria (2 participants), rhinorrhoea (2 participants), and oropharyngeal pain (2 participants).

There were no deaths, serious adverse events, or adverse events leading to study discontinuation through data cutoff date (March 31, 2021). Adverse events leading to discontinuation of the second dose occurred in 3 participants in the vaccine group. The adverse events consisted of injection site rash (2 participants), which was reported as an unsolicited adverse event; injection site pain (1 participant), fatigue (1 participant), arthralgia (1 participant), headache (1 participant), and axillary pain (1 participant), all of which were reported as a solicited adverse event in a single participant. All those events were considered causally related to study vaccine and had an outcome of "resolved."

7.2 Foreign phase I study (CTD 5.3.5.1.1, Study 20-0003 [101], ongoing since March 2020 [data cutoff date of October 7, 2020 [safety] or October 15, 2020 [immunogenicity])

An open-label, dose-ranging study was conducted at 4 sites in the US to evaluate the safety and immunogenicity

of mRNA-1273 in healthy adults aged ≥18 years (target sample size, 155 participants). This study was originally designed to administer mRNA-1273 at 3 dose levels of 25, 100, and 250 μg to participants aged 18 to 55 years (target sample size, 45 participants), but age cohorts of 56 to 70 years and ≥71 years were also included for evaluation in the elderly population (Protocol Version 3, March 30, 2020). Then, the dose levels of 10 μg (18-55 years only) and 50 μg were added (Protocol Version 4, May 20, 2020), and the target sample size was changed to 155. Participants were enrolled in these cohorts sequentially. Of 15 participants who received 250 μg of mRNA-1273 in the cohort of 18 to 55 years, 4 had severe solicited adverse events during the study. For this reason, no participants were enrolled in the 250 μg group for the cohorts of 56 to 70 years and ≥71 years. Taking account of the results of interim analysis of immunogenicity of 25, 50 and 100 μg, no participants were enrolled in the 10 μg group.

Study vaccine (25 μg, 50 μg, 100 μg, or 250 μg mRNA-1273) was to be administered intramuscularly as a series of 2 doses 28 days apart (Days 1 and 29; The window for receiving the second dose was −2 to +2 days around Day 29).

All of 120 participants enrolled in the study (18-55 years of age, 15 each in the 25 μg, 50 μg, 100 μg, and 250 μg groups; 56-70 years of age, 10 each in the 25 μg, 50 μg, and 100 μg groups; ≥71 years of age, 10 each in the 25 μg, 50 μg, and 100 μg groups) received at least 1 dose of study vaccine and were included in the Safety Set.

The safety follow-up period is shown below. Severity grading of adverse events[25] occurred according to the FDA guidance on the toxicity grading scale in preventive vaccine clinical trials.[23]

- The following solicited adverse events: through 8 days after each dose of study vaccine (Days 1-8 and Days 29-36)
  - Local (injection site): pain, erythema/redness, and edema/induration
  - Systemic: headache, fatigue, myalgia, arthralgia, nausea, fever, and chills
- Unsolicited adverse events (excluding solicited adverse events occurring through 8 days after each dose of study vaccine): through 29 days after each dose of study vaccine (Days 1-29, Days 29-57)
- Serious adverse events: from the first dose of study vaccine through 12 months after the second dose (Days 1-394)

Solicited adverse events occurring through 8 days after each dose of study vaccine are shown in Table 13.

[25] All adverse events were coded using MedDRA Version 23.0.

Table 13. Solicited adverse events through 8 days after each dose of study vaccine (Foreign Study 101: Safety Set)

		18-55 years				56-70 years			≥71 years		
Dose level		25 μg	50 μg	100 μg	250 μg	25 μg	50 μg	100 μg	25 μg	50 μg	100 μg
Vaccination	1	N = 15	N = 15	N = 15	N = 15	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10
	2	N = 13	N = 15	N = 15	N = 14	N = 10	N = 10	N = 9	N = 10	N = 10	N = 10
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Solicited local (injection site) adverse events											
Pain	Dose 1	10 (66.7)	13 (86.7)	14 (93.3)	15 (100)	3 (30.0)	6 (60.0)	8 (80.0)	6 (60.0)	7 (70.0)	8 (80.0)
	Dose 2	10 (76.9)	13 (86.7)	15 (100)	14 (100)	5 (50.0)	8 (80.0)	8 (88.9)	6 (60.0)	4 (40.0)	10 (100)
Erythema/ Redness	Dose 1	0	0	2 (13.3)	1 (6.7)	0	0	0	0	0	0
	Dose 2	0	0	2 (13.3)	3 (21.4)	1 (10.0)	1 (10.0)	1 (11.1)	2 (20.0)	0	2 (20.0)
Swelling/ Induration	Dose 1	0	1 (6.7)	2 (13.3)	3 (20.0)	1 (10.0)	2 (20.0)	0	0	1 (10.0)	0
	Dose 2	0	0	1 (6.7)	3 (21.4)	2 (20.0)	1 (10.0)	1 (11.1)	2 (20.0)	0	3 (30.0)
Solicited systemic adverse events											
Headache	Dose 1	3 (20.0)	3 (20.0)	4 (26.7)	7 (46.7)	2 (20.0)	1 (10.0)	0	3 (30.0)	1 (10.0)	0
	Dose 2	3 (23.1)	10 (66.7)	9 (60.0)	14 (100)	3 (30.0)	3 (30.0)	7 (77.8)	2 (20.0)	0	4 (40.0)
Fatigue	Dose 1	4 (26.7)	8 (53.3)	4 (26.7)	5 (33.3)	2 (20.0)	1 (10.0)	3 (30.0)	2 (20.0)	4 (40.0)	3 (30.0)
	Dose 2	5 (38.5)	10 (66.7)	12 (80.0)	10 (71.4)	4 (40.0)	5 (50.0)	7 (77.8)	1 (10.0)	5 (50.0)	7 (70.0)
Myalgia	Dose 1	1 (6.7)	2 (13.3)	1 (6.7)	4 (26.7)	2 (20.0)	1 (10.0)	1 (10.0)	3 (30.0)	0	2 (20.0)
	Dose 2	3 (23.1)	6 (40.0)	8 (53.3)	13 (92.9)	6 (60.0)	2 (20.0)	7 (77.8)	1 (10.0)	2 (20.0)	6 (60.0)
Arthralgia	Dose 1	0	2 (13.3)	2 (13.3)	1 (6.7)	3 (30.0)	0	0	1 (10.0)	1 (10.0)	0
	Dose 2	2 (15.4)	2 (13.3)	2 (13.3)	8 (57.1)	1 (10.0)	1 (10.0)	2 (22.2)	0	0	2 (20.0)
Nausea	Dose 1	1 (6.7)	1 (6.7)	0	1 (6.7)	0	2 (20.0)	0	0	0	0
	Dose 2	1 (7.7)	2 (13.3)	7 (46.7)	4 (28.6)	2 (20.0)	0	4 (44.4)	0	0	1 (10.0)
Fever[a)]	Dose 1	0	0	0	0	0	0	0	0	0	0
	Dose 2	0	1 (6.7)	6 (40.0)	8 (57.1)	1 (10.0)	1 (10.0)	1 (11.1)	0	0	1 (10.0)
Chills	Dose 1	0	0	1 (6.7)	2 (13.3)	0	0	0	0	0	1 (10.0)
	Dose 2	1 (7.7)	3 (20.0)	12 (80.0)	12 (85.7)	2 (20.0)	2 (20.0)	5 (55.6)	0	0	4 (40.0)

N = Number of participants analyzed, n = Number of participants with event
a) ≥38°C (oral temperature)

The incidences of unsolicited adverse events and adverse reactions through 29 days after any injection of study vaccine are shown in Table 14.

Table 14. Unsolicited adverse events and adverse reactions through 29 days after any study vaccine injection (Foreign Study 101: Safety Set)

	18-55 years				56-70 years			≥71 years		
Dose level	25 μg N = 15	50 μg N = 15	100 μg N = 15	250 μg N = 15	25 μg N = 10	50 μg N = 10	100 μg N = 10	25 μg N = 10	50 μg N = 10	100 μg N = 10
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	12 (80.0)	10 (66.7)	11 (73.3)	11 (73.3)	7 (70.0)	7 (70.0)	8 (80.0)	9 (90.0)	6 (60.0)	8 (80.0)
Adverse reactions	4 (26.7)	6 (40.0)	3 (20.0)	7 (46.7)	2 (20.0)	1 (10.0)	1 (10.0)	4 (40.0)	0	3 (30.0)

N = Number of participants analyzed, n = Number of participants with event

There were no serious adverse events or deaths through data cutoff date (October 7, 2020).

Although there were no adverse events leading to study discontinuation, 3 participants did not receive the second dose due to adverse events (lower limb urticaria [1 participant in the 25 μg group], sore throat [1 participant in the 250 μg group], rash maculo-papular [1 participant in the 100 μg group]), and 1 participant owing to contact with a person with COVID-19 (25 μg group).

7.3 Foreign phase IIa study (CTD 5.3.5.1.2, Study mRNA-1273-P201, ongoing since May 2020 [data cutoff date of November 5, 2020])

A randomized, observer-blind, placebo-controlled, parallel-group study was conducted at 8 sites in the US to evaluate the safety and immunogenicity of mRNA-1273 in healthy adults aged ≥18 years (target sample size, 600 participants [200 each in the 50 μg, 100 μg, and placebo groups]). The participants, investigator, study staff, and sponsor (excluding the personnel responsible for study vaccine preparation or administration and the personnel who needs to perform unblinded duties) were blinded to study vaccine assignment.

Study vaccine (50 or 100 μg mRNA-1273 or placebo) was to be administered intramuscularly as a series of 2 doses 28 days apart (Days 1 and 29; The window for receiving the second dose was +7 days).

A total of 600 participants were enrolled in the study and randomized to any of treatment groups (≥18 and <55 years of age, 100 participants each in the 50 μg, 100 μg, and placebo groups; ≥55 years of age, 100 participants each in the 50 μg, 100 μg, and placebo groups). All of the participants received at least 1 dose of study vaccine and were included in the Safety Set. All participants contributed any solicited adverse event data in the participant diary and were included in the Solicited Safety Set. A total of 560 participants who were randomized, received planned doses of study vaccine and had their blood collected for immunogenicity assessment per schedule, had at least 1 valid result after study vaccination, had baseline SARS-CoV-2 negative status, and had no major protocol deviations (185 in the 50 μg group, 189 in the 100 μg group, 186 in the placebo group) were included in the PP Set and in the Immunogenicity Subset.

The primary immunogenicity endpoints of GMT of SARS-CoV-2 S protein-specific binding antibody on Day 57 (28 days after the second dose of study vaccine) [two-sided 95% confidence interval (CI)] and GMFR from pre-first dose baseline to Day 57 [two-sided 95% CI] were 123.89 [113.07, 135.75] and 20.39 [18.31, 22.70], respectively, in the 50 μg group (176 participants with results available), 147.42 [134.47, 161.61] and 25.04 [22.51, 27.86], respectively, in the 100 μg group (177 participants with results available), and 5.86 [5.46, 6.29] and 0.98 [0.94, 1.03], respectively, in the placebo group (175 participants with results available). GMT of SARS-CoV-2-specific neutralizing antibody (microneutralization assay using SARS-CoV-2) [two-sided 95% CI] and GMFR from pre-first dose baseline to Day 57 [two-sided 95% CI] were 1,091.0 [1,035.5, 1,149.5] and 53.65 [50.54, 56.95], respectively, in the 50 μg group (150 participants with results available), 1,095.8 [1,038.8, 1,155.9] and 54.79 [51.94, 57.80], respectively, in the 100 μg group (152 participants with results available), and 21.2 [19.8, 22.6] and 1.06 [0.99, 1.13], respectively, in the placebo group (171 participants with results available).

The safety follow-up period is shown below. Severity grading of adverse events[25)] occurred according to the FDA guidance on the toxicity grading scale in preventive vaccine clinical trials.[23)]

- The following solicited adverse events: through 7 days after each dose of study vaccine (Days 1-7 and Days 29-35)
  - Local (injection site): pain, erythema/redness, swelling/induration, and lymphadenopathy[24)]

- Systemic: headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, fever, and rash

- Unsolicited adverse events (excluding solicited adverse events occurring through 7 days after each dose of study vaccine): through 28 days after each dose of study vaccine (Days 1-28, Days 29-56)
- Serious adverse events: from the first dose of study vaccine through 12 months after the second dose (Days 1-394)

Solicited adverse events occurring through 7 days after each dose of study vaccine are shown in Table 15.

Table 15. Solicited adverse events through 7 days after each dose of study vaccine (Foreign Study 201: Solicited Safety Set)

	Dose 1			Dose 2		
	50 μg N = 200 n (%)	100 μg N = 200[c)] n (%)	Placebo N = 199 n (%)	50 μg N = 195 n (%)	100 μg N = 198 n (%)	Placebo N = 194 n (%)
Solicited local (injection site) adverse events						
Pain	131 (65.5)	166 (83.4)	21 (10.6)	155 (79.5)	169 (85.4)	15 (7.7)
Erythema/Redness	5 (2.5)	5 (2.5)	1 (0.5)	10 (5.1)	15 (7.6)	0
Swelling/Induration	8 (4.0)	8 (4.0)	1 (0.5)	12 (6.2)	21 (10.6)	1 (0.5)
Lymphadenopathy[a)]	10 (5.0)	18 (9.0)	5 (2.5)	19 (9.7)	20 (10.1)	1 (0.5)
Solicited systemic adverse events						
Headache	58 (29.0)	43 (21.6)	36 (18.1)	96 (49.2)	104 (52.5)	33 (17.0)
Fatigue	48 (24.0)	50 (25.1)	35 (17.6)	104 (53.3)	128 (64.6)	41 (21.1)
Myalgia	21 (10.5)	28 (14.1)	14 (7.0)	81 (41.5)	104 (52.5)	15 (7.7)
Arthralgia	18 (9.0)	18 (9.0)	10 (5.0)	68 (34.9)	77 (38.9)	13 (6.7)
Nausea/Vomiting	11 (5.5)	6 (3.0)	10 (5.0)	25 (12.8)	41 (20.7)	2 (1.0)
Chills	13 (6.5)	10 (5.0)	6 (3.0)	49 (25.1)	78 (39.4)	5 (2.6)
Fever[b)]	0	1 (0.5)	0	12 (6.2)	26 (13.1)	1 (0.5)
Rash	6 (3.0)	5 (2.5)	5 (2.5)	10 (5.1)	6 (3.0)	1 (0.5)

N = Number of participants analyzed, n = Number of participants with event
a) Localized axillary swelling or tenderness ipsilateral to the injected arm
b) ≥38°C (oral temperature)
c) N = 199 for analysis of events other than swelling/induration

The incidences of unsolicited adverse events and adverse reactions through 28 days after any injection of study vaccine were 28.5% (57 of 200 participants) and 8.0% (16 of 200 participants), respectively, in the 50 μg group, 28.0% (56 of 200 participants) and 13.5% (27 of 200 participants), respectively, in the 100 μg group, and 25.5% (51 of 200 participants) and 6.5% (13 of 200 participants), respectively, in the placebo group.

There were no deaths or adverse events leading to study discontinuation through data cutoff date (November 5, 2020).

As a serious adverse event, pneumonia was reported by 1 participant in the 50 μg group (≥55 years of age). Its causal relationship to study vaccine was ruled out, and its outcome was reported as “resolved.”

7.4 Foreign phase III study (CTD 5.3.5.1.3, Study mRNA-1273-P301, ongoing since May 2020 (Data snapshots, November 11, 2020 [DS1][26] [interim analysis] and November 25, 2020 [DS2][27] [primary analysis])

A randomized, observer-blind, placebo-controlled, parallel-group study was conducted at 99 sites in the US to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 in individuals 18 years of age or older (target sample size, 30,000 participants [15,000 each in the vaccine and placebo groups]). A target sample size of 30,000 was chosen, considering that a total of 151 cases of confirmed COVID-19 would provide 90% power to detect 60% vaccine efficacy (VE), rejecting the null hypothesis H0: VE ≤30%, with a one-sided significance level of 2.5% and taking account of COVID-19 incidence rate and other data. In this study, the investigator, study staff, participants, and sponsor (excluding the personnel for study vaccine preparation or administration and the personnel who needs to perform unblinded duties) were blinded to study vaccine assignment.

Study vaccine (100 μg mRNA-1273 or placebo) was to be administered intramuscularly as a series of 2 doses 28 days apart (Days 1 and 29; The window for receiving the second dose was −3 to +7 days).

Randomization was stratified based on age (18 to <65 years or ≥65 years) and, if they were <65 years of age, based on the presence or absence of risk factors for severe COVID-19 (chronic lung disease or moderate to severe asthma, significant cardiac disease, severe obesity [BMI ≥40 kg/m^2], diabetes, liver disease, HIV infection).

For early detection of the efficacy of mRNA-1273, 2 interim analyses were planned at 35% (53 cases) and 70% (106 cases) of the target total number of confirmed COVID-19 cases (151 cases). There was no intention to stop the study early even if the efficacy had been demonstrated at any of the interim analyses. The results of this interim analysis were to be handled as the primary results of the study, and the subsequent interim analysis and primary analysis was to be considered supportive analyses. The Lan-DeMets O'Brien-Fleming α-spending function was used to control the type I error rate for interim analyses. The nominal one-sided α at the first and second interim and the primary analyses was 0.0002, 0.0073, and 0.0227, respectively. However, due to the rapid accrual of COVID-19 cases before the data cutoff date for the first interim analysis, 95 adjudicated cases of COVID-19 were included in the interim analysis. A one-sided α of 0.0047 was used for this interim analysis (DS1), and the second interim analysis was dropped.

Randomized participants who received at least 1 dose of study vaccine were included in the FAS and in the Safety Set. As of the first interim analysis (DS1) and the primary analysis (DS2), 30,418 and 30,420 participants, respectively, were randomized, of whom 30,350 participants (15,180 in the vaccine group, 15,170 in the placebo group) and 30,351 participants (15,181 in the vaccine group, 15,170 in the placebo group) who received at least 1 dose of study vaccine, respectively, were included in the FAS. In the Safety Set, participants were to be included in the treatment group corresponding to the study vaccine that they actually received, and 30,351 participants were included in the Safety Set at the primary analysis (DS2) (15,185 in the vaccine group,

[26] Data cutoff date of November 7, 2020
[27] Data cutoff date of November 21, 2020

15,166 in the placebo group). Of whom, 30,342 participants who contributed any solicited adverse event data in the participant diary (15,179 in the vaccine group, 15,163 in the placebo group) were included in the Solicited Safety Set.

All participants in the FAS who had no immunologic or virologic evidence of SARS-CoV-2 infection at baseline were included in the modified intention-to-treat (mITT) Set. All participants in the mITT Set who received planned doses of study vaccine per schedule and had no major protocol deviations through 14 days after the second dose were included in the PP Set, which was used as the primary efficacy analysis population. At the first interim analysis (DS1), 27,817 participants (13,934 in the vaccine group, 13,883 in the placebo group) in the FAS were included in the PP Set, and 2,533 participants were excluded from analysis (1,668 participants with positive or unknown baseline SARS-CoV-2 status [868 in the vaccine group, 800 in the placebo group], 12 participants who received incorrect injection [5 in the vaccine group, 7 in the placebo group], 339 participants who discontinued without receiving the second dose [136 in the vaccine group, 203 in the placebo group], 179 participants who received the second dose out of window[28)] [81 in the vaccine group, 98 in the placebo group], 299 participants who did not receive the second dose or were out of window [+14 days][28)] as of the data cutoff date [144 in the vaccine group, 155 in the placebo group], and 36 participants who had other major protocol deviations[29)] [12 in the vaccine group, 24 in the placebo group]). At the primary analysis (DS2), 28,207 participants (14,134 in the vaccine group, 14,073 in the placebo group) in the FAS were included in the PP Set and 2,144 participants were excluded from analysis (1,203 participants with positive or unknown baseline SARS-CoV-2 status [631 in the vaccine group, 572 in the placebo group], 13 participants who received incorrect injection [6 in the vaccine group, 7 in the placebo group], 399 participants who discontinued without receiving the second dose [168 in the vaccine group, 231 in the placebo group], 202 participants who received the second dose out of window[28)] [93 in the vaccine group, 109 in the placebo group], 292 participants who did not receive the second dose or were out of window [+14 days][28)] as of the data cutoff date [138 in the vaccine group, 154 in the placebo group], and 35 participants who had other major protocol deviations[30)] [11 in the vaccine group, 24 in the placebo group]).

Efficacy evaluation was based on the data obtained up to the data cutoff date, and safety evaluation was based on the data obtained up to the date of data snapshot.

The primary efficacy endpoint was VE based on confirmed COVID-19 cases (COVID-19 starting 14 days after the second dose of study vaccine) in participants with no known history of SARS-CoV-2 infection prior to the first dose of study vaccine (at baseline) (VE = 1 − hazard ratio [mRNA-1273 vaccine vs. placebo]).

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28) The dosing window allowed for inclusion in the PP Set was changed from −3 to +7 days to −7 to +14 days before the first interim analysis (blinded).

29) A breakdown: 16 subjects who received study vaccine impacted by a temperature excursion, 4 subjects who met the exclusion criteria, 4 subjects who received the second dose out of window, 4 subjects who received prohibited concomitant medication or vaccine, 4 subjects who did not attend a scheduled visit or visited out of window, 1 subject who did not meet the inclusion criteria, 1 subject who was not prescribed correct study vaccine, 1 subject who did not complete 2 doses of study vaccine, 1 subject who did not provide sample for PCR testing as specified

30) A breakdown: 16 subjects who received study vaccine impacted by a temperature excursion, 4 subjects who met the exclusion criteria, 3 subjects who received the second dose out of window, 4 subjects who received prohibited concomitant medication or vaccine, 4 subjects who did not attend a scheduled visit or visited out of window, 1 subject who did not meet the inclusion criteria, 1 subject who was not prescribed correct study vaccine, 1 subject who did not complete 2 doses of study vaccine, 1 subject who did not provide sample for PCR testing as specified (1 subject who received the second dose out of window was excluded from DS1, but included in DS2 analyses because the subject was found to have no major protocol deviation prior to database lock for DS2)

COVID-19 cases were adjudicated by the Adjudication Committee, based on the following definitions:

- At least 2 of the following systemic symptoms: fever [≥38°C], chills, myalgia, headache, sore throat, new olfactory or taste disorder; OR
- At least 1 of the following respiratory signs/symptoms: cough, shortness of breath, difficulty breathing; OR clinical or radiographical evidence of pneumonia; AND
- At least 1 nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR

At the first interim analysis (DS1), VE based on COVID-19 incidence rate [two-sided 99.1% CI] was 94.5% [81.8, 98.3] (Table 16), and the lower limit of the two-sided 99.1% confidence interval was above the pre-specified threshold of 30% (based on discussion with FDA and FDA Guidance on Development and Licensure of Vaccines to Prevent COVID-19 [Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry, June 2020][31)]).

Table 16. VE to prevent COVID-19 starting 14 days after second dose (Foreign Study 301: PP Set, Interim analysis [DS1])

	N	Confirmed COVID-19 cases	VE[a)] (%) [Two-sided 99.1% CI]	*P*-value[a, b)]
Vaccine	13,934	5	94.5 [81.8, 98.3]	< 0.0001
Placebo	13,883	90		

N = Number of participants analyzed

a) A Cox proportional hazard model with treatment group as a covariate stratified by age/risk for severe COVID-19 (18-64 years of age [absence of risk factors for severe COVID-19], 18-64 years of age [presence of risk factors for severe COVID-19], ≥65 years of age)

b) One-sided α of 0.0047 (null hypothesis, VE ≤0.3)

The primary analysis was planned when ≥151 confirmed COVID-19 cases had accrued. VE at the primary analysis (DS2) after accrual of 196 cases is shown in Table 17.

Table 17. VE to prevent COVID-19 starting 14 days after second dose (Foreign Study 301: PP Set, Primary analysis [DS2])

	N	Confirmed COVID-19 cases	VE[a)] (%) [Two-sided 95% CI]
Vaccine	14,134	11	94.1 [89.3, 96.8]
Placebo	14,073	185	

N = Number of participants analyzed

a) A Cox proportional hazard model with treatment group as a covariate stratified by age/risk for severe COVID-19 (18-64 years of age [absence of risk factors for severe COVID-19], 18-64 years of age [presence of risk factors for severe COVID-19], ≥65 years of age)

The safety follow-up period is shown below. Severity grading of adverse events[25)] occurred according to the FDA guidance on the toxicity grading scale in preventive vaccine clinical trials.[23)]

- The following solicited adverse events: through 7 days after each dose of study vaccine (Days 1-7 and Days 29-35)
  - Local (injection site): pain, erythema/redness, swelling/induration, and lymphadenopathy[24)]
  - Systemic: headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever
- Unsolicited adverse events (excluding solicited adverse events occurring through 7 days after each dose of study vaccine): through 28 days after each dose of study vaccine (Days 1-28, Days 29-56)

31) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19 (last access on April 23, 2021)

- Serious adverse events: from the first dose of study vaccine through 24 months after the second dose (Days 1-759)

The median safety follow-up after the second dose of study vaccine was 2 months at the primary analysis (DS2), and the main results are shown below.

Solicited adverse events occurring through 7 days after each dose of study vaccine are shown in Table 18.

Table 18. Solicited adverse events through 7 days after each dose of study vaccine (Foreign Study 301: Solicited Safety Set, Primary analysis [DS2])

Event term	Dose 1		Dose 2	
	Vaccine (N = 15,168)	Placebo (N = 15,155)	Vaccine (N = 14,677)	Placebo (N = 14,566)
	n (%)	n (%)	n (%)	n (%)
Solicited local (injection site) adverse events				
	N = 15,164	N = 15,151	N = 14,673	N = 14,562
Any	12,765 (84.2)	2,997 (19.8)	13,006 (88.6)	2,735 (18.8)
Pain	12,690 (83.7)	2,658 (17.5)	12,943 (88.2)	2,477 (17.0)
Erythema/Redness	430 (2.8)[c)]	67 (0.4)	1,257 (8.6)	56 (0.4)
Swelling/Induration	932 (6.1)[c)]	52 (0.3)	1,789 (12.2)	49 (0.3)
Lymphadenopathy[a)]	1,553 (10.2)[c)]	722 (4.8)	2,090 (14.2)	567 (3.9)
Solicited systemic adverse events				
	N = 15,167	N = 15,155	N = 14,677	N = 14,565
Any	8,320 (54.9)	6,399 (42.2)	11,652 (79.4)	5,323 (36.5)
Headache	4,951 (32.7)[c)]	4,027 (26.6)[e)]	8,602 (58.6)[g)]	3,410 (23.4)[j)]
Fatigue	5,635 (37.2)[c)]	4,133 (27.3)[e)]	9,582 (65.3)[g)]	3,403 (23.4)[j)]
Myalgia	3,441 (22.7)[c)]	2,071 (13.7)[e)]	8,508 (58.0)[g)]	1,809 (12.4)[j)]
Arthralgia	2,511 (16.6)[c)]	1,783 (11.8)[e)]	6,284 (42.8)[g)]	1,569 (10.8)[j)]
Nausea/Vomiting	1,262 (8.3)[c)]	1,074 (7.1)[e)]	2,785 (19.0)[g)]	934 (6.4)[j)]
Chills	1,253 (8.3)[c)]	878 (5.8)[e)]	6,482 (44.2)[g)]	809 (5.6)[j)]
Fever[b)]	115 (0.8)[d)]	44 (0.3)[f)]	2,278 (15.5)[h)]	43 (0.3)[k)]

N = Number of participants analyzed, n = Number of participants with event
a) Localized axillary swelling or tenderness ipsilateral to the injected arm
b) ≥38°C (oral temperature)
c) N = 15,163, d) N = 15,164, e) N = 15,150, f) N = 15,153, g) N = 14,673, h) N = 14,669, i) N = 14,562, j) N = 14,560, k) N = 14,559

The incidences of unsolicited adverse events and adverse reactions through 28 days after any injection of study vaccine were 23.9% (3,632 of 15,185 participants) and 8.2% (1,242 of 15,185 participants), respectively, in the vaccine group and 21.6% (3,277 of 15,166 participants) and 4.5% (686 of 15,166 participants), respectively, in the placebo group. Adverse events or adverse reactions reported by ≥1% of participants in either group through 28 days after study vaccination are shown in Table 19.

Table 19. Unsolicited adverse events or adverse reactions reported by ≥1% of participants in either group through 28 days after any study vaccine injection (Foreign Study 301: Safety Set, Primary analysis [DS2])

	Adverse events		Adverse reactions	
	Vaccine (N = 15,185)	Placebo (N = 15,166)	Vaccine (N = 15,185)	Placebo (N = 15,166)
Event term	n (%)	n (%)	n (%)	n (%)
Any	3,632 (23.9)	3,277 (21.6)	1,242 (8.2)	686 (4.5)
Headache	466 (3.1)	458 (3.0)	211 (1.4)	143 (0.9)
Fatigue	372 (2.4)	336 (2.2)	222 (1.5)	178 (1.2)
Arthralgia	207 (1.4)	167 (1.1)	121 (0.8)	77 (0.5)
Myalgia	200 (1.3)	181 (1.2)	97 (0.6)	90 (0.6)
Diarrhoea	189 (1.2)	162 (1.1)	40 (0.3)	30 (0.2)
Cough	164 (1.1)	156 (1.0)	13 (<0.1)	6 (<0.1)
Oropharyngeal pain	147 (1.0)	203 (1.3)	11 (<0.1)	16 (0.1)
Injection site pain	151 (1.0)	54 (0.4)	120 (0.8)	38 (0.3)

N = Number of participants analyzed, n = Number of participants with event

As of December 3, 2020, there were 6 deaths in the vaccine group (cardio-respiratory arrest, completed suicide, head injury, myocardial infarction, multiple organ dysfunction syndrome, and death NOS [1 participant each]) and 7 deaths in the placebo group (myocardial infarction [2 participants]; and gastric perforation, cardio-respiratory arrest, COVID-19, and death NOS [1 participant each]; and 1 participant with systemic inflammatory response syndrome and dermatitis bullous). All events were considered unrelated to study vaccine.

As of the primary analysis (DS2), serious adverse events occurred in 147 of 15,185 participants (1.0%) in the vaccine group and 153 of 15,166 participants (1.0%) in the placebo group. A causal relationship to study vaccine could not be ruled out for the events reported by 7 participants in the vaccine group (swelling face [2 participants]; and autonomic nervous system imbalance, dyspnoea, nausea, vomiting, rheumatoid arthritis, oedema peripheral, and B-cell small lymphocytic lymphoma [1 participant each]) and the events reported by 5 participants in the placebo group (paraesthesia, pulmonary embolism, polymyalgia rheumatica, swelling face, feeling hot, immunisation anxiety related reaction, procedural haemorrhage, acute myocardial infarction, hypomagnesaemia, acute kidney injury, atrial fibrillation, organising pneumonia, and respiratory failure [1 participant each]). All those events except for autonomic nervous system imbalance, rheumatoid arthritis, and B-cell small lymphocytic lymphoma, had an outcome of "resolved" or "improved."

As of the primary analysis (DS2), adverse events leading to study discontinuation occurred in 2 of 15,185 participants (<0.1%) in the vaccine group and 3 of 15,166 participants (<0.1%) in the placebo group. There were no adverse events leading to study discontinuation for which a causal relationship to study vaccine could not be ruled out in the vaccine or placebo group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and review strategy

In order to accelerate SARS-CoV-2 vaccine development, the International Coalition of Medicines Regulatory Authorities (ICMRA),[32] the WHO,[33] and local regulatory authorities[34] have published guidance on vaccine development, etc. In Japan, PMDA published the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2"[35] on September 2, 2020. The guidance states the following principles for clinical trials:

- In principle, clinical trials that aim to assess the vaccine efficacy to prevent COVID-19 must be conducted to evaluate the efficacy of the SARS-CoV-2 vaccine candidate (Section 3.1.3).
- There may be a high need of evaluating the efficacy and safety of the vaccine in Japanese participants by conducting a clinical trial(s) in Japan, even if a large-scale confirmatory trial is conducted overseas to evaluate the vaccine efficacy to prevent COVID-19 (Section 3).

32) "Global regulatory workshop on COVID-19 vaccine development" (March 18, 2020 and June 22, 2020)
33) "Target Product Profiles for COVID-19 Vaccines, WHO R&D Blueprint, 29 April 2020" and "An international randomised trial of candidate vaccines against COVID-19, WHO R&D Blueprint, 28 May 2020"
34) FDA, "Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, CBER FDA, June 2020;" EMA, "EMA considerations on COVID-19 vaccine approval; etc.
35) https://www.pmda.go.jp/files/000236327.pdf (last accessed on April 23, 2021)

- When a large-scale confirmatory clinical trial of the vaccine candidate is conducted overseas using the efficacy of the vaccine candidate to prevent COVID-19 as the primary endpoint, it may be sufficient to conduct a Japanese clinical trial to confirm the immunogenicity and safety of the vaccine candidate in Japanese participants without conducting a confirmatory clinical trial in Japan to evaluate its efficacy to prevent COVID-19 in Japanese participants (Section 3.2.3).

The applicant planned and conducted a Japanese clinical study to evaluate the immunogenicity and safety of mRNA-1273, in accordance with the above guidance documents. The clinical data package for the present application consists of the following evaluation data: a foreign phase III study to evaluate the efficacy of mRNA-1273 to prevent COVID-19 (Study mRNA-1273-P301 [hereinafter referred to as "Foreign Study 301"]) and a foreign phase I study (Study 20-0003 [101] [hereinafter referred to as "Foreign Study 101"]), a foreign phase II study (Study mRNA-1273-P201 [hereinafter referred to as "Foreign Study 201"), and a Japanese phase I/II study (Study TAK-919-1501 [hereinafter referred to as "Japanese Study 1501") to evaluate the safety and immunogenicity of mRNA-1273 [see Section 7, Table 11].

PMDA's view on the review strategy for mRNA-1273:
The clinical data package prepared by the applicant based on the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" is acceptable. PMDA will evaluate the efficacy and safety of mRNA-1273 based on the pivotal data from the foreign confirmatory study that evaluated the efficacy of mRNA-1273 to prevent COVID-19 (Foreign Study 301). In addition, PMDA will review the immunogenicity and safety of mRNA-1273 in Japanese participants based on the data from the Japanese clinical study (Japanese Study 1501) to evaluate the efficacy and safety of mRNA-1273 in the Japanese population. PMDA will also use foreign post-marketing information etc. for safety review.

Since the results of Foreign Study 301 demonstrated the efficacy of mRNA-1273 at the first interim analysis (DS1), the results of the interim analysis (DS1) were handled as the primary efficacy results, as pre-specified [see Section 7.4]. In this review, detailed evaluation of the efficacy of mRNA-1273 and safety evaluation will be performed based on the results of analysis of the data as of November 25, 2020 (DS2) because the data as of November 25, 2020 (DS2) at the originally planned primary analysis timepoint contain more efficacy and safety information than the data as of November 11, 2020 (DS1) at the interim analysis, though the primary efficacy evaluation will be based on the results of the interim analysis (DS1).

7.R.2 Efficacy

PMDA's view:
According to the submitted study results and the following considerations, the results of Foreign Study 301 demonstrated the efficacy of mRNA-1273 to prevent COVID-19. The immunogenicity results of Foreign Study 201 and Japanese Study 1501 suggest similar efficacy in the Japanese population.

However, the currently available information on the long-term efficacy of mRNA-1273 is limited, and with regard to the efficacy of mRNA-1273 against SARS-CoV-2 variants, newly emerging variants of SARS-CoV-2 are anticipated. Thus, the applicant should collect post-marketing information and communicate any new information to healthcare professionals in clinical practice or take other appropriate action, if a new finding becomes available.

A final decision on the efficacy of mRNA-1273 will be made, taking account of comments from the Expert Discussion.

7.R.2.1 Efficacy endpoint

In the pivotal clinical study (Foreign Study 301) in the development program, the primary efficacy endpoint was VE based on confirmed COVID-19 cases starting 14 days after the second dose of study vaccine in the PP Set.

The applicant's explanation about selection of the primary endpoint:
Confirmed COVID-19 was defined as symptomatic COVID-19 adjudicated by the Adjudication Committee, meeting the following criteria (a) OR (b), AND (c), using the case definition in the Standardized surveillance case definition and national notification for 2019 novel coronavirus disease (COVID-19) of the Council of State and Territorial Epidemiologists (CSTE).[36)]

(a) At least 2 of the following systemic symptoms: fever [≥38°C], chills, myalgia, headache, sore throat, new olfactory or taste disorder
(b) At least 1 of the following respiratory symptoms: cough, shortness of breath, difficulty breathing; OR clinical or radiographical evidence of pneumonia
(c) At least 1 of the following: nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR

This definition is consistent with COVID-19 case definition[37)] for efficacy evaluation in SARS-CoV-2 vaccine clinical trials recommended by the FDA guidance on Development and Licensure of Vaccines to Prevent COVID-19[31)] and defines clinical symptoms so as to detect COVID-19 more specifically than the FDA guidance.

The evaluation period for accrual of confirmed COVID-19 cases was defined as "≥14 days after the second dose" during which an immune response to mRNA-1273 occurs because titers of neutralizing antibodies induced by mRNA-1273 vaccination peaked at approximately 14 days after the second dose in Foreign Study 101 (Table 20).

36) https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/Interim-20-ID-01_COVID-19.pdf (last accessed on April 23, 2021)
37) For efficacy evaluation in clinical trials, FDA recommends that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with one or more of the following clinical symptoms:
fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea

Table 20. Neutralizing antibody titers (50% inhibitory dilution)[a] (Foreign Study 101: mITT Set[b])

Age	Dose (mRNA-1273)	N	GMT [Two-sided 95% CI]				
			Before Dose 1	28 days after Dose 1	7 days after Dose 2	14 days after Dose 2	28 days after Dose 2
18-55 years	25 μg	15	10 [NE]	12 [10, 14]	106 [70, 160][c]	112 [71, 177][c]	90 [57, 143][c]
	50 μg	15	10 [NE]	14 [9, 21]	294 [178, 487]	351 [214, 575][d]	234 [153, 358]
	100 μg	15	10 [NE]	18 [12, 27]	263 [188, 368]	360 [273, 476][d]	276 [193, 393][d]
	250 μg	15	10 [NE]	21 [13, 32][d]	378 [306, 468][d]	342 [267, 438][d]	277 [231, 332][d]
56-70 years	25 μg	10	10 [NE]	10 [NE]	85 [51, 142]	119 [68, 209]	100 [49, 204]
	50 μg	10	10 [NE]	12 [9, 16]	108 [56, 211]	220 [162, 299]	163 [115, 230]
	100 μg	10	10 [NE]	11 [10, 12]	340 [219, 527][e]	404 [292, 561][e]	424 [267, 673][e]
≥71 years	25 μg	10	10 [NE]	11 [9, 12]	121 [69, 211]	112 [67, 188]	100 [56, 179]
	50 μg	10	10 [NE]	12 [9, 17]	75 [30, 190]	217 [86, 542]	150 [53, 419]
	100 μg	10	10 [NE]	20 [12, 33]	310 [202, 475]	317 [198, 508]	231 [150, 356]

N = Number of participants analyzed, NE: Not evaluable
a) Pseudovirus luciferase assay
b) All of participants who received at least 1 dose of mRNA-1273, provided serum samples prior to and after vaccination for immunogenicity assessment, and had valid test results
c) 13 participants with results available
d) 14 participants with results available
e) 9 participants with results available

Since participants who did not complete 2 doses of study vaccine or who had major protocol deviations were considered to potentially impact efficacy evaluation, a population after excluding these participants (PP Set) was used as the analysis population.

PMDA considers that the efficacy of mRNA-1273 to prevent COVID-19 can be evaluated based on the primary endpoint selected for Foreign Study 301.

7.R.2.2 Efficacy to prevent COVID-19

The applicant's explanation about the efficacy of mRNA-1273 to prevent COVID-19:

(a) Vaccine efficacy (VE)

At the planned first interim analysis (DS1) in Foreign Study 301, the primary endpoint of VE based on confirmed COVID-19 cases starting 14 days after the second dose in the PP Set with no evidence of prior SARS-CoV-2 infection [two-sided 99.1% CI] was 94.5% [81.8%, 98.3%], and the lower limit of the two-sided 99.1% CI was above the pre-specified threshold (30%), demonstrating its efficacy [see Section 7.4]. VE [two-sided 95% CI] based on the data as of November 25, 2020 (DS2) was 94.1% [89.3%, 96.8%], which was supportive analysis and similar to the results of the interim analysis (DS1).

A secondary endpoint of confirmed COVID-19 cases starting 14 days after the second dose (DS2) in all participants regardless of evidence of prior SARS-CoV-2 infection (FAS) was analyzed, and there were 12 cases in the vaccine group (N = 15,181) and 187 cases in the placebo group (N = 15,170) with VE [two-sided 95% CI] of 93.6% [88.6%, 96.5%], which was similar to the results of the primary endpoint. The number of participants with evidence of prior SARS-CoV-2 infection (seropositive participants) in the FAS was as small as 343 participants in the vaccine group and 337 participants in the placebo group,[38] and there was only 1 case

[38] In Foreign Study 301, subjects with a known history of SARS-CoV-2 infection were excluded at screening, but subjects enrolled in the study who were found to have a history of SARS-CoV-2 infection at baseline testing were included.

of confirmed COVID-19 in the placebo group. Thus, there are limitations to interpreting the efficacy results of mRNA-1273 in participants with a history of SARS-CoV-2 infection.

The cumulative incidence rates of confirmed COVID-19 in the mITT Set are shown in Figure 2. The curves of the vaccine and placebo groups diverge at 14 days after the first dose of study vaccine, suggesting that the efficacy of mRNA-1273 starts before the second dose.

VE based on COVID-19 cases after randomization by time to onset in the PP Set is shown in Table 21. VE by time to onset is based on symptomatic COVID-19 regardless of whether cases were adjudicated by the Adjudication Committee ("confirmed COVID-19" was defined as symptomatic COVID-19 with systemic or respiratory symptoms and a positive sample for SARS-CoV-2 by RT-PCR, adjudicated by the Adjudication Committee [see Section 7.R.2.1]).

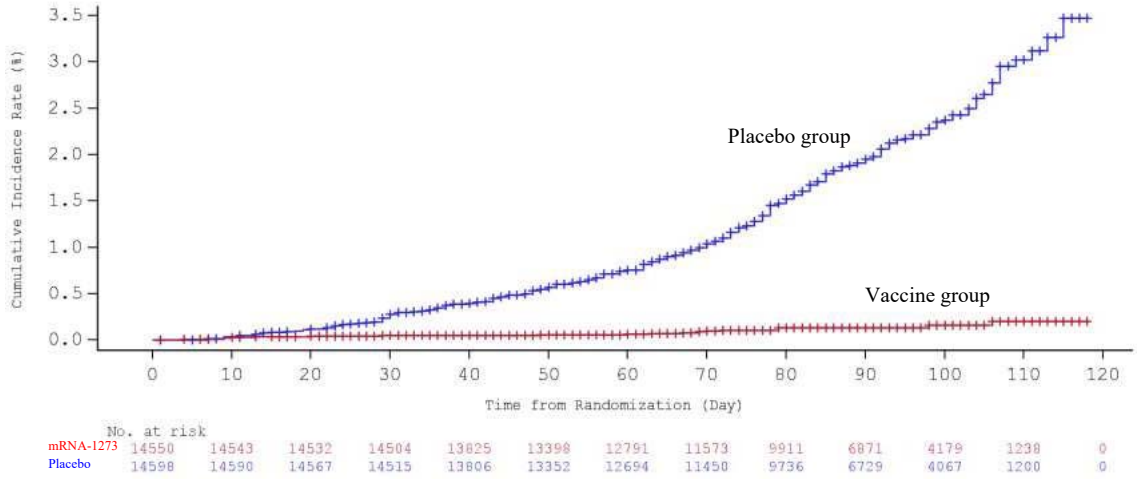

Figure 2. Cumulative incidence rates of confirmed COVID-19 after randomization (Foreign Study 301: mITT Set [DS2])

Table 21. Occurrence of symptomatic COVID-19 by time to onset (Foreign Study 301: PP Set [DS2])

		Vaccine	Placebo	VE (%)[a)]
Number of participants analyzed		14,134	14,073	[Two-sided 95% CI]
Symptomatic COVID-19 (by time to onset)	Entire period (after randomization)	12	225	94.8 [90.6, 97.1]
	≥14 days after Dose 1	11	225	95.2 [91.2, 97.4]
	From Dose 1 to before Dose 2[b)]	1	4	74.9 [-124.2, 97.2]
	From Dose 2 to 13 days after Dose 2	0	19	100 [NE, 100]
	≥14 days after Dose 2	11	202	94.7 [90.2, 97.1]

NE: Not evaluable

a) A Cox proportional hazard model with treatment group as a covariate stratified by age and risk for severe COVID-19 (18-64 years of age [absence of risk factors for severe COVID-19], 18-64 years of age [presence of risk factors for severe COVID-19], ≥65 years of age)

b) Participants who did not develop event by the day of Dose 2 were censored on the day before Dose 2.

Efficacy results in subgroups are shown in Table 22. There were no major differences in VE across all subgroups based on age, sex, race, risk factors for severe COVID-19, and age and risk for severe COVID-19.

Table 22. COVID-19 cases starting 14 days after the second dose of study vaccine by subgroup (Foreign Study 301: PP Set [DS2])

		Vaccine		Placebo		VE (%)[a] [Two-sided 95% CI]
		N (%)	Confirmed COVID-19 cases	N (%)	Confirmed COVID-19 cases	
Overall population		14,134	11	14,073	185	94.1 [89.3, 96.8]
Age	18 to <65 years	10,551 (74.6)	7	10,521 (74.8)	156	95.6 [90.6, 97.9]
	≥65 years	3,583 (25.4)	4	3,552 (25.2)	29	86.4 [61.4, 95.2]
	18-19 years	92 (0.7)	0	116 (0.8)	2	100 [NE, 100]
	20-64 years	10,459 (74.0)	7	10,405 (73.9)	154	95.5 [90.5, 97.9]
	65 to <75 years	2,953 (20.9)	4	2,864 (20.4)	22	82.4 [48.9, 93.9]
	≥75 years	630 (4.5)	0	688 (4.9)	7	100 [NE, 100]
Sex	Male	7,366 (52.1)	4	7,462 (53.0)	87	95.4 [87.4, 98.3]
	Female	6,768 (47.9)	7	6,611 (47.0)	98	93.1 [85.2, 96.8]
Race	White	11,253 (79.6)	11	11,174 (79.4)	166	93.5 [88.0, 96.5]
	Black or African American	1,385 (9.8)	0	1,349 (9.6)	6	100 [NE, 100]
	Asian	620 (4.4)	0	689 (4.9)	5	100 [NE, 100]
	Others[b]/Unknown	876 (6.2)	0	861 (6.1)	8	100 [NE, 100]
Risk factors for severe COVID-19	Yes	3,206 (22.7)	4	3,167 (22.5)	43	90.9 [74.7, 96.7]
	No	10,928 (77.3)	7	10,906 (77.5)	142	95.1 [89.6, 97.7]
Age and risk for severe COVID-19	18-64 years of age Absence of risk factors	8,396 (59.4)	5	8,403 (59.7)	121	95.9 [90.0, 98.3][c]
	18-64 years of age Presence of risk factors	2,155 (15.2)	2	2,118 (15.1)	35	94.4 [76.9, 98.7][c]
	≥65 years of age	3,583 (25.4)	4	3,552 (25.2)	29	86.4 [61.4, 95.2][c]

N = Number of participants analyzed, NE: Not evaluable

a) A Cox proportional hazard model with treatment group as a covariate stratified by age and risk for severe COVID-19 (18-64 years of age [absence of risk factors for severe COVID-19], 18-64 years of age [presence of risk factors for severe COVID-19], ≥65 years of age)

b) Other than White, Black or African American, and Asian

c) A Cox proportional hazard model with treatment group as a covariate

Although Japanese Study 1501 did not evaluate the efficacy of mRNA-1273 to prevent COVID-19, information on the onset and diagnosis of COVID-19 during the study period was to be collected as adverse events, and no COVID-19 cases were reported (data cutoff date of March 31, 2021).

(b) Immunogenicity

S protein-specific binding and neutralizing antibody titers in Foreign Study 201 and Japanese Study 1501 are shown in Table 23 and Table 24, respectively.

Table 23. Antibody titers at 28 days after the second dose of study vaccine (Foreign Study 201: PP Set for S protein-specific binding or neutralizing antibodies)

		S protein-specific binding antibody titer[a)]				Neutralizing antibody titer (50% neutralization titer [MN_{50}])[b, c)]			
		N	n	GMT (μg/mL) [Two-sided 95% CI]	GMFR [Two-sided 95% CI]	N	n	GMT [Two-sided 95% CI]	GMFR [Two-sided 95% CI]
mRNA-1273 100 μg	All age groups	189	177	147.42 [134.47, 161.61]	25.04 [22.51, 27.86]	186	152	1,655.1 [1,563.2, 1,752.4]	36.3 [34.3, 38.5]
	18-54 years	95	87	181.15 [164.17, 199.88]	29.13 [25.68, 33.03]	95	82	1,691.9 [1,585.7, 1,805.3]	37.1 [34.8, 39.6]
	≥55 years	94	90	120.79 [104.60, 139.49]	21.63 [18.29, 5.59]	91	70	1,612.9 [1,460.0, 1,781.9]	35.4 [32.1, 39.1]
Placebo	All age groups	186	175	5.86 [5.46, 6.29]	0.98 [0.94, 1.03]	181	171	47.8 [45.2, 50.5]	1.1 [1.0, 1.1]
	18-54 years	92	84	6.54 [5.91, 7.23]	1.01 [0.95, 1.08]	92	84	48.5 [44.4, 53.0]	1.1 [1.0, 1.2]
	≥55 years	94	91	5.30 [4.81, 5.84]	0.96 [0.90, 1.01]	89	87	47.1 [44.0, 50.5]	1.0 [1.0, 1.1]

N = Number of participants analyzed, n = Number of participants with results available
GMT, 28 days after Dose 2; GMFR, 28 days after Dose 2/before Dose 1
Antibody values below the LLOQ were replaced by 0.5 × LLOQ for analyses.
a) Coating antigen, commercially available S-2P protein (S1+S2 ECD, His-tag); Assay reference material, monoclonal antibody; Detection limit, 0.49 μg/mL; Assay range, 3.9-487 μg/mL
b) Microneutralization assay
c) Host cells, BBRC VERO E6 cells; Assay positive control sera, pooled convalescent sera from COVID-19 patients; Detection limit, 70.08; Assay range, 91.10-2,031.87

Table 24. Antibody titers at 28 days after the second dose of study vaccine (Japanese Study 1501: PP Set)

		S protein-specific binding antibody titer[a)]				Neutralizing antibody titer (50% neutralization titer [MN_{50}])[b, c)]			
		N	n	GMT (AU/mL) [Two-sided 95% CI]	GMFR [Two-sided 95% CI]	N	n	GMT [Two-sided 95% CI]	GMFR [Two-sided 95% CI]
mRNA-1273 (100 μg)	All age groups	147	147	813.05 [759.31, 870.60]	1,009.25 [865.11, 1177.40]	147	146	1731.1 [1579.0, 1897.8]	21.7 [19.8, 23.8]
	20-64 years	98	98	810.61 [750.45, 875.60]	1,037.79 [867.37, 1241.69]	98	97	1727.4 [1549.0, 1926.5]	21.6 [19.4, 24.1]
	≥65 years	49	49	817.95 [711.35, 940.52]	954.51 [706.61, 1289.37]	49	49	1738.3 [1459.9, 2069.8]	21.8 [18.3, 25.9]
Placebo	All age groups	49	49	0.60 [0.53, 0.68]	0.90 [0.83, 0.98]	49	49	79.9 [79.9, 79.9]	1.0 [1.0, 1.0]
	20-64 years	39	39	0.59 [0.52, 0.67]	0.88 [0.79, 0.98]	39	39	79.9 [79.9, 79.9]	1.0 [1.0, 1.0]
	≥65 years	10	10	0.66 [0.48, 0.91]	1.00 [0.93, 1.07]	10	10	79.9 [79.9, 79.9]	1.0 [1.0, 1.0]

N = Number of participants analyzed, n = Number of participants with results available
GMT, 28 days after Dose 2; GMFR, 28 days after Dose 2/before Dose 1
Antibody values below the LLOQ were replaced by 0.5 × LLOQ for analyses.
a) Coating antigen, S-2P protein; Assay reference material, pooled convalescent sera from COVID-19 patients; Detection limit, 0.24 AU/mL; Assay range, 1.0-2,052AU/mL (The same assay method as in Foreign Study 301)
b) Microneutralization assay
c) Host cells, Quidel VERO E6 cells; Assay positive control sera, pooled sera from participants in the mRNA-1273 group of a foreign clinical study; Detection limit, 82.11; Assay range, 159.79-11,173.11 (The same assay method as in Foreign Study 301)

In Foreign Study 201 and Japanese Study 1501, GMTs of S protein-specific binding and neutralizing antibodies at 28 days after the second dose and GMFRs from pre-first dose baseline to 28 days after the second dose were markedly higher in the vaccine group than in the placebo group. In both studies, the seroconversion rate in the vaccine group was 100%. In both studies, GMTs of S protein-specific binding and neutralizing antibodies were comparable for the younger age group (16-55 years or 20-64 years) and the older age group (≥56 years or ≥65 years). The immunogenicity results of Foreign Study 301 are not available at present.

While the data beyond 28 days after the second dose of study vaccine are not available from Foreign Study 201 or Japanese Study 1501, the data up to 180 days after the second dose have been obtained from Foreign Study 101. The time course of neutralizing antibody titer in the mRNA-1273 100 μg group is shown in Table 25. S protein-specific binding and neutralizing antibodies were detected even at 180 days after the second dose (*N Engl J Med*. 2021; 384: 80-2, *N Engl J Med*. 2021; doi: 10.1056/NEJMc2103916), and GMTs at 90 days after the second dose exceeded GMTs in convalescent sera[39] (106 [60, 189]). Other studies will also assess the durability of immunogenicity.

Table 25. Time course of neutralizing antibody titer (50% inhibitory dilution)[a] beyond 28 days after Dose 2 (Foreign Study 101: mITT Set[b])

	mRNA-1273 100 μg		
	18-55 years (N = 15)	56-70 years (N = 10)	≥71 years (N = 10)
	GMT [Two-sided 95% CI]	GMT [Two-sided 95% CI]	GMT [Two-sided 95% CI]
Before Dose 1	10 [NE]	10 [NE]	10 [NE]
28 days after Dose 1	18 [12, 27]	11 [10, 12]	20 [12, 33]
7 days after Dose 2	263 [188, 368]	340 [219, 527][d]	310 [202, 475]
14 days after Dose 2	360 [273, 476][c]	404 [292, 561][d]	317 [198, 508]
28 days after Dose 2	276 [193, 393][c]	424 [267, 673][d]	231 [150, 356]
90 days after Dose 2	182 [112, 296]	167 [88, 318][d]	109 [68, 175]
180 days after Dose 2[e]	80 [48, 135]	57 [30, 106][d]	59 [29, 121][d]

N = Number of participants analyzed, NE: Not evaluable

a) Pseudovirus luciferase assay
b) All of participants who received at least 1 dose of mRNA-1273, provided serum samples prior to and after vaccination for immunogenicity assessment, and had valid test results
c) 14 participants with results available
d) 9 participants with results available
e) Abstracted from *N Engl J Med*. 2021; doi: 10.1056/NEJMc2103916 Supplemental Table 2

A discussion on the relationship between neutralizing antibody titers and the prevention of SARS-CoV-2 infection/COVID-19 after vaccination with mRNA-1273 has not yet reached a conclusion that neutralizing antibody titers are correlated with the prevention of COVID-19. However, taking account of the results of non-clinical challenge studies [see Section 3.1.3], and given that marked increases in antibody titers were seen after the second dose of mRNA-1273 in clinical studies and that Foreign Study 301 demonstrated VE to prevent COVID-19, increases in antibody titers following mRNA-1273 vaccination may suggest its relationship with the prevention of COVID-19.

An investigation will be continued for the relationship between the prevention of COVID-19 and S protein-specific binding or neutralizing antibody titers.

(c) Efficacy in the Japanese population

In Japanese Study 1501, S protein-specific binding and neutralizing antibody titers rose markedly in the vaccine group compared with the placebo group [see Table 24]. The seroconversion rate in the vaccine group was 100% as in Foreign Study 201. Since the assay methods for S protein-specific binding and neutralizing antibodies were different between Foreign Study 201 and Japanese Study 1501, direct comparison of GMT and GMFR between the 2 studies is difficult.

39) Sera collected from 41 COVID-19 convalescent donors between 20 and 77 years of age (a median of 49 years) with a median of 34 days (23-54 days) since diagnosis (symptom onset or positive PCR test result).

Given that increases in S protein-specific binding and neutralizing antibody titers were seen in Japanese Study 1501 as in Foreign Study 201, and that Foreign Study 301 demonstrated the efficacy of mRNA-1273,mRNA-1273 is expected to exhibit similar efficacy in the Japanese population, as in the case of Foreign Study 301.

PMDA's view on the efficacy of mRNA-1273:
The results of Foreign Study 301 demonstrated VE of mRNA-1273 to prevent COVID-19 in the overall population. Foreign Study 301 was conducted in the US only, and there was an imbalance in the race distribution of participants enrolled in the study (White participants accounted for 79.2% of the analysis population). However, no marked differences in VE to prevent COVID-19 were observed across all subgroups including the race, within the scope investigated in this study.

As explained by the applicant, the assay methods for S protein-specific binding and neutralizing antibodies were different between Foreign Study 201 and Japanese Study 1501, and thus direct comparison of GMT and GMFR between these studies is not suitable for evaluation. However, S protein-specific binding and neutralizing antibody titers increased after the second dose of mRNA-1273 in Japanese Study 1501, as in Foreign Study 201 [see Table 23 and Table 24].

Based on the above, VE of mRNA-1273 to prevent COVID-19 is promising in the Japanese population as the immunogenicity of mRNA-1273 was found to be similar in Japanese participants and non-Japanese participants.

Though no information on the long-term efficacy of mRNA-1273 is currently available, antibody titers similar to or higher than those of convalescent sera persisted through 90 days after the second dose of 100 μg, and neutralizing antibodies were detected even at 180 days after the second dose in Foreign Study 101 (Table 25, *N Engl J Med*. 2021; doi: 10.1056/NEJMc2103916). Assuming that there is a relationship between the prevention of COVID-19 and antibody titers, VE of mRNA-1273 may be expected to persist for a certain period of time. However, given a decline over time in neutralizing antibody titers, the applicant should continue to investigate the long-term efficacy of mRNA-1273.

Since Foreign Study 301 and Japanese Study 1501 will be continued also after marketing, the applicant should provide the obtained information on the efficacy of mRNA-1273 to healthcare professionals in clinical practice and others, as appropriate. The applicant should continue an investigation of the relationship between the prevention of COVID-19 and neutralizing antibody titers etc., and should communicate any new information to healthcare professionals in clinical practice if it becomes available.

Because the effect of mRNA-1273 in preventing SARS-CoV-2 infection was not assessed in clinical studies, at present, it is important to continue infection control measures even after vaccination with mRNA-1273. This issue should be communicated appropriately to healthcare professionals and vaccine recipients.

7.R.2.3 Efficacy to prevent severe COVID-19

The applicant's explanation:

In Foreign Study 301, in order to evaluate the vaccine efficacy of mRNA-1273 to prevent severe COVID-19, the occurrence of severe COVID-19 adjudicated by the Adjudication Committee was analyzed. Severe COVID-19 was defined as meeting any one of the following criteria:

- Clinical signs indicative of severe systemic illness (respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, $SpO_2 \leq 93\%$ 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 neurologic dysfunction
- Admission to an intensive care unit
- Death

This definition has been developed in accordance with FDA Guidance on Development and Licensure of Vaccines to Prevent COVID-19[31)] and includes the terms "admission to an intensive care unit" and "mechanical ventilator required," which represent the clinical state of severe cases defined in the Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers (Version 4.1)[40)] used in Japan. The use of this definition for adjudication of severe COVID-19 is appropriate. No participants in the vaccine group and 30 participants in the placebo group had severe COVID-19 based on this definition (DS2), with VE of 100%.

Although 1 participant in the vaccine group had severe COVID-19 by the data cutoff date for DS2, this case was not included in the above analysis because the RT-PCR result of the participant was not reported by the data cutoff date.

PMDA's view:

As Foreign Study 301 was not intended to confirm the efficacy of mRNA-1273 to prevent severe COVID-19, the results should be interpreted carefully. However, the presented results suggest the efficacy of mRNA-1273 in the prevention of severe COVID-19. If a new finding on the efficacy of mRNA-1273 or SARS-CoV-2 vaccines in the prevention of severe COVID-19 becomes available, the applicant should consider the revision of the information materials distributed, or take other appropriate actions.

7.R.2.4 Efficacy against variants

In Japan, the B.1.1.284 and B.1.1.214 lineages with D614G mutation were dominant as of January 2021,[41)] but new variants, such as the UK variant or VOC-202012/01 (the B.1.1.7 lineage), the South African variant 501Y.V2 (the B.1.351 lineage), and the Brazil variant 501Y.V3 (the P.1 lineage), with multiple mutations in

40) https://www.mhlw.go.jp/content/000712473.pdf (last accessed on April 23, 2021)
41) https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2488-idsc/iasr-news/10152-493p01.html (last accessed on April 23, 2021)

the S protein, have been reported since late December 2020. Especially, VOC-202012/01 accounted for ≥90% of all variants identified in Japan (1,076 of 1,141 cases, as of April 13)[42] and its number has been increasing continuously.[43] These variants have been classified as variants of concern (VOC)[44] by WHO, all of which have N501Y mutation that may increase infectivity/transmissibility, and the 501Y.V2 and 501Y.V3 variants have also E484K mutation, which may drive immune escape. The severity of COVID-19, infectivity/transmissibility, and other characteristics have been reported as follows:

- VOC-202012/01 (the B.1.1.7 lineage): Increases in infectivity/transmissibility have been reported compared to previously circulating strains (*Science*. 2021; 372: eabg3055). It is likely that infection with VOC B.1.1.7 is associated with an increased risk of death and hospitalization compared to infection with non-VOC viruses (The New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG): Update note on B.1.1.7 severity, 11 February 2021[45]).
- 501Y.V2 (the B.1.351 lineage): Increased infectivity/transmissibility is suggested compared to previously circulating strains, and since E484K is present, immune escape may also occur (*Nature*. 2021; 592: 438-43). No definitive information suggestive of a change in severity has been obtained (Centre for Mathematical Modelling of infectious Diseases, Estimates of severity and transmissibility of novel SARS-CoV-2 variant 501Y.V2 in South Africa, 11 Jan 2021[46]).
- 501Y.V3 (the P.1 lineage): Since 501Y.V3 and 501Y.V2 share the same mutations in the receptor-binding domain (RBD) (K417T, E484K, N501Y), there is a concern about potentially increased infectivity/transmissibility and immune escape. No definitive information suggestive of a change in severity has been obtained (Rapid risk assessment. SARS-CoV-2-Increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update. 15 Feb 2021[47]).

In addition to these variants, the recent variants identified in Japan include the P.3 lineage reported in the Philippines and the B.1.427/B.1.429 lineage detected mainly in California, the US.[43]

PMDA asked the applicant to explain the efficacy of mRNA-1273 against variants.

The applicant's explanation using the literature (Kai, W et al.) (*N Engl J Med*. 2021; 384: 1468-70):

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42) https://www.mhlw.go.jp/content/10900000/000769042.pdf (last accessed on April 23, 2021)
43) https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/10280-covid19-41.html (last accessed on April 23, 2021)
44) WHO defines VOC and VOI as follows (https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update [last accessed on April 23, 2021]):
VOI: A SARS-CoV-2 isolate is a variant of interest (VOI) if it is phenotypically changed compared to a reference isolate or has a genome with mutations that lead to amino acid changes associated with established or suspected phenotypic implications
AND
has been identified as a variant that causes community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries
OR
is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Working Group.
VOC: A VOI is a variant of concern (VOC) if, through a comparative assessment, it has been demonstrated to be associated with
● Increase in transmissibility or detrimental change in COVID-19 epidemiology
● Increase in virulence or change in clinical disease presentation, or
● Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics
OR
assessed to be a VOC by WHO in consultation with the WHO SARS-CoV-2 Virus Working Group.
45) https://www.gov.uk/government/publications/nervtag-update-note-on-b117-severity-11-february-2021 [last accessed on April 23, 2021])
46) https://cmmid.github.io/topics/covid19/sa-novel-variant.html (last accessed on April 23, 2021)
47) https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-variants-vaccine-fourteenth-update-february-2021 (last accessed on April 23, 2021)

In order to assess the neutralizing activity elicited by mRNA-1273 against variants, the neutralizing activity against recombinant vesicular stomatitis virus-based SARS-CoV-2 (a pseudovirus-based model) in serum samples obtained from 8 participants in Foreign Study 101 was assayed. The samples were obtained 1 week after the participants had received the second dose of 100 μg mRNA-1273. Pseudoviruses bearing the spike proteins from the original Wuhan-1 isolate (wild-type), the B.1.1.7, B.1.351, P.1, and B.1.427/B.1.429 variants, the D614G variant, the EU1 variant, the EU2 variant, the N439K-D614G variant, and the mink cluster 5 variant were tested. All pseudoviruses tested were neutralized (Kai, W et al's report, Figure 1 and Figure S4). Although the neutralizing activity against the B.1.351 variant was lower than that against the D614G variant, GMT of ID_{50} (50% inhibitory dilution against the pseudovirus) was 1:290. Because all the serum samples neutralized the pseudovirus, the neutralizing activity is considered to be retained.

However, the applicant will continue monitoring for newly emerging variants, and collect post-marketing information on the neutralizing activity against variants with increased transmission potential.

The circulating strain during clinical studies of mRNA-1273 is assumed to be the D614G variant. At present, virus strains from COVID-19 cases in Foreign Study 301 are being assessed, and the efficacy of mRNA-1273 against the above-mentioned variants has not been evaluated.

PMDA's view:
The serum samples obtained from participants immunized with mRNA-1273 neutralized the pseudoviruses incorporating D614G or the spike mutations. This and other findings suggest a certain level of efficacy of mRNA-1273 against variants that were circulating as of April 2021. However, since the emergence of new variants is anticipated in future, the applicant should continue to watch for the emergence and prevalence of variants, and should investigate and collect information on the neutralizing activity and clinical efficacy of mRNA-1273 against variants. The applicant should provide information, as needed, or take other appropriate actions, if a new finding becomes available.

7.R.3 Safety

The applicant's explanation about safety in clinical studies and post-marketing experience:
Based on Sections 7.R.3.1 to 7.R.3.5, the currently available information indicates that the benefits of mRNA-1273 outweigh its risks.

PMDA reviewed the safety of mRNA-1273 based on the submitted data and the applicant's explanation in Sections 7.R.3.1 to 7.R.3.5, and then concluded as follows:
According to the safety data from clinical studies submitted, there were no major differences in safety profile between Japanese and non-Japanese populations. Given the incidences of other adverse events and serious adverse events, the incidences by age group, and other data, no serious concerns were identified. Adverse events such as anaphylaxis, which were not detected in clinical studies, have been reported under the

emergency use authorization or in post-marketing settings overseas, but no events unique to mRNA-1273 have been observed so far.

Based on the above, there are no safety concerns about mRNA-1273, on the premise that appropriate precautions and information are provided.

However, all of the clinical studies of mRNA-1273 are ongoing, and there are limited long-term safety data from the Japanese and foreign clinical studies submitted. Thus, the applicant should collect post-marketing long-term safety information. The applicant also collect other necessary information, make a decision to provide an additional precaution or information according to the obtained findings, or take other appropriate actions.

A final decision on the safety of mRNA-1273 will be made, taking account of comments from the Expert Discussion.

7.R.3.1 Safety in clinical studies

The applicant's explanation about safety in clinical studies is presented in sections below.

7.R.3.1.1 Adverse events

(a) Foreign Study 301

In Foreign Study 301, pre-specified solicited local (injection site) adverse events (pain, erythema/redness, swelling/induration, lymphadenopathy) and solicited systemic adverse events (headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, fever) were recorded using participant diaries through 7 days after each dose of study vaccine. The recorded information was analyzed. Solicited adverse events through 7 days after each dose of study vaccine are shown in Table 18 [see Section 7.4], and Grade ≥3 solicited adverse events are shown in Table 26. Many participants in the vaccine group experienced at least 1 solicited adverse event, and the incidence of each specific event was higher in the vaccine group than in the placebo group. The most common solicited local adverse event in the vaccine group was pain, and the incidence of pain after the first injection (83.7%) was similar to that after the second injection (88.2%). In the vaccine group, solicited systemic adverse events were reported at a higher incidence after the second injection (79.4%) than after the first injection (54.9%). The majority of solicited adverse events observed in the vaccine group were Grade 1 to Grade 2 in severity, and the severity of all those events increased after the second injection. The incidences of Grade ≥3 events observed in the vaccine group were all <1% after the first injection, except for pain (2.7%), headache (1.8%), and fatigue (1.0%). On the other hand, the incidences of Grade ≥3 events observed in the vaccine group after the second injection were all higher than those after the first injection. The events reported by ≥1% of participants after the second injection were fatigue (9.7%), myalgia (9.0%), arthralgia (5.2%), headache (4.5%), pain (4.1%), erythema/redness (2.0%), swelling/induration (1.7%), fever (1.5%), and chills (1.3%). After the first or second injection, Grade 4 solicited adverse events were reported by 19 participants in the vaccine group, which were all systemic events, including fever reported by 17 participants.

Table 26. Grade ≥3 solicited adverse events (Foreign Study 301: Solicited Safety Set [DS2])

	After Dose 1		After Dose 2		After either Dose 1 or 2	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Solicited local (injection site) adverse events						
	N = 15,164	N = 15,151	N = 14,673	N = 14,562	N = 15,179	N = 15,162
Any	529 (3.5)	78 (0.5)	1,020 (7.0)	72 (0.5)	1,418 (9.3)	145 (1.0)
Pain	416 (2.7)	55 (0.4)	604 (4.1)	40 (0.3)	922 (6.1)	92 (0.6)
Erythema/Redness	42 (0.3)[c)]	13 (<0.1)	287 (2.0)	15 (0.1)	324 (2.1)	27 (0.2)
Swelling/Induration	82 (0.5)[c)]	6 (<0.1)	254 (1.7)	11 (<0.1)	326 (2.1)	16 (0.1)
Lymphadenopathy[a)]	49 (0.3)[c)]	27 (0.2)	67 (0.5)	19 (0.1)	110 (0.7)	45 (0.3)
Solicited systemic adverse events						
	N = 15,167	N = 15,155	N = 14,677	N = 14,565	N = 15,179	N = 15,163
Any	452 (3.0)	314 (2.1)	2,339 (15.9)	285 (2.0)	2,629 (17.3)	565 (3.7)
Headache	271 (1.8)[c)]	196 (1.3)[e)]	659 (4.5)[g)]	162 (1.1)[i)]	869 (5.7)	341 (2.2)[m)]
Fatigue	151 (1.0)[c)]	105 (0.7)[e)]	1,428 (9.7)[g)]	106 (0.7)[j)]	1,529 (10.1)	200 (1.3)[m)]
Myalgia	90 (0.6)[c)]	47 (0.3)[e)]	1,318 (9.0)[g)]	52 (0.4)[j)]	1,382 (9.1)	98 (0.6)[m)]
Arthralgia	61 (0.4)[c)]	37 (0.2)[e)]	770 (5.2)[g)]	44 (0.3)[j)]	813 (5.4)	80 (0.5)[m)]
Nausea/Vomiting	10 (<0.1)[c)]	12 (<0.1)[e)]	21 (0.1)[g)]	11 (<0.1)[j)]	30 (0.2)	23 (0.2)[m)]
Chills	24 (0.2)[c)]	14 (<0.1)[e)]	191 (1.3)[g)]	17 (0.1)[j)]	211 (1.4)	31 (0.2)[m)]
Fever[b)]	15 (<0.1)[d)]	8 (<0.1)[f)]	215 (1.5)[h)]	5 (<0.1)[k)]	229 (1.5)[l)]	13 (<0.1)[m)]

N = Number of participants analyzed, n = Number of participants with event
a) Localized axillary swelling or tenderness ipsilateral to the injected arm
b) Grade 3, 39°C-40°C; Grade 4, >40°C
c) N = 15,163, d) N = 15,164, e) N = 15,150, f) N = 15,153, g) N = 14,673, h) N = 14,669, i) N = 14,562, j) N = 14,560, k) N = 14,559, l) N = 15,178, m) N=15,162

The majority of solicited local adverse events (17,711 of 18,477 cases) occurred within the first 1 to 2 days after injection and persisted for a median of 1.0 to 3.0 days, though some persisted for approximately 3 months or had an unknown outcome. The majority of solicited systemic adverse events occurred within the first 1 to 2 days after injection and persisted for a median of 1.0 to 2.0 days, though some persisted for approximately 2 months or longer or had an unknown outcome.

The incidences of unsolicited adverse events through 28 days after any study vaccine injection (excluding solicited adverse events occurring through 7 days after each dose of study vaccine) were 23.9% (3,632 of 15,185 participants) in the vaccine group and 21.6% (3,277 of 15,166 participants) in the placebo group. The events reported by ≥1% of participants in the vaccine group were headache, fatigue, arthralgia, myalgia, diarrhoea, cough, oropharyngeal pain, and injection site pain, and the proportion of participants with those events considered causally related to mRNA-1273 was approximately 50% for headache, fatigue, arthralgia, myalgia, and injection site pain, 25% for diarrhoea, and ≤10% for cough and oropharyngeal pain [see Section 7.4, Table 19]. The incidence of Grade ≥3 unsolicited adverse events was low (1.5% [234 of 15,185 of participants] in the vaccine group, 1.3% [202 of 15,166 of participants] in the placebo group), with no notable differences between the vaccine and placebo groups.

In Foreign Study 301, local reactions that began ≥7 days after each dose of study vaccine (Day 7 and Day 35) (delayed local reactions) occurred in 1.2% (189 of 15,185) of participants in the vaccine group and 0.4% (54 of 15,166) of participants in the placebo group (Table 27), and no serious cases were reported. In the vaccine group, delayed local reactions were noted in 166 participants (209 events) after the first injection and 25

participants (28 events) after the second injection, and local corticosteroids, diphenhydramine, or other medications were reported to be used to treat those reactions. Among the 166 participants with those events after the first injection, 160 (96.4%) received the second dose and 2 of them experienced the same delayed local reaction also after the second injection (pain [1 participant] and axillary pain [1 participant]), both of which were mild in severity. Severe events were reported by 10 participants (11 events) in the vaccine group. A causal relationship to mRNA-1273 could not be ruled out for those reported by 8 participants, but their outcomes were all reported as "resolved" or "improved." All of the 10 participants experienced those events after the first injection, of whom 2 did not receive the second dose.

Table 27. Delayed local reactions after study vaccination (Foreign Study 301: Safety Set [DS2])

	Vaccine N = 15,185	Placebo N = 15,166
	n (%)	n (%)
Any delayed local reaction	189 (1.2)	54 (0.4)
Pain	70 (0.5)	37 (0.2)
Erythema	92 (0.6)	13 (<0.1)
Swelling	60 (0.4)	8 (<0.1)
Lymphadenopathy[a)]	7 (<0.1)	2 (<0.1)

N = Number of participants analyzed, n = Number of participants with event

a) Localized axillary swelling or tenderness ipsilateral to the injected arm

(b) Japanese Study 1501

In Japanese Study 1501, solicited adverse events through 7 days after each dose of study vaccine are shown in Table 12 [see Section 7.1]. Solicited local and systemic adverse events were reported by the majority of participants in the vaccine group, and the incidence of each specific event was higher in the vaccine group than in the placebo group. As in Foreign Study 301, the incidences of most solicited adverse events increased after the second injection, and the severity of all events increased after the second injection. Grade ≥3 solicited adverse events are shown in Table 28. Grade ≥3 events reported by ≥5% of participants in the vaccine group after any study vaccine injection were injection site pain, headache, fatigue, myalgia, arthralgia, and fever, and the incidences of all those events increased after the second injection.

Table 28. Grade ≥3 solicited adverse events (Japanese Study 1501: Safety Set)

	After Dose 1		After Dose 2		After either Dose 1 or 2	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Solicited local (injection site) adverse events						
	N = 150	N = 50	N = 147	N = 50	N = 150	N = 50
Any	4 (2.7)	0	15 (10.2)	0	18 (12.0)	0
Pain	2 (1.3)	0	6 (4.1)	0	8 (5.3)	0
Erythema/Redness	0	0	5 (3.4)	0	5 (3.3)	0
Swelling	2 (1.3)	0	4 (2.7)	0	5 (3.3)	0
Induration	0	0	0	0	0	0
Lymphadenopathy[a)]	0	0	0	0	0	0
Solicited systemic adverse events						
	N = 150	N = 50	N = 147	N = 50	N = 150	N = 50
Any	2 (1.3)	1 (2.0)	38 (25.9)	0	39 (26.0)	1 (2.0)
Headache	0	0	10 (6.8)	0	10 (6.7)	0
Fatigue	0	0	26 (17.7)	0	26 (17.3)	0
Myalgia	1 (0.7)	0	10 (6.8)	0	11 (7.3)	0
Arthralgia	0	0	11 (7.5)	0	11 (7.3)	0
Nausea/Vomiting	0	0	0	0	0	0
Chills	0	0	7 (4.8)	0	7 (4.7)	0
Fever[b)]	1 (0.7)	1 (2.0)	8 (5.4)	0	9 (6.0)	1 (2.0)

N = Number of participants analyzed, n = Number of participants with event
a) Localized axillary swelling or tenderness ipsilateral to the injected arm
b) Grade 3, 39℃ to 40℃; Grade 4, >40℃

The majority of solicited local and systemic adverse events occurred within the first 1 to 2 days after study vaccine injection. Solicited local adverse events persisted for a median of 1.0 to 3.0 days, and solicited systemic adverse events persisted for a median of 1.0 to 2.0 days.

The incidences of unsolicited adverse events through 28 days after any study vaccine injection (excluding solicited adverse events occurring through 7 days after each dose of study vaccine) were 30.0% (45 of 150 participants) in the vaccine group and 22.0% (11 of 50 participants) in the placebo group. The events reported by ≥2 participants in the vaccine group were injection site pruritus (9 participants); nasopharyngitis (4 participants); headache (4 participants); diarrhoea (3 participants); and vertigo, dental caries, fatigue, chest discomfort, injection site warmth, injection site rash, dizziness, pollakiuria, rhinorrhoea, and oropharyngeal pain (2 participants each).

Delayed local reactions were noted in 8 participants (10 reactions) in the vaccine group, all of which occurred after the first injection, had an onset 8 to 22 days after injection, and persisted for 2 to 15 days. Among the 8 participants, 2 did not receive the second injection in the judgment of the investigator and 6 did not experience a similar event after the second injection. A causal relationship to mRNA-1273 could not be rule out for all those events, except for 1 event reported by 1 participant, but those events were all mild or moderate in severity, with an outcome of "resolved."

7.R.3.1.2 Serious adverse events

In Foreign Study 101 (data cutoff date of October 26, 2020), no deaths or serious adverse events were reported.
In Foreign Study 201 (data cutoff date of November 5, 2020), 1 participant aged ≥55 years in the mRNA-1273 vaccine 50 μg group had a serious adverse event of pneumonia (negative for SARS-CoV-2 until recovery), but its causal relationship to study vaccine was denied. The outcome of the event was reported as "resolved." There were no deaths.

In Foreign Study 301 (data snapshot date of November 25, 2020), serious adverse events occurred in 147 of 15,185 participants (1.0%) in the vaccine group and 153 of 15,166 participants (1.0%) in the placebo group. A causal relationship to study vaccine could not be ruled out for those events reported by 7 participants in the vaccine group (swelling face [2 participants]; and autonomic nervous system imbalance, dyspnoea, nausea, vomiting, rheumatoid arthritis, oedema peripheral, and B-cell small lymphocytic lymphoma [1 participant each]) and those reported by 5 participants in the placebo group (paraesthesia, pulmonary embolism, polymyalgia rheumatica, swelling face, feeling hot, immunisation anxiety related reaction, procedural haemorrhage, acute myocardial infarction, hypomagnesaemia, acute kidney injury, atrial fibrillation, organising pneumonia, and respiratory failure [1 participant each]), and their outcomes were reported as "resolved" or "improved" except for autonomic nervous system imbalance, rheumatoid arthritis, and B-cell small lymphocytic lymphoma. Through December 3, 2020, 6 deaths occurred in the vaccine group (cardio-respiratory arrest, completed suicide, head injury, myocardial infarction, multi-system organ failure syndrome, death NOS [1 participant each]) and 7 deaths in the placebo group (myocardial infarction [2 participants]; gastric perforation, cardio-respiratory arrest, COVID-19, and death NOS [1 participant each]; and 1 participant with systemic inflammatory response syndrome and dermatitis bullous). A causal relationship to study vaccine was denied for all cases.

In Japanese Study 1501, no deaths or serious adverse events were reported (data cutoff date of March 31, 2021).

7.R.3.1.3 Adverse events by age group

Solicited adverse events by age group are shown in Table 29 (Foreign Study 301) and Table 30 (Japanese Study 1501).

Table 29. Solicited adverse events through 7 days after each dose of study vaccine (Foreign Study 301: Solicited Safety Set [DS2])

	Event term	Dose number	Vaccine			Placebo		
			Overall	18-64 years	≥65 years	Overall	18-64 years	≥65 years
			Dose 1 N = 15,168	Dose 1 N = 11,406	Dose 1 N = 3,762	Dose 1 N = 15,155	Dose 1 N = 11,407	Dose 1 N = 3,748
			Dose 2 N = 14,677	Dose 2 N = 10,985	Dose 2 N = 3,692	Dose 2 N = 14,566	Dose 2 N = 10,918	Dose 2 N = 3,648
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local	Pain	Dose 1	12,690 (83.7)[b)]	9,908 (86.9)[g)]	2,782 (74.0)	2,658 (17.5)[o)]	2,177 (19.1)[u)]	481 (12.8)[x)]
		Dose 2	12,943 (88.2)[c)]	9,873 (89.9)[h)]	3,070 (83.2)[l)]	2,477 (17.0)[p)]	2,040 (18.7)[v)]	437 (12.0)
	Erythema/Redness	Dose 1	430 (2.8)[d)]	344 (3.0)[g)]	86 (2.3)[k)]	67 (0.4)[o)]	47 (0.4)[u)]	20 (0.5)[x)]
		Dose 2	1,257 (8.6)[c)]	982 (8.9)[h)]	275 (7.5)[l)]	56 (0.4)[p)]	43 (0.4)[v)]	13 (0.4)
	Swelling/Induration	Dose 1	932 (6.1)[d)]	767 (6.7)[g)]	165 (4.4)[k)]	52 (0.3)[o)]	34 (0.3)[u)]	18 (0.5)[x)]
		Dose 2	1,789 (12.2)[c)]	1,389 (12.6)[h)]	400 (10.8)[l)]	49 (0.3)[p)]	36 (0.3)[v)]	13 (0.4)
	Lymphadenopathy[a)]	Dose 1	1,553 (10.2)[d)]	1,322 (11.6)[g)]	231 (6.1)[k)]	722 (4.8)[o)]	567 (5.0)[u)]	155 (4.1)[x)]
		Dose 2	2,090 (14.2)[c)]	1,775 (16.2)[h)]	315 (8.5)[l)]	567 (3.9)[p)]	470 (4.3)[v)]	97 (2.7)
Systemic	Headache	Dose 1	4,951 (32.7)[d)]	4,030 (35.3)[g)]	921 (24.5)[k)]	4,027 (26.6)[q)]	3,304 (29.0)[u)]	723 (19.3)[y)]
		Dose 2	8,602 (58.6)[e)]	6,898 (62.8)[h)]	1,704 (46.2)[l)]	3,410 (23.4)[p)]	2,760 (25.3)[v)]	650 (17.8)
	Fatigue	Dose 1	5,635 (37.2)[d)]	4,384 (38.4)[g)]	1,251 (33.3)[k)]	4,133 (27.3)[q)]	3,282 (28.8)[u)]	851 (22.7)[y)]
		Dose 2	9,582 (65.3)[e)]	7,430 (67.6)[h)]	2,152 (58.3)[l)]	3,403 (23.4)[r)]	2,687 (24.6)[w)]	716 (19.6)
	Myalgia	Dose 1	3,441 (22.7)[d)]	2,699 (23.7)[g)]	742 (19.7)[k)]	2,071 (13.7)[q)]	1,628 (14.3)[u)]	443 (11.8)[y)]
		Dose 2	8,508 (58.0)[e)]	6,769 (61.6)[h)]	1,739 (47.1)[l)]	1,809 (12.4)[r)]	1,411 (12.9)[w)]	398 (10.9)
	Arthralgia	Dose 1	2,511 (16.6)[d)]	1,893 (16.6)[g)]	618 (16.4)[k)]	1,783 (11.8)[q)]	1,327 (11.6)[u)]	456 (12.2)[y)]
		Dose 2	6,284 (42.8)[e)]	4,993 (45.5)[h)]	1,291 (35.0)[l)]	1,569 (10.8)[r)]	1,172 (10.7)[w)]	397 (10.9)
	Nausea/Vomiting	Dose 1	1,262 (8.3)[d)]	1,068 (9.4)[g)]	194 (5.2)[k)]	1,074 (7.1)[q)]	908 (8.0)[u)]	166 (4.4)[y)]
		Dose 2	2,785 (19.0)[e)]	2,348 (21.4)[h)]	437 (11.8)[l)]	934 (6.4)[r)]	801 (7.3)[w)]	133 (3.6)
	Chills	Dose 1	1,253 (8.3)[d)]	1,051 (9.2)[g)]	202 (5.4)[k)]	878 (5.8)[q)]	730 (6.4)[u)]	148 (4.0)[y)]
		Dose 2	6,482 (44.2)[e)]	5,341 (48.6)[h)]	1,141 (30.9)[l)]	809 (5.6)[r)]	658 (6.0)[w)]	151 (4.1)
	Fever	Dose 1	115 (0.8)[b)]	105 (0.9)[j)]	10 (0.3)[m)]	44 (0.3)[s)]	37 (0.3)[u)]	7 (0.2)
		Dose 2	2,278 (15.5)[f)]	1,908 (17.4)[j)]	370 (10.0)[n)]	43 (0.3)[t)]	39 (0.4)[w)]	4 (0.1)[z)]

N = Number of participants analyzed, n = Number of participants with event

a) Localized axillary swelling or tenderness ipsilateral to the injected arm

b) N = 15,164, c) N = 14,673, d) N = 15,163, e) N = 14,673, f) N = 14,669, g) N = 11,402, h) N = 10,984, i) N = 11,404, j) N = 10,979, k) N = 3,761, l) N = 3,689, m) N = 3,760, n) N = 3,690, o) N = 15,151, p) N = 14,562, q) N = 15,150, r) N = 14,560, s) N = 15,153, t) N = 14,559, u) N = 11,405, v) N = 10,914, w) N = 10,912, x) N = 3,746, y) N = 3,745, z) N = 3,647

Table 30. Solicited adverse events through 7 days after each dose of study vaccine (Japanese Study 1501: Safety Set)

	Event term	Dose number	Vaccine			Placebo		
			Overall	20-64 years	≥65 years	Overall	20-64 years	≥65 years
			Dose 1 N = 150	Dose 1 N = 100	Dose 1 N = 50	Dose 1 N = 50	Dose 1 N = 40	Dose 1 N = 10
			Dose 2 N = 147	Dose 2 N = 98	Dose 2 N = 49	Dose 2 N = 50	Dose 2 N = 40	Dose 2 N = 10
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local	Pain	Dose 1	124 (82.7)	88 (88.0)	36 (72.0)	3 (6.0)	3 (7.5)	0
		Dose 2	125 (85.0)	81 (82.7)	44 (89.8)	1 (2.0)	0	1 (10.0)
	Erythema/Redness	Dose 1	3 (2.0)	2 (2.0)	1 (2.0)	0	0	0
		Dose 2	26 (17.7)	13 (13.3)	13 (26.5)	0	0	0
	Swelling	Dose 1	16 (10.7)	8 (8.0)	8 (16.0)	0	0	0
		Dose 2	24 (16.3)	10 (10.2)	14 (28.6)	0	0	0
	Induration	Dose 1	9 (6.0)	3 (3.0)	6 (12.0)	0	0	0
		Dose 2	19 (12.9)	7 (7.1)	12 (24.5)	0	0	0
	Lymphadenopathy[a)]	Dose 1	17 (11.3)	12 (12.0)	5 (10.0)	2 (4.0)	1 (2.5)	1 (10.0)
		Dose 2	15 (10.2)	12 (12.2)	3 (6.1)	3 (6.0)	0	3 (30.0)
Systemic	Headache	Dose 1	20 (13.3)	18 (18.0)	2 (4.0)	0	0	0
		Dose 2	70 (47.6)	53 (54.1)	17 (34.7)	5 (10.0)	5 (12.5)	0
	Fatigue	Dose 1	28 (18.7)	21 (21.0)	7 (14.0)	5 (10.0)	3 (7.5)	2 (20.0)
		Dose 2	93 (63.3)	64 (65.3)	29 (59.2)	4 (8.0)	4 (10.0)	0
	Myalgia	Dose 1	56 (37.3)	41 (41.0)	15 (30.0)	2 (4.0)	2 (5.0)	0
		Dose 2	73 (49.7)	43 (43.9)	30 (61.2)	5 (10.0)	2 (5.0)	3 (30.0)
	Arthralgia	Dose 1	12 (8.0)	9 (9.0)	3 (6.0)	0	0	0
		Dose 2	47 (32.0)	34 (34.7)	13 (26.5)	0	0	0
	Nausea/Vomiting	Dose 1	1 (0.7)	1 (1.0)	0	0	0	0
		Dose 2	6 (4.1)	3 (3.1)	3 (6.1)	0	0	0
	Chills	Dose 1	8 (5.3)	5 (5.0)	3 (6.0)	1 (2.0)	0	1 (10.0)
		Dose 2	74 (50.3)	58 (59.2)	16 (32.7)	0	0	0
	Fever	Dose 1	3 (2.0)	2 (2.0)	1 (2.0)	1 (2.0)	0	1 (10.0)
		Dose 2	59 (40.1)	42 (42.9)	17 (34.7)	0	0	0

N = Number of participants analyzed, n = Number of participants with event
a) Localized axillary swelling or tenderness ipsilateral to the injected arm

In the vaccine group of Foreign Study 301, all solicited adverse events were more common in younger participants than in older participants. In the vaccine group of Japanese Study 1501, some events were more common in older participants than in younger participants. None of Grade ≥3 solicited adverse events were reported at a markedly higher incidence in older participants in either study.

No evident differences between age groups in the trend of unsolicited adverse events that occurred through 28 days after each dose of study vaccine (excluding solicited adverse events occurring through 7 days after each dose of study vaccine) were observed in Foreign Study 301 or Japanese Study 1501.

The applicant's explanation about the safety of mRNA-1273 on the basis of the clinical study results:
In Japanese and foreign clinical studies, solicited adverse events were reported by the majority of participants, but most events were mild or moderate in severity and resolved within several days (persisted for a median of 1-3 days). The incidences of death and serious adverse events were low, and a causal relationship to mRNA-1273 was denied for most cases. The incidence of solicited adverse events tended to be higher in younger participants than in older participants, and there were no differences in the incidence of unsolicited adverse events according to age group. In vaccine recipients aged ≥18 years, no serious concerns about the safety profile of mRNA-1273 were identified, and its tolerability was demonstrated.

Delayed local reactions observed in Foreign Study 301 have been reported also by the Swiss authority (as of

February 19, 2021)[48] and a published article (*N Engl J Med*. 2021; 384: 1273-77). Some cases have been assessed as skin hypersensitivity reactions by a skin pathologist based on the image and clinical findings, suggesting that the events are unlikely to raise long-term safety concerns. At present, there is no need for including a precaution specifically about delayed local reactions in the package insert, for the following reasons: (1) delayed local reactions have yet to be classified as definitive adverse reactions to mRNA-1273; (2) most cases were mild or moderate in severity; (3) individuals with a delayed local reaction after the first dose can receive the second dose; and (4) the package insert and information materials etc. will include a precaution about local reactions following vaccination with mRNA-1273.

PMDA's view:
According to the safety information from clinical studies submitted, solicited local and systemic adverse events were reported by the majority of participants, but most of the events were mild or moderate in severity and resolved; and there were no major differences in safety profile between Japanese and non-Japanese populations. Given these findings, the incidences of other adverse events and serious adverse events, the incidences by age group, and other data, no serious concerns have been identified so far.

However, systemic reactions observed in many participants may affect daily living activities; a certain proportion of participants experienced Grade 3 solicited systemic adverse events, and some events were more common after the second injection than after the first injection. These findings are important information for vaccine recipients, and this information should be disseminated. Although delayed local reactions tended to occur more frequently after the first injection, most of the events were mild or moderate in severity, and all events, including severe ones, resolved. Based on the currently available information, the applicant's opinion (the package insert will include a precaution about local reactions following vaccination with mRNA-1273, and a precaution specifically about delayed local reactions is unnecessary) is acceptable. Note that information materials etc. should advise that individuals who experienced a delayed local reaction after the first dose of vaccination do not necessarily have to skip the second dose.

7.R.3.2 Events of special interest

7.R.3.2.1 Shock/anaphylaxis

The applicant's explanation about hypersensitivity reactions following vaccination with mRNA-1273:
In Foreign Study 201, the incidence of events coded to the MedDRA SMQ "hypersensitivity" was similar between the vaccine group (the 50 μg and 100 μg groups) (2.8% [11 of 400 participants]) and the placebo group (3.0% [6 of 200 participants]). A causal relationship to study vaccine was denied for the 11 cases in the vaccine group. Anaphylaxis was not reported in any group.

In Foreign Study 301, the incidence of events coded to the MedDRA SMQ "hypersensitivity" was similar between the vaccine group (1.5% [233 of 15,185 participants]) and the placebo group (1.1% [166 of 15,166 participants]). A causal relationship between study vaccine and some cases could not be ruled out (98 cases in

[48] https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/sicherheit-covid-19-impfstoffe-verzoegert-lokalreaktionen.html (last accessed on April 23, 2021)

the vaccine group and 19 cases in the placebo group). The majority of the events observed in the vaccine group were Grade 1 or 2 in severity. A Grade 4 event was rash vesicular (1 participant), and Grade 3 events were rash (3 participants), Type IV hypersensitivity reaction (1 participant), swelling face (1 participant), rash macular (1 participant) injection site rash (1 participant), and dermatitis (1 participant). A causal relationship between mRNA-1273 and the following events could not be ruled out: rash, Type IV hypersensitivity reaction, swelling face, rash macular, injection site rash, and dermatitis (1 participant each), but their outcomes were all reported as "resolved" or "improved." Anaphylaxis was reported by 1 participant in the vaccine group (with onset 63 days after study vaccination, Grade 2) and 1 participant in the placebo group (with onset 11 days after study vaccination, Grade 3). A causal relationship to study vaccine was denied for both events, and both events had an outcome of "resolved."

Foreign Study 301 included 83 participants in the vaccine group and 85 participants in the placebo group who had a history of the MedDRA SMQ "hypersensitivity" (including 0 participants in the vaccine group and 4 participants in the placebo group who had a history of the MedDRA SMQ "anaphylaxis"). No allergy-related events (the MedDRA SMQ "hypersensitivity") which were considered related to study vaccine were reported by these participants.

In Japanese Study 1501 (data cutoff date of March 31, 2021), the incidence of events coded to the MedDRA SMQ "hypersensitivity" was 3.3% (5 of 150 participants) in the vaccine group, and no events were reported in the placebo group. A causal relationship to study vaccine could not be ruled out for injection site rash reported by 2 participants (both moderate in severity) in the vaccine group, and both events had an outcome of "resolved." A causal relationship to study vaccine was denied for allergic conjunctivitis, contact dermatitis, and eczema (1 participant each, all mild in severity), and all those events had an outcome of "resolved." No anaphylaxis was reported.

According to foreign post-authorization or post-marketing spontaneous reports, 10 cases of anaphylaxis were reported after administration of a reported 4,041,396 first doses of COVID-19 Vaccine Moderna (between December 21, 2020 and January 10, 2021), and the incidence rate was 2.5 cases per million doses administered (*MMWR*. 2021; 70: 125-9). The latest safety report (as of April 15, 2021) was used to investigate spontaneous reports received between December 18, 2020 and March 31, 2021. Cases identified by the MedDRA SMQ "anaphylactic reaction" were classified using the Brighton Collaboration Anaphylaxis Case Definition (*Vaccine*. 2007; 25: 5675-84). There were 244 cases with a definitive diagnosis of anaphylaxis meeting the Brighton criteria for levels 1 to 3 (level 1, 99 cases; level 2, 120 cases; level 3, 25 cases). The majority of these cases occurred in women (79.5%). The interval from vaccine receipt to symptom onset is shown in Table 31. Symptom onset occurred on or later than the day after vaccination in some cases.

Table 31. Interval from vaccine receipt to onset of anaphylaxis
(Foreign post-authorization or post-marketing spontaneous reports, December 18, 2020 to March 31, 2021)

Brighton classification	≤15 minutes after vaccination	15-60 minutes after vaccination	1-4 hours after vaccination	Day of vaccination	Day after vaccination	Later than day after vaccination	Unknown
Overall (244 cases)	46	18	15	90	34	30	11
Level 1 (99 cases)	9	5	4	37	20	17	7
Level 2 (120 cases)	27	11	10	45	14	10	3
Level 3 (25 cases)	10	2	1	8	0	3	1

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Using the 244 cases spontaneously reported during this period, the reporting rate of anaphylaxis was determined based on the 0- to 2-day risk window. The reporting rate with COVID-19 Vaccine Moderna was calculated to be 37.85 cases/100,000 person-years, which was higher than the background incidence rate of anaphylaxis in European countries (a maximum of 24.43 cases/100,000 person-years)[49)] provided by ACCESS (vACcine Covid-19 monitoring readinESS).

In Japanese or foreign clinical studies, shock or anaphylaxis which were considered related to mRNA-1273 was not reported. Meanwhile, according to foreign post-authorization or post-marketing safety information, serious anaphylaxis and anaphylactic shock have been reported. Since these are potentially life-threatening and need medical interventions, shock and anaphylaxis will be classified as important identified risks, monitoring for the occurrence of these events will be continued also after marketing, and the package insert will provide a relevant precaution.

PMDA accepted the applicant's explanation and considers as follows:
The package insert should include a precaution about shock and anaphylaxis, and healthcare professionals should be advised to check the vaccine recipient's medical history and relevant information before vaccination, to monitor the vaccine recipient for a certain period of time after vaccination, and to take appropriate medical care promptly if any abnormality is observed. Since a certain number of cases with symptom onset occurring ≥1 hour after vaccination or on or later than the day after vaccination have also been reported, vaccine recipients should be advised to watch out for any change in their health on their way home or at home and seek medical attention promptly if any abnormality is observed.

7.R.3.2.2 Facial paralysis (Bell's palsy)

The applicant's explanation about facial paralysis (Bell's palsy):
In Foreign Study 301, facial paralysis occurred in 0.02% (3 of 15,184) of participants in the vaccine group and 0.007% (1 of 15,165) of participants in the placebo group (a median follow-up of 9 weeks). Among the 3 participants with the event in the vaccine group, one had Grade 4 event, and the other two had Grade 2 event. Their outcomes were reported as "resolved" or "improved," but one Grade 2 event unresolved. A causal relationship to study vaccine was denied for all those events.

49) http://www.encepp.eu/documents/DraftReport.pdf (last accessed on April 25, 2021)

No facial paralysis was reported in Foreign Study 101 (the results of analysis up to Day 119), Foreign Study 201 (the results of analysis up to Day 57), or Japanese Study 1501 (as of March 31, 2021).

According to foreign post-authorization or post-marketing spontaneous reports (between December 18, 2020 and March 31, 2021), 249 cases of facial paralysis were reported, which included 246 serious cases.

The incidence rate of Bell's palsy in the general population was determined based on the published literature. Even the conservative estimate of the incidence rate was 11.5 cases per 100,000 person-years (*J Neurol*. 2020; 267: 1896-905, *Eur J Neurol*. 2002; 9: 63-7, etc.). The incidence rate of facial paralysis in clinical studies of mRNA-1273 and foreign post-authorization or post-marketing experience (5.52 cases per 100,000 person-years) is lower than that estimate, and no particular signals for facial paralysis have been detected. According to risk assessment for COVID-19 vaccines using Vaccine Safety Datalink (VSD) in the US (as of February 13, 2021, assessment of COVID-19 Vaccine Moderna and COMIRNATY intramuscular injection), no increased risk was detected for Bell's palsy (https://www.fda.gov/media/146269/download [last accessed on April 23, 2021]).

Study participants and vaccine recipients are closely monitored for facial paralysis as an adverse event of special interest in clinical studies and post-marketing surveillance, and the package insert needs to include a relevant precaution. The applicant will continue to collect data on the risk of facial paralysis associated with COVID-19 Vaccine Moderna, and will consider the need for an additional precaution if new information becomes available.

PMDA accepted the applicant's explanation.

7.R.3.3 Safety in special populations

7.R.3.3.1 Individuals with underlying medical conditions

The applicant's explanation about safety in individuals with underlying medical conditions:
Foreign Study 301 enrolled not only healthy subjects but also individuals with underlying medical conditions at increased risk of severe COVID-19 for whom SARS-CoV-2 vaccination is highly recommended.

The data from Foreign Study 301 were used to retrospectively evaluate participants with underlying medical conditions at study participation and participants with obesity, a risk factor for severe COVID-19 (BMI ≥40 kg/m^2). Participants with underlying medical conditions evaluated (6,817 participants, including 1,244 participants with more than 1 comorbidity) included 1,454 participants with chronic lung disease, 1,496 participants with cardiac disease, 2,046 participants with severe obesity, 2,875 participants with diabetes, 196 participants with liver disease, and 179 participants with HIV infection. Some of the medical conditions were

consistent with underlying diseases or state[50)] that are listed as risk factors for severe COVID-19 in Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers (Version 4.1).[40)]

Among these subgroups, the incidences of unsolicited adverse events and adverse reactions (adverse events for which a causal relationship to study vaccine could not be ruled out) were 26.1% (888 of 3,399 participants) and 8.3% (283 of 3,399 participants), respectively, in the vaccine group and 23.6% (806 of 3,418 participants) and 4.8% (163 of 3,418 participants), respectively, in the placebo group. The incidences of serious adverse events and serious adverse reactions were 1.0% (34 of 3,399 participants) and 0.1% (2 of 3,399 participants), respectively, in the vaccine group and 1.3% (43 of 3,418 participants) and 0.1% (2 of 3,418 participants), respectively, in the placebo group. Although the incidences of unsolicited adverse events and adverse reactions tended to be slightly higher in the vaccine group than in the placebo group, the incidence of serious adverse events was comparable for the vaccine and placebo groups. These results were similar to the results of the overall population of Foreign Study 301 [see Section 7.R.3.1.2]. Based on the above findings, there are no safety concerns about the use of mRNA-1273 in individuals with underlying medical conditions who are at risk for severe COVID-19. Meanwhile, participants with underlying medical conditions who were in stable condition were enrolled in Foreign Study 301, and information on individuals with severe and unstable underlying medical conditions is limited. Thus, the applicant will collect post-marketing information on the safety of COVID-19 Vaccine Moderna in individuals with underlying medical conditions who are at increased risk for severe COVID-19.

PMDA accepted the applicant's explanation. It is envisaged that individuals with underlying medical conditions who are in various state will receive the vaccine in the post-marketing setting. The applicant should collect information on the safety of COVID-19 Vaccine Moderna in people with underlying medical conditions at increased risk for severe COVID-19, make a decision to provide an additional precaution or information, based on the obtained information, and take other appropriate measures.

7.R.3.3.2 Pregnant and breastfeeding women

The applicant's explanation about safety in pregnant and breastfeeding women:
Pregnant women were excluded from clinical studies of mRNA-1273. In Foreign Study 301, female participants were required to have a negative pregnancy test at screening and to continue adequate contraception through 3 months following the second dose of study vaccine. In Foreign Study 301, 13 pregnancies were reported in participants who received at least 1 dose of study vaccine (6 in the vaccine group, 7 in the placebo group), of which 10 pregnancies were progressing without complications as of December 2, 2020, and the remaining 3 pregnancies (spontaneous abortion, elective abortion, and lost to follow up [1 participant each]) were in the placebo group.

[50)] The following risk factors for severe COVID-19 are listed: the elderly ≥65 years of age, malignancies, chronic obstructive pulmonary disease, chronic renal disease, type 2 diabetes mellitus, hypertension, obesity (BMI ≥30 kg/m^2), smoking, and immunodeficiency after solid organ transplantation.

According to foreign post-authorization or post-marketing spontaneous reports (submitted between December 18, 2020 and March 31, 2021), there were 1,334 reports of pregnancy and accompanying pregnancy outcomes in 1,255 recipients. The events with ≥50 reports were exposure during pregnancy (1,071 cases), pregnancy (99 cases), and maternal exposure during pregnancy (71 cases). There were 69 serious events, and the most common event was spontaneous abortion (23 cases), which occurred in the first trimester except for 2 cases. Although some events reported were not observed in clinical studies, the reports of pregnancy and pregnancy outcomes currently show no evidence suggesting the relationship between pregnancy-related events or abortion after vaccination and COVID-19 Vaccine Moderna.

There were 161 reports of breastfeeding in 152 vaccine recipients.

Although there is no clear relationship between pregnancy and severe COVID-19 or no clear basis showing that SARS-CoV-2 infection affects pregnancy outcomes and fetuses, some studies suggest that pregnant women may be at increased risk for severe COVID-19, premature delivery, or other severe outcomes (*MMWR*. 2020: 69; 1635-40, *MMWR*. 2020: 69; 1641-7). Safety information from pregnant vaccine recipients is limited, but a reproductive and developmental toxicity study raised no particular concerns [see Section 5.5]. Thus, pregnant women may receive COVID-19 Vaccine Moderna if the benefits of vaccination are considered to outweigh its risks. The package insert will advise that pregnant women or women who may be pregnant should be vaccinated if the benefits of vaccination are considered to outweigh its risks. There is limited clinical experience with the use of COVID-19 Vaccine Moderna in breastfeeding women, and milk excretion of COVID-19 Vaccine Moderna and antibodies induced by the vaccine is unknown. The package insert will also advise that breastfeeding women should decide to continue or discontinue breastfeeding, taking account of the benefits of vaccination and the benefits of breastfeeding nutrition.

Although no clinical studies of the mRNA-1273 vaccine in pregnant women have been planned, a foreign clinical study is following outcomes for all pregnancies reported after vaccination. The applicant will evaluate data from vaccinated pregnant and breastfeeding women. A foreign observational pregnancy outcome study in females exposed to COVID-19 Vaccine Moderna during pregnancy to evaluate outcomes of pregnancies and infant outcomes up to 12 months of infant age has been planned. In Japan, the safety of COVID-19 Vaccine Moderna in pregnant and breastfeeding women will be listed as important missing information. Information collected as spontaneous reports etc. through routine pharmacovigilance practices will be evaluated to identify the occurrence of adverse reactions including pregnancy outcomes. Information regarding pregnant and breastfeeding women will be collected also via general use-results survey and specified use-results survey of COVID-19 Vaccine Moderna.

PMDA accepted the applicant's explanation. The US Centers for Disease Control and Prevention (CDC) used the data from multiple adverse reaction reporting systems such as the Vaccine Adverse Event Reporting System (VAERS) to evaluate the safety of mRNA SARS-CoV-2 vaccines (COVID-19 Vaccine Moderna or Comirnaty intramuscular injection) in pregnant persons. The CDC published an article on findings from the research and

concluded as follows: “The findings did not show obvious safety signals. However, more longitudinal follow-up is necessary” (*N Engl J Med.* 2021; doi: 10.1056/NEJMoa2104983). Taking also account of the above, the applicant should determine the need for an additional precaution or take other appropriate measures if a new finding becomes available from post-marketing information.

7.R.3.4 Disease enhancement risk for COVID-19 Vaccine Moderna

The applicant’s explanation about the disease enhancement risk for COVID-19 Vaccine Moderna:
The potential risk of SARS-CoV-2 vaccine-associated disease enhancement is unknown at present. The risk of vaccine-associated disease enhancement in animal studies has been reported with SARS-CoV, which is similar to SARS-CoV-2, and the induction of a Th2-type immune response is potentially linked to it (*PLoS ONE*. 2012; 7: e35421). If SARS-CoV-2 vaccines induce Th1 predominant responses, the risk of disease enhancement upon infection with SARS-CoV-2 will be reduced (*Vaccine.* 2020; 38: 4783-91).

At present, the risk of mRNA-1273-associated enhanced disease should be low for the following reasons.

- In non-clinical pharmacology studies, mRNA-1273 induced a Th1-directed response in mice and hamsters. In virus challenge studies, mRNA-1273 did not promote vaccine-associated enhancement of disease in mice, hamsters, and NHPs as demonstrated by the absence of increased lung pathology and controlled viral replication after viral challenge [see Section 3.R.2].
- In Foreign Study 101, peripheral blood mononuclear cells obtained from participants in the mRNA-1273 group were stimulated with the antigen to measure CD4+ and CD8+ T-cell responses by intracellular cytokine straining. mRNA-1273 elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines.
- In Foreign Study 301, 30 cases of confirmed severe COVID-19 reported by the data cutoff date for DS2 were all in the placebo group [see Section 7.R.2.3]. In the vaccine group, only 1 participant had severe COVID-19, which was reported after the data cutoff date for DS2, and no signs of disease enhancement were observed. A long-term follow-up is required to assess the risk of disease enhancement. As the currently available information from clinical studies is based on the data through 2 months after vaccination with mRNA-1273, information collection will be continued.

According to the foreign post-authorization or post-marketing experience (between December 18, 2020 and March 31, 2021), 1,659 COVID-19 cases were reported during the period covered. Based on the Guidance: a Brighton Collaboration Case Definition of the term “Vaccine Associated Enhanced Disease” (*Vaccine*. 2021; S0264-410X(21)00094-3. doi:10.1016/j.vaccine.2021.01.055.), the day of onset of COVID-19 and adverse events consistent with clinical symptoms of interest in the Guidance were evaluated for 1,018 cases with information regarding the time to onset of COVID-19 after vaccination. No cases of vaccine-associated enhanced disease were identified. At present, no particular signals for disease enhancement-related events have been detected.

Based on the above facts, vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease will be categorized as an important potential risk, and information will be collected via Japanese and foreign post-marketing clinical studies and post-marketing surveillance.

PMDA accepted the applicant's explanation. The applicant should collect post-marketing information on the disease enhancement risk for COVID-19 Vaccine Moderna in humans, including information from abroad, and should provide new information promptly if it becomes available.

7.R.3.5 Foreign post-authorization or post-marketing safety information

The applicant's explanation about foreign post-authorization or post-marketing safety information:
As of March 31, 2021, COVID-19 Vaccine Moderna has been granted a conditional marketing authorization or an Emergency Use Authorization in 10 countries or regions, and supplied to 35 countries. Approximately 124,025,500 doses have been shipped, and an estimated 78,494,588 doses have been administered. Approximately 89% of the total shipment has been delivered to the US.

Between December 18, 2020 (the date of EUA in the US) and March 31, 2021, there were 217,685 spontaneous reports from 61,121 vaccine recipients. The main reports are summarized below.

There were 1,137 deaths and 2,482 adverse events with a fatal outcome (including 1,065 medically confirmed events) reported. The terms for the adverse events with a fatal outcome included death (702 events), dyspnoea (83 events), cardiac arrest (78 events), unresponsive to stimuli (75 events), and COVID-19 (50 events). Among the cases of death, 911 were individuals aged 65 years or older (including 679 individuals aged ≥75 years). Among the cases of death, 681 had at least 1 underlying medical condition as a risk factor for death. The common underlying medical conditions included cardiovascular disease (359 recipients), hypertension (340 recipients), diabetes and its associated diseases (214 recipients), chronic renal disease (125 recipients), arrhythmia (124 recipients), and neurological disorder (124 recipients), and 425 recipients were ≥75 years of age.

Among the cases of death, 1,057 (93.0%) were reported from the US, and the adverse events with a fatal outcome showed a similar distribution to the events generally reported as the most common causes of death in the US.[51)] The demographic characteristics (age, sex, underlying medical conditions, etc.) of the deaths were consistent with the main distribution of Moderna vaccine recipients in the US and were also consistent with the baseline population at increased risk of death. The predicted death rates for Moderna vaccine recipients, calculated using the age distribution of people with at least 1 dose administered in the US (as of March 8, 2021),[52)] for all age groups, were lower than the age-specific death rates in the US.[53)] Based on the above

51) Age-adjusted death rates for the 10 leading causes of death in the US in 2019 (deaths per 100,000 US standard population): heart disease, 161.5; cancer, 146.2; unintentional injuries, 49.3; chronic lower respiratory disease, 38.2; stroke, 37.0; Alzheimer disease, 29.8; diabetes, 21.6; kidney disease, 12.7; influenza and pneumonia, 12.3; suicide, 13.9 (https://www.cdc.gov/nchs/products/databriefs/db395.htm [last accessed on April 25, 2021])
52) https://covid.cdc.gov/covid-data-tracker/#vaccination-demoqraphic (last accessed on April 25, 2021)
53) https://www.cdc.gov/nchs/products/databriefs/db395.htm (last accessed on April 25, 2021)

findings, there is no sufficient evidence suggesting a potential causal relationship between COVID-19 Vaccine Moderna and death.

Adverse events of special interest (shock/anaphylaxis and facial paralysis [Bell's palsy]) are described in Section 7.R.3.2.

Thirty events of immune thrombocytopenia were reported by 30 recipients, all of which were serious events. Ninety-five cases of thrombocytopenia (including immune thrombocytopenia)[54)] were reported, and 0.66 per 100,000 person-years calculated from this number of events reported is less than the lowest reporting rate of 20.24 per 100,000 person-years in the 2019 UK Clinical Practice Research Datalink (CPRD) obtained from ACCESS. Thus, COVID-19 Vaccine Moderna is not associated with the risk of thrombocytopenia at present.

There were 605 events of thromboembolism in 505 recipients (through March 22, 2021). The events with ≥10 reports (MedDRA preferred terms) were cerebrovascular accident (138 events), pulmonary embolism (79 events), myocardial infarction (52 events), thrombosis (49 events), hemiparesis (46 events), deep vein thrombosis (35 events), acute myocardial infarction (27 events), transient ischaemic attack (22 events), hemiplegia (19 events), monoplegia (17 events), and ischaemic stroke (10 events). The events occurred during the period from the day of the first vaccination through 39 days after the second vaccination, and there was no clear trend in the time to onset.

Among frail individuals, 22,281 adverse events were reported by 5,207 recipients, of which 7,979 events in 2,415 recipients were serious. The main events included headache (851 events), pyrexia (837 events), fatigue (708 events), and chills (637 events). There were 573 deaths of frail individuals, of whom 354 were aged ≥75 years, and 562 had underlying medical conditions as a risk factor for death. Most of the reported adverse events were consistent with solicited adverse events reported in clinical studies of mRNA-1273 or symptoms commonly observed in frail or elderly individuals (asthenia, cough, fall, etc.). An increased risk of death is associated with underlying medical conditions, and there is no particular risk associated with vaccination of frail individuals at present.

Reports on pregnant and breastfeeding women are described in Section 7.R.3.3.2.

The foreign post-authorization or post-marketing safety information obtained to date indicates that the benefit-risk balance of COVID-19 Vaccine Moderna is favorable.

PMDA reviewed the foreign post-authorization or post-marketing safety information and accepted the applicant's explanation. Events of special interest, and safety in pregnant and breastfeeding women are described in Sections 7.R.3.2 and 7.R.3.3.2, respectively.

54) Including haematopoietic thrombocytopenia (SMQ) (SMQ level 2-broad, excluding PT thrombocytopenia neonatal), immune thrombocytopenia (PT), HELLP syndrome (PT), thrombotic thrombocytopenic purpura (PT), and thrombocytopenic purpura (PT).

7.R.4 Clinical positioning

PMDA's view on the clinical positioning of COVID-19 Vaccine Moderna:

As of April 26, 2021, a total of 564,211 people in Japan have been infected with SARS-CoV-2 (those testing positive by PCR). Of them, 898 had severe COVID-19 and 9,969 died.[55] Because of the inability to identify all asymptomatic patients, the total number of both symptomatic and asymptomatic patients is presumed to be much greater than the above figure. People in their 20s make up the largest age group, followed by 30s, 40s, and 50s, whereas death and severe COVID-19 occurred predominantly in those aged ≥60 years.[56]

The incubation period from the exposure to SARS-CoV-2 to symptom onset is 1 through 14 days, usually around 5 days.[57] People infected with SARS-CoV-2 become infectious before symptom onset and especially highly infectious early after the onset before diagnosis. This is considered to be the cause of community transmission (Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers [Version 4.1][40]).

In Japan, an antiviral agent, remdesivir or Veklury for Intravenous Injection 100 mg (Solution)/Veklury for Intravenous Injection 100 mg (Lyophilized powder) was approved for the treatment of disease caused by SARS-CoV-2 infection (COVID-19) on May 7, 2020, and baricitinib or Olumiant tablets 2 mg/4 mg was approved for use in combination with remdesivir for the treatment of "pneumonia caused by SARS-CoV-2 infection (COVID-19) (limited to patients requiring supplemental oxygen)" on April 23, 2021. Dexamethasone can be used within the approved indications. Other various drugs are also used in clinical practice, depending on the severity and symptoms of the disease (Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers [Version 4.1][40]). However, despite treatment with these drugs, the numbers of infected people, patients with severe COVID-19, and fatal cases keep rising in Japan as of April 2021, putting the nation's medical system under severe strain in some areas. Furthermore, it has been reported that some patients who recovered from COVID-19 have prolonged symptoms such as dysosmia, dysgeusia, dyspnoea, and hair loss even after viral clearance, though the cause is unclear (*Open Forum Infect Dis*. 2020; 7: ofaa507). The prevention of COVID-19 through vaccination is extremely important because (1) COVID-19 may result in severe illness or death and (2) prolonged sequelae has been reported even in non-severe COVID-19 cases.

According to "COVID-19 Vaccination (dated February 9, 2021, Cabinet Secretariat/MHLW),"[58] the objective of vaccination is "to prevent COVID-19 and reduce the number of deaths and severe cases as far as possible and thereby to prevent the prevalence of COVID-19." Although Comirnaty Intramuscular Injection (Pfizer Japan Inc.) was approved as a vaccine for the prevention of COVID-19 on February 14, 2021, rapid supply of multiple types of vaccines is needed in Japan due to the prevalence of SARS-CoV-2 infection, the persistent and rapid spread of the infection, the tremendous impact of the pandemic on the healthcare system and society and economy, and the issue of supply associated with worldwide vaccination.

55) https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html#h2_1 (last accessed on April 26, 2021)
56) https://www.mhlw.go.jp/content/10906000/000759133.pdf (last accessed on April 23, 2021)
57) https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations (last accessed on April 23, 2021)
58) https://www.cas.go.jp/jp/seisaku/ful/bunkakai/wakuchin_sesyu.pdf (last accessed on April 23, 2021)

The results of Foreign Study 301 demonstrated the efficacy of mRNA-1273 to prevent COVID-19, and increases in S protein-specific binding and neutralizing antibody titers were seen in Japanese Study 1501 as in Foreign Study 201. These results are expected to demonstrate similar vaccine efficacy to prevent COVID-19 in the Japanese population [see Section 7.R.2]. Further, there are no safety or tolerability problems that might affect the approval of mRNA-1273 [see Section 7.R.3]. Despite the fact that the long-term efficacy and safety of mRNA-1273 is unknown [see Sections 7.R.2 and 7.R.3] and that it is necessary to continue to investigate the efficacy of mRNA-1273 against SARS-CoV-2 variants and collect information thereon [see Section 7.R.2.4], vaccination with mRNA-1273 is expected to prevent COVID-19 and reduce the number of patients with COVID-19 in Japan. mRNA-1273 also prevent severe COVID-19, suggesting the possibility that the number of severe COVID-19 cases will be reduced. At present, only one COVID-19 vaccine has been approved. It is important to make more SARS-CoV-2 vaccines available in a swift manner during the epidemic of COVID-19, and offering COVID-19 Vaccine Moderna to medical practice in order to contribute to a stable supply of vaccines has its high significance.

7.R.5 Indication

PMDA's view on the indication of COVID-19 Vaccine Moderna:

The results of Foreign Study 301 demonstrated the efficacy of mRNA-1273 to prevent COVID-19, and increases in S protein-specific binding and neutralizing antibody titers were seen in Japanese Study 1501 as in Foreign Study 201 These results are expected to demonstrate similar efficacy against COVID-19 in the Japanese population [see Section 7.R.2]. In accordance with the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" and given the indications of the currently approved SARS-CoV-2 vaccine and other vaccines for the prevention of infections, the proposed indication of "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" is appropriate.

7.R.6 Dosage and administration

7.R.6.1 Dosing rationale

The applicant's justification for the proposed vaccine dose and schedule, "2 intramuscular injections of 100 μg, 28 days apart":

In Foreign Study 101, participants aged 18 to 55 years received 2 injections of mRNA-1273, 28 days apart, at a dose of 25 μg, 100 μg, or 250 μg. The interim data comparing the 3 dose groups showed a dose response for immunogenicity, and furthermore, the following safety and immunogenicity results were obtained.

- Two injections of 100 μg stimulated S protein-specific binding antibody titers greater than 2 injections of 25 μg at 28 days after the second dose (Table 32).

Table 32. S protein-specific binding antibody titers (Foreign Study 101: mITT Set [18-55 years of age])

Dose (mRNA-1273)	N	GMT [Two-sided 95% CI]				
		Before Dose 1	28 days after Dose 1	7 days after Dose 2	14 days after Dose 2	28 days after Dose 2
25 μg	15	116 [72, 187]	40,227 [29,094, 55,621]	391,018 [267,402, 571,780][a)]	379,764 [281,597, 512,152][a)]	299,751 [206,070, 436,020][a)]
100 μg	15	131 [65, 266]	109,209 [79,051, 150,874]	781,399 [606,247, 1,007,156]	811,119 [656,336, 1,002,404][b)]	782,719 [619,310, 989,244][b)]
250 μg	15	178 [81, 392]	213,526 [128,832, 353,896][b)]	1,261,975 [973,972, 1,635,140][b)]	994,629 [806,189, 1,227,115][b)]	1,255,376 [969,516, 1,625,521][b)]

N = Number of participants analyzed; NE, Not evaluable
a) 13 participants with results available, b) 14 participants with results available

- Two injections of 100 μg induced neutralizing antibody responses similar to those measured in recipients of 2 injections of 250 μg [see Section 7.R.2.1, Table 20].
- Safety data showed that 2 injections of 100 μg led to a lower incidence of solicited adverse events than 2 injections of 250 μg [see Section 7.2, Table 13].

Based on the above findings, Foreign Study 301 was conducted using the dosing regimen of 2 doses, 100 μg each, administered intramuscularly 28 days apart (the acceptable window, −3 to +7 days). The study demonstrated the efficacy of mRNA-1273 [see Section 7.R.2] and its acceptable safety and tolerability [see Section 7.R.3]. Foreign Study 201 was initiated as a dose-confirmation study, at the same time as Foreign Study 301. This study showed increases in S protein-specific binding and neutralizing antibody titers in the 100 μg group [see Section 7.R.2.2, Table 23] and raised no safety concerns [see Section 7.3], which supported dose selection for Foreign Study 301.

Japanese Study 1501 was also conducted using the same dosing regimen as that used in Foreign Study 301. The immunogenicity results indicate that the efficacy of mRNA-1273 to prevent COVID-19 is promising also in the Japanese population [see Section 7.R.2.2], and there were no safety or tolerability concerns unique to the Japanese population [see Section 7.R.3].

In Foreign Study 301, 2 doses were separated by 28 days (the second dose on Day 29), and the acceptable window was −3 to +7 days (Day 26 to Day 36). Initially, the dosing window allowed for inclusion in the PP Set was also the same. But in order to include more participants in the analyses, the dosing window allowed for inclusion in the PP Set was changed to −7 to +14 days (Day 22 to Day 43) prior to unblinding for the interim analysis, and efficacy analyses were performed. Among participants who received the second dose, 94.9% (27,832 of 29,328 participants) received their second dose within the window of −3 to +7 days and 99.2% (29,105 of 29,328 participants) received their second dose within the window of −7 to +14 days. Among participants who received their second dose at an interval of ≥43 days (out of window [+14 days]) not included in the PP Set, no COVID-19 cases confirmed by the Adjudication Committee were reported in the vaccine or placebo group. In contrast, a secondary endpoint of symptomatic COVID-19 reported based on clinical symptoms[59)] and a positive RT-PCR result (not adjudicated by the Adjudication Committee) occurred in 0 of 101 participants in the vaccine group and 2 of 122 participants in the placebo group, with VE of 100%. Among

59) At least 1 of the following: fever (≥38˚C), chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, sore throat, new loss of taste or smell, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea

participants who received their second dose at an interval of ≥36 days (out of window [+7 days]), confirmed COVID-19 occurred in 0 of 262 participants in the vaccine group and 2 of 277 participants in the placebo group, with VE of 100%. Although interpretation of the results has limitations due to a small number of events, longer interval between doses did not result in decreased VE. There are currently no data showing decreased efficacy of mRNA-1273 in participants who received their second dose at an interval of ≥36 or ≥43 days.

The applicant considers that the dosing regimen of COVID-19 Vaccine Moderna can be selected based on the results of the above clinical studies.

7.R.6.2 Age limit for vaccination

The applicant's explanation about the age limit for vaccination with COVID-19 Vaccine Moderna:
Japanese Study 1501 enrolled adults aged ≥20 years and evaluated the safety, tolerability, and immunogenicity of mRNA-1273 in Japanese participants. On the other hand, Foreign Study 301 demonstrated the efficacy and safety of mRNA-1273 in adults aged ≥18 years, and evaluation by age group raised no clinical concerns [see Sections 7.R.2.2 and 7.R.3.1.3]. Thus, COVID-19 Vaccine Moderna may be indicated for individuals aged ≥18 years in Japan, as well. For the clinical development of the vaccine for individuals aged <18 years, a study in adolescents aged 12 to 17 years and a study in children aged 6 months to 11 years are ongoing overseas.

Based on the above Sections 7.R.6.1 and 7.R.6.2, the following dosage and administration statement was proposed: "For individuals 18 years of age and older, COVID-19 Vaccine Moderna is administered intramuscularly as a series of 2 doses (0.5 mL each) at an interval of 4 weeks."

PMDA's view on dosage and administration:
Based on the results of evaluation of the efficacy [see Section 7.R.2] and safety [see Section 7.R.3] of mRNA-1273, the proposed dosing regimen of mRNA-1273 administered intramuscularly in two 100 μg (0.5 mL) doses given 4 weeks apart is acceptable. Japanese Study 1501 enrolled adults aged ≥20 years, and there are no data from Japanese participants aged 18 to 19 years. However, the vaccine may be indicated for individuals aged ≥18 years, given the applicant's explanation in Section 7.R.6.2 and the current epidemic of SARS-CoV-2 in Japan, and taking account that (1) Japanese Study 1501 demonstrated the immunogenicity of mRNA-1273 in Japanese participants and (2) no major differences were observed in safety profile between Japanese and non-Japanese populations.

In all clinical studies of mRNA-1273, mRNA-1273 was administered as 2 doses, 28 days apart, and the efficacy of 1 dose only of mRNA-1273 was not evaluated. Approximately 95% of participants received their second dose at an interval of ≤35 days, though the efficacy analysis population included participants who received their second dose at an interval of ≤42 days. The efficacy of mRNA-1273 when administered at an interval of ≥36 days or ≥43 days has not been well established. Thus, mRNA-1273 should be administered as a series of 2 doses, 4 weeks apart, based on the schedule used in clinical studies.

Based on the above considerations and the dosage and administration statements for the currently approved SARS-CoV-2 vaccine and other vaccines for the prevention of infections, the dosage and administration statement in the package insert should be modified as follows.

- **Dosage and Administration**
  COVID-19 Vaccine Moderna is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.
- **Precautions Concerning Dosage and Administration**
  COVID-19 Vaccine Moderna is approved for use in individuals 18 years of age and older.

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing surveillance for COVID-19 Vaccine Moderna:
Only limited information on the safety of mRNA-1273 in the Japanese population including long-term data is obtained by the time of marketing approval [see Section 7.R.3]. There is also a theoretical risk of enhanced disease upon infection with SARS-CoV-2 after vaccination with mRNA-1273 [see Section 3.R.2]. Therefore, the applicant plans to conduct a general use-results survey to assess the safety of COVID-19 Vaccine Moderna through 12 months after the last vaccination. This survey is planned as a follow-up of the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan (Research on Emerging and Re-emerging Infectious Diseases and Immunization funded by 2020 Health, Labour and Welfare Policy Research Grant). For persons with underlying medical conditions at increased risk of severe COVID-19 [see Section 7.R.3.3.1], a specified use-results survey to assess the safety of COVID-19 Vaccine Moderna through 1 month after the last vaccination is planned separately.

In addition to these surveys, Japanese Study 1501 will be reclassified as a post-marketing clinical study after the approval of COVID-19 Vaccine Moderna, and foreign clinical studies are ongoing. The information from these surveys, studies, etc., will be used to assess the safety and other aspects of COVID-19 Vaccine Moderna.

In order to promote the proper use of COVID-19 Vaccine Moderna and ensure its safety, the applicant will take the following actions as additional risk minimization activities: To develop and distribute information materials to healthcare professionals and vaccine recipients, and to periodically prepare a tabular listing of adverse reactions to COVID-19 Vaccine Moderna and provide the latest safety information to healthcare professionals.

PMDA's view:
The applicant's proposal about the plan for post-marketing surveillance and other activities is acceptable. However, the population for a general use-results survey depends on the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan and may be subject to change according to the progress of vaccination with the currently approved SARS-CoV-2 vaccine. Thus, the post-marketing surveillance plan needs to be reviewed depending on the situation. The applicant should also continuously assess the safety of COVID-19 Vaccine

Moderna on the basis of the obtained information including that obtained within Japan and that obtained from abroad (foreign clinical studies, foreign post-authorization or post-marketing investigation, etc.) and make a decision to provide a further precaution or information or take other appropriate actions.

The above conclusion by PMDA will be discussed at 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 COVID-19 Vaccine Moderna has efficacy in the prevention of disease caused by SARS-CoV-2 infection, and that COVID-19 Vaccine Moderna has acceptable safety in view of its benefits. Under the current situation where rapid supply of multiple types of vaccines is needed for the prevention of COVID-19, offering COVID-19 Vaccine Moderna to medical practice has its significance. PMDA considers that dosage and administration, precautionary statements in the package insert, post-marketing investigations, etc., need to be further discussed.

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)

May 17, 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	March 5, 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 Efficacy

The applicant additionally submitted part of immunogenicity data from Foreign Study 301, i.e., S protein-specific binding antibody titers at 28 days after the second dose (data cutoff date of March 31, 2021). The results are shown in Table 33. The immunogenicity analysis population of Foreign Study 301 was the PP random subcohort. The PP random subcohort was defined as participants selected by stratified random sampling (stratified by treatment group, baseline SARS-CoV-2 status, age and at risk for severe COVID-19, and racial minority) from all participants, who received 2 doses of study vaccine, received their second dose at 21 to 42 days after the first dose, and had no major protocol deviations that might impact key study data. S protein-specific binding antibody titers in Foreign Study 301 were measured by the same assay method as that used in Japanese Study 1501.

Table 33. S protein-specific binding antibody titers at 28 days after the second dose of study vaccine[a)] (Foreign Study 301: PP random subcohort)

		N	n	GMT [Two-sided 95% CI]	GMFR [Two-sided 95% CI]	Seroconversion rate[b)] (%) [Two-sided 95% CI]
mRNA-1273 (100 μg)	All age groups	1,055	1,051	694.93 [664.87, 726.35]	971.09 [914.34, 1031.37]	99.6 [99.0, 99.9]
	18-64 years	700	697	740.67 [702.09, 781.36]	1,003.84 [928.98, 1084.72]	99.4 [98.5, 99.8]
	≥65 years	355	354	612.98 [567.50, 662.10]	909.21 [828.36, 997.95]	100 [99.0, 100.0]
Placebo	All age groups	142	141	0.71 [0.61, 0.84]	1.06 [0.92, 1.23]	7.1 [3.5, 12.7]
	18-64 years	94	93	0.69 [0.57, 0.84]	1.01 [0.84, 1.22]	4.3 [1.2, 10.8]
	≥65 years	48	48	0.76 [0.55, 1.03]	1.17 [0.91, 1.49]	12.5 [4.7, 25.2]

N = Number of participants analyzed, n = Number of participants with results available
GMT, 28 days after Dose 2; GMFR: 28 days after Dose 2/before Dose 1
Antibody values below the LLOQ were replaced by 0.5 × LLOQ for analyses.
a) The same assay method as that used in Japanese Study 1501 [see Section 7.R.2.2, Table 24 in the Report (1)]
b) Percentage of participants with a change from below the LLOQ to equal to or above the LLOQ, or at least a 4-fold rise from baseline

GMT of S protein-specific binding antibody in Japanese Study 1501 (Section 7.R.2.2, Table 24 in the Report (1)) was similar to or higher than that in Foreign Study 301. PMDA's conclusion ("the efficacy of mRNA-1273 is promising in the Japanese population") remains unchanged, as presented in Section "7.R.2 Efficacy" in the Report (1).

The expert advisors made the following comments on efficacy:

- According to immunogenicity assessment in Foreign Study 101, the neutralizing antibody titer decreased at 180 days after the second dose (Section 7.R.2.2, Table 25 in the Report (1)), and the duration of efficacy is unknown. An investigation of the long-term efficacy of mRNA-1273 should be continued, and the obtained information should be communicated to healthcare professionals in clinical practice. The need for and timing of further booster doses of the vaccine should be determined, as needed.
- An investigation of the efficacy of mRNA-1273 against new variants, including the B.1.617 variant that is spreading in the India and its neighboring countries, should be continued, and the results of the investigation should be disseminated to healthcare professionals in clinical practice and people in Japan.

PMDA asked the applicant to explain the evaluation of the long-term efficacy of mRNA-1273 and a booster dose of the vaccine.

The applicant's explanation:
Additional efficacy data with a median follow-up of approximately 6 months post second dose have been obtained from Foreign Study 301 (data cutoff date of April 7, 2021), though the data was based on a post-hoc, preliminary assessment (not adjusted for person time). Among participants with negative SARS-CoV-2 status at baseline (mITT Set, 14,550 in the vaccine group and 14,598 in the placebo group), there were 70 cases of COVID-19 starting 14 days after the second dose in the vaccine group and 759 cases of COVID-19 starting 14 days after the second dose in the placebo group. Three participants in the vaccine group and 106 participants in the placebo group had severe COVID-19 starting 14 days after the second dose. Based on these results, the efficacy of mRNA-1273 at approximately 6 months after the second dose was comparable to that at DS2 (data cutoff date of November 21, 2020).

For evaluation of a booster dose to address waning antibody titers, the protocol for Foreign Study 201 was revised to give a booster dose of COVID-19 Vaccine Moderna (mRNA-1273), a booster candidate based on the B.1.351 variant of SARS-CoV-2 (mRNA-1273.351), or a multivalent candidate as a combination of mRNA-1273 plus mRNA-1273.351 (mRNA-1273.211), at approximately 6 months after the second dose of mRNA-1273. Although no conclusion on the need for or timing of a booster dose of mRNA-1273 has been reached, the currently available preliminary data showed that mRNA-1273 and the variant vaccine candidate boosted neutralization of the wild-type original strain and variants (medRxiv [60] preprint doi: 10.1101/2021.05.05.21256716).

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.2 Efficacy" in the Report (1), taking account of the above information.

After the Expert Discussion, the applicant presented additional data evaluating the neutralizing activity of mRNA-1273 against variants including the B.1.617 lineage, which is the latest information on variants, and provided the following explanation:
As with assessment of the neutralizing activity against different variants in Section "7.R.2.4 Efficacy against variants" in the Report (1), serum samples obtained from participants in Foreign Study 101 (the samples were collected 1 week after the participants had received the second dose of 100 μg mRNA-1273) were used to assess the neutralizing activity against pseudoviruses bearing the S proteins from different variants including the B.1.617 lineage.[61] All pseudoviruses tested were neutralized. Although the neutralizing activities against the B.1.617.1-v1 and B.1.617.1-v2 variants were 2.9-fold and 2.8-fold lower,[62] respectively, than that against the D614G variant, GMTs of ID_{50} (50% inhibitory dilution against the pseudovirus) were 1:546 and 1:567, respectively, suggesting that the neutralizing activity is retained.

PMDA reviewed the additional data on the efficacy of mRNA-1273 against variants and accepted the applicant's explanation ("the neutralizing activity against the variants tested is retained"). However, since the emergence of new variants is anticipated in future, PMDA considers that it is necessary to continue to watch for the emergence of variants and that appropriate action should be taken to address it.

PMDA requested the applicant to address the comments from the expert advisors, i.e., to determine the duration of efficacy and the need for and timing of a booster dose and to continue an investigation of the efficacy against variants. The applicant agreed to respond to them appropriately.

1.2 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.3 Safety" in the Report (1).

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60) medRxiv (The Preprint Server For Health Sciences): https://www.medrxiv.org/ (last accessed on May 13, 2021)
61) D614G variant, B.1.351 lineage, B.1.526-v1 variant, NY-2 variant, B.1.525 lineage, A.23.1-v1 variant, A.23.1-v3 variant, B.1.617.1-v1 variant, B.1.617.1-v2 variant, and A.VOI.V2 variant were tested.
62) In the same test system, there was a 6.8-fold reduction in neutralizing activity against the B.1.351 lineage compared to that against the D614G variant.

Based on the currently available post-marketing information on a SARS-CoV-2 vaccine in Japan, the expert advisors added the following comments.

- The incidence of adverse events following vaccination tends to be higher in women. If there is a sex difference in the incidence of adverse events also following vaccination with COVID-19 Vaccine Moderna, this information should be communicated to vaccine recipients and healthcare professionals.
- For frail individuals, adverse events following vaccination is a concern. Caution is required when administering COVID-19 Vaccine Moderna to the population.

PMDA asked the applicant to explain sex differences in the incidences of adverse events in clinical studies of mRNA-1273.

The applicant's explanation:
In both Foreign Study 301 and Japanese Study 1501, the incidences of solicited adverse events and unsolicited adverse events occurring through 28 days after study vaccination were higher in female participants than in male participants, though the difference varied among the specific events. In Japanese Study 1501 (the Safety Set of the vaccine group, 65 female participants and 85 male participants), solicited adverse events reported at a ≥10% higher incidence in female participants than in male participants after the first dose were headache (21.5% [14 of 65 female participants] vs. 7.1% [6 of 85 male participants]), fatigue (24.6% [16 of 65 participants] vs. 14.1% [12 of 85 participants]), and myalgia (44.6% [29 of 65 participants] vs. 31.8% [27 of 85 participants]). Solicited adverse events reported at a ≥10% higher incidence in female participants than in male participants after the second dose were erythema/redness (28.6% [18 of 63 participants] vs. 9.5% [8 of 84 participants]), swelling (25.4% [16 of 63 participants] vs. 9.5% [8 of 84 participants]), headache (60.3% [38 of 63 participants] vs. 38.1% [32 of 84 participants]), fatigue (71.4% [45 of 63 participants] vs. 57.1% [48 of 84 participants]), myalgia (58.7% [37 of 63 participants] vs. 42.9% [36 of 84 participants]), arthralgia (46.0% [29 of 63 participants] vs. 21.4% [18 of 84 participants]), chills (58.7% [37 of 63 participants] vs. 44.0% [37 of 84 participants]), and pyrexia (57.1% [36 of 63 participants] vs. 27.4% [23 of 84 participants]). The possible reasons for the sex differences in the incidences of adverse events were as follows: In vaccine clinical studies, spontaneous reporting of adverse events tends to be elevated among females compared to males (*Vaccine*. 2017; 35: 2600-4, *J Infect Dis*. 2014; 209(S3): S114-9, etc.), and females tend to develop higher antibody response and, relatedly, more side-effects (*Lancet.* 2021; 397: 966-7).

PMDA instructed the applicant to inform healthcare professionals and vaccine recipients of sex differences in the incidences of some adverse events and collect and provide post-marketing information on the safety of COVID-19 Vaccine Moderna in frail individuals. The applicant agreed to respond appropriately.

During the preparation of the Report (1), the applicant explained that a precaution focused on delayed local reactions would not be included in the package insert (Section 7.R.3.1 in the Report (1)). However, as a result of a review of the latest safety information accumulated overseas and other data, the applicant decided to

provide a precaution about delayed local reactions in the package insert as well as in information materials. PMDA accepted it, and the expert advisors supported it at the Expert Discussion.

1.3 Clinical positioning, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the clinical positioning (Section 7.R.4), indication (Section 7.R.5), and dosage and administration (Section 7.R.6) of COVID-19 Vaccine Moderna presented in the Report (1).

1.4 Risk management plan (draft)

As described in Section "7.R.7 Post-marketing investigations" in the Report (1), PMDA has concluded that the risk management plan (draft) for COVID-19 Vaccine Moderna should include the safety specification presented in Table 34, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 35, Table 36, and Table 37.

Table 34. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
Shock, anaphylaxis	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 35. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance · General use-results survey (a follow-up of participants in the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan) · Specified use-results survey (persons with underlying medical conditions who are at increased risk of severe COVID-19) · Post-marketing clinical study (Japanese Study 1501) · Foreign phase III study (Foreign Study 301)	· Disseminate data gathered during early post-marketing phase vigilance · Develop and distribute information materials for healthcare professionals. · Develop and distribute information materials for vaccine recipients · Publish information on reported adverse reactions periodically.

Table 36. Outline of general use-results survey (draft)

Objective	To assess long-term safety through 12 months after the last vaccination with COVID-19 Vaccine Moderna (as a follow-up after the completion of the observation period [through approximately 1 month after the last vaccination] of the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan)
Population	Individuals who gave consent to participate in the present survey after completion of the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan
Observation period	From the day after the completion of the observation period (through approximately 1 month after the last vaccination) of the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan until 12 months after the last vaccination
Planned sample size	All individuals who gave consent to participate in the present survey after completion of the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan
Main survey items	Characteristics of vaccine recipients (medical history, comorbidities, a history of allergy, pregnancy/breastfeeding status for women only, etc.), status of vaccination with COVID-19 Vaccine Moderna, use of other vaccines, concomitant medications, serious adverse events, information on COVID-19 (test for SARS-CoV-2, presence or absence of symptoms in those testing positive for SARS-CoV-2, date of diagnosis, treatments given, outcome), etc.

Table 37. Outline of specified use-results survey (draft)

Objective	To assess safety of COVID-19 Vaccine Moderna in persons with underlying medical conditions who are at increased risk of severe COVID-19.
Survey method	Central registry system
Population	COVID-19 Vaccine Moderna recipients with underlying medical conditions who are at increased risk of severe COVID-19
Observation period	From the day of the first dose of COVID-19 Vaccine Moderna until 28 days after the last vaccination
Planned sample size	1,000 individuals
Main survey items	Characteristics of vaccine recipients (medical history, comorbidities, a history of allergy, pregnancy/breastfeeding status for women only, etc.), status of vaccination with COVID-19 Vaccine Moderna, use of other vaccines, concomitant medications, adverse events, information on COVID-19 (test for SARS-CoV-2, presence or absence of symptoms in those testing positive for SARS-CoV-2, date of diagnosis, treatments given, outcome), etc.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

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 5.3.5.1.4) 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 on the submitted data, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The vaccine product and its active substance are both classified as powerful drugs.

Indication

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

Dosage and Administration

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

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 1
   The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. After the market launch, the applicant is required to continue to collect information on the quality aspects of the product and take necessary measures.
   (2) 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.
   (3) 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.
   (4) 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 product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. After the market launch, the applicant is required to continue to collect information on the quality aspects of the product and take necessary measures.
   (5) 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.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 8 months after the approval. If new data, etc., submitted in accordance with the above, necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

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.

List of Abbreviations

ACE2	Angiotensin-converting enzyme 2
Active substance	CX-024414
ADE	Antibody-dependent enhancement
AEX-HPLC	Anion exchange chromatography-high performance liquid chromatography
APTT	Activated partial thromboplastin time
ATP	Adenosine triphosphate
AUC_{0-t}	Area under the concentration versus time curve from the start of dose administration to the time after dosing at which the last quantifiable concentration was observed
BAL	Bronchoalveolar lavage
BME	2-mercaptoethanol
BMI	Body mass index
BZ	Benzonase
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)
CAD	Charged aerosol detection
CI	Confidence interval
CMA	Critical material attribute
COVID-19	Coronavirus disease
COVID-19 Vaccine Moderna or mRNA-1273	COVID-19 Vaccine Moderna Intramuscular Injection
CTD	Common technical document
CQA	Critical quality attribute
CX-024414	mRNA that encodes the S protein of SARS-CoV-2
DTT	Dithiothreitol
DNA	Deoxyribonucleic acid
[redacted]	[redacted]
DTPA	Diethylenetriamine pentaacetic acid
DS1	Data Snapshot 1 (date: November 11, 2020)
DS2	Data Snapshot 2 (date: November 25, 2020)
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
ELISA	Enzyme-linked immunosorbent assay
ESI MS	ElectroSpray ionization-mass spectrometry
EUA	Emergency use authorization
FAS	Full Analysis Set
FDA	US Food and Drug Administration
gB/ gH/ gL	Glycoprotein B/ H/ L
GC	Gas chromatography
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
ICMRA	International Coalition of Medicines Regulatory Authorities
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IL-1β/2/4/5/13/21	Interleukin 1β/2/4/5/13/21
IP	Interferon inducible protein
Lipid Mixture	Mixture of 4 lipid components (SM-102, cholesterol, DSPC, PEG2000-DMG)

LNP	Lipid nanoparticle
LOD	Limit of detection
MCP-1	Monocyte chemotactic protein 1
MedDRA	Medical Dictionary for Regulatory Activities
Ministerial Ordinance for Enforcement of Pharmaceuticals and Medical Devices Act	Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance of the Ministry of Health and Welfare No. 1 of February 1, 1961)
MIP-1α	Macrophage inflammatory protein 1α
mITT	Modified intention-to-treat
mRNA	Messenger RNA
mRNA-1273 LNP	CX-024414-Lipid Mixture complex
MS	Mass spectrometry
2'-O-MT	2'-*O*-methyltransferase
N1-Me-ΨTP	N^1-methylpseudouridine triphosphate
NE	Not evaluable
NTD	N-terminal domain
PaO_2/FiO_2	Partial pressure of arterial oxygen/Fraction of inspiratory oxygen
PEG2000-DMG	1,2-Dimyristoyl-*rac*-glycero-3-methylpolyoxyethylene
PFU	Plaque-forming units
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
PDE1	Phosphodiesterase I
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
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)
PP Set	Per-protocol set
PPiase	Inorganic pyrophosphatase
QbD	Quality by design
QCIP	Quick calf intestinal phosphatase
qPCR	Quantitative polymerase chain reaction
RBD	Receptor binding domain
Report (1)	Report on Special Approval for Emergency (1)
Report (2)	Report on Special Approval for Emergency (2)
RNA	Ribonucleic acid
RT-PCR	Reverse transcription PCR
RP-HPLC	Reversed phase-high performance liquid chromatography
S1	Amino-terminal region of the S protein containing the RBD
S2	Carboxy-terminal region of the S protein containing a membrane-spanning region
S-2P	Spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
SARS	Severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SEC	Size exclusion chromatography
sgRNA	subgenomic RNA
SM-102	Heptadecan-9-yl 8- ((2-hydroxyethyl) (6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SpO_2	Oxygen saturation of peripheral artery
S protein	Spike protein
T7 RNP	T7 RNA polymerase

Th1/2	T helper cell type 1/2
TNF-α	Tumor necrosis factor-alpha
TLR	Toll-like receptors
UL128	Unique long 128
UL130	Unique long 130
UL131A	Unique long 131A
UTP	Uridine triphosphate
UV	Ultraviolet
VCE	Vaccinia virus capping enzyme
VE	Vaccine efficacy
VOC	Variants of concern
VOI	Variants of interest
WHO	World Health Organization