Report on Special Approval for Emergency

July 12, 2023
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	Spikevax Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine (Active ingredients: (a) Elasomeran [JAN*]; (b) Elasomeran [JAN*] and Imelasomeran [JAN*]; (c) Elasomeran [JAN*] and Davesomeran [JAN*])
Applicant	Moderna Japan Co., Ltd.
Date of Application	February 9, 2023
Dosage Form/Strength	(a) Suspension for injection: Each vial (5 mL) contains 1.0 mg of Elasomeran. (b) Suspension for injection: Each vial (2.5 mL) contains 0.125 mg of Elasomeran and 0.125 mg of Imelasomeran. (c) Suspension for injection: Each vial (2.5 mL) contains 0.125 mg of Elasomeran and 0.125 mg of Davesomeran.
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as the "Pharmaceuticals and Medical Devices Act"), pursuant to the provisions of Article 14-3, Paragraph 1 of the Act ("Handling of Drugs Submitted for Special Approval for Emergency (Request)" [PSEHB/PED No. 0502-5, dated on May 2, 2023]).
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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) in children 6 years through 11 years of age, 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)

The indication applies to the following vaccine products:

- Vaccine product containing messenger ribonucleic acid (mRNA) encoding the spike protein of SARS-CoV-2 (original strain)
- Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

(No change)

Dosage and Administration

- Vaccine product containing mRNA encoding the spike protein of SARS-CoV-2 (original strain)

Individuals 12 years of age and older

For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 years of age and older but younger than 12 years of age

For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (0.25 mL each) at a recommended interval of 4 weeks.

- Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

Individuals 12 years of age and older

For a booster dose, a single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children 6 years of age and older but younger than 12 years of age

For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

(Underline denotes changes.)

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 3 of the Pharmaceuticals and Medical Devices Act.

(1) Matters related to Item 2

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

(2) Matters related to Item 3

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

(3) Matters related to Item 4

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

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

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

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

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

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

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

**Japanese Accepted Name (modified INN)*

Attachment

Report on Special Approval for Emergency (1)

June 15, 2023

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	Spikevax Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (At the time of submission) (Active ingredients: (a) Elasomeran; (b) Elasomeran and Imelasomeran; (c) Elasomeran and Davesomeran)
Applicant	Moderna Japan Co., Ltd.
Date of Application	February 9, 2023
Dosage Form/Strength	(a) Suspension for injection: Each vial (5 mL) contains 1.0 mg of Elasomeran. (b) Suspension for injection: Each vial (2.5 mL) contains 0.125 mg of Elasomeran and 0.125 mg of Imelasomeran. (c) Suspension for injection: Each vial (2.5 mL) contains 0.125 mg of Elasomeran and 0.125 mg of Davesomeran.

Proposed Indication

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

The indication applies to the following vaccine products:

- Vaccine product containing mRNA encoding the spike protein of SARS-CoV-2 (original strain)
- Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

(No change)

Proposed Dosage and Administration

- Vaccine product containing mRNA encoding the spike protein of SARS-CoV-2 (original strain)

Adults

For the primary series for adults, Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

For a booster dose in adults, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children

For the primary series for children 12 years of age and older, Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

For a booster dose for children 12 years of age and older, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

For the primary series for children 6 years of age and older but younger than 12 years of age, Spikevax is administered intramuscularly as a series of 2 doses (0.25 mL each) at a recommended interval of 4 weeks.

• Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

Adults

For a booster dose for adults, a single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children

For a booster dose for children 12 years of age and older, a single dose (0.5 mL) of Spikevax is administered intramuscularly.

For a booster dose for children 6 years of age and older but younger than 12 years of age, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

Several therapeutic agents and vaccines have been developed to tackle the global pandemic of disease caused by SARS-CoV-2 infection (COVID-19) that broke out in January 2020, and various measures including vaccination roll-out programs have been implemented to control COVID-19. While the World Health Organization (WHO) declared an end to COVID-19 as a public health emergency of international concern on May 5, 2023, it also stated that COVID-19 is now an established and ongoing health issue, and State Parties should maintain efforts to increase SARS-CoV-2 vaccine coverage, conduct epidemiological monitoring, and facilitate the development of new vaccines and therapeutic drugs.[1)]

In Japan, beginning on May 8, 2023, COVID-19 has been reclassified as a Class V infectious disease under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Disease Control Act), though it was previously classified in the category of "Novel influenza and other diseases." SARS-CoV-2 vaccination is still offered as a special temporary vaccination program under the Immunization Act ("Guidelines for implementation of temporary vaccination against novel coronavirus infection" [dated May 8, 2023] [2)]). As of the end of May 2023, 80.1% of people had completed the primary series of an approved SARS-CoV-2 vaccine and 68.7% of people received a booster dose (first booster) of such vaccine.[3)] The proportions of children aged 5 to 11 years who completed the primary series and a booster dose (first booster) of an approved SARS-CoV-2 vaccine are 23.4% and 9.7%, respectively.

Spikevax Intramuscular Injection (hereinafter also referred to as "Spikevax") is a vaccine product containing the messenger RNA (mRNA) encoding the spike protein of SARS-CoV-2 as the active ingredient. Spikevax was approved in Japan in May 2021 for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)." Currently, individuals aged ≥12 years are eligible for vaccination with Spikevax. As of May 2023, vaccines that have been approved in Japan for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" in children under 12 years of age are "Comirnaty Intramuscular Injection for 5 to 11 years old" and "Comirnaty Intramuscular Injection for 6 months to 4 years old."

The applicant has recently submitted a partial change application for Spikevax to add dosage and administration for children aged 6 to 11 years, based on data including the results from Study mRNA-1273-P204 (Study P204), a foreign phase I/II study on the monovalent (Original) vaccine in children aged 6 to 11 years.

As of May 2023, Spikevax has been approved in ≥90 countries or regions. Spikevax products approved in Europe or authorized in the US for use in children aged 6 to 11 years are as follows: In Europe, Spikevax monovalent (Original) vaccine was approved for the primary series in March 2022, and

1) https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic (last accessed on June 6, 2023)
2) https://www.mhlw.go.jp/content/000971377.pdf (last accessed on June 6, 2023)
3) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (last accessed on May 31, 2023)

Spikevax bivalent (Original/Omicron BA.1) vaccine and Spikevax bivalent (Original/Omicron BA.4-5) vaccine were approved for a booster dose in December 2022 and May 2023, respectively; and in the US, Spikevax monovalent (Original) vaccine for the primary series was authorized under the emergency use authorization (EUA) in June 2022, and Spikevax bivalent (Original/Omicron BA.4-5) vaccine for a booster dose in October 2022.

This report contains the result of the 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 No. 0502-5, dated on May 2, 2023).

2. Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for a new dosage, no data relating to quality were submitted.

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

Although the present application is intended for a new dosage, no new data were submitted under this section because the non-clinical pharmacology data had already been evaluated during the review process for the initial approval.

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

Although the present application intended for a new dosage, no new data were submitted under this section because the non-clinical pharmacokinetic data had already been evaluated during the review process for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new dosage, no data relating to toxicity were submitted.

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

No data relating to biopharmaceutic studies and associated analytical methods and clinical pharmacology were submitted in the present application.

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 results from 2 studies (Table 1). In Study P204, the study population evaluated included healthy children of different age groups (children aged 6 months to 1 year, 2 to 5 years, and 6 to 11 years). The applicant submitted data from children aged 6 to 11 years for the present application. The data from the monovalent (Original) vaccine group in Cohort 2 in Part F[4)] of Study mRNA-1273-P205 (Study P205) served as the control for immunogenicity analyses in Part H of Study P205. The data have been already submitted for the review

[4)] Part F was established to evaluate the efficacy of the monovalent vaccine against Omicron BA.1 lineage. The first booster dose was studied in Cohort 1 and the second booster dose in Cohort 2.

of the application filed for approval of Spikevax bivalent (Original/Omicron BA.1) vaccine (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on September 7, 2022).

Table 1. Overview of clinical studies

Data category	Country	Study ID	Phase	Study population	Number of participants	Dosage regimen	Study objective
Evaluation	US and Canada	mRNA-1273-P204	II/III	Healthy children aged 6 to 11 years[a)]	Part 1: Monovalent (Original) vaccine 50 µg: 380 Monovalent (Original) vaccine 100 µg: 371 Part 2: Monovalent (Original) vaccine 50 µg: 3012 Placebo: 1004	Part 1: 2 doses of monovalent (Original) vaccine 50 µg[b)] or 100 µg administered intramuscularly, 28 days apart Part 2: 2 doses of monovalent (Original) vaccine 50 µg[b)] or placebo[c)] administered intramuscularly, 28 days apart	Safety Immunogenicity
				Healthy children aged 6 to 11 years[a)] who completed the primary series in Part 1 or Part 2	1294	A single dose of monovalent (Original) vaccine 25 µg[d)] administered intramuscularly	
Evaluation	US	mRNA-1273-P205 Part H	II/III	Adults aged ≥18 years who received 2 doses of monovalent (Original) vaccine 100 µg as the primary series, and 1 booster dose of the monovalent (Original) vaccine 50 µg	511	A single dose of bivalent (Original/Omicron BA.4-5) vaccine[e)] 50 µg administered intramuscularly	Safety Immunogenicity

a) Including children with stable underlying medical conditions
b) A vaccine product containing 100 µg of elasomeran per 0.5 mL was diluted to contain 50 µg of elasomeran per 0.5 mL and used for injection
c) Physiological saline
d) A vaccine product containing 100 µg of elasomeran per 0.5 mL was diluted to contain 25 µg of elasomeran per 0.5 mL and used for injection
e) A vaccine product containing 25 µg of elasomeran and 25 µg of davesomeran per 0.5 mL

7.1 Foreign phase II/III study (CTD 5.3.5.1.1, Study mRNA-1273-P204, ongoing since March 2021 [data cut-off date for interim analysis, November [redacted], 2021 for the primary series, and May [redacted], 2022 for a booster dose)

Study P204 (Parts 1 and 2) was initiated as a study investigating the primary series in healthy children aged 6 months to 11 years. Initially, the study included a follow-up of 12 months after the second dose of the study vaccine. However, the study design was changed during the follow-up period to allow administration of a booster dose at least 6 months after the completion of the primary series so as to evaluate the safety and immunogenicity of the study vaccine as a booster dose (Protocol Version 7 prepared on February [redacted], 2022).

7.1.1 Study P204 (Primary series)

The study consisting of an open label, uncontrolled, dose-escalation phase (Part 1) and a randomized, observer-blind, placebo-controlled parallel-group phase (Part 2) was conducted at 45 study centers in the US and 77 study centers in Canada. Part 1 and 2 phases were conducted in healthy children aged 6

to 11 years, including children with stable underlying medical conditions (Part 1: a target sample size of approximately 750 participants, approximately 375 participants each for the monovalent [Original] vaccine 50 µg and 100 µg groups; Part 2: a target sample size of a maximum of 4,000 participants, a maximum of 3,000 participants in the monovalent [Original] vaccine 50 µg group and a maximum of 1,000 participants in the placebo group) to investigate the safety and immunogenicity of the monovalent (Original) vaccine.

1) Part 1

Participants were to receive 2 doses of the monovalent (Original) vaccine 50 µg[5)] or 100 µg intramuscularly, 28 days apart.

All 751 participants who received the study vaccine at least once (380 participants in the monovalent [Original] vaccine 50 µg group and 371 participants in the monovalent [Original] vaccine 100 µg group) were included in the full analysis set (FAS) and safety analysis set. Of the participants included in the safety analysis set, those who had provided solicited adverse event data from their participant diary were included in the solicited adverse event analysis set. Part 1 consists of 2 subparts, the dose-selection and extension subparts. In the dose-selection subpart, the study vaccine was administered to 75 participants in each group, while in the extension subpart, approximately 300 participants were additionally enrolled in each group to evaluate the safety and immunogenicity of the study vaccine. In the dose-selection subpart, 75 of 75 participants in the monovalent (Original) vaccine 50 µg group and 61 of 75 participants in the monovalent (Original) vaccine 100 µg groups had had evaluable immunogenicity data at 28 days after the second study vaccination and were included in the immunogenicity subset. Of them, 67 participants (50 µg) and 57 participants (100 µg) were included in the per-protocol immunogenicity subset (PPIS) while the remaining 8 participants (50 µg) and 4 participants (100 µg) were excluded from the analysis because they had positive SARS-CoV-2 status before the first study vaccination. In the extension subpart, only participants in the monovalent (Original) vaccine 50 µg group underwent immunogenicity analysis.[6)] Of the participants receiving the monovalent (Original) vaccine 50 µg who were included in the FAS, the first 145 participants who entered the extension subpart and had provided evaluable immunogenicity data at 28 days after the second study vaccination were included in the immunogenicity subset. Of the 145 participants, 134 participants were included in the PPIS, while the remaining 11 participants (10 participants with positive SARS-CoV-2 status before the first study vaccination and 1 participant receiving the second study vaccination outside the allowable time window) were excluded from the analysis. In the SARS-CoV-2 test, reverse transcription polymerase chain reaction (RT-PCR) testing and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were used. Participants who had negative results of both RT-PCR and antibody testing were considered SARS-CoV-2 negative, and those who had a positive result of RT-PCR or antibody testing were considered SARS-CoV-2 positive.

[5)] A vaccine product containing 100 µg of elasomeran per 0.5 mL was diluted to contain 50 µg of elasomeran per 0.5 mL and used for injection.

[6)] In the dose-selection subpart, immunogenicity data from the first 75 participants who had received 50 µg were evaluated when 28 days after the second dose had elapsed. Based on the results, the dose of 50 µg was selected for children aged 6 to 11 years.

The safety follow-up period was as follows:

- Solicited adverse events[7] (local adverse events: pain, erythema [redness], swelling/induration, and lymphadenopathy[8]; and systemic adverse events: fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills): Reported through 7 days after each dose of the study vaccine (collected from diaries of parents/guardians)
- Unsolicited adverse events (excluding solicited adverse events reported through 7 days after study vaccination): Reported through 28 days after each dose of the study vaccine
- Serious adverse events, acute myocarditis or pericarditis,[9] and adverse events of special interest (AESIs), [10] adverse events requiring treatment: Reported throughout the study period after the first dose of the study vaccine

Table 2 shows the incidence of solicited adverse events reported through 7 days after each dose of the study vaccine.

[7] The severity of adverse events was evaluated according to the Food and Drug Administration (FDA) Guidance (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials: https://www.fda.gov/media/73679/download [last accessed on June 5, 2023]).

[8] This event was reported as axillary swelling or tenderness ipsilateral to the injection site in the participant diary.

[9] Regarding myocarditis and pericarditis reported after vaccination against COVID-19, the protocol was amended before the start of Part 2 (Protocol Version 3 prepared on July [redacted], 2021) according to the definition of the US Centers for Disease Control and Prevention (CDC) (*MMWR Morb Mortal Wkly Rep.* 2021;70:977-82). On and after July [redacted], 2021, in the safety communication by phone (phone communication on safety during the 7 days or later after each dose of the vaccine), parents/guardians of participants were interviewed about the following: chest pain, chest pressure, chest discomfort, shortness of breath, tachypnoea at rest, or pain when breathing, increased heart rate, cardiac flutter, or palpitations.

[10] The AESIs include the following adverse events: anosmia, ageusia, subacute thyroiditis, acute pancreatitis, appendicitis, rhabdomyolysis, acute respiratory distress syndrome, coagulation disorders, acute cardiovascular injury, acute kidney injury, acute liver injury, dermatologic findings, multisystem inflammatory disorders, thrombocytopenia, acute aseptic arthritis, new onset or worsening of neurologic disease, and anaphylaxis.

Table 2. The incidence of solicited adverse events reported through 7 days after each dose of the study vaccine (Study P204 Part 1: Solicited adverse event analysis set)

Event	First dose				Second dose			
	Monovalent (Original) 50 μg N = 378		Monovalent (Original) 100 μg N = 369		Monovalent (Original) 50 μg N = 379		Monovalent (Original) 100 μg N = 371	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any local adverse event	339 (89.7)	4 (1.1)	347 (94.0)	12 (3.3)	355 (93.7)	10 (2.6)	348 (93.8)	30 (8.1)
Pain	336 (88.9)	2 (0.5)	341 (92.4)	10 (2.7)	350 (92.3)	8 (2.1)	346 (93.3)	14 (3.8)
Erythema (redness)	39 (10.3)	2 (0.5)	63 (17.1)	0	81 (21.4)	2 (0.5)	108 (29.1)	16 (4.3)
Swelling/induration	40 (10.6)	2 (0.5)	57 (15.4)	2 (0.5)	82 (21.6)	1 (0.3)	92 (24.8)	6 (1.6)
Lymphadenopathy[a)]	41 (10.8)	0	54 (14.6)	1 (0.3)	46 (12.1)	0	63 (17.0)	1 (0.3)
Any systemic adverse event	207 (54.8)	8 (2.1)	223 (60.4)	17 (4.6)	284 (74.9)	36 (9.5)	312 (84.1)	66 (17.8)
Fever[b)]	11 (2.9)	1 (0.3)	24 (6.5)	2 (0.5)	78 (20.6)	10 (2.6)	110 (29.6)	22 (5.9)
Headache	109 (28.8)	4 (1.1)	129 (35.0)	6 (1.6)	188 (49.6)	10 (2.6)	226 (60.9)	19 (5.1)
Fatigue	154 (40.7)	4 (1.1)	167 (45.3)	10 (2.7)	216 (57.0)	26 (6.9)	236 (63.6)	36 (9.7)
Myalgia	40 (10.6)	0	58 (15.7)	6 (1.6)	89 (23.5)	7 (1.8)	112 (30.2)	13 (3.5)
Arthralgia	27 (7.1)	0	39 (10.6)	4 (1.1)	43 (11.3)	2 (0.5)	68 (18.3)	4 (1.1)
Nausea/vomiting	36 (9.5)	0	26 (7.0)	1 (0.3)	79 (20.8)	2 (0.5)	113 (30.5)	3 (0.8)
Chills	33 (8.7)	0	40 (10.8)	1 (0.3)	77 (20.3)	1 (0.3)	135 (36.4)	2 (0.5)

N =number of participants analyzed, n = number of participants with the event

a) Axillary swelling or tenderness ipsilateral to the injection site

b) ≥38°C (oral temperature)

The incidence of unsolicited adverse events reported through 28 days after study vaccination (monovalent [Original] vaccine) was 31.3% (119 of 380 participants) in the 50 μg group and 27.0% (100 of 371 participants) in the 100 μg group, while the incidence of unsolicited adverse events classified as adverse reactions was 11.6% (44 of 380 participants) in the 50 μg group and 12.7% (47 of 371 participants) in the 100 μg group. Unsolicited adverse events occurring in >1% of participants in the monovalent (Original) vaccine 50 μg group were injection site erythema (4.2%, 16 participants), upper respiratory tract infection (3.7%, 14 participants), nasal congestion (2.9%, 11 participants), oropharyngeal pain (2.9%, 11 participants), cough (1.8%, 7 participants), headache (1.6%, 6 participants), fatigue (1.6%, 6 participants), injection site lymphadenopathy (1.6%, 6 participants), nasopharyngitis (1.3%, 5 participants), otitis externa (1.3%, 5 participants), rhinorrhoea (1.3%, 5 participants), vomiting (1.3%, 5 participants), fever (1.1%, 4 participants), and lymphadenopathy (1.1%, 4 participants). Among these events, a causal relationship to the study vaccine could not be ruled out for the following events: injection site erythema (16 participants), injection site lymphadenopathy (6 participants), headache (3 participants), fatigue (3 participants), lymphadenopathy (3 participants), vomiting (2 participants), and fever (2 participants). Unsolicited adverse events occurring in >1% of participants in the monovalent (Original) vaccine 100 μg group were injection site erythema (3.8%, 14 participants), upper respiratory tract infection (3.5%, 13 participants), nasal congestion (2.7%, 10 participants), fever (2.4%, 9 participants), cough (1.9%, 7 participants), rhinorrhoea (1.9%, 7 participants), injection site rash (1.9%, 7 participants), headache (1.6%, 6 participants), injection site induration (1.3%, 5 participants), injection site lymphadenopathy (1.1%, 4 participants), and fatigue (1.1%, 4 participants). Among these events, a causal relationship to the study vaccine could not be ruled

out for the following events: injection site erythema (14 participants), injection site rash (7 participants), injection site induration (5 participants), injection site lymphadenopathy (4 participants), headache (4 participants), fatigue (2 participants), nasal congestion (1 participant), fever (1 participant), and cough (1 participant).

An adverse event (urticaria papular) led to study discontinuation in 1 participant in the monovalent (Original) vaccine 50 μg group. Its causal relationship to the study vaccine could not be ruled out and the outcome was reported as resolved. There were no reports of death.

Serious adverse events occurred in 4 participants in the monovalent (Original) vaccine 50 μg group (appendicitis [2 participants], foreign body ingestion [1 participant], and optic disc drusen [1 participant]) and 2 participants in the monovalent (Original) vaccine 100 μg group (constipation [1 participant] and pancreatitis acute [1 participant]). A causal relationship to the study vaccine was ruled out for all the events. The outcome was reported as resolved; however, optic disc drusen and pancreatitis acute resolved with sequelae.

The results for immunogenicity were analyzed. The geometric mean titer (GMT) [two-sided 95% confidence interval (CI)] of neutralizing antibodies (as measured by pseudovirus neutralization assay [PsVNA], 50% inhibitory dilution) against the original strain at 28 days after the second dose of the study vaccine in the PPIS was 1,204.647 [1,047.150, 1,385.831] in the monovalent (Original) vaccine 50 μg group (N = 67) and 1,887.744 [1,606.495, 2,218.231] in the monovalent (Original) vaccine 100 μg group (N = 57) in the dose-selection subpart; 1,964.601 [1,722.357, 2,240.915] in the monovalent (Original) vaccine 50 μg group (N = 134) in the extension subpart. The seroresponse rate[11)] [two-sided 95% CI] was 100% [94.6, 100.0] (67 of 67 participants) in the monovalent (Original) vaccine 50 μg group and 100% [93.7, 100.0] (57 of 57 participants) in the monovalent (Original) vaccine 100 μg group in the dose-selection subpart; and 99.3% [95.9, 100.0] (133 of 134 participants) in the monovalent (Original) vaccine 50 μg group in the extension subpart.

2) Part 2

Participants were to receive 2 doses of the monovalent (Original) vaccine 50 μg[5)] or placebo intramuscularly, 28 days apart.

Of the 4,016 randomized participants (3,012 participants in the monovalent [Original] vaccine 50 μg group and 1,004 participants in the placebo group), 4,002 participants who had received at least 1 dose of the study vaccine were included in the FAS (3,005 participants in the monovalent [Original] vaccine 50 μg group and 997 participants in the placebo group) and also in the safety analysis set (3,007 participants in the monovalent [Original] vaccine 50 μg group and 995 participants in the placebo group). Analyses on the FAS were performed according to the study vaccine group as randomized (which may

[11)] The seroresponse rate was defined as the proportion of participants who had a ≥4-fold rise in neutralizing antibody titer from the pre-first dose (if the neutralizing antibody titer is below LLOQ, a ≥4-fold rise from the LLOQ).

be different from the study vaccine they received); conversely, safety analyses were performed based on the study vaccine they actually received. Of the participants included in the safety analysis set, those who had provided solicited adverse event data from their participant diary were all included in the solicited adverse event analysis set. Of the participants included in the FAS, 364 participants in the monovalent (Original) vaccine 50 μg group from whom specimens for immunogenicity assessment after study vaccination had been obtained were included in the immunogenicity subset. The PPIS consisted of 320 participants[12)] while the remaining 44 participants were excluded from the analysis (positive SARS-CoV-2 status before the first study vaccination [38 participants], missing immunogenicity data at 28 days after the second dose of the study vaccine [4 participants], serious protocol deviation [1 participant], and the second study vaccination outside the allowable time window [1 participant]). In the SARS-CoV-2 test, RT-PCR testing and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were performed. Participants who had negative results of both RT-PCR and antibody testing were considered SARS-CoV-2 negative, and those who had a positive result of RT-PCR or antibody testing were considered SARS-CoV-2 positive. Of the participants included in the FAS, those with negative SARS-CoV-2 status before the first dose of the study vaccine were included in the modified intention-to-treat (mITT) set (2,701 participants in the monovalent [Original] vaccine 50 μg group and 882 participants in the placebo group). Among the participants in the mITT set, those who had received the study vaccine as planned (2,687 participants in the monovalent [Original] vaccine 50 μg group and 880 participants in the placebo group) were included in the mITT1 set.

The primary immunogenicity endpoints were the GM value of neutralizing antibodies (as measured by PsVNA, 50% inhibitory dilution) against the original strain and seroresponse rate at 28 days after the second dose of the study vaccine. The non-inferiority of the immunogenicity data from participants in the monovalent (Original) vaccine 50 μg group in Study P204 to the immunogenicity data from participants aged 18 to 25 years in Study P301 (data at 28 days after the second dose of the primary series of the monovalent [Original] vaccine 100 μg) was evaluated based on the geometric mean ratio (GMR) of neutralizing antibodies (the ratio of Study P204 [6 to 11 years] to Study P301 [18 to 25 years]) and the difference in seroresponse rates (Study P204 [6 to 11 years] minus Study P301 [18 to 25 years]). Seroresponse was defined as a ≥4-fold rise in neutralizing antibody titers from pre-first dose (if neutralizing antibody titer reported was below the lower limit of quantification [LLOQ], a ≥4-fold rise from the LLOQ). The non-inferiority of the results of Study P204 was considered to be demonstrated if both of the following non-inferiority success criteria are met.

12) The number of participants necessary for immunogenicity analysis of the primary series in Study P204 was determined as follows: If the PPIS of Study P204 and the PPIS of the age group of 18 to 25 years in Study P301 both consist of approximately 289 participants receiving the monovalent (Original) vaccine, assuming a GMR of 1, a non-inferiority margin of 0.67, a point estimate minimum threshold of 0.8, and a standard deviation of the natural log-transformed level of 1.5, there would be 90% power to demonstrate the non-inferiority of the immune response as measured by the antibody geometric mean (GM) levels in the pediatric population at a two-sided α of 0.05, compared to that in the age group of 18 to 25 years in Study P301. If approximately 289 participants each in the PPIS of Study P204 and in the PPIS of the age group of 18 to 25 years in Study P301 receive the monovalent (Original) vaccine, there would be at least 90% power to demonstrate the non-inferiority of the seroresponse rate in the pediatric population at a two-sided α of 0.05, compared to that in the age group of 18 to 25 years receiving the monovalent (Original) vaccine in Study P301, assuming a seroresponse rate of ≥95% in the age group of 18 to 25 years in Study P301 and a true seroresponse rate of ≥95% in children, a true between-group difference of ≤4%, a non-inferiority margin for the seroresponse rate difference of 10%, and a point estimate minimum threshold for the seroresponse rate difference of −5%.

1) As for the GM values of neutralizing antibodies, the lower bound of the two-sided 95% CI of the GMR is >0.67 based on the non-inferiority margin of 1.5, and the GMR point estimate ≥0.8.
2) As for the neutralizing antibody seroresponse rate, the lower bound of the two-sided 95% CI of the seroresponse rate difference is >−10% based on the non-inferiority margin of 10%, and the seroresponse rate difference point estimate is >−5%.

Table 3 shows the results of the primary immunogenicity endpoints at 28 days after study vaccination. The lower bound of the two-sided 95% CI for the GMR of neutralizing antibodies against the original strain and the lower bound of the two-sided 95% CI for difference in the seroresponse rate of neutralizing antibodies against the original strain were greater than the non-inferiority margins. The GMR point estimate was ≥0.8 and the seroresponse rate difference point estimate was >−5%, indicating that the results met the prespecified success criteria for non-inferiority.

Table 3. Comparison of serum neutralizing antibody titers against the original strain (Study P204 Part 2: PPIS)

	P204 (6-11 years)	P301 (18-25 years)
	Monovalent (Original) 50 μg N = 320	Monovalent (Original) 100 μg N = 295
Pre-first dose		
n	317	295
GMT [two-sided 95% CI][a)]	9.250 [NE, NE]	9.285 [9.216, 9.355]
28 days post-second dose		
n	319	295
GMT [two-sided 95% CI][a)]	1610.203 [1456.623, 1779.976]	1299.855 [1170.622, 1443.354]
GMFR [two-sided 95% CI][a)]	173.972 [157.238, 192.487]	139.990 [126.103, 155.405]
GLSM [two-sided 95% CI][b)]	1610.203 [1456.589, 1780.017]	1299.855 [1171.156, 1442.696]
GMR [two-sided 95% CI][b)]	1.239 [1.072, 1.432]	
Seroresponse rate		
N1	316	295
n[c)]	313	292
Seroresponse rate (%) [two-sided 95% CI][d)]	99.1 [97.3, 99.8]	99.0 [97.1, 99.8]
Difference in seroresponse rate [two-sided 95% CI][e)]	0.1 [−1.9, 2.1]	

PsVNA (50% inhibitory dilution)
Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Values greater than the upper limit of quantification [ULOQ] were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 18.5-45118).
N = number of participants evaluated; N1 = number of participants with non-missing data both before the primary series and after the second booster dose; n = number of participants with non-missing data at the evaluation timepoint
NE = not estimable
GMR = the ratio of Study P204 to Study P301; seroresponse rate difference = Study P204 minus Study P301
a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or the fold rise in antibody titer, and then back-transformed to the original scale for representation.
b) An analysis of covariance model with the titers at 28 days post-second dose in Studies P204 and P301 as the dependent variable and the group variable (children aged 6-11 years in Study P204 and adults aged 18-25 years in Study P301) as fixed effect
c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series baseline (if below the LLOQ, a ≥4-fold rise from the LLOQ)
d) Two-sided 95% CI was calculated using the Clopper-Pearson method.
e) Two-sided 95% CI was calculated using the Miettinen-Nurminen method.

The grading scale used for the assessment of the severity of adverse events and safety follow-up period were similar to those of Part 1.

Table 4 shows the incidence of solicited adverse events reported through 7 days after each dose of the study vaccine.

Table 4. The incidence of solicited adverse events reported through 7 days after each dose of the study vaccine (Study P204 Part 2: Solicited adverse event analysis set)

Event	First dose							
	Monovalent (Original) 50 μg N = 3004				Placebo N = 993			
	All Grades		Grade ≥3		All Grades		Grade ≥3	
	N1	n (%)	N1	n (%)	N1	n (%)	N1	n (%)
Any local adverse event	3004	2814 (93.7)	3004	54 (1.8)	993	480 (48.3)	993	3 (0.3)
Pain	3004	2796 (93.1)	3004	28 (0.9)	993	465 (46.8)	993	0
Erythema (redness)	3004	349 (11.6)	3004	16 (0.5)	993	13 (1.3)	993	1 (0.1)
Swelling/induration	3004	354 (11.8)	3004	19 (0.6)	993	12 (1.2)	993	1 (0.1)
Lymphadenopathy[a)]	3004	465 (15.5)	3004	3 (<0.1)	993	84 (8.5)	993	1 (0.1)
Any systemic adverse event	3004	1740 (57.9)	3004	53 (1.8)	993	518 (52.2)	993	13 (1.3)
Fever[b)]	3003	99 (3.3)	3003	17 (0.6)	993	15 (1.5)	993	3 (0.3)
Headache	3002	938 (31.2)	3002	18 (0.6)	993	306 (30.8)	993	4 (0.4)
Fatigue	3002	1298 (43.2)	3002	31 (1.0)	993	334 (33.6)	993	8 (0.8)
Myalgia	3002	438 (14.6)	3002	11 (0.4)	993	96 (9.7)	993	1 (0.1)
Arthralgia	3002	260 (8.7)	3002	3 (<0.1)	993	75 (7.6)	993	1 (0.1)
Nausea/vomiting	3002	325 (10.8)	3002	5 (0.2)	993	107 (10.8)	993	0
Chills	3002	309 (10.3)	3002	3 (<0.1)	993	67 (6.7)	993	0
Event	Second dose							
	Monovalent (Original) 50 μg N = 2988				Placebo N = 969			
	All Grades		Grade ≥3		All Grades		Grade ≥3	
	N1	n (%)	N1	n (%)	N1	n (%)	N1	n (%)
Any local adverse event	2988	2849 (95.3)	2988	122 (4.1)	969	490 (50.6)	969	5 (0.5)
Pain	2988	2832 (94.8)	2988	81 (2.7)	969	480 (49.5)	969	2 (0.2)
Erythema (redness)	2988	559 (18.7)	2988	33 (1.1)	969	10 (1.0)	969	1 (0.1)
Swelling/induration	2988	507 (17.0)	2988	20 (0.7)	969	12 (1.2)	969	0
Lymphadenopathy[a)]	2988	537 (18.0)	2988	3 (0.1)	969	65 (6.7)	969	2 (0.2)
Any systemic adverse event	2988	2335 (78.1)	2988	364 (12.2)	969	485 (50.1)	969	14 (1.4)
Fever[b)]	2988	714 (23.9)	2988	113 (3.8)	969	19 (2.0)	969	2 (0.2)
Headache	2986	1622 (54.3)	2986	119 (4.0)	969	275 (28.4)	969	8 (0.8)
Fatigue	2986	1925 (64.5)	2986	191 (6.4)	969	335 (34.6)	969	8 (0.8)
Myalgia	2986	843 (28.2)	2986	71 (2.4)	969	105 (10.8)	969	1 (0.1)
Arthralgia	2986	482 (16.1)	2986	25 (0.8)	969	84 (8.7)	969	0
Nausea/vomiting	2986	716 (24.0)	2986	19 (0.6)	969	97 (10.0)	969	0
Chills	2986	904 (30.3)	2986	19 (0.6)	969	74 (7.6)	969	0

N = number of participants analyzed; N1 = number of participants who submitted any data for the event; n = number of participants with the event

a) Axillary swelling or tenderness ipsilateral to the injection site

b) ≥38°C (oral temperature)

Table 5 shows the incidence of unsolicited adverse events (occurring at ≥2% in either group) reported through 28 days after study vaccination and the incidence of unsolicited adverse events classified as adverse reactions.

Table 5. The incidence of unsolicited adverse events occurring in ≥2% in either group reported through 28 days after study vaccination and the incidence of the unsolicited adverse events classified as adverse reactions (Study P204 Part 2: Safety analysis set)

Event	Unsolicited adverse event		Adverse reaction	
	Monovalent (Original) 50 μg (N = 3007)	Placebo (N = 995)	Monovalent (Original) 50 μg (N = 3007)	Placebo (N = 995)
	n (%)	n (%)	n (%)	n (%)
Total	891 (29.6)	250 (25.1)	319 (10.6)	50 (5.0)
Upper respiratory tract infection	116 (3.9)	25 (2.5)	4 (0.1)	2 (0.2)
Injection site erythema	94 (3.1)	1 (0.1)	91 (3.0)	1 (0.1)
Headache	77 (2.6)	29 (2.9)	39 (1.3)	16 (1.6)
Oropharyngeal pain	68 (2.3)	30 (3.0)	2 (<0.1)	2 (0.2)
Nasal congestion	65 (2.2)	26 (2.6)	2 (<0.1)	1 (0.1)
Cough	64 (2.1)	22 (2.2)	3 (<0.1)	0
Rhinorrhoea	62 (2.1)	23 (2.3)	1 (<0.1)	0
COVID-19	11 (0.4)	22 (2.2)	0	0

N = number of participants analyzed; n = number of participants with the event
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Adverse events led to study discontinuation in 4 participants in the monovalent (Original) vaccine 50 μg group (rash pruritic [1 participant], urticaria/asthma exercise induced [1 participant], rash [1 participant], inflammatory bowel disease[13)] [1 participant]) and 2 participants in the placebo group (COVID-19 [2 participants]). Except for urticaria (no report on causal relationship) in the monovalent (Original) vaccine 50 μg group, a causal relationship to the study vaccine was ruled out for the events.

Serious adverse events occurred in 6 participants in the monovalent (Original) vaccine 50 μg group (appendicitis [2 participants], cellulitis [1 participant], cellulitis orbital [1 participant], type 1 diabetes mellitus [1 participant], pyelonephritis/urosepsis [1 participant]) and 2 participants in the placebo group (affective disorder [1 participant] and COVID-19 [1 participant]). A causal relationship to the study vaccine was ruled out for all these events, and the outcome was reported as resolved. However, type 1 diabetes mellitus in the monovalent (Original) vaccine 50 μg group and affective disorder in the placebo group were reported as resolved with sequelae. There were no reports of death.

7.1.2 Study P204 (booster dose)

The safety and immunogenicity of the monovalent (Original) vaccine administered ≥6 months after the second dose of the primary series were evaluated in participants aged 6 to 11 years[14)] who had received 2 doses of the monovalent (Original) vaccine 50 μg as the primary series in Part 1 or Part 2 and who

[13)] At 21 days after the second dose, the study was discontinued in this participant due to inflammatory bowel disease. According to additional information, endoscopy examination showed granuloma but no evidence of inflammatory bowel disease. Furthermore, additional immunological examination and genetic examination revealed that this participant did not show an immune response to general vaccines given previously, leading to a new tentative diagnosis of "immunodeficiency common variable."

[14)] The protocol allowed any participants aged 6 to 11 years who had been enrolled in Study P204 Part 1 or Part 2 to start receiving a booster dose of the monovalent (Original) vaccine 25 μg at ≥6 months after completion of the second dose of the primary series. Since an EUA was issued for the primary series in children aged 6 to 11 years in the US, participants who had been assigned to receive placebo in Study P204 were allowed to receive the primary series of the monovalent (Original) vaccine and the study of participants in the placebo group continued. However, the data from the participants who had previously received placebo and then received the monovalent (Original) vaccine were not included in the immunogenicity analysis for the booster dose.

provided informed consent to receiving a booster dose. This study was conducted in an open-label fashion at 69 study centers in the US and Canada.

Participants were to receive 1 dose of monovalent (Original) vaccine 25 μg[15)] intramuscularly.

The FAS included 1,294 participants who had provided informed consent to receiving the booster dose and received at least one dose of the study vaccine as the booster dose (176 participants who received the monovalent [Original] vaccine 50 μg as their primary series in Part 1; and 1,115 participants who received the monovalent [Original] vaccine 50 μg as their primary series and 3 participants who received placebo[16)] in Part 2), all of whom were included in the safety analysis set. Of the participants included in the safety analysis set, those who had provided solicited adverse event data from their participant diary were all included in the solicited adverse event analysis set. Of the participants in the FAS who had been assigned to the monovalent (Original) vaccine 50 μg for the primary series and whose antibody data after the booster dose had been evaluated at least once, the first 154 participants in the order of enrollment (62 participants who received their primary series in Part 1; 92 participants who received their primary series in Part 2) were included in the immunogenicity subset. Of the 154 participants, 25 participants (positive SARS-CoV-2 status before the primary series [11 participants], missing data on neutralizing antibody titers at 28 days after the second dose of the study vaccine [10 participants], and wrong booster dose level [4 participants]) were excluded from the analysis, and the remaining 129 participants were included in the PPIS. Of the 129 participants, 95 with negative for SARS-CoV-2 status before the booster dose were included in the Per-protocol immunogenicity subset - SARS-CoV-2 negative at baseline (PPIS-Neg), which served as the primary immunogenicity subset.[17)] In the SARS-CoV-2 test, RT-PCR testing and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were performed. Participants who had negative results of both RT-PCR and antibody testing were considered SARS-CoV-2 negative, and those who tested a positive result of RT-PCR or antibody testing were considered SARS-CoV-2 positive.

The median interval between the second dose of the primary series and the booster dose was 225.0 days (range, 124-378 days) in the safety analysis set and 224.0 days (range, 202-367 days) in the PPIS-Neg.

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15) A vaccine product containing 100 μg of elasomeran per 0.5 mL was diluted to contain 25 μg per 0.5 mL and used for injection.

16) After SARS-CoV-2 vaccination had been approved in Europe and the US for the age group investigated in Study P204, the protocol was amended to offer the primary series vaccination with the monovalent (Original) vaccine to participants assigned to placebo in the study. These 3 participants had been assigned to placebo and then received the monovalent (Original) vaccine 50 μg as the primary series after the protocol amendment.

17) The sample size necessary for immunogenicity analysis of the booster dose in Study P204 was determined as follows: If approximately 289 participants each are included in the PPIS-Neg of Study P204 and in the age group of 18 to 25 years in the PPIS of Study 301, assuming a GMR of 1, a non-inferiority margin of 0.67, and a standard deviation of the natural log-transformed level of 1.5, there would be 90% power to demonstrate the non-inferiority of the immune response as measured by GM antibody levels in the pediatric population at a two-sided α of 0.05, compared to that in the age group of 18 to 25 years in Study P301. The sample size of approximately 289 participants each in the PPIS-Neg of Study P204 and in the age group of 18 to 25years in the PPIS of Study 301 would provide at least 90% power to demonstrate the non-inferiority of the seroresponse rate in the pediatric population receiving the booster dose at a two-sided α of 0.05, compared to the seroresponse rate in the age group of 18 to 25 years in Study P301 that received the primary series of mRNA-1273, assuming a seroresponse rate of ≥95% in the age group of 18 to 25 years in Study P301 and a true seroresponse rate of ≥95% in children, a true between-group difference of ≤4%, and a non-inferiority margin for the seroresponse rate difference of 10%.

The primary immunogenicity endpoints were the GM value of neutralizing antibodies (PsVNA [antibody level]) against the original strain and seroresponse rate at 28 days after the booster dose. The non-inferiority of the post-booster immunogenicity data in Study P204 to the immunogenicity data from participants aged 18 to 25 years in Study P301 (data at 28 days after the second dose of the primary series of the monovalent [Original] vaccine 100 μg) was evaluated based on the GMR of neutralizing antibodies (the ratio of Study P204 [6 to 11 years] to Study P301 [18 to 25 years]) and the difference in seroresponse rates (Study P204 [6 to 11 years] minus Study P301 [18 to 25 years]). Seroresponse was defined as a ≥4-fold rise in neutralizing antibody levels from pre-primary series (if neutralizing antibody level reported was below the LLOQ, a ≥4-fold rise from the LLOQ). The non-inferiority of the results was considered to be demonstrated if both of the following non-inferiority success criteria were met.

1) As for the GM values of neutralizing antibodies, the lower bound of the two-sided 95% CI of the GMR is >0.67 based on the non-inferiority margin of 1.5.
2) As for the neutralizing antibody seroresponse rate, the lower bound of the two-sided 95% CI of the seroresponse rate difference is >−10% based on the non-inferiority margin of 10%.

Table 6 shows the results of the primary immunogenicity endpoints at 28 days after the booster dose. The lower bound of the two-sided 95% CI for the GMR of neutralizing antibodies against the original strain and the lower bound of the two-sided 95% CI of the difference in the seroresponse rate of neutralizing antibodies against the original strain were greater than the non-inferiority margins, indicating that the results met the prespecified success criteria for non-inferiority.

Table 6. Comparison of serum neutralizing antibody levels against the original strain (Study P204 [booster dose]: PPIS-Neg)

	P204 (6-11 years)	P301 (18-25 years)
	Monovalent (Original) Booster dose 25 μg N = 95	Monovalent (Original) Primary series 100 μg N = 295
28 days post-booster (Study P204) or 28 days post-second dose of primary series (Study P301)		
N1	95	294
GMC [two-sided 95% CI][a)]	5847.487 [5212.299, 6560.079]	1400.411 [1272.681, 1540.961]
GLSM [two-sided 95% CI][b)]	5847.487 [4999.636, 6839.118]	1400.411 [1281.102, 1530.832]
GMR [two-sided 95% CI][b)]	4.176 [3.487, 5.000]	
Seroresponse rate		
N1	88	294
n[c)]	88	292
Seroresponse rate (%) [two-sided 95% CI][d)]	100 [95.9, 100.0]	99.3 [97.6, 99.9]
Seroresponse rate difference [two-sided 95% CI][e)]	0.7 [−3.5, 2.4]	

PsVNA (antibody level)

Antibody levels reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Antibody levels greater than the ULOQ were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 10-281600).

N = number of participants evaluated; N1 = number of participants with non-missing data at the evaluation time point

GMR = the ratio of Study P204 to Study P301; seroresponse rate difference = Study P204 minus Study P301

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for geometric mean antibody level, and then back-transformed to the original scale for representation.

b) An analysis of covariance model with the antibody level at 28 days post-booster dose in Study P204 and 28 days post-second dose of the primary series in Study P301 as the dependent variable, and the group variable (children aged 6-11 years in Study P204 and adults aged 18-25 years in Study P301) as the fixed effect

c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody levels from the pre-primary series (if below the LLOQ, a ≥4-fold rise from the LLOQ)

d) Two-sided 95% CI was calculated using the Clopper-Pearson method.

e) Two-sided 95% CI was calculated using the Miettinen-Nurminen method.

The grading scale used for the assessment of the severity of adverse events and the safety follow-up period were similar to those used in the evaluation of the primary series [see Section 7.1.1].

Table 7 shows the incidence of solicited adverse events reported through 7 days post-booster dose.

Table 7. The incidence of solicited adverse events reported through 7 days post-booster dose (Study P204 [booster dose]: Solicited adverse event analysis set)

Event	P204 (6-11 years)		
	Monovalent (Original) 25 μg N = 1280		
		All Grades	Grade ≥3
	N1	n (%)	n (%)
Any local adverse event	1279	1165 (91.1)	33 (2.6)
Pain	1279	1152 (90.1)	24 (1.9)
Erythema (redness)	1279	137 (10.7)	4 (0.3)
Swelling/induration	1279	139 (10.9)	4 (0.3)
Lymphadenopathy[a)]	1279	355 (27.8)	4 (0.3)
Any systemic adverse event	1280	823 (64.3)	78 (6.1)
Fever[b)]	1276	108 (8.5)	17 (1.3)
Headache	1280	489 (38.2)	22 (1.7)
Fatigue	1279	625 (48.9)	47 (3.7)
Myalgia	1280	269 (21.0)	19 (1.5)
Arthralgia	1279	160 (12.5)	12 (0.9)
Nausea/vomiting	1279	168 (13.1)	6 (0.5)
Chills	1279	179 (14.0)	4 (0.3)

N = number of participants analyzed; N1 = number of participants who submitted any data for the event; n = number of participants with the event
a) Axillary swelling or tenderness ipsilateral to the injection site
b) ≥38°C (oral temperature)

The incidence of unsolicited adverse events reported through 28 days post-booster dose was 13.1% (169 of 1,294 participants) and the incidence of unsolicited adverse events classified as adverse reactions was 4.0% (52 of 1,294 participants). Unsolicited adverse events occurring in ≥1% of participants were COVID-19 (1.9%, 25 participants), upper respiratory tract infection (1.3%, 17 participants), headache (1.2%, 15 participants), and fatigue (1.0%, 13 participants). Among these events, those for which a causal relationship to the study vaccine could not be ruled out were fatigue (13 participants), headache (12 participants), and COVID-19 (4 participants).

No adverse events leading to death occurred, nor did any adverse events lead to study discontinuation.

Serious adverse events occurred in 1 participant (abdominal pain). A causal relationship of the event to the study vaccine was ruled out and the outcome of the event was reported as resolved.

7.2 Foreign phase II/III study (CTD 5.3.5.1.2, Study mRNA-1273-P205, ongoing since May 2021 [data cut-off date for interim analysis, September [redacted], 2022 (Part H)])

Study P205 was an open-label phase II/III study consisting of 8 parts, Parts A through H, conducted in adults aged ≥18 years to evaluate the safety and immunogenicity of a booster dose of mRNA vaccines[18)] against SARS-CoV-2 variants. Initially, Study P205 was commenced as a study to investigate the first booster dose, and the study design was changed during the study period to add the evaluation of the second booster dose (Protocol Amendments: addition of Part F Cohort 2[19)] and changes to study plan

[18)] In addition to the bivalent (Original/Omicron BA.4-5) vaccine, the bivalent vaccine against Beta (B.1.351) variant, the monovalent and bivalent vaccines against Delta (B.1.617.2) variant, and the monovalent and bivalent vaccines against Omicron BA.1.
[19)] In Part F Cohort 2, the monovalent vaccine against Omicron BA.1 administered as a second booster dose was also evaluated; however, the data submitted for the present application do not include the data on vaccination with the monovalent vaccine.

on January [redacted], 2022 and February [redacted], 2022; addition of Part H and changes to study plan on August [redacted], 2022 and September [redacted], 2022).

7.2.1 Study P205 Part H

Study P205 Part H was conducted at 23 study centers in the US to evaluate the safety and immunogenicity of the bivalent (Original/Omicron BA.4-5) vaccine administered as a second booster dose at ≥3 months post-first booster dose in participants aged ≥18 years who had received 2 doses of the monovalent (Original) vaccine 100 μg as the primary series and 1 booster dose of the monovalent (Original) vaccine 50 μg (target sample size, 500 participants[20)]). The immunogenicity was evaluated using data from the monovalent (Original) vaccine group in Part F Cohort 2 as a comparator group (the group of participants aged ≥18 years who received the monovalent [Original] vaccine as a second booster dose following 2 doses of the monovalent [Original] vaccine 100 μg as the primary series and 1 booster dose of the monovalent [Original] vaccine 50 μg; hereinafter referred to as Part F). The participants were to receive 1 dose of the bivalent (Original/Omicron BA.4-5) vaccine 50 μg intramuscularly.

Of the 511 enrolled participants,[21)] 511 participants received the study vaccine and were included in the FAS and the safety analysis set. Of the participants in the safety analysis set, 508 participants provided solicited adverse event data from their participant diary and were included in the solicited adverse event analysis set. Of the participants included in the FAS, 490 participants were included in the PPIS, and the remaining 21 participants (missing data on neutralizing antibody titers against Omicron BA.4-5 lineage at pre-study vaccination baseline and 28 days post-study vaccination [19 participants], serious protocol deviations [1 participant], and human immunodeficiency virus (HIV) infection [1 participant]) were excluded from the analysis. Of the participants included in the PPIS, 209 participants with negative SARS-CoV-2 status before study vaccination were included in the PPIS-Neg, which served as the primary immunogenicity subset. A target sample size of 375 was selected for Part F as a comparator group.[20)] The FAS comprised 376 participants, of whom 366 were included in the PPIS, and the remaining 10 participants were excluded from the analysis (missing data on neutralizing antibody titers against Omicron BA.4-5 at pre-study vaccination baseline and 28 days post-study vaccination [6 participants], serious protocol deviations [1 participant], HIV infection [1 participant], and the blood

[20)] The results shown below were assumed for the evaluation of neutralizing antibodies, the primary objective, at 28 days after study vaccination. To demonstrate the non-inferiority or superiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine at a two-sided α of 0.05, approximately 300 and 260 participants in Part H and Part F Cohort 2, respectively, would provide approximately 60% power for detection in the overall study. Assuming 40% of participants in Part H and 20% of participants in Part F Cohort 2 would be excluded from the PPIS-Neg, target sample sizes of 500 and 375 were selected for Part H and Part F Cohort 2, respectively.

- Assuming that the GMR of neutralizing antibodies against Omicron BA.4-5 (the ratio of the bivalent [Original/Omicron BA.4-5] vaccine to the monovalent [Original] vaccine) after the second booster dose (primary endpoint) is 1.5 and that the standard deviation for the log-transformed value is 1.5, the result is assessed for non-inferiority with a non-inferiority margin of 0.67.
- Assuming that the post-second booster seroresponse rates against Omicron BA.4-5 and the original strain (primary endpoint) are 95% both for participants receiving the bivalent (Original/Omicron BA.4-5) vaccine and those receiving the monovalent (Original) vaccine, the difference in seroresponse rate (the bivalent [Original/Omicron BA.4-5] vaccine minus the monovalent [Original] vaccine) is assessed for non-inferiority with a non-inferiority margin of −5% (against Omicron BA.4-5) and −10% (against original strain).
- Assuming that the GMR of post-second booster neutralizing antibodies against the original strain (the ratio of the bivalent [Original/Omicron BA.4-5] vaccine to the monovalent [Original] vaccine) (primary endpoint) is 1, and that the standard deviation for the log-transformed value is 1.5, the result is assessed for non-inferiority with a non-inferiority margin of 0.67.

[21)] The enrolled participants included participants who had received the primary series and the first booster dose in Study P301 that evaluated the efficacy of the monovalent (Original) vaccine and those who had received the primary series and the first booster dose under EUA in the US.

sample scheduled to be obtained at 28 days post-study vaccination was taken outside the allowable time window [2 participants]). Of the participants included in the PPIS, 259 participants with negative for SARS-CoV-2 status before study vaccination were included in the PPIS-Neg. In the SARS-CoV-2 test, RT-PCR testing and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were performed. Participants who had negative results of both RT-PCR and antibody testing were considered SARS-CoV-2 negative, and those who a positive result of RT-PCR or antibody testing were considered SARS-CoV-2 positive.

The median interval between the first booster dose and the second booster dose in the safety analysis set was 289.0 days (range, 103-371 days) in Part H and 134.0 days (range, 90-310 days) in Part F, while that in the PPIS-Neg was 288 days (range, 138-334 days) in Part H and 133 days (range, 90-310 days) in Part F.

The primary immunogenicity endpoints consisted of the following: the GMR (the ratio of the bivalent [Original/Omicron BA.4-5] vaccine to the monovalent [Original] vaccine) for neutralizing antibodies (as measured by PsVNA at 50% inhibitory dilution) against Omicron BA.4-5; the difference in seroresponse rate (the bivalent [Original/Omicron BA.4-5] vaccine minus the monovalent [Original] vaccine); the GMR (the ratio of the bivalent [Original/Omicron BA.4-5] vaccine to the monovalent [Original] vaccine) for neutralizing antibodies against the original strain; and the difference in seroresponse rate (the bivalent [Original/Omicron BA.4-5] vaccine minus the monovalent [Original] vaccine). The seroresponse was defined as a ≥4-fold rise in neutralizing antibody titers from pre-primary series (if neutralizing antibody titers reported were below the LLOQ, a ≥4-fold rise from the LLOQ). Participants who did not have pre-primary series antibody titer data and who had a negative SARS-CoV-2 status before the primary series were considered to have a pre-primary series antibody titer of <LLOQ. Participants who did not have pre-primary series antibody titer data and who had a positive SARS-CoV-2 status before the primary series were handled as those with missing pre-primary series antibody titer data, who were not evaluable for seroresponse. If the participant did not have any information on the pre-primary series antibody titer or SARS-CoV-2 status, the pre-second booster SARS-CoV-2 test result was to be imputed as the pre-primary series SARS-CoV-2 test result.

For the primary endpoints, the 5 main hypotheses shown below, 1 through 5, were tested. The superiority of the bivalent (Original/Omicron BA.4-5) vaccine described in Hypothesis 5 would be assessed only if the non-inferiority of the bivalent (Original/Omicron BA.4-5) vaccine was demonstrated for all Hypotheses 1 through 4 at each analysis time point.

1. Non-inferiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine based on the GMR of neutralizing antibodies against Omicron BA.4-5 (non-inferiority margin of 0.667)
2. Non-inferiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine based on the difference in the neutralizing antibody seroresponse rate against Omicron BA.4-5 (non-inferiority margin of −5%)

3. Non-inferiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine based on the GMR of neutralizing antibodies against the original strain (non-inferiority margin of 0.667)
4. Non-inferiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine based on the difference in the neutralizing antibody seroresponse rate against the original strain (non-inferiority margin of −10%)
5. Superiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine based on the GMR of neutralizing antibody against Omicron BA.4-5

Table 8 shows the results for the primary immunogenicity endpoints at 28 days after study vaccination. The lower bound of the two-sided 95% CI of the GMR of neutralizing antibodies against Omicron BA.4-5 and that against the original strain were all greater than the non-inferiority margin of 0.667. The lower bound of the two-sided 95% CI of the difference in the neutralizing antibody seroresponse rate against Omicron BA.4-5 and that against the original strain were greater than the non-inferiority margin of −5% and −10%, respectively. The prespecified success criteria for non-inferiority were met. The lower bound of the two-sided 95% CI of the GMR of neutralizing antibodies against Omicron BA.4-5 was greater than the superiority margin of 1. The prespecified success criterion for superiority was met.

Table 8. Comparison of serum neutralizing antibody titers against Omicron BA.4-5 and the original strain (Study P205: PPIS-Neg)

	Omicron BA.4-5		Original strain	
	Part H	Part F	Part H	Part F
	Bivalent (Original/Omicron BA.4-5) 50 μg N = 209	Monovalent (Original) 50 μg N = 259	Bivalent (Original/Omicron BA.4-5) 50 μg N = 209	Monovalent (Original) 50 μg N = 259
Pre-second booster dose				
n	209	259	209	259
GMT [two-sided 95% CI][a)]	87.9 [72.2, 107.1]	136.1 [116.3, 159.3]	796.9 [678.7, 935.8]	1515.4 [1347.5, 1704.2]
28 days post-second booster dose				
n	209	259	209	259
GMT [two-sided 95% CI][a)]	2324.6 [1921.2, 2812.7]	488.5 [427.4, 558.4]	7322.4 [6386.2, 8395.7]	5651.4 [5055.7, 6317.3]
GMFR [two-sided 95% CI][a)]	26.4 [22.0, 31.9]	3.6 [3.3, 4.0]	9.2 [7.9, 10.6]	3.7 [3.4, 4.1]
GLSM [two-sided 95% CI][b)]	2747.3 [2399.2, 3145.9]	436.7 [389.1, 490.0]	9555.8 [8593.6, 10625.7]	4882.2 [4457.7, 5347.1]
GMR [two-sided 95% CI][b)]	6.29 [5.27, 7.51]		1.96 [1.70, 2.25]	
Seroresponse rate				
N1	209	257	209	259
n[c)]	205	222	209	259
Seroresponse rate (%) [two-sided 95% CI][d)]	98.1 [95.2, 99.5]	86.4 [81.6, 90.3]	100 [98.3, 100]	100 [98.6, 100]
Difference in seroresponse rate [two-sided 95% CI][e)]	12.1 [6.9, 17.3]		0	

PsVNA (50% inhibitory dilution)

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Values greater than the ULOQ were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 36.7-13705 [Omicron BA.4-5], 18.5-45118 [original strain]).

N = number of participants evaluated; N1 = number of participants with non-missing data both before the primary series and after the second booster dose; n = number of participants with non-missing data at the evaluation timepoint

GMR = the ratio of the bivalent (Original/Omicron BA.4-5) vaccine to monovalent (Original) vaccine; difference in seroresponse rate = the bivalent (Original/Omicron BA.4-5) vaccine minus monovalent (Original) vaccine

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or the fold rise in antibody titer and back-transformed to the original scale for representation.

b) An analysis of covariance model with adjustment for age group (<65 years vs. ≥65 years) and pre-second booster titer, with the post-second booster titer as the dependent variable and study vaccine group (bivalent [Original/Omicron BA.4-5] vaccine vs. monovalent [Original] vaccine) as the fixed effect

c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from the pre-primary series (if below the LLOQ, a ≥4-fold rise from the LLOQ). Participants who did not have pre-primary series antibody titer data and who had a negative SARS-CoV-2 status before the primary series were considered to have a pre-primary series antibody titer of <LLOQ. Participants who did not have pre-primary series antibody titer data and who had a positive SARS-CoV-2 status before the primary series were handled as those with missing pre-primary series antibody titer data, who were not evaluable for seroresponse. If the participant did not have any information on pre-primary series SARS-CoV-2 status, the pre-second booster SARS-CoV-2 test result was to be imputed as the pre-primary series SARS-CoV-2 test result.

d) Two-sided 95% CI was calculated using the Clopper-Pearson method.

e) Two-sided 95% CI was calculated using the stratified Miettinen-Nurminen method adjusted by age group.

The safety follow-up period was as follows:

- Solicited adverse events[7)] (local adverse event: pain, erythema [redness], swelling/induration, and lymphadenopathy[8)]; and systemic adverse event: fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills): Reported through 7 days after study vaccination
- Unsolicited adverse events (excluding solicited adverse events reported through 7 days after study

vaccination): Reported through 28 days after study vaccination

- Serious adverse events, acute myocarditis or pericarditis,[9] and AESI,[10] adverse events requiring treatment: Reported from study vaccination throughout of the study period

Table 9 shows the incidence of solicited adverse events reported through 7 days after study vaccination.

Table 9. The incidence of solicited adverse events reported through 7 days after study vaccination (Study P205, Solicited adverse event analysis set)

Event	Part H		
	Bivalent (Original/Omicron BA.4-5) 50 μg N = 508		
		All Grades	Grade ≥3
	N1	n (%)	n (%)
Any local adverse event	507	420 (82.8)	28 (5.5)
Pain	507	418 (82.4)	20 (3.9)
Erythema (redness)	507	23 (4.5)	5 (1.0)
Swelling/induration	507	40 (7.9)	5 (1.0)
Lymphadenopathy[a)]	507	106 (20.9)	1 (0.2)
Any systemic adverse event	508	372 (73.2)	35 (6.9)
Fever[b)]	507	20 (3.9)	1 (0.2)
Headache	507	249 (49.1)	12 (2.4)
Fatigue	508	304 (59.8)	17 (3.3)
Myalgia	507	235 (46.4)	20 (3.9)
Arthralgia	507	177 (34.9)	9 (1.8)
Nausea/vomiting	507	71 (14.0)	1 (0.2)
Chills	507	112 (22.1)	4 (0.8)

N = number of participants analyzed; N1 = number of participants who submitted any data for the event;
n = number of participants with the event
a) Axillary swelling or tenderness ipsilateral to the injection site
b) ≥38°C (oral temperature)

The incidence of unsolicited adverse events reported through 28 days after study vaccination was 22.7% (116 of 511 participants) and the incidence of unsolicited adverse events classified as adverse reactions was 7.8% (40 of 511 participants). Unsolicited adverse events occurring in >1% of participants were fatigue (4.3%, 22 participants), headache (2.9%, 15 participants), COVID-19 (2.2%, 11 participants), rhinovirus infection (1.4%, 7 participants), and upper respiratory tract infection (1.4%, 7 participants). Among these events, those for which a causal relationship to the study vaccine could not be ruled out were fatigue (22 participants) and headache (12 participants).
Until the data cut-off date (September [redacted], 2022), serious adverse events occurred in 3 participants (anginal equivalent/syncope [1 participant], subarachnoid haemorrhage [1 participant], and anaemia [1 participant]). A causal relationship to the study vaccine was ruled out for all the events. The outcome of the event in one of the participants (subarachnoid haemorrhage) was reported as “death.” No adverse events led to study discontinuation.

A serious adverse event resulting in death (1 participant) was reported after the data cut-off date (September [redacted], 2022). This participant died at home and the cause of death was unknown because autopsy results have not been made available yet. However, given that the participant’s medical history

includes depression, anxiety neurosis, bipolar II disorder, and drug/alcohol dependence, and that there was a possibility of drug overdose preceding the death according to the family's explanation, the death was considered unrelated to the study vaccine by the investigator.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and review strategy

The applicant's explanation about the clinical data package for children aged 6 to 11 years:
The development of Spikevax, including the development of vaccines for children, has been accelerated to address the global public health emergency caused by the SARS-CoV-2 pandemic.

In the development program for the monovalent (Original) vaccine for the primary series in children aged 6 to 11 years, a foreign phase II/III study (Study P024) was conducted in children aged 6 months to ≤12 years to investigate the immunogenicity and safety of Spikevax, and the data of the age group of 6 to 11 years were subjected to analysis. Based on the "Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19"[22)] and "Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19,"[23)] Study P204 was designed to evaluate clinical efficacy by adopting an immunobridging approach that uses clinical immunogenicity data for efficacy evaluation. The applicant extensively discussed with the regulatory agencies of other countries for development of the Study P204 protocol. Part 1 was conducted to find the optimal dose for children aged 6 to 11 years, and the 50 μg dose was selected based on the evaluation of safety and immunogenicity data [see Section 7.1.1]. Subsequently, Part 2 was planned to compare the immunogenicity data from children aged 6 to 11 years to the immunogenicity data from adults aged 18 to 25 years from Study P301.

During the surge of the Omicron variant, published literature reported that although the effectiveness of the monovalent (Original) vaccine used as the primary series in adults aged ≥18 years wanes over time, the monovalent (Original) vaccine used as a booster dose increased vaccine effectiveness against the Omicron variant (*Nature Medicine* 2022;28:1063-71). Based on this finding, the protocol of Study P204 was amended for the development of a booster dose for the pediatric population (Protocol Version 7 prepared on February [redacted], 2022) to facilitate an evaluation of the safety and immunogenicity of the monovalent (Original) vaccine 25 μg as a booster dose in children aged 6 to 11 years who had completed the primary series.

The immunobridging success criteria (the lower bound of the two-sided 95% CI of GMR is >0.67, and the lower bound of the two-sided 95% CI of difference in seroresponse rate is >−10%) were established based on the FDA's guidance document on COVID-19 vaccine development.[23)] The results of immunogenicity analyses comparing data on the primary series in Study P204 (Part 2) to data on the booster dose in adults aged 18 to 25 years in Study P301 showed that the immunobridging success

[22)] https://www.fda.gov/media/139638/download (last accessed on June 6, 2023)
[23)] https://www.fda.gov/media/142749/download (last accessed on June 6, 2023)

criteria were met, suggesting that the monovalent (Original) vaccine in children aged 6 to 11 years is expected to be effective [see Sections 7.1.1, 7.1.2, and 7.R.2]. The safety profiles showed no significant concerns and the results demonstrated the vaccine is tolerable in the pediatric population [see Section 7.R.3].

In light of the circulation of SARS-CoV-2 variants, the applicant began to consider the development of a COVID-19 vaccine targeting variants for use in adults, and decided to develop a bivalent vaccine containing the mRNA encoding the spike protein of the original strain and the mRNA encoding the spike protein of the variant in equal amounts to address the Omicron variant. The bivalent (Original/Omicron BA.1) vaccine induced not only seroresponse against Omicron BA.1 and the original strain, but also induced seroresponse against Omicron BA.4-5 in adults aged ≥18 years regardless of their pre-booster SARS-CoV-2 infection status (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated September 7, 2022). In Study P205 Part H, which enrolled adults aged ≥18 years, the efficacy of the bivalent (Original/Omicron BA.4-5) vaccine as a booster dose was investigated based on the immunogenicity analyses, as is the case of the bivalent (Original/Omicron BA.1) vaccine. The results indicated not only the induction of seroresponse against Omicron BA.4-5 and the original strain, but also the induction of seroresponse against the Omicron BQ.1.1 and XBB.1 lineages [see Section 7.R.2]. Although no clinical studies have been planned or conducted to evaluate the bivalent (Original/Omicron BA.1) vaccine or bivalent (Original/Omicron BA.4-5) vaccine in children aged 6 to 11 years,[24)]the applicant considers that bivalent vaccine data in adults (≥18 years) from Study P205 can be extrapolated to the pediatric age group (6–11 years), and that the efficacy and safety of the bivalent vaccine in children aged 6 to 11 years can be inferred from the results for the booster dose of the monovalent (Original) vaccine in children aged 6 to 11 years from Study P204 conducted based on the FDA's guidance document.[23)]

In Japan, data from the phase I/II study in adults aged ≥20 years (Study TAK-919-1501) demonstrated the immunogenicity and safety of the vaccine in the Japanese population; therefore, no new clinical studies in children aged 6 to 11 years were planned in the development program.

Based on the above, the present application was filed on the basis of the immunogenicity and safety results from Studies P204 and P205 Part H to obtain approval for the indications and dosage and administration of the primary series of the monovalent (Original) vaccine and the booster dose of the bivalent vaccine in children aged 6 to 11 years.

PMDA's view:

The FDA's "Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19 for Use in Pediatric Populations"[25)] states that if the efficacy of a vaccine has been demonstrated in any other

[24)] Following the amendment of Study P204 protocol (Protocol Amendment dated August [redacted], 2022), approximately 130 participants aged 6 to 11 years received the bivalent (Original/Omicron BA.1) vaccine as a booster dose. Safety data from these participants will be available when the study ends.

[25)] https://www.fda.gov/media/149935/download (last accessed on June 6, 2023)

population such as adults, it is possible to infer the vaccine efficacy in a pediatric population by evaluating the GMT of neutralizing antibodies and seroresponse rate through an immunobridging approach. This is based on the following findings: (i) children are less susceptible to SARS-CoV-2 infection and often have a milder COVID-19 disease course, possibly making it difficult to conduct a clinical study with adequate power to demonstrate the efficacy of SARS-CoV-2 vaccines in pediatric populations; and (ii) it has been demonstrated that the neutralizing antibodies serve as a biomarker to infer the efficacy of SARS-CoV-2 vaccines (*Nat Med.* 2021;27:1205-11). In Japan, PMDA issued a document titled "Principles for the Evaluation of Vaccines Against Novel Coronavirus SARS-CoV-2 (Appendix 3): Evaluation of SARS-CoV-2 vaccines based on immunogenicity" on October 22, 2021 (Office of Vaccines and Blood Products, PMDA), which contains PMDA's current thinking. Since it has been gradually revealed that the neutralizing antibody titer after SARS-CoV-2 vaccination is correlated with the vaccine efficacy for the prevention of COVID-19 (*Vaccine.* 2021;39:4423-8, *Nat Med*. 2021;27:1205-11), PMDA's Appendix 3 document states that in the development of a novel SARS-CoV-2 vaccine, it is acceptable to employ an immunobridging approach that uses an immunogenicity index to evaluate the efficacy of the novel vaccine versus an approved SARS-CoV-2 vaccine as the control. The Appendix 3 document also states that immunobridging analysis can be used to evaluate the efficacy of a vaccine in an age group if the analysis uses data from a study in which the efficacy of the vaccine has been evaluated in different age groups. Thus, in the evaluation of data for the expansion of the indication to include children, it is acceptable to evaluate the efficacy of the monovalent (Original) vaccine in pediatric populations through an immunobridging approach because the vaccine efficacy has already been demonstrated in the population ≥18 years of age.

For the above reasons, the following evaluation policies of the applicant are acceptable: in the development of the monovalent (Original) vaccine for use in children aged 6 to 11 years, the neutralizing antibody titers are assessed in a pediatric clinical study and the efficacy of the primary series in children aged 6 to 11 years is evaluated by comparing the pediatric data to the data of a different age group in which the efficacy of the vaccine has already been demonstrated. Furthermore, in light of the information presented in the guidance documents mentioned above, the efficacy of the primary series and the booster dose can be evaluated according to the prespecified immunobridging success criteria.

For the regulatory submission for use of the bivalent vaccine in children aged 6 to 11 years, the clinical study on the booster dose in the pediatric population aged 6 to 11 years was conducted using the monovalent (Original) vaccine, but no pediatric data were available from studies with the bivalent (Original/Omicron BA.1) vaccine or the bivalent (Original/Omicron BA.4-5) vaccine.[24)] However, in Japan, Spikevax has already been granted regulatory approval for its use as a booster dose in individuals aged ≥12 years, and the efficacy of the bivalent (Original/Omicron BA.4-5) vaccine during the Omicron surge has been reported (*MMWR Morb Mortal Wkly Rep*. 2022;71:1526-30). Outside Japan, a bivalent vaccine and the bivalent (Original/Omicron BA.4-5) vaccine are available in Europe and the US, respectively, for a booster dose in children aged 6 to 11 years. Given this situation, it is meaningful to provide this age group with access to an Omicron-adapted bivalent vaccine in Japan. Evaluation of the

efficacy of the booster dose of the monovalent (Original) vaccine is addressed in the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1): Evaluation of vaccines against variants" (Office of Vaccines and Blood Products, PMDA, dated on April 5, 2021), which recommends evaluating the post-booster efficacy of a variant-adapted vaccine based on comparison of post-booster immunogenicity data and those on immunogenicity after the primary series with the parent vaccine. Based on the above information as well as the details in the Appendix 3 document, it is acceptable to assess the immunogenicity of the booster dose in Study P204 and to evaluate the efficacy of the booster dose in pediatric population by comparing the post-booster immunogenicity data to the post-primary series data in participants aged 18 to 25 years from Study P301. Study P205 Part H evaluated the booster dose of the bivalent (Original/Omicron BA.4-5) vaccine. PMDA issued a document titled "Principles for the Evaluation of Vaccine Against the Novel Coronavirus SARS-CoV-2 (Appendix 4): Immunogenicity-based evaluation of variant vaccines modified from parent vaccines and booster vaccines with new active ingredients" on July 15, 2022. According to the Appendix 4 document, the efficacy of the bivalent (Original/Omicron BA.4-5) vaccine can be evaluated by verifying the superiority (based on GMR) and non-inferiority (difference in the seroresponse rate) of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine in terms of neutralizing antibody titers against Omicron BA.4-5. The applicant used Part F as the non-concurrent control to evaluate the data from Part H in Study P205. Although a concurrent control should have been established within Part H under normal circumstances, the study conducted according to the applicant's plan was considered acceptable because the situation required urgent development of variant-adapted vaccines. Thus, the submitted data were subjected to review.

Accordingly, PMDA decided to evaluate the efficacy and safety of the booster dose of the bivalent vaccine in the pediatric population aged 6 to 11 years based on data that included the following: data from Study P204, which evaluated the efficacy and safety of the monovalent (Original) vaccine in the pediatric population aged 6 to 11 years; immunogenicity and safety data from Study P205 Part H, a clinical study of the bivalent (Original/Omicron BA.4-5) vaccine in adults aged ≥18 years, and currently available study data on the bivalent (Original/Omicron BA.1) vaccine.

7.R.2 Efficacy

The applicant's explanation about the efficacy of Spikevax in children aged 6 to 11 years:

(1) Primary series (monovalent [Original] vaccine)

The results for the primary endpoints of Study P204 Part 2, the GM value of neutralizing antibodies against the original strain and seroresponse rate at 28 days after the second dose of the study vaccine, met the prespecified success criteria [see Section 7.1.1]. The demographics and baseline characteristics of Study P204 Part 2 participants were similar to those of the control, participants aged 18 to 25 years enrolled in Study P301, except for body weight (Table 10).

Table 10. Comparison of demographics and baseline characteristics of participants (Study P204 Part 2: PPIS)

		P204 (6-11 years) Monovalent (Original) 50 µg N = 320	P301 (18-25 years) Monovalent (Original) 100 µg N = 295
		n (%)	n (%)
Sex	Male	168 (52.5)	142 (48.1)
	Female	152 (47.5)	153 (51.9)
Race	White	220 (68.8)	206 (69.8)
	Black	36 (11.3)	29 (9.8)
	Asian	23 (7.2)	30 (10.2)
	Multiracial	29 (9.1)	14 (4.7)
	Other[a)] or unknown	12 (3.8)	16 (5.4)
Ethnicity	Hispanic or Latino	51 (15.9)	78 (26.4)
	Non-Hispanic or non-Latino	266 (83.1)	215 (72.9)
	Unknown	3 (0.9)	2 (0.7)
Body weight (kg)	Median (range)	31.33 (16.8, 112.0)	73.62 (44.0, 158.2)

N = number of participants evaluated; n = number of participants applicable

a) American Indians, Alaska natives, Native Hawaiians, and others

The incidence rate of SARS-CoV-2 infection and the incidence rate of COVID-19, the secondary endpoints of Study P204 Part 2 (primary series) were evaluated. In Study P204, the protocol allowed unblinding following the issuance of the EUA for the SARS-CoV-2 vaccine and administration of the monovalent (Original) vaccine to participants in the placebo group after the unblinding. The study was conducted under blinded conditions with a relatively short follow-up period, and the follow-up period was further shortened due to unblinding of the participants because the SARS-CoV-2 vaccine for use in children was authorized under the EUA (the median follow-up period was 51 days after the second dose of the study vaccine). At ≥14 days after the second dose of the study vaccine, only 7 participants had COVID-19 (3 participants in the monovalent [Original] vaccine group, an incidence rate of 5.043/1,000 person-years; and 4 participants in the placebo group, an incidence rate of 21.716/1,000 person-years). Because this result was not sufficient for a meaningful analysis, vaccine efficacy (VE) was evaluated for the period starting 14 days after the first dose of the study vaccine. Table 11 shows the results of evaluation of VE starting 14 days after the first dose of the study vaccine.

Table 11. VE starting 14 days after the first dose of the study vaccine (Study P204 Part 2: mITT1)

	Monovalent (Original) 50 µg N = 2687	Placebo N = 880
Case definition in Study P301		
Confirmed COVID-19 according to the case definition[a)] in Study P301 n/N1 (%)	4/2681 (0.1)	15/877 (1.7)
VE [two-sided 95% CI][b)]	0.918 [0.742, 0.980]	
CDC case definition		
Confirmed COVID-19 according to the CDC case definition[c)] n/N1 (%)	7/2680 (0.3)	18/875 (2.1)
VE [two-sided 95% CI][b)]	0.880 [0.700, 0.958]	
SARS-CoV-2 infection (regardless of symptoms)		
Confirmed SARS-CoV-2 infection[d)] n/N1 (%)	34/2678 (1.3)	40/875 (4.6)
VE [two-sided 95% CI][b)]	0.740 [0.579, 0.841]	

N = number of participants evaluated; N1 = number of participants at risk at 14 days after the first dose for specific endpoint; n = number of participants with SARS-CoV-2 infection according to the respective definition

VE = 1 minus the incidence rate ratio (i.e., the ratio of monovalent [Original] vaccine 50 µg to placebo)

a) Had a positive post-first dose RT-PCR test result AND eligible symptoms as follows:
At least 2 systemic symptoms: fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory or taste disorder; OR
At least one of the following respiratory signs/symptoms: cough, shortness of breath, difficulty breathing; or clinical or radiographical evidence of pneumonia

b) The incidence rate for each group was defined as the number of participants with confirmed COVID-19 divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The two-sided 95% CI of VE was calculated using the exact method conditional on the total number of confirmed cases, adjusted by person-years.

c) Had at least 1 positive RT-PCR test result for SARS-CoV-2, and at least 1 symptom (lasting ≥48 hours) from the following prescribed list of COVID-19 symptoms derived from the CDC case definition:
Systemic symptoms: fever (≥38°C) or chills (of any duration including ≤48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea or vomiting, poor appetite or poor feeding, OR respiratory signs/symptoms: cough (of any duration including ≤48 hours), shortness of breath or difficulty breathing (of any duration including ≤48 hours)

d) A negative antibody test result based on binding antibodies specific to SARS-CoV-2 nucleocapsid pre-first dose that became positive post-first dose, OR a positive RT-PCR test result post-first dose.

An exploratory analysis was performed in participants in the PPIS of Part 1 (134 participants in the 50 µg group) for neutralizing antibody titers against the Delta variant, which was circulating during the study period of Study P204 Part 2. At 28 days after the second dose of the monovalent (Original) vaccine, the GMT, GMFR, and seroresponse rate of neutralizing antibody against the Delta variant and their two-sided 95% CI were as follows: GMT: 756.36 [650.99, 878.77], GMFR: 81.77 [70.38, 95.00], seroresponse rate: 99.3% [95.9%, 100.0%], indicating the induction of immunity against the Delta variant.

The neutralizing antibody titers against Omicron BA.1 were evaluated using specimens from 20 participants aged 6 to 11 years in Study P204 Part 1. At 28 days after the second dose of the monovalent (Original) vaccine, the GMT of neutralizing antibodyies against the original strain (ID_{50} Log_{10}) was 2,102, while that against Omicron BA.1 (ID_{50} Log_{10}) was 95. The GMT of neutralizing antibodies against the original strain (ID_{50} Log_{10}) measured concurrently in 20 adults from Study P301 was 1,039, while that against Omicron BA.1 was 36, indicating that the GMT against Omicron BA.1 (ID_{50} Log_{10}) in the pediatric population (6 to 11 years of age) was 2.5 times that in the adult population (medRxiv 2022; https://doi.org/10.1101/2022.01.24.22269666).

Taken together, the primary series vaccination with the monovalent (Original) vaccine is expected to be effective in children aged 6 to 11 years, based on the following findings: (1) the non-inferiority of the immunogenicity data in the pediatric population aged 6 to 11 years in Study P204 to that in the population aged 18 to 25 years in Study P301 has been demonstrated; (2) based on COVID-19 cases occurring at least 14 days after the first dose of the study vaccine, the VE in the pediatric population is comparable to the VE [two-sided 99.1% CI] in adults aged ≥18 years from Study P301 (VE in COVID-19 cases occurring at least 14 days after the second dose of the study vaccine), which is 94.5% [81.8%, 98.3%], although it is a secondary endpoint with a different evaluation period (Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated on May 17, 2021); and (3) an increase in neutralizing antibody titer against variants was observed.

(2) Booster dose (monovalent [Original] vaccine)

The evaluation of the booster dose in Study P204 showed that the GM value of the neutralizing antibody level and seroresponse rate against the original strain at 28 days after the booster dose, the primary immunogenicity endpoints, met the prespecified non-inferiority success criteria [see Section 7.1.2]. Table 12 shows the neutralizing antibody levels against the original strain and the Omicron BA.1 by SARS-CoV-2 status. Not only the neutralizing antibody levels against the original strain but also those against Omicron BA.1 were increased by the booster dose of the monovalent (Original) vaccine.

Table 12. Neutralizing antibody levels by pre-booster SARS-CoV-2 status (Study P204 [booster dose]: PPIS)

	Original strain			Omicron BA.1		
	SARS-CoV-2 negative	SARS-CoV-2 positive	PPIS total	SARS-CoV-2 negative	SARS-CoV-2 positive	PPIS total
	Monovalent (Original) 25 μg N = 95	Monovalent (Original) 25 μg N = 27	Monovalent (Original) 25 μg N = 129	Monovalent (Original) 25 μg N = 95	Monovalent (Original) 25 μg N = 27	Monovalent (Original) 25 μg N = 129
Pre-booster dose						
n	95	27	129	92	27	124
GMC [two-sided 95% CI][a)]	485.6 [423.1, 557.3]	4513.3 [2979.3, 6837.1]	780.3 [635.5, 958.2]	53.0 [45.3, 61.9]	1360.6 [939.5, 1970.4]	108.5 [82.4, 143.0]
28 days post-booster dose						
n	95	27	129	95	27	129
GMC [two-sided 95% CI][a)]	5847.5 [5212.3, 6560.1]	8903.7 [6736.9, 11767.6]	6586.1 [5906.6, 7343.8]	632.6 [546.7, 731.9]	2362.9 [1778.0, 3140.4]	860.6 [737.0, 1004.9]
GMFR [two-sided 95% CI][a)]	12.0 [10.3, 14.1]	2.0 [1.4, 2.8]	8.4 [7.0, 10.2]	12.1 [9.7, 15.0]	1.7 [1.3, 2.3]	8.1 [6.5, 10.1]
Seroresponse rate						
N1	88	25	120	50	19	70
n[b)]	88	25	120	50	19	70
Seroresponse rate (%) [two-sided 95% CI][c)]	100 [95.9, 100.0]	100 [86.3, 100.0]	100 [97.0, 100.0]	100 [92.9, 100.0]	100 [82.4, 100.0]	100 [94.9, 100.0]

PsVNA (antibody level)

Antibody levels reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Antibody levels greater than the ULOQ were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 10-281600 [Original strain]; 8-41984 [Omicron BA.1]).

N = number of participants evaluated; N1 = number of participants with non-missing data both before the primary series and after the booster dose; n = number of participants with non-missing data at the evaluation timepoint

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody level or the fold rise in antibody level, and back-transformed to the original scale for representation.

b) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody levels from the pre-primary series (if below the LLOQ, a ≥4-fold rise from the LLOQ)

c) Two-sided 95% CI was calculated using the Clopper-Pearson method.

Published literature has reported that administration of a booster dose of the monovalent (Original) vaccine to adults countered a decline in serum neutralizing antibody titers, increasing clinical effectiveness in the prevention of COVID-19, hospitalization, and COVID-19-related death (*Nat Med.* 2022;28:1042-9, *Nat Med.* 2022;28:1063-71). The results from Study P204 support the efficacy of the booster dose of the monovalent (Original) vaccine in children aged 6 to 11 years.

(3) Booster dose (bivalent vaccine)

The evaluation of the booster dose of the bivalent (Original/Omicron BA.4-5) vaccine in Study P205 Part H showed that all of the 4 prespecified success criteria for the non-inferiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine (primary immunogenicity endpoints) were met. Furthermore, the superiority of the bivalent (Original/ Omicron BA.4-5) vaccine to the monovalent (Original) vaccine in terms of GMR was also demonstrated [see Section 7.2.1]. The results, therefore, demonstrated that the bivalent (Original/Omicron BA.4-5) vaccine induced a higher seroresponse against Omicron BA.4-5 compared to the monovalent (Original) vaccine.

Table 13 shows the results for neutralizing antibody titers in the group regardless of pre-second booster SARS-CoV-2 status. The results are similar to those for the primary analysis set (PPIS-Neg) (Table 8).

Table 13. Comparison of serum neutralizing antibody titers against Omicron BA.4-5 and the original strain (Study P205: PPIS)

	Omicron BA.4-5		Original strain	
	Part H	Part F	Part H	Part F
	Bivalent (Original/Omicron BA.4-5) 50 μg N = 490	Monovalent (Original) 50 μg N = 366	Bivalent (Original/Omicron BA.4-5) 50 μg N = 490	Monovalent (Original) 50 μg N = 366
Pre-second booster dose				
n	490	366	490	366
GMT [two-sided 95% CI][a)]	284.2 [243.9, 331.3]	205.3 [175.8, 239.8]	1619.7 [1439.3, 1822.8]	1941.0 [1721.5, 2188.4]
28 days post-second booster dose				
n	490	366	490	366
GMT [two-sided 95% CI][a)]	4289.4 [3789.0, 4855.9]	642.5 [567.1, 727.9]	9318.9 [8541.0, 10167.7]	6050.2 [5466.3, 6696.4]
GMFR [two-sided 95% CI][a)]	15.1 [13.3, 17.1]	3.1 [2.9, 3.4]	5.8 [5.2, 6.3]	3.1 [2.9, 3.4]
GLSM [two-sided 95% CI][b)]	4198.3 [3819.2, 4615.2]	725.7 [653.2, 806.4]	10658.0 [9909.2, 11463.3]	5609.4 [5165.8, 6091.2]
GMR [two-sided 95% CI][b)]	5.79 [5.05, 6.63]		1.90 [1.71, 2.11]	
Seroresponse rate				
N1	375	341	387	346
n[c)]	370	304	387	346
Seroresponse rate (%) [two-sided 95% CI][d)]	98.7 [96.9, 99.6]	89.1 [85.4, 92.2]	100 [99.1, 100]	100 [98.9, 100.0]
Difference in seroresponse rate [two-sided 95% CI][e)]	8.7 [5.1, 12.3]		0	

PsVNA (50% inhibitory dilution)

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Values greater than the ULOQ were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 36.7-13705 [Omicron BA.4-5], 18.5-45118 [original strain]).

N = number of participants evaluated; N1= number of participants with non-missing data both before the primary series and after the second booster dose; n = number of participants with non-missing data at the evaluation timepoint

GMR = the ratio of the bivalent (Original/Omicron BA.4-5) vaccine to monovalent (Original) vaccine; seroresponse rate difference = the bivalent (Original/Omicron BA.4-5) vaccine minus monovalent (Original) vaccine

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or the fold rise in antibody titer and back-transformed to the original scale for representation.

b) An analysis of covariance model with adjustment for age group (<65 years vs. ≥65 years) and pre-second booster titer, with the post-second booster titer as the dependent variable and study vaccine group (bivalent [Original/Omicron BA.4-5] vaccine vs. monovalent [Original] vaccine) as the fixed effect

c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from the pre-primary series (if below the LLOQ, a ≥4-fold rise from the LLOQ). Participants who did not have pre-primary series antibody titer data and who had a negative SARS-CoV-2 status before primary series were considered to have a pre-primary series antibody titer of <LLOQ. Participants who did not have pre-primary series antibody titer data and who had a positive SARS-CoV-2 status before the primary series were handled as those with missing pre-primary series antibody titer data, who were not evaluable for seroresponse. If the participant did not have any information on pre-primary series SARS-CoV-2 status, the pre-second booster SARS-CoV-2 test result was to be imputed as the pre-primary series SARS-CoV-2 test result.

d) Two-sided 95% CI was calculated using the Clopper-Pearson method.

e) Two-sided 95% CI was calculated using the stratified Miettinen-Nurminen method adjusted by age group.

Table 14 shows the neutralizing antibody titers by pre-second booster SARS-CoV-2 status. The results by pre-second booster status show an overall tendency towards higher GMT in the SARS-CoV-2 positive group than in the SARS-CoV-2 negative group, while GMR and the seroresponse rate in the

SARS-CoV-2 positive group are similar to those in the SARS-CoV-2 negative group (PPIS-Neg). The bivalent (Original/Omicron BA.4-5) vaccine elicited a greater rise in neutralizing antibody titers compared to the monovalent (Original) vaccine.

Table 14. Neutralizing antibody titers by pre-second booster SARS-CoV-2 test result status (Study P205, PPIS)

	Omicron BA.4-5				Original strain			
	SARS-CoV-2 negative		SARS-CoV-2 positive		SARS-CoV-2 negative		SARS-CoV-2 positive	
	Part H	Part F	Part H	Part F	Part H	Part F	Part H	Part F
	Bivalent (Original/Omicron BA.4-5) 50 μg N = 209	Monovalent (Original) 50 μg N = 259	Bivalent (Original/Omicron BA.4-5) 50 μg N = 274	Monovalent (Original) 50 μg N = 99	Bivalent (Original/Omicron BA.4-5) 50 μg N = 209	Monovalent (Original) 50 μg N = 259	Bivalent (Original/Omicron BA.4-5) 50 μg N = 274	Monovalent (Original) 50 μg N = 99
Pre-second booster dose								
N	209	259	274	99	209	259	274	99
GMT [two-sided 95% CI][a)]	87.9 [72.2, 107.1]	136.1 [116.3, 159.3]	710.2 [606.9, 831.1]	616.8 [453.1, 839.8]	796.9 [678.7, 935.8]	1515.4 [1347.5, 1704.2]	2841.1 [2475.0, 3261.4]	3649.5 [2758.5, 4828.2]
28 days post-second booster dose								
N	209	259	274	99	209	259	274	99
GMT [two-sided 95% CI][a)]	2324.6 [1921.2, 2812.7]	488.5 [427.4, 558.4]	6964.5 [6043.7, 8025.4]	1280.2 [996.7, 1644.3]	7322.4 [6386.2, 8395.7]	5651.4 [5055.7, 6317.3]	11197.9 [10035.1, 12495.5]	6979.3 [5585.6, 8720.9]
GMFR [two-sided 95% CI][a)]	26.4 [22.0, 31.9]	3.6 [3.3, 4.0]	9.8 [8.4, 11.4]	2.1 [1.8, 2.4]	9.2 [7.9, 10.6]	3.7 [3.4, 4.1]	3.9 [3.5, 4.4]	1.9 [1.6, 2.2]
GLSM [two-sided 95% CI][b)]	2747.3 [2399.2, 3145.9]	436.7 [389.1, 490.0]	7607.7 [6607.4, 8759.5]	1490.2 [1217.3, 1824.4]	9555.8 [8593.6, 10625.7]	4882.2 [4457.7, 5347.1]	12659.4 [11361.6, 14105.4]	6872.8 [5877.7, 8036.2]
GMR [two-sided 95% CI][b)]	6.29 [5.27, 7.51]		5.11 [4.10, 6.36]		1.96 [1.70, 2.25]		1.84 [1.56, 2.18]	
Seroresponse rate								
N1	209	257	162	76	209	259	174	79
n[c)]	205	222	162	74	209	259	174	79
Seroresponse rate (%) [two-sided 95% CI][d)]	98.1 [95.2, 99.5]	86.4 [81.6, 90.3]	100 [97.7, 100]	97.4 [90.8, 99.7]	100 [98.3, 100]	100 [98.6, 100]	100 [97.9, 100]	100 [95.4, 100]
Difference in seroresponse rate [two-sided 95% CI][e)]	12.1 [6.9, 17.3]		5.5 [0.5, 10.5]		0		0	

PsVNA (50% inhibitory dilution)

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Values greater than the ULOQ were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 36.7-13705 [Omicron BA.4-5], 18.5-45118 [original strain]).

N = number of participants evaluated; N1 = number of participants with non-missing data both before the primary series and after the second booster dose; n = number of participants with non-missing data at the evaluation timepoint

GMR = the ratio of the bivalent (Original/Omicron BA.4-5) vaccine to monovalent (Original) vaccine; difference in seroresponse rate = the bivalent (Original/Omicron BA.4-5) vaccine minus monovalent (Original) vaccine

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or the fold rise in antibody titer and back-transformed to the original scale for representation.

b) An analysis of covariance model with adjustment for age group (<65 years vs. ≥65 years) and pre-second booster titer, with the post-second booster titer as the dependent variable and study vaccine group (bivalent [Original/Omicron BA.4-5] vaccine vs. monovalent [Original] vaccine) as the fixed effect.

c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from the pre-primary series (if below the LLOQ, a ≥4-fold rise from the LLOQ). Participants who did not have pre-primary series antibody titer data and who had a negative SARS-CoV-2 status before the primary series were considered to have a pre-primary series antibody titer of <LLOQ. Participants who did not have pre-primary series antibody titer data and who had a positive SARS-CoV-2 status before the primary series were handled as those with missing pre-primary series antibody titer data, who were not evaluable for seroresponse. If the participant did not have any information on the pre-primary series SARS-CoV-2 status, the pre-second booster SARS-CoV-2 test result was to be imputed as the pre-primary series SARS-CoV-2 test result.

d) Two-sided 95% CI was calculated using the Clopper-Pearson method.

e) Two-sided 95% CI was calculated using the stratified Miettinen-Nurminen method adjusted by age group.

Table 15 shows the results of neutralizing antibody titers at 28 days after the second booster dose by age group. Although the analysis included only a limited number of participants aged 18 to 25 years, which

precludes stringent comparison, the immune response tended to be higher in participants aged 18 to 25 years than in other age groups.

Table 15. Comparison of serum neutralizing antibody titers by age group (Study P205, PPIS-Neg)

	Part H					
	Bivalent (Original/Omicron BA.4-5) 50 μg					
	Omicron BA.4-5			Original strain		
	18-25 years N = 6	26-64 years N = 150	≥65 years N = 53	18-25 years N = 6	26-64 years N = 150	≥65 years N = 53
Pre-second booster dose						
N	6	150	53	6	150	53
GMT [two-sided 95% CI][a)]	90.2 [20.3, 402.0]	83.9 [67.0, 105.2]	99.9 [64.1, 155.6]	515.5 [212.6, 1250.4]	741.3 [620.4, 885.6]	1027.7 [703.1, 1502.0]
28 days post-second booster dose						
n	6	150	53	6	150	53
GMT [two-sided 95% CI][a)]	5148.6 [2428.1, 10917.2]	2219.7 [1791.6, 2750.2]	2421.0 [1548.4, 3785.2]	10950.2 [3330.5, 36002.8]	6406.3 [5510.6, 7447.5]	10212.9 [7531.1, 13849.6]
GMFR [two-sided 95% CI][a)]	57.1 [9.6, 340.2]	26.4 [21.4, 32.7]	24.2 [16.2, 36.4]	21.2 [5.8, 77.9]	8.6 [7.4, 10.1]	9.9 [7.1, 14.0]
Seroresponse rate						
N1	6	150	53	6	150	53
n[b)]	6	137	47	5	124	39
Seroresponse rate (%) [two-sided 95% CI][c)]	100 [54.1, 100.0]	91.3 [85.6, 95.3]	88.7 [77.0, 95.7]	83.3 [35.9, 99.6]	82.7 [75.6, 88.4]	73.6 [59.7, 84.7]

PsVNA (50% inhibitory dilution)

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Values greater than the ULOQ were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 36.7-13705 [Omicron BA.4-5], 18.5-45118 [original strain]).

N = number of participants evaluated; N1 = number of participants with non-missing data both before the primary series and after the second booster dose; n = number of participants with non-missing data at the evaluation timepoint

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or the fold rise in antibody titer and back-transformed to the original scale for representation.

b) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from the pre-primary series (if below the LLOQ, a ≥4-fold rise from the LLOQ). Participants who did not have pre-primary series antibody titer data and who had a negative SARS-CoV-2 status before primary series were considered to have a pre-primary series antibody titer of <LLOQ. Participants who did not have pre-primary series antibody titer data and who had a positive SARS-CoV-2 status before the primary series were handled as those with missing pre-primary series antibody titer data, who were not evaluable for seroresponse. If the participant did not have any information on the pre-primary series SARS-CoV-2 status, the pre-second booster SARS-CoV-2 test result was to be imputed as the pre-primary series SARS-CoV-2 test result.

c) Two-sided 95% CI was calculated using the Clopper-Pearson method.

The cross-neutralizing ability of the bivalent (Original/Omicron BA.4-5) vaccine against the emerging Omicron lineages, BQ.1.1 and XBB.1, was evaluated in an exploratory manner. Table 16 shows neutralizing antibody titers against Omicron BQ.1.1 and XBB.1 in randomly sampled participants by pre-second booster SARS-CoV-2 status (40 SARS-CoV-2 negative participants and 20 SARS-CoV-2 positive participants). The booster dose of the bivalent (Original/Omicron BA.4-5) vaccine led to an increase in seroresponse not only to Omicron BA.4-5 and original strain, but also to Omicron BQ.1.1 and XBB.1.

Table 16. Serum neutralizing antibody titers against Omicron BA.4-5, BQ.1.1 and XBB.1 (Study P205: PPIS)

	Part H					
	Bivalent (Original/Omicron BA.4-5) 50 μg					
	SARS-CoV-2 negative N = 40			SARS-CoV-2 positive N = 20		
	BA.4-5	BQ.1.1	XBB.1	BA.4-5	BQ.1.1	XBB.1
Pre-second booster dose						
GMT [two-sided 95% CI][a)]	122.8 [74.3, 203.1]	31.7 [19.6, 51.3]	18.1 [12.0, 27.1]	833.7 [422.5, 1645.1]	124.7 [61.4, 253.2]	55.4 [28.4, 108.0]
28 days post-second booster dose						
GMT [two-sided 95% CI][a)]	3355.4 [2109.9, 5336.2]	621.9 [422.2, 916.2]	222.3 [147.4, 335.2]	8871.8 [4809.7, 16364.8]	1093.5 [536.8, 2227.9]	381.4 [198.1, 734.4]
GMFR [two-sided 95% CI][a)]	27.3 [15.9, 47.0]	19.6 [11.7, 32.8]	12.3 [7.4, 20.5]	10.6 [6.4, 17.6]	8.8 [5.0, 15.5]	6.9 [4.0, 11.7]
GMT (%) vs BA.4-5	–	18.5	6.6	–	12.3	4.3

PsVNA (50% inhibitory dilution)

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ for analyses. Values greater than the ULOQ were replaced by the ULOQ for analyses if measurements were not available (quantification range [LLOQ-ULOQ]: 36.7-13705 [Omicron BA.4-5]; limit of detection: 10 [BQ.1.1 and XBB.1]).

N = number of participants evaluated

–: not applicable

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or the fold rise in antibody titer and back-transformed to the original scale for representation.

In Study P205, the evaluation of the efficacy of the booster dose of vaccines was not planned. Table 17 shows the SARS-CoV-2 infections occurring at least 14 days after the second dose in Part H. None of the participants with COVID-19 required a visit to the emergency room or hospitalization due to COVID-19.

Table 17. SARS-CoV-2 infections starting 14 days after the second booster dose (Study P205)

	Part H	
Analysis set	PPES[a)] N = 216	FAS N = 511
Confirmed COVID-19 according to the case definition[b)] in Study P301 n (%)	5 (2.3)	6 (1.2)
Confirmed COVID-19 according to the CDC case definition[c)] n (%)	7 (3.2)	8 (1.6)
Confirmed SARS-CoV-2 infection[d)] n (%)	12 (5.6)	17 (3.3)

N = number of participants evaluated; n = number of participants who had the disease defined according to the definition

a) An efficacy analysis set comprising participants in the FAS who had received the study vaccine as planned and who had a negative pre-second booster SARS-CoV-2 status as set out in the protocol.

b) Had a positive post-second booster RT-PCR test result AND eligible symptoms as follows: At least 2 systemic symptoms: fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory or taste disorder; OR
At least one of the following respiratory signs or symptoms: cough, shortness of breath, difficulty breathing; or clinical or radiographical evidence of pneumonia

c) Had at least 1 positive RT-PCR test result for SARS-CoV-2, and at least 1 symptom (lasting ≥48 hours) from the following prescribed list of COVID-19 symptoms derived from the CDC case definition:
Systemic symptoms: fever (≥38°C) or chills (of any duration including ≤48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea or vomiting, poor appetite or poor feeding, OR respiratory signs or symptoms: cough (of any duration including ≤48 hours), shortness of breath or difficulty breathing (of any duration including ≤48 hours)

d) A negative antibody test result based on binding antibodies specific to SARS-CoV-2 nucleocapsid that became positive after the second booster dose, OR a positive RT-PCR test result after the second booster dose.

Although no data from an efficacy (immunogenicity) study of the bivalent vaccine in children aged 6 to 11 years are available, the immunogenicity of the bivalent vaccine as a booster dose is promising in this age group as is the case of adults aged ≥18 years, based on the following grounds: (1) Study P205 Part G (bivalent [Original/Omicron BA.1] vaccine) and Part H (bivalent [Original/Omicron B.4-5] vaccine), which evaluated the booster dose in adults aged ≥18 years, demonstrated the superiority of the bivalent vaccines to the monovalent (Original) vaccine in terms of the neutralizing antibody titers against Omicron variants (BA.1 or B.4-5), and the non-inferiority of the bivalent vaccines to the monovalent (Original) vaccine in terms of the neutralizing antibody titers against the original strain; and (2) Study P204, which evaluated the booster dose of the monovalent (Original) vaccine, demonstrated the non-inferiority of the neutralizing antibody titers against the original strain in the age group of 6 to 11 years to those in the age group of 18 to 25 years.

A small fraction of children and adolescents develop multisystem inflammatory syndrome in children (MIS-C), a post-COVID-19 complication (*Vaccine*. 2021;39:3037-49). According to the publication of CDC (*MMWR Morb Mortal Wkly Rep.* 2022;71:52-8), during the period between July and December 2021, persons aged 12 to 17 years received 2 doses of another COVID-19 mRNA vaccine, which was shown to be 91% effective against MIS-C. In the same study, all of the seriously affected MIS-C patients requiring life support were unvaccinated. The findings suggest that vaccination is expected to be effective in preventing COVID-19 as well as long COVID in children aged 6 to 11 years.

Based on the above, the primary series of the monovalent (Original) vaccine and the booster dose of the bivalent vaccine are expected to be effective in children aged 6 to 11 years.

PMDA's view:
The primary series immunogenicity data of the age group of 6 to 11 years in Study P204 Part 2 can be compared to those of the age group of 18 to 25 years in Study P301, for the following reasons: (i) The demographics and baseline characteristics of participants, such as the sex and race, in the age group of 6 to 11 years in Study P204 Part 2 were generally similar to those in the age group of 18 to 25 years in Study P301 except for body weight (Table 10); and (ii) the subgroup analysis in Study P301 also demonstrated high vaccine effectiveness in the prevention of COVID-19 regardless of the demographics and baseline characteristics of participants (Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated on May 17, 2021, *N Engl J Med.* 2021;384:1576-7), suggesting that the differences in the demographics and baseline characteristics are unlikely to lead to a clinically significant difference in immune response.

The primary series of the monovalent (Original) vaccine is expected to have a certain level of efficacy in children aged 6 to 11 years, based on the following grounds: (1) The immunogenicity analyses comparing the GMR of the neutralizing antibody titers and the difference in seroresponse rate at 28 days after the second dose of the monovalent (Original) vaccine in the age group of 6 to 11 years in Study P204 Part 2 to the immunogenicity data of the age group of 18 to 25 years from Study P301 (control)

met the immunobridging success criteria [see Section 7.1.1]; (2) the VE for the prevention of COVID-19, a secondary endpoint, in children aged 6 to 11 years in Study P204 Part 2 was similar to the VE in Study P301, though the endpoint was not prespecified and its evaluation period was different; and (3) the effectiveness of the monovalent (Original) vaccine for the prevention of COVID-19 was demonstrated in adults aged ≥18 years in Study 301, whose data served as the control.

The applicant submitted the data from the study on the booster dose of the monovalent (Original) vaccine in children aged 6 to 11 years and from the study on the booster dose of the bivalent (Original/Omicron BA.4-5) vaccine in adults aged ≥18 years. The present application is intended for addition of dosage and administration for the use of the bivalent vaccine as a booster dose in children aged 6 to 11 years.

The immunogenicity analyses comparing the booster dose of the monovalent (Original) vaccine in children aged 6 to 11 years in Study P204 to the primary series in the age group of 18 to 25 years from Study P301 (control) met the immunobridging success criteria [see Section 7.1.2]. Given that the neutralizing antibody titers increased after the booster dose of the monovalent (Original) vaccine regardless of the pre-booster SARS-CoV-2 status (Table 12), the booster dose of the monovalent (Original) vaccine is expected to be effective in children aged 6 to 11 years.

PMDA considers that the booster dose of the bivalent (Original/Omicron BA.1) vaccine is expected to have a certain level of efficacy in in children aged 6 to 11 years because the prespecified success criteria were met in the clinical study involving adults aged ≥18 years, which compared the booster dose of the bivalent (Original/Omicron BA.1) vaccine to the monovalent (Original) vaccine (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated September 7, 2022). The booster dose of the bivalent (Original/Omicron BA.4-5) vaccine was evaluated in Study P205 Part H in adults aged ≥18 years, and the results demonstrated the non-inferiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine in terms of the immune response against the original strain and the superiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine in terms of the immune response against the Omicron BA.4-5 variant [see Section 7.2.1]. Although the success criteria in Study P205 Part H aimed to test 4 non-inferiority hypotheses, the superiority of the bivalent (Original/Omicron BA.4-5) vaccine to the monovalent (Original) vaccine in terms of the immunogenicity against Omicron BA.4-5 should be demonstrated to support the clinical significance of the bivalent (Original/Omicron BA.4-5) vaccine. Therefore, the study plan should have included the testing of the superiority in the success criteria of Study P205 Part H. Taken together, however, PMDA concluded that the bivalent (Original/Omicron BA.4-5) vaccine also has a certain level of efficacy in adults aged ≥18 years, in view of the following: (a) the situation required urgent development of variant-adapted vaccines; (b) the circumstances of the COVID-19 pandemic and plan to develop variant-adapted vaccines were constantly changing globally; and (c) in light of the overall endpoint data obtained, the results for the primary endpoints in Study P205 Part H met not only all the prespecified non-inferiority criteria but also the superiority criterion for the GMR against Omicron BA.4-5.

No data have been submitted from a clinical study that evaluated the immunogenicity of the bivalent vaccine in children aged 6 to 11 years; however, the data of the booster dose of the monovalent (Original) vaccine from Study P204 [see Section 7.1.2] and the results from Study P205 indicate that both the booster dose of the bivalent (Original/Omicron BA.1) vaccine and the booster dose of the bivalent (Original/Omicron BA.4-5) vaccine could be effective in adults aged ≥18 years (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on September 7, 2022) [see Section 7.2.1]. Additionally, it has been reported that during the surge of the Omicron variant, the efficacy of the monovalent (Original) vaccine in children aged 5 to 11 years was similar to that in children 12 to 15 years and in adults aged ≥18 years (ACIP [Sep/1/2022] Updates on COVID-19 Vaccine Effectiveness During Omicron,[26] *JAMA.* 2022;327:2210-9); therefore, the applicant's opinion on the expected efficacy of the bivalent vaccine in children 6 to 11 years is acceptable.

Although no data on vaccination with Spikevax in Japanese children are available, Japanese and foreign clinical studies conducted in the development of the vaccine as the primary series in adults confirmed that the immune response elicited in Japanese participants was similar to that in non-Japanese participants (Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated on May 17, 2021). Based on this and other data, including data from Study P204 and data by age group from Study P205 Part H, Spikevax is expected to elicit a high immune response and accordingly be effective in Japanese children aged 6 to 11 years.

Spikevax monovalent (Original) vaccine, Spikevax bivalent (Original/Omicron BA.1) vaccine, and Spikevax bivalent (Original/Omicron BA.4-5) vaccine have all been approved with the dosage and administration as a booster dose for individuals aged ≥12 years. However, the applicant plans to recommend only the use of the bivalent vaccines as a booster dose in children aged 6 to 11 years. Given the current circumstances of circulating variants in Japan (Summary of SARS-CoV-2 variants of concern for increased infectivity/transmissibility and antigenic changes, No. 27. April 21, 2023. National Institute of Infectious Diseases, Japan), and the situation[27] where the mRNA SARS-CoV-2 vaccines derived from the original strain are not used in the special temporary vaccination program, the applicant's plan is reasonable.

Circulating variants of SARS-CoV-2 are changing, and other lineages and new variants will emerge. In addition, it has been reported that the vaccine effectiveness wanes in other ages groups over time after the booster dose (e.g., *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). In view of these situations, the applicant should gather information constantly from the data being accrued worldwide and from published reports regarding the efficacy of Spikevax administered as a booster dose in children aged 6 to 11 years, with an eye on the emergence and circulation of variants, and should take measures to address the situation as necessary based on the information so obtained.

[26] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/04-covid-link-gelles-508.pdf (last accessed on June 6, 2023)
[27] https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_supply.html (last accessed on June 6, 2023)

7.R.3 Safety

7.R.3.1 Safety profile

The applicant's explanation about the safety of Spikevax in children aged 6 to 11 years:

(1) Monovalent (Original) vaccine as the primary series

In Study P204 Part 1, the incidence of local solicited adverse events after the first dose is comparable to that after the second dose both in the 50 μg group and 100 μg group, while the incidence of systemic solicited adverse events occurred more frequently after the second dose than after the first dose (Table 2). The median time to onset of local solicited adverse events after the first dose and second dose was 1.0 day (range, 1-3 days) and 1.0 day (range, 1-7 days), respectively, in the 50 μg group; and 1.0 day (range, 1-5 days) and 1.0 day (range, 1-3 days), respectively, in the 100 μg group. The median time to onset of systemic solicited adverse events after the first dose and second dose was 1.0 day (range, 1-7 days) and 1.0 day (range, 1-6 days), respectively, in the 50 μg group; and 1.0 day (range, 1-7 days) and 1.0 day (range, 1-7 days), respectively, in the 100 μg group. The median duration of local solicited adverse events after the first dose and second dose was 2.0 days (range, 1-24 days) and 2.0 days (range, 1-28 days), respectively, in the 50 μg group; and 3.0 days (range, 1-15 days) and 3.0 days (range, 1-17 days), respectively, in the 100 μg group. The median duration of systemic solicited adverse events after the first dose and second dose was 2.0 days (range, 1-10 days) and 2.0 days (range, 1-10 days), respectively, in the 50 μg group; and 2.0 days (range, 1-9 days) and 2.0 days (range, 1-10 days), respectively, in the 100 μg group. After both the first dose and second dose, local and systemic Grade ≥3 solicited adverse events occurred more frequently in the 100 μg group than in the 50 μg group.

In Study P204 Part 2, data from the monovalent (Original) 50 μg group were analyzed. The median time to onset of local solicited adverse events after the first dose and second dose was 1.0 day (range, 1-7 days) and 1.0 day (range, 1-6 days), respectively, while the median time to onset of systemic solicited adverse events after the first dose and second dose was 1.0 day (range, 1-7 days) and 1.0 day (range, 1-7 days), respectively. The median duration of local solicited adverse events after the first dose and second dose was 2.0 days (range, 1-34 days) and 3.0 days (range, 1-28 days), respectively, while the median duration of systemic solicited adverse events after the first dose and second dose was 2.0 days (1-18 days) and 2.0 days (1-18 days), respectively. Similarly to Part 1, the incidence of local solicited adverse events after the first dose is comparable to that after the second dose, while the incidence of systemic solicited adverse events occurred more frequently after the second dose than after the first dose (Table 4). The local and systemic solicited adverse events that occurred most frequently after either dose were injection site pain (local), and headache and fatigue (systemic).

The incidence of solicited adverse events in Study P204 Part 2 was comparable to that in the age group of 18 to 25 years in Study P301, which served as the control in the immunobridging analyses (Table 18). In addition, the majority of solicited adverse events occurring in Study P204 Part 2 were Grade 1 or Grade 2, and disappeared within a short period of time after the onset of symptoms. This is similar to previously reported safety profiles in the age group of ≥18 years.

Table 18. The incidence of solicited adverse events reported through 7 days after either dose of the primary series (Solicited adverse event analysis set)

Event	P204 Part 2 (6-11 years) Monovalent (Original) 25 μg N = 3006			P301 (18-25 years) Monovalent (Original) 100 μg N = 878		
		All Grades	Grade ≥3		All Grades	Grade ≥3
	N1	n (%)	n (%)	N1	n (%)	n (%)
Any local adverse event	3006	2963 (98.6)	167 (5.6)	878	826 (94.1)	100 (11.4)
Pain	3006	2957 (98.4)	101 (3.4)	878	821 (93.5)	87 (9.9)
Erythema (redness)	3006	722 (24.0)	49 (1.6)	878	83 (9.5)	9 (1.0)
Swelling/induration	3006	671 (22.3)	39 (1.3)	878	123 (14.0)	12 (1.4)
Lymphadenopathy[a)]	3006	811 (27.0)	6 (0.2)	878	245 (27.9)	5 (0.6)
Any systemic adverse event	3006	2603 (86.6)	404 (13.4)	878	782 (89.1)	206 (23.5)
Fever[b)]	3006	772 (25.7)	128 (4.3)	878	159 (18.1)	10 (1.1)
Headache	3004	1866 (62.1)	134 (4.5)	878	648 (73.8)	73 (8.3)
Fatigue	3004	2196 (73.1)	216 (7.2)	878	641 (73.0)	103 (11.7)
Myalgia	3004	1059 (35.3)	82 (2.7)	878	555 (63.2)	100 (11.4)
Arthralgia	3004	639 (21.3)	28 (0.9)	878	392 (44.6)	50 (5.7)
Nausea/vomiting	3004	879 (29.3)	24 (0.8)	878	290 (33.0)	0
Chills	3004	1038 (34.6)	22 (0.7)	878	471 (53.6)	11 (1.3)

N = number of participants analyzed; N1 = number of participants who submitted any data for the event; n = number of participants with the event

a) Axillary swelling or tenderness ipsilateral to the injection site

b) ≥38°C (oral temperature)

The incidence of unsolicited adverse events occurring in the monovalent (Original) vaccine 50 μg group in Study P204 Part 1 and Part 2 is generally similar to that in the placebo group in Part 2. The majority of the unsolicited adverse events were Grade 1 or 2. No serious adverse events considered possibly related to the study vaccine were reported [see Section 7.1.1]. Based on the above and other data, currently, there are no serious concerns about the safety of the monovalent (Original) vaccine in children aged 6 to 11 years, indicating the tolerability of the primary series in the pediatric population.

(2) Monovalent (Original) vaccine as booster dose

Table 7 shows the incidence of solicited adverse events reported after the booster dose in Study P204, with the most common solicited adverse events being injection site pain (local), and headache and fatigue (systemic). The majority of solicited adverse events reported after the booster dose were Grade 1 or Grade 2. The median time to onset of local and systemic solicited adverse events after the booster dose was 1.0 day (range, 1-6 days) for local events and 1.0 day (range, 1-7 days) for systemic events, while the median duration of solicited adverse events after the booster dose was 3.0 days (range, 1-27 days) for local events and 2.0 days (1-14 days) for systemic events.

Table 19 shows the incidence of solicited adverse events after the primary series and booster dose in Study P204. While solicited adverse events were reported in a large proportion of participants who had received the monovalent (Original) vaccine as a booster dose, there was no trend towards increasing incidence after the booster dose compared to after the primary series, The incidence of solicited adverse events tended to be highest after the second dose of the primary series.

Table 19. The incidence of solicited adverse events reported through 7 days after each dose (Study P204, solicited adverse event analysis set)

	Primary series (Part 2)						Booster dose		
	Monovalent (Original) 50 μg N = 3004			Monovalent (Original) 50 μg N = 2988			Monovalent (Original) 25 μg N = 1280		
Dose number	Dose 1			Dose 2			Dose 3		
Event		All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3
	N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)
Any local adverse event	3004	2814 (93.7)	54 (1.8)	2988	2849 (95.3)	122 (4.1)	1279	1165 (91.1)	33 (2.6)
Pain	3004	2796 (93.1)	28 (0.9)	2988	2832 (94.8)	81 (2.7)	1279	1152 (90.1)	24 (1.9)
Erythema (redness)	3004	349 (11.6)	16 (0.5)	2988	559 (18.7)	33 (1.1)	1279	137 (10.7)	4 (0.3)
Swelling/induration	3004	354 (11.8)	19 (0.6)	2988	507 (17.0)	20 (0.7)	1279	139 (10.9)	4 (0.3)
Lymphadenopathy[a)]	3004	465 (15.5)	3 (<0.1)	2988	537 (18.0)	3 (0.1)	1279	355 (27.8)	4 (0.3)
Any systemic adverse event	3004	1740 (57.9)	53 (1.8)	2988	2335 (78.1)	364 (12.2)	1280	823 (64.3)	78 (6.1)
Fever[b)]	3003	99 (3.3)	17 (0.6)	2988	714 (23.9)	113 (3.8)	1276	108 (8.5)	17 (1.3)
Headache	3002	938 (31.2)	18 (0.6)	2986	1622 (54.3)	119 (4.0)	1280	489 (38.2)	22 (1.7)
Fatigue	3002	1298 (43.2)	31 (1.0)	2986	1925 (64.5)	191 (6.4)	1279	625 (48.9)	47 (3.7)
Myalgia	3002	438 (14.6)	11 (0.4)	2986	843 (28.2)	71 (2.4)	1280	269 (21.0)	19 (1.5)
Arthralgia	3002	260 (8.7)	3 (<0.1)	2986	482 (16.1)	25 (0.8)	1279	160 (12.5)	12 (0.9)
Nausea/vomiting	3002	325 (10.8)	5 (0.2)	2986	716 (24.0)	19 (0.6)	1279	168 (13.1)	6 (0.5)
Chills	3002	309 (10.3)	3 (<0.1)	2986	904 (30.3)	19 (0.6)	1279	179 (14.0)	4 (0.3)

N = number of participants analyzed; N1 = number of participants who submitted any data for the event; n = number of participants with the event

a) Axillary swelling or tenderness ipsilateral to the injection site

b) ≥38°C (oral temperature)

The incidence of unsolicited adverse events after the booster dose in Study P204 was lower than that after either dose of the primary series. The majority of the unsolicited adverse events were Grade 1 or Grade 2, and no serious adverse events considered related to the study vaccine were reported [see Section 7.1.2]. The safety profile was similar to that of Spikevax reported in persons aged ≥12 years. Based on the above, currently, there are no serious concerns about the safety of the monovalent (Original) vaccine as a booster dose in children aged 6 to 11 years, indicating the tolerability of the monovalent (Original) vaccine 25 μg as a booster dose.

(3) Bivalent vaccine as booster dose

The incidence of solicited adverse events after the second booster dose of the bivalent (Original/Omicron BA.4-5) vaccine 50 μg in Study P205 Part H was similar to the incidence of solicited adverse events in Part F, in which participants received the monovalent (Original) vaccine 50 μg as the second booster dose (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on September 7, 2022). There was no trend towards an increasing incidence of Grade ≥3 events (Table 9). The median time to onset of local and systemic solicited adverse events after the booster dose was 1.0 day (range, 1-5 days) for local events and 2.0 days (range, 1-7 days) for systemic events, while the median duration of solicited adverse events after the booster dose was 3.0 days (range, 1-22 days) for local events and 3.0 days (range, 1-38 days) for systemic events.

The incidence of solicited adverse events in Study P205 Part H tended to be similar to or lower than that after the monovalent (Original) vaccine 50 μg as the first booster dose in Study P201 Part B, and similar

to or lower than that after the monovalent (Original) vaccine 100 μg as the second dose of the primary series in Study P301 (Table 20).

Table 20. The incidence of solicited adverse events reported through 7 days after the bivalent (Original/Omicron BA.4-5) vaccine or monovalent (Original) vaccine by dose number (Solicited adverse event analysis set; ≥18 years of age)

Study	P205 Part H			P201 Part B			P301		
Type of vaccination	Bivalent (Original/Omicron BA.4-5) Second booster dose 50 μg N = 508			Monovalent (Original) First booster dose 50 μg N = 167			Monovalent (Original) Primary series (second) 100 μg N = 14691		
Event		All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3
	N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)
Any local adverse event	507	420 (82.8)	28 (5.5)	167	143 (85.6)	8 (4.8)	14688	13029 (88.7)	1023 (7.0)
Pain	507	418 (82.4)	20 (3.9)	167	140 (83.8)	6 (3.6)	14688	12964 (88.3)	606 (4.1)
Erythema (redness)	507	23 (4.5)	5 (1.0)	167	8 (4.8)	1 (0.6)	14687	1274 (8.7)	287 (2.0)
Swelling/induration	507	40 (7.9)	5 (1.0)	167	9 (5.4)	1 (0.6)	14687	1807 (12.3)	255 (1.7)
Lymphadenopathy[a)]	507	106 (20.9)	1 (0.2)	167	34 (20.4)	1 (0.6)	14687	2092 (14.2)	68 (0.5)
Any systemic adverse event	508	372 (73.2)	35 (6.9)	167	126 (75.4)	12 (7.2)	14690	11678 (79.5)	2350 (16.0)
Fever[b)]	507	20 (3.9)	1 (0.2)	166	11 (6.6)	2 (1.2)	14682	2276 (15.5)	216 (1.5)
Headache	507	249 (49.1)	12 (2.4)	167	92 (55.1)	2 (1.2)	14687	8637 (58.8)	666 (4.5)
Fatigue	508	304 (59.8)	17 (3.3)	167	98 (58.7)	7 (4.2)	14687	9607 (65.4)	1433 (9.8)
Myalgia	507	235 (46.4)	20 (3.9)	167	82 (49.1)	5 (3.0)	14687	8529 (58.1)	1321 (9.0)
Arthralgia	507	177 (34.9)	9 (1.8)	167	69 (41.3)	5 (3.0)	14687	6303 (42.9)	775 (5.3)
Nausea/vomiting	507	71 (14.0)	1 (0.2)	167	19 (11.4)	0	14687	2794 (19.0)	22 (0.1)
Chills	507	112 (22.1)	4 (0.8)	167	59 (35.3)	0	14687	6500 (44.3)	191 (1.3)

N = number of participants analyzed; N1 = number of participants who submitted any data for the event; n= number of participants with the event

a) Axillary swelling or tenderness ipsilateral to the injection site

b) ≥38°C (oral temperature)

Table 21 shows the incidence of solicited adverse events after the booster dose of the bivalent (Original/Omicron BA.4-5) vaccine in Study P205 Part H by age group. Although the limited number of participants aged 18 to 25 years precluded a stringent evaluation, there were no clear difference by age.

Table 21. The incidence of solicited adverse events reported through 7 days after administration of the study vaccine, sorted by age group (Study P205 Part H: solicited adverse event analysis set)

Event	Bivalent (Original/Omicron BA.4-5) 50 μg								
	18-25 years N = 17			26-64 years N = 386			≥65 years N = 105		
		All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3
	N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)
Any local adverse event	17	15 (88.2)	1 (5.9)	385	332 (86.2)	22 (5.7)	105	73 (69.5)	5 (4.8)
Pain	17	15 (88.2)	1 (5.9)	385	332 (86.2)	18 (4.7)	105	71 (67.6)	1 (1.0)
Erythema (redness)	17	1 (5.9)	0	385	16 (4.2)	3 (0.8)	105	6 (5.7)	2 (1.9)
Swelling/induration	17	3 (17.6)	0	385	29 (7.5)	2 (0.5)	105	8 (7.6)	3 (2.9)
Lymphadenopathy[a)]	17	8 (47.1)	0	385	83 (21.6)	1 (0.3)	105	15 (14.3)	0
Any systemic adverse event	17	13 (76.5)	2 (11.8)	386	294 (76.2)	28 (7.3)	105	65 (61.9)	5 (4.8)
Fever[b)]	17	0	0	385	16 (4.2)	1 (0.3)	105	4 (3.8)	0
Headache	17	10 (58.8)	1 (5.9)	385	200 (51.9)	10 (2.6)	105	39 (37.1)	1 (1.0)
Fatigue	17	10 (58.8)	0	386	233 (60.4)	14 (3.6)	105	61 (58.1)	3 (2.9)
Myalgia	17	10 (58.8)	1 (5.9)	385	187 (48.6)	16 (4.2)	105	38 (36.2)	3 (2.9)
Arthralgia	17	6 (35.3)	0	385	139 (36.1)	9 (2.3)	105	32 (30.5)	0
Nausea/vomiting	17	3 (17.6)	0	385	64 (16.6)	1 (0.3)	105	4 (3.8)	0
Chills	17	5 (29.4)	0	385	91 (23.6)	3 (0.8)	105	16 (15.2)	1 (1.0)

N = number of participants analyzed; N1= number of participants who submitted any data for the event; n= number of participants with the event

a) Axillary swelling or tenderness ipsilateral to the injection site

b) ≥38°C (oral temperature)

Furthermore, the incidence of unsolicited adverse events in Study P205 Part H was similar to that of solicited adverse events in Part F, in which the monovalent (Original) vaccine 50 μg was administered as the second booster dose (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on September 7, 2022), and the majority of the unsolicited adverse events were Grade 1 or 2. No serious adverse events considered related to the study vaccine were reported [see Section 7.2.1], and the safety profile was similar to that of Spikevax reported in persons aged ≥12 years.

As discussed above, (1) the safety of the bivalent (Original/Omicron BA.4-5 or Original/Omicron BA.1) vaccine as a booster dose in adults aged ≥18 years was similar to the safety of the monovalent (Original) vaccine as the primary series or booster dose (Table 20 and Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on September 7, 2022); (2) the analyses by age group in Study P205 Part H indicated no difference in the safety of the bivalent (Original/Omicron BA.4-5) vaccine between age groups (Table 21); and (3) the safety of the monovalent (Original) vaccine as the booster dose in children aged 6 to 11 years was similar to known safety profiles reported earlier in other clinical studies. Based on these findings, the safety profile of the bivalent vaccine in children aged 6 to 11 years is inferred from the previously reported safety profiles of Spikevax products, and the bivalent (Original/Omicron BA.1) vaccine and the bivalent (Original/Omicron BA.4-5) vaccine are also considered tolerable in children aged 6 to 11 years.

(4) Foreign post-marketing safety information

According to the post-marketing safety data on Spikevax (Monthly Summary Safety Report 22, for events reported from March [redacted] to April [redacted], 2023), an estimated ≥774 million doses of the monovalent (Original) vaccine, ≥70 million doses of the bivalent (Original/Omicron BA.1) vaccine, and ≥117 million doses of the bivalent (Original/Omicron BA.4-5) vaccine were administered as of April [redacted], 2023. As the post-marketing safety information on Spikevax, a total of 2,660,539 reports from 693,535 recipients (including 439,895 serious adverse events in 142,480 recipients; 18,237 reports of death in 6,777 recipients) were submitted. There were a total of 1,388,781 adverse events in 373,114 recipients of any age (574 adverse events in 321 recipients aged 6 to 11 years) after the first or second dose of the monovalent (Original) vaccine, a total of 234,281 adverse events in 77,290 recipients of any age (88 adverse events in 50 recipients aged 6 to 11 years) after the third or subsequent doses, and 985,738 adverse events in 298,807 recipients (465 adverse events in 232 recipients aged 6 to 11 years) after an unknown number of doses. There were 38,511 adverse events in 11,230 recipients of any age (2 adverse events in 1 recipient aged 6 to 11 years) after administration of the bivalent (Original/Omicron BA.1) vaccine, and 13,228 adverse events in 5,015 recipients of any age (139 adverse events in 63 recipients aged 6 to 11 years) after administration of the bivalent (Original/Omicron BA.4-5) vaccine. Commonly reported events included “no adverse event,” “wrong product administered,” and “use of the product in a patient of ineligible age,” which were mostly associated with vaccine administration, while commonly reported reactogenicity-related events were fever, chest pain, headache, and rash.

According to the analyses for children aged 6 to 11 years, 195 serious adverse events were reported in 107 recipients after administration of the monovalent (Original) vaccine. The outcomes of the events were reported as “death” (2 recipients; death [1 recipient] and sudden death [1 recipient]),[28)] “unresolved” (11 recipients; fall/seizure [1 recipient], condition aggravated/device connection issue/seasonal allergy/underdose/urticaria [1 recipient], chest pain/tension headache [1 recipient], asthma/chills/palpitations/fever [1 recipient], immune thrombocytopenia [1 recipient], oral lichen planus [1 recipient], eczema [1 recipient], myocarditis [1 recipient], erythema multiforme [1 recipient], facial paralysis [1 recipient], and immunisation reaction [1 recipient]), “resolved or resolving” (93 recipients), and “unknown” (1 recipient). Among these, events with ≥4 reports were fever (34 reports), chest pain (14 reports), vomiting (11 reports), myocarditis (10 reports), rash (8 reports), nausea (8 reports), abdominal pain (6 reports), palpitations (5 reports), vaccination site pain (4 reports), vaccination site swelling (4 reports), headache (4 reports), seizure (4 reports), dyspnoea (4 reports), and pruritus (4 reports). After vaccination with the bivalent (Original/Omicron BA.4-5) vaccine, 41 serious adverse events were reported in 22 recipients, and the outcomes were reported as “death” (0 recipients), “unresolved” (2 recipients; Kawasaki’s disease [1 recipient] and seizure [1 recipient]), “resolved or resolving” (20 recipients), and “unknown” (0 recipients). Among these, events with ≥4 reports were fever (7 reports) and rash (4 reports).

[28)] The causes of death were classified as “not reported” (death) and cardio-respiratory arrest (sudden death), and only little information was available for both cases; therefore, the causal relationship was determined to be “unassessable.”

PMDA's view:

In Study P204, in which the monovalent (Original) vaccine was administered, solicited adverse events (local and systemic) occurred in a large number of recipients both after the dose of the primary series and after the booster dose, but the majority of the events were Grade 1 or Grade 2 and resolved. The unsolicited adverse events reported were anticipated from available safety information obtained in persons aged ≥12 years, with the majority being Grade 1 or Grade 2. The safety of the primary series was evaluated by comparing the incidence of solicited adverse events in Study P204 to that in the age group of 18 to 25 years from Study P301 (control), while confirming that safety data showed no clear difference between the booster dose and the primary series. Therefore, currently available information shows no serious concerns about the safety of the monovalent (Original) vaccine in children aged 6 to 11 years.

Acceptable safety of the bivalent (Original/Omicron BA.1) vaccine or bivalent (Original/Omicron BA.4-5) vaccine as a booster dose in children aged 6 to 11 years is inferred based on the following grounds: (1) The safety of the bivalent (Original/Omicron BA.1) vaccine or the bivalent (Original/Omicron BA.4-5) vaccine as a booster dose in adults aged ≥18 years, did not differ markedly from that of the monovalent (Original) vaccine; (2) safety data from Study P204 of the monovalent (Original) vaccine administered as the primary series or booster dose in children aged 6 to 11 years serve as the supportive data; and (3) post-marketing data, albeit limited, indicate no new safety concerns.

However, there is limited information on the safety of the monovalent (Original) vaccine in children aged 6 to 11 years, and no data from clinical studies on the bivalent (Original/Omicron BA.1) vaccine or the bivalent (Original/Omicron BA.4-5) vaccine in children aged 6 to 11 years have been submitted. The applicant should therefore gather information on the safety of Spikevax in children aged 6 to 11 years from ongoing/planned clinical studies and surveys, as well as the post-marketing safety information, and should take appropriate measures based on the information obtained. Furthermore, the applicant should appropriately inform healthcare professionals, vaccine recipients, and their parents and guardians that solicited adverse events (local and systemic) have been reported in many participants, and that some adverse events occur more frequently after the second dose than after the first dose, together with information on the time to onset and the duration of common adverse events.

7.R.3.2 Safety in children with underlying medical conditions

The applicant's explanation about vaccination with Spikevax in children with underlying medical conditions:

Some children with underlying medical conditions or obesity are at an increased risk of severe COVID-19.[29)] Study P204 allowed enrollment of children with underlying medical conditions as long as their condition was stable. Safety data were analyzed by defining the following conditions as risk factors for

[29)] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (last accessed on June 6, 2023)

severe COVID-19: obesity,[30] chronic lung disease, asthma, cardiac disorders, diabetes mellitus, and HIV infection. Among the participants included in the safety analysis set[31] for evaluation of the primary series in Study P204, the proportions of participants who had had risk factors for severe COVID-19 before receiving the first dose were 28.5% (965 of 3,387) in the monovalent (Original) vaccine 50 μg group and 26.1% of (260 of 995) in the placebo group. The underlying medical conditions seen in participants in the monovalent (Original) vaccine 50 μg group and in the placebo group were as follows: obesity (20.6%, 697 of 3,387 participants [vaccine] and 19.6%, 195 of 995 participants [placebo]), chronic lung disease (9.7%, 329 of 3,387 participants [vaccine] and 9.0%, 90 of 995 participants [placebo]), asthma (8.7%, 295 of 3,387 participants [vaccine] and 8.3%, 83 of 995 participants [placebo]), cardiac disorders (0.6% (22 of 3,387 participants [vaccine] and 0.7%, 7 of 995 participants [placebo]), diabetes mellitus (0.3%, 9 of 3,387 participants [vaccine] and 0.5%, 5 of 995 participants [placebo]), HIV infection (0.1%, 4 of 3,387 participants [vaccine] and 0%, 0 of 995 participants [placebo]). In the monovalent (Original) vaccine 50 μg group in Part 2, 27.9% (840 of 3,007) of participants had at least one risk factor for severe COVID-19. In the safety analysis set for the evaluation of the booster dose, 30.6% (396 of 1294) of participants had had risk factors for severe COVID-19 before receiving the first dose.

Subgroup analyses were performed for local and systemic solicited adverse events reported in children with risk factors for severe COVID-19zed. In Part 2 (primary series), the incidences of local and systemic solicited adverse events in the monovalent (Original) vaccine 50 μg group were 94.6% (794 of 839 participants) and 58.9% (494 of 839 participants), respectively, after the first dose, and 94.0% (783 of 833 participants) and 75.0% (625 of 833 participants), respectively, after the second dose; and, after the booster dose, the incidences of local and systemic solicited adverse events were 90.0% (350 of 389 participants) and 63.8% (248 of 389 participants), respectively. The majority of the events were Grade 1 or Grade 2, and the incidence of such adverse events in the subgroup of children with risk factors for severe COVID-19 was similar to that in the overall population for both of studies on the primary series and the booster dose [see Section 7.1]. Serious adverse events occurred in 0.5% (4 of 840) of participants in Part 2; however, a causal relationship to the study vaccine was ruled out for all events. No serious adverse events were reported in the study of the booster dose. Based on the above, the safety profile of Spikevax does not pose any particular concerns in children with risk factors for severe COVID-19.

In Study P204, the small number of participants who had COVID-19 [see Section 7.R.2] precluded a subgroup analysis for efficacy based on the status of underlying medical conditions. However, the results of Study P301 in adults aged ≥18 years showed that the efficacy of the vaccine in participants with risk factors for severe COVID-19 was similar to that in the overall population (Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated on May 17, 2021).

[30] At or above the body mass index (BMI) 95th percentile on the CDC growth chart. https://www.cdc.gov/growthcharts/extended-bmi.htm (last accessed on June 6, 2023)
[31] Total of Part 1 (monovalent [Original] vaccine 50 μg group only) and Part 2

PMDA's view:
The safety profile of the vaccine product in participants with risk factors for severe COVID-19 enrolled in Study P204 was similar to that of the overall population. However, given that only a small number of participants were evaluated; and that the study only enrolled children whose underlying medical conditions were stable while children with different underlying medical conditions will be vaccinated in the post-marketing setting, the applicant should collect data on the safety of Spikevax in children with underlying medical conditions and take appropriate measures based on the data obtained.

7.R.3.3 Myocarditis/pericarditis

Post-marketing data on SARS-CoV-2 vaccines including Spikevax suggest concerns about the increased risk of myocarditis/pericarditis following vaccination with mRNA vaccines against SARS-CoV-2. Myocarditis/pericarditis has been reported in young males more frequently after the second dose.

The applicant's explanation about the risk for myocarditis/pericarditis in children aged 6 to 11 years:
In children aged 6 to 11 years enrolled in Study P204, no case of myocarditis/pericarditis has been reported nor were there any children with conditions suggestive of myocarditis/pericarditis.

According to the post-marketing safety data on Spikevax (Monthly Summary Safety Report 22, for events reported from March [redacted] to April [redacted], 2023), cases of myocarditis or pericarditis occurring in children aged 6 to 11 years until April [redacted], 2023 were reported in 11 recipients (10 recipients had myocarditis and 1 recipient had pericarditis) and all cases were medically confirmed. Of the 11 recipients, 10 were from Taiwan, and the remaining 1 was from Australia. All of the cases were reported until October 2022 (6 recipients in July 2022 and 4 recipients between August and October 2022), and there have been no reports thereafter. The details of the recipients were as follows: myocarditis/pericarditis occurred in 10 recipients after the second dose and 1 recipient after unknown number of doses; 7 boys and 4 girls with the median age of 10 years (range, 6-11 years). The time to onset in the 10 recipients who had myocarditis/pericarditis after the second dose was ≤7 days of vaccination (the median time to onset from vaccination was 2 days), and the time to onset in the recipient with an unknown number of doses was 7 to 13 days after vaccination. The outcomes were reported as resolved or resolving.

According to the report by the CDC, a large-scale cohort study has provided evidence of an increased risk of myocarditis in all age groups of persons with a diagnosis of COVID-19, and it has been shown that persons aged ≤15 years infected with COVID-19 were at a ≥36-fold higher risk than that in the group of COVID-19 non-infected hospital inpatients adjusted for age and sex as a comparator group (*MMWR Morb Mortal Wkly Rep.* 2021;70:1228-32). There is an increase in the risk of myocarditis in recipients of COVID-19 mRNA vaccines, especially in males aged 12 to 29 years, and an estimated 39-47 cases of myocarditis, pericarditis, and myopericarditis occur per million doses of COVID-19 mRNA vaccine (*MMWR Morb Mortal Wkly Rep.* 2021;70:977-82). A study conducted in Israel showed that COVID-19 mRNA vaccination was associated with an elevated risk of myocarditis (risk ratio, 3.24

[95% CI: 1.55 to 12.44]), and SARS-CoV-2 infection was a stronger risk factor for myocarditis (risk ratio, 18.28 [95% CI: 3.95 to 25.12]) (*N Engl J Med.* 2021;385:1078-90). In the meeting of the Advisory Committee on Immunization Practices held on June 23, 2021, the Advisory Committee concluded that the benefits of COVID-19 vaccination clearly outweigh the risks of myocarditis associated with vaccination.

According to the post-marketing safety data on Spikevax, more than 3 million children aged 5 to 11 years are estimated to have completed the primary series with Spikevax in the US, where there have been no reports of myocarditis or pericarditis. Of the reported cases of myocarditis/pericarditis (11 recipients), those reported in Taiwan were concentrated during a specific time span, and the frequency of reported cases appears to be decreasing over time. Taken together, the overall number of reports is small; the reporting rate has been decreasing with increasing exposure to COVID-19 mRNA vaccine in the post-marketing setting; and published literature suggests that the incidence of myocarditis in children aged 5 to 11 years after SARS-CoV-2 infection or after receiving COVID-19 mRNA vaccine is lower than that in persons aged ≥12 years (*MMWR Morb Mortal Wkly Rep.* 2022;71:517-23). In light of the above and other factors, the risk of myocarditis/pericarditis in children aged 5 to 11 years is considered to be low, and the benefits of Spikevax vaccine outweigh the risks.

The post-marketing safety studies are ongoing/planned in the US and Europe to further clarify the risk of myocarditis/pericarditis, and data obtained may provide more findings including the post-booster risk of myocarditis/pericarditis and the clinical characteristics.

PMDA's conclusion:
In Japan, myocarditis and pericarditis are included in the reporting criteria for suspected adverse reactions, and reported cases of myocarditis/pericarditis after SARS-CoV-2 vaccination have been evaluated on a regular basis. The details of such cases were reported in the joint meeting[32)] of the Adverse Reaction Working Group of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (81st meeting) and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (sixth meeting of FY2022). The number of suspected cases of myocarditis or pericarditis (per million doses)[33)] after administration of Spikevax (monovalent [Original] vaccine), reported by the marketing authorization holder (MAH) (for those reported from May 22, 2021 to June 12, 2022) was 2.6 for myocarditis and 0.6 for pericarditis following the first dose, 12.9 for myocarditis and 2.6 for pericarditis after the second dose, and 1.1 for myocarditis and 0.5 for pericarditis following the third dose. Further information on such cases were reported in the joint meeting[34)] of the Adverse Reaction Working Group of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (93rd meeting) and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs

[32)] https://www.mhlw.go.jp/stf/shingi2/0000208910_00044.html (last accessed on June 6, 2023)
[33)] Classification by Brighton Collaboration (*Vaccine.* 2022;40:1499-1511). Total number of reports including Level 4 and Level 5.
[34)] https://www.mhlw.go.jp/stf/shingi2/0000208910_00060.html (last accessed on June 6, 2023)

Department of the Pharmaceutical Affairs and Food Sanitation Council (first meeting of FY2023). The number of suspected cases of myocarditis or pericarditis (per million doses)[33] after administration of Spikevax reported by the MAH (for those reported from December 6, 2021 to March 12, 2023) was 0.6 for myocarditis and 0.1 for pericarditis following the fourth dose, 0 cases for both myocarditis and pericarditis after the fifth dose. Of these cases, the number of cases in recipients of the bivalent (Original/Omicron BA.1) vaccine (regardless of dose number) was 0.1 for both myocarditis and pericarditis, and the number of cases in recipients of the bivalent (Original/Omicron BA.4-5) vaccine (regardless of dose number) was 0 for both myocarditis and pericarditis. At both Working Group/Subcommittee meetings, it was concluded that there were no serious concerns affecting the vaccination program at that time. The incidence of myocarditis/pericarditis in young people is lower after vaccination than after SARS-CoV-2 infection (e.g., *Circulation.* 2021;144:471-84, *MMWR Morb Mortal Wkly Rep.* 2022;71:517-23). Based on the incidence of myocarditis/pericarditis in children aged 6 to 11 years from foreign post-marketing safety information, the incidence of myocarditis/pericarditis in children aged 6 to 11 years who received mRNA vaccines approved in Japan, and the risk of myocarditis/pericarditis associated with SARS-CoV-2 infection, currently, there is no information suggesting that Spikevax represents an unacceptable risk in children aged 6 to 11 years.

Nevertheless, the applicant should continue collecting safety information including the incidence of myocarditis/pericarditis in children aged 6 to 11 years, and provide cautionary statements.

7.R.4 Clinical positioning

PMDA's conclusion on the clinical positioning of Spikevax:

While the WHO declared an end to COVID-19 as a public health emergency of international concern on May 5, 2023, it also stated that COVID-19 is now an established and ongoing health issue, and State Parties should maintain efforts to increase SARS-CoV-2 vaccine coverage, conduct epidemiological monitoring, and facilitate the development of new vaccines and therapeutic drugs.[1] In Japan, beginning on May 8, 2023, COVID-19 has been reclassified as a Class V Infectious Disease under the Infectious Disease Control Act, though it was previously classified in the category of "Novel Influenza Infection and other diseases." SARS-CoV-2 vaccination is still offered as a special temporary vaccination program under the Immunization Act ("Guidelines for implementation of temporary vaccination against novel coronavirus infection" [dated May 8, 2023][35]). Following an increase in the total number of people infected with SARS-CoV-2 during the surge of the Omicron variant, the number of children with severe COVID-19 and fatal cases also increased in Japan.[36] The events reported in children included MIS-C, which is a condition associated with COVID-19 and accompanied by fever and multiorgan disorder (Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children [MIS-C] in the United States[37]); long COVID characterized by persistent symptoms such as fatigue, headache, and shortness of breath after SARS-CoV-2 infection (*Lancet Child Adolesc Health.*

[35] https://www.mhlw.go.jp/content/000971377.pdf (last accessed on June 6, 2023)
[36] https://covid19.mhlw.go.jp/ (last accessed on June 6, 2023)
[37] https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (last accessed on June 6, 2023)

2022;6:240-8); and acute encephalopathy (*Front Neurosci*. 2023;17:1085082). Several variants of SARS-CoV-2 are anticipated to circulate in the future. Although children account for low proportions of total severe COVID-19 and fatal cases, the number of cases will increase with an increase in the number of persons infected with SARS-CoV-2. Therefore, vaccination is an important measure to prevent COVID-19 in children. The Japan Pediatric Society states that SARS-CoV-2 vaccination continue to be recommended in all children aged 6 months to 17 years since COVID-19 remains a threat to children in Japan ("On novel coronavirus vaccination in children: 2023.6 Supplement," dated June 9, 2023, issued by the Committee on Immunization and Prevention of Infectious Diseases, Japan Pediatric Society [in Japanese][38]).

Following a booster dose with monovalent mRNA vaccine targeting the original strain, there was some increase in vaccine effectiveness against the Omicron variant, which was the predominant strain worldwide in 2022, but the vaccine effectiveness is reported to be lower and of shorter duration than that against the other variants circulating in the past (Delta variant) (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). Omicron BA.4/BA.5 lineages, in particular, have higher infectivity and immune evasion capability than other Omicron sublineages (*Nature.* 2022;608:603-8). In this context, Omicron-adapted vaccines were developed by modifying the monovalent mRNA vaccines against the original strain. In Japan, as of May in 2023, Comirnaty RTU Intramuscular Injection and other products (bivalent vaccine targeting the original strain/Omicron BA.1 and bivalent vaccine targeting the original strain/Omicron BA.4-5) for use in persons aged ≥5 years,[39] and Spikevax Intramuscular Injection (bivalent vaccine targeting the original strain/Omicron BA.1 and bivalent vaccine targeting the original strain/Omicron BA.4-5) for use in persons aged ≥12 years are available. Currently, the bivalent mRNA (Original/Omicron BA.4-5) vaccines are widely used. There are studies on the effectiveness of the bivalent vaccine in the prevention of symptomatic SARS-CoV-2 infections during the predominance of the Omicron variant and in the prevention of visits to the emergency room or hospitalization due to COVID-19-like disease in the US. The bivalent mRNA (Original/Omicron BA.4-5) vaccine was administered as a booster dose to adults who had already received the monovalent mRNA vaccine targeting the original strain, in whom additional protection against COVID-19 was observed compared with those receiving no booster dose of the bivalent vaccine (e.g., *MMWR Morb Mortal Wkly Rep*. 2022;71:1526-30, *MMWR Morb Mortal Wkly Rep.* 2022;71:1616-24).

In the review of the present application, from the results from Study P204, it was concluded that the monovalent (Original) vaccine as the primary series coupled with the booster dose is expected to be effective in children aged 6 to 11 years [see Section 7.R.2] and that the vaccine has acceptable safety. The results from Study P205 and other findings suggest that the bivalent vaccine is effective in children aged 6 to 11 years and that its safety profile is generally similar to that of the monovalent (Original)

[38] http://www.jpeds.or.jp/uploads/files/20230609_vaccine_hoi.pdf (last accessed on June 14, 2023)
[39] "Comirnaty Intramuscular Injection for 5 to 11 years old" (bivalent vaccine for the original strain/Omicron BA.4-5) is the only Omicron-adapted vaccine approved for children aged 5 to 11 years.

vaccine [see Section 7.R.3]. “Comirnaty Intramuscular Injection for 5 to 11 years old” is the only SARS-CoV-2 vaccine available for children aged 6 to 11 years in Japan; therefore, given the supply and other factors, it is clinically significant to provide children aged 6 to 11 years with access to Spikevax as an option.

Circulating variants are changing and new variants are likely to emerge in the future. In addition, the benefit of a vaccine may change depending on variants; therefore, the vaccination strategy should be updated according to the situation.

7.R.5 Dosage and administration

During the review, the applicant explained that the proposed dosage and administration statement would be changed as shown below:

• Vaccine product containing mRNA encoding the spike protein of SARS-CoV-2 (original strain)

Individuals 12 years of age and older

For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 years of age and older but younger than 12 years of age

For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (0.25 mL each) at a recommended interval of 4 weeks.

• Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

Individuals 12 years of age and older

For a booster dose, a single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children 6 years of age and older but younger than 12 years of age

For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

(Underline denotes changes.)

7.R.5.1 Dosage and administration

The applicant’s explanation about the proposed dosage and administration:

• Primary series

In Study P204 Part 1 for dose selection, a pre-planned immunogenicity assessment for dose selection was performed on data from 75 participants in the monovalent (Original) vaccine 50 µg group at 28 days after the second dose.[40)] Results were obtained from 67 participants included in the PPIS, and were compared with the immunogenicity data in 295 participants (PPIS) aged 18 to 25 years from Study P301. The GMR (the pediatric participants in the 50 µg group of Study P204 to the participants aged 18 to 25

[40)] The results of neutralizing antibody titers in the monovalent (Original) vaccine 100 µg group were obtained after 50 µg had been selected as the dose level for Study P204 Part 2.

years in Study P301) for neutralizing antibody titers against the original strain at 28 days after the second dose of the study vaccine was 0.93 [two-sided 95% CI: 0.74, 1.16] and the between-group difference in seroresponse rate was 1.0% [two-sided 95% CI: −4.4%, 3.0%]. While these results met the success criteria for non-inferiority established in Study P204 Part 2, the results suggested that vaccination at a dose <50 μg is likely to meet the success criteria for non-inferiority established for Part 2; in addition, the monovalent (Original) vaccine 50 μg was well tolerated. Consequently, a dose of 50 μg was selected for Study P204 Part 2.

In Study P204 Part 2, the monovalent (Original) vaccine 50 μg was administered to children aged 6 to 11 years as a series of 2 doses, 28 days apart, and its immunogenicity and safety were evaluated. The results of the immunogenicity assessment met the prespecified success criteria for non-inferiority and the safety data did not raise any particular concerns. Based on these results, one dose of 0.25 mL (equivalent to 50 μg) was selected, and "the monovalent (Original) vaccine is administered intramuscularly as a series of 2 doses (0.25 mL each) at a recommended interval of 4 weeks" was defined as the dosage regimen for the monovalent (Original) vaccine as the primary series in children aged 6 to 11 years.

• Booster dose

Based on the evidence suggesting that a booster dose increased vaccine effectiveness in adults, the protocol of Study P204 was amended to allow all participants aged 6 to 11 years enrolled in Study P204 to receive the monovalent (Original) vaccine 25 μg as a booster dose at least 6 months following completion of the second dose of the primary series. The dose level of the booster dose (a dose of 25 μg which is half the 50 μg dose as the primary series) for children aged 6 to 11 years was determined based on the following ground: The adult data showed a decrease in reactogenicity after receiving a booster dose lower than the dose level of the primary series while a higher neutralizing antibody titer was induced, and therefore, 2 doses of100 μg as the primary series followed by a booster dose of 50 μg was selected for adults(Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated on December 9, 2021). The evaluation of immunogenicity and safety of the monovalent (Original) vaccine 25 μg as a booster dose in children aged 6 to 11 years in Study P204 showed that the immunogenicity data met the prespecified success criteria for non-inferiority [see Section 7.1.2] and the safety profile was generally consistent with the known safety profile for the monovalent (Original) vaccine as the primary series in children aged 6 to 11 years and raised no new concerns.

Based on the results for the monovalent (Original) vaccine as a booster dose in Study P204, the bivalent vaccines (25 μg) were approved as a booster dose for children aged 6 to 11 years in Europe and the bivalent (Original/Omicron BA.4-5) vaccine (25 μg) was authorized under the EUA in the US. Accordingly, a dose of 25 μg (injection volume of 0.25 mL) was selected as a booster dose in Japan.

Study mRNA-1273-P306 is ongoing to evaluate the safety and efficacy of the bivalent (Original/Omicron BA.1) vaccine as the primary series and a booster dose in children aged 6 months to 5 years. Based on the results of the study, the applicant plans to expand the indication of Spikevax to include children aged 6 months to 5 years.

PMDA's view:
Based on results of the clinical studies submitted, in addition to the applicant's explanation, it is acceptable to select the proposed dosage and administration of Spikevax in children aged 6 to 11 years.

7.R.5.2 Timing of booster dose (interval between the previous dose and the booster dose)

The timing of the booster dose in persons aged ≥12 years was discussed in the meeting of the Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council held on October 19, 2022. The proposed interval of ≥5 months from the preceding dose was changed to ≥3 months in light of the situation in foreign countries. The timing of the booster dose for "Comirnaty Intramuscular Injection for 5 to 11 years old" is "≥3 months after the preceding dose of SARS-CoV-2 vaccination," as is the case of that specified for "Comirnaty RTU Intramuscular Injection," which is indicated for persons aged ≥12 years.

PMDA asked the applicant to explain whether there is any impact on the efficacy and safety of the booster dose in children aged 6 to 11 years if the interval between the previous dose and the booster dose is changed to ≥3 months.

The applicant's explanation:
Study P204 did not evaluate the case where the interval between the completion of the primary series and the booster dose is changed to 3 months in participants aged 6 to 11 years. Published literature has reported that vaccine effectiveness wanes after receiving a booster dose as well as after receiving the primary series, and the decline in vaccine effectiveness is more significant against Delta and Omicron variants (*Nat Med.* 2022;28:1063-71). Because it was desirable that a booster dose should be administered as early as possible, an interval of ≥3 months from the previous dose (first booster dose) was selected for Part F, Part G, and Part H of Study P205. Neutralizing antibody titers increased in participants who received a booster dose after an interval of 3 months, and the post-booster neutralizing antibody titers were similar regardless of the duration of interval, suggesting that the duration of interval from the previous dose is unlikely to affect the seroresponse after the booster dose. The safety data from these studies raised no new concerns. The efficacy and safety of SARS-CoV-2 vaccines as a booster dose were evaluated in a clinical study in which participants received a SARS-CoV-2 vaccine at an interval of 3 months between the completion of the primary series and the booster dose, and the results showed that the immune response increased with no new safety concerns (*medRxiv.* 2021; https://doi:org/10.1101/2021.10.10.21264827). Outside Japan, the recommended interval between the completion of the primary series and the booster dose for children aged 6 to 11 years varies from 3 to 6 months, depending on the particular country. In the post-marketing period, safety data are collected

regardless of the duration of interval; nevertheless, no new safety concerns have been reported. While there is no established immunogenicity threshold, data have demonstrated that neutralizing antibody response to Spikevax is correlated with its effectiveness in the prevention of COVID-19 (*Science.* 2022;375:43-50), and therefore, the booster dose is expected to reduce the risk of SARS-CoV-2 infection and severe COVID-19, which may prevent transmission of SARS-CoV-2. Thus, it is beneficial to provide children with access to a booster dose as soon as clinically feasible. Based on the above, an interval of ≥3 months from the previous dose can be selected for children aged 6 to 11 years, as is the case of that specified for persons aged ≥12 years.

Based on the applicant's explanation, PMDA concluded that it is acceptable to select ≥3 months as the interval between the previous dose and the booster dose in children aged 6 to 11 years as is the case of persons aged ≥12 years.

7.R.6 Post-marketing investigation

7.R.6.1 Post-marketing surveillance

The applicant's explanation about the post-marketing surveillance of Spikevax:

Although there were no serious concerns about the safety of the monovalent (Original) vaccine in children aged 6 to 11 years in Study P204, no clinical studies have been conducted to investigate the safety and efficacy (immunogenicity) of the bivalent vaccine in children aged 6 to 11 years, consequently, no safety information on Spikevax is available in Japanese children aged 6 to 11 years. For this reason, the applicant plans to conduct a specified use-results survey in children aged 6 to 11 years (target sample size, 100 participants; survey period, 8 months) to collect and evaluate safety data, including adverse events after vaccination with Spikevax and vaccine administration errors, as well as information on the incidence of COVID-19 in the post-marketing clinical setting. Currently, the monovalent (Original) vaccine is not distributed in Japan, and the distribution volume of the bivalent (Original/Omicron BA.1) vaccine and the bivalent (Original/Omicron BA.4-5) vaccine in the future has not been determined; therefore, the vaccine product distributed during the specified use-results survey will be subjected to the survey.

PMDA's view:

As discussed in Section 7.R.3, in light of the currently available study results, the safety of Spikevax in children aged 6 to 11 years is acceptable. However, given that safety data on Spikevax in Japanese children are not currently available, the applicant should keep track of the safety data on Spikevax in the post-marketing clinical setting and evaluate the safety of Spikevax based on the data accrued. Therefore, the applicant's plan of conducting a specified use-results survey presented as an additional pharmacovigilance activity is acceptable. The applicant should develop a specific survey plan including determination of the sample size, according to the Government's policy on the SARS-CoV-2 vaccination program in children aged 6 to 11 years in Japan, estimated number of vaccine recipients, and vaccine products to be distributed during the survey period.

The appropriateness of the post-marketing investigation will be finalized taking into account the comments from the Expert Discussion.

7.R.6.2 Measures to prevent vaccine administration errors

The injectable volume for children aged 6 to 11 years differs from that for persons aged ≥12 years, and currently distributed vaccine products can only be used as booster doses. The applicant provided the following explanation about the measures to prevent vaccine administration errors for the expansion of indication to include children:

The dose levels differ between the age groups. It is assumed that the volume to be withdrawn from the vial will be checked by a healthcare professional to ensure that the correct volume is administered. However, to prevent the syringe filled with the vaccine from being used for the wrong person, the applicant will prepare adhesive tabs to be affixed to syringes for pediatric use to distinguish the syringes for children aged 6 to 11 years from those for persons aged ≥12 years. The applicant also plans to add information on the proper use of the vaccine for children aged 6 to 11 years to the current proper use guide. Furthermore, the applicant will prepare a leaflet to address information on the prevention of administration errors.

PMDA's view:

To expand the indication of Spikevax to include children aged 6 to 11 years, the applicant plans to appropriately inform healthcare professionals that dose levels differ depending on the age group, and introduce new means to prevent administration errors in healthcare settings to ensure proper use. The applicant's plan is considered appropriate. Spikevax is the second SARS-CoV-2 vaccine that can be used in children aged 6 to 11 years in Japan, and healthcare professionals should be alerted to the fact that the eligible age groups differ from those for the approved vaccine. In the future, the applicant should continue to collect data on the proper use of Spikevax and take further safety measures as necessary.

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 new drug application data were subjected to a document-based 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.

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that

there were no obstacles to conducting its review based on the application documents submitted.

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 Spikevax has a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in children aged 6 to 11 years, and that the vaccine has acceptable safety with no significant safety concerns. Providing children aged 6 to 11 years with access to Spikevax has clinical significance, based on the assessment of its benefit-risk balance taking into account the circulation of SARS-CoV-2 variants and the characteristics of individual vaccine recipients.

PMDA has concluded that Spikevax Intramuscular Injection may be approved if it is not considered to have any particular problems based on comments from the Expert Discussion.

Report on Special Approval for Emergency (2)

July 11, 2023

Product Submitted for Approval

Brand Name	Spikevax Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Moderna Japan Co., Ltd.
Date of Application	February 9, 2023

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).

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Sections "7.R.3 Safety," "7.R.4 Clinical positioning," and "7.R.5 Dosage and administration" in the Report on Special Approval for Emergency (1).

1.1 Efficacy

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Section "7.R.2 Efficacy" in the Report on Special Approval for Emergency (1) and also commented that the efficacy of Spikevax against new variants of SARS-CoV-2 should continue to be evaluated in the future.

PMDA instructed the applicant to gather and analyze information and data from clinical studies, post-marketing surveillance, safety information, literature, and other sources if a new variant of SARS-CoV-2 emerges, so as evaluate the efficacy of Spikevax against the new variant, and then provide information about the findings so obtained. The applicant agreed to respond appropriately.

1.2 Risk management plan (draft)

At the Expert Discussion, the expert advisors made the comments below, while supporting PMDA's conclusions presented in Section "7.R.6 Post-marketing investigation" in the Report on Special Approval for Emergency (1).

- It is important to conduct post-marketing surveillance and gather data because of no experience with the use of Spikevax in Japanese children aged 6 to 11 years and of insufficient available information.
- Since there is no safety data on Spikevax in Japanese children aged 6 to 11 years, a larger sample size is preferred for the specified use-results survey.

PMDA asked the applicant to re-examine the proposed target sample size for the specified use-results survey (N = 100), taking into account of the sample size used in surveys for approved vaccines and the feasibility of the survey. After re-examination, the applicant responded that they would increase the sample size for the specified use-results survey to 200 individuals because the Japan Pediatric Society stated that SARS-CoV-2 vaccination continues to be recommended in children ("On novel coronavirus vaccination in children: 2023.6 Supplement," dated June 9, 2023, issued by the Committee on Immunization and Prevention of Infectious Diseases, Japan Pediatric Society[38)] [in Japanese]), implying that vaccine coverage is expected to grow in the roll-out program beginning in fall 2023, and that a larger sample size is feasible.

Based on the above discussion, PMDA has concluded that the current risk management plan (draft) for Spikevax should include the safety and efficacy specifications presented in Table 22, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities as presented in Table 23. The specified use-results survey with the target sample size presented by the applicant is acceptable. However, when the vaccine product to be distributed during the survey period and its distribution volume become clear, whether the survey should be conducted and the detailed plan should be discussed based on the plan of the Government-led cohort study in children aged 6 to 11 years, and the Japanese Government's policy on vaccination program in future.

Table 22. Safety and efficacy specifications in the risk management plan (draft)

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

No changes in the present application

Table 23. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (bivalent [Original/Omicron] vaccine) • Early post-marketing phase vigilance (in pediatric recipients aged 6 to 11 years) • General use-results survey (a follow-up of participants in the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan) (monovalent [Original] vaccine) • Specified use-results survey (in pediatric recipients aged 6 to 11 years) • Post-marketing database survey: shock, anaphylaxis (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) (monovalent [Original] vaccine) • Post-marketing database survey: acute phase solicited adverse events (primary series) (monovalent [Original] vaccine) • Post-marketing database survey: non-acute phase hospitalization events (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) (monovalent [Original] vaccine) • Post-marketing clinical study (Study TAK-919-1501) (primary series) (monovalent [Original] vaccine) • Foreign phase III study (Study P301) (primary series) (monovalent [Original] vaccine)	• Disseminate data gathered during early post-marketing phase vigilance (bivalent [Original/Omicron] vaccine) • Disseminate data gathered during early post-marketing phase vigilance (pediatric recipients aged 6 to 11 years) • Develop and distribute information materials for healthcare professionals • Develop and distribute information materials for vaccine recipients • Develop and distribute information materials for vaccine recipients (Children who receive the SARS-CoV-2 vaccine, Spikevax Intramuscular Injection, and their parents or guardians) • Publish information on reported adverse reactions periodically (bivalent [Original/Omicron] vaccine) • Publish information on reported adverse reactions periodically (in pediatric recipients aged 6 to 11 years) (Spikevax Intramuscular Injection)

Underline denotes changes in content for the present application.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. The re-examination period for the present application should be the remainder of the ongoing re-examination period (until May 20, 2029).

Indication

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

The indication applies to the following vaccine products:

- Vaccine product containing mRNA encoding the spike protein of SARS-CoV-2 (original strain)
- Vaccine product containing mRNA encoding the spike protein of SARS-CoV-2 (original strain and Omicron variant)

(No change)

Dosage and Administration

- Vaccine product containing mRNA encoding the spike protein of SARS-CoV-2 (original strain)

Individuals 12 years of age and older

For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 years of age and older but younger than 12 years of age

For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (0.25 mL each) at a recommended interval of 4 weeks.

• Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

Individuals 12 years of age and older

For a booster dose, a single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children 6 years of age and older but younger than 12 years of age

For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.

(Underline denotes changes.)

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 3 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (2) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (3) Matters related to Item 4
   The applicant is required to report the quantity sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals

and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

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

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

List of Abbreviations

Adverse reaction	Adverse event for which a causal relationship to the study vaccine cannot be ruled out
AESI	Adverse events of special interest
Bivalent (Original/Omicron BA.1) vaccine	Bivalent vaccine containing elasomeran and imelasomeran at a mass ratio of 1:1
Bivalent (Original/Omicron BA.4-5) vaccine	Bivalent vaccine containing elasomeran and davesomeran at a mass ratio of 1:1
Bivalent vaccine(s)	Bivalent (Original/Omicron BA.1) vaccine and/or bivalent (Original/Omicron BA.4-5) vaccine
Cabinet Order for Enforcement of the 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 1961)
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GLSM	Geometric least squares mean
GM	Geometric mean
GMFR	Geometric mean fold rise
GMR	Ratio of Geometric mean titers
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
Infectious Disease Control Act	Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Act No. 114 of 1998)
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	Multisystem inflammatory syndrome in children
mITT	Modified intention-to-treat
Monovalent (Original) vaccine	Monovalent vaccine containing elasomeran
mRNA	Messenger RNA
Original strain	Wuhan-Hu-1 strain (D614G)
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
PPES	Per-protocol efficacy set
PPIS	Per-protocol immunogenicity subset
PPIS-Neg	Per-protocol immunogenicity subset - SARS-CoV-2 negative at baseline
PsVNA	Pseudovirus neutralization assay
RNA	Ribonucleic acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Spikevax	Spikevax Intramuscular Injection
Study P201	Study mRNA-1273-P201
Study P204	Study mRNA-1273-P204
Study P205	Study mRNA-1273-P205

Study P301	Study mRNA-1273-P301
ULOQ	Upper limit of quantification
VE	Vaccine efficacy
WHO	World Health Organization