Report on Special Approval for Emergency

October 5, 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*], (d) Andusomeran [JAN*])
Applicant	Moderna Japan Co., Ltd.
Date of Application	May 25, 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 (d) Suspension for injection: Each vial (2.5 mL) contains 0.25 mg of Andusomeran
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. 0613-1, dated on June 13, 2023])
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the primary series of the vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (Omicron variant) has a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in children aged 6 months to 5 years, and all age groups 6 years and older, and that the product has acceptable safety with no significant safety concerns (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)

(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

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

  Individuals 12 years of age and older

  <u>For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (1 mL each) at a recommended interval of 4 weeks.</u>

  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

  <u>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.</u>

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

  <u>Children 6 months of age and older but younger than 6 years</u>

  <u>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.</u>

(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 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 the cases 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)

August 29, 2023

The following is an outline of the data submitted by the applicant and the 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 (SARS-CoV-2) RNA Vaccine (Active ingredients: (a) Elasomeran, (b) Elasomeran and Imelasomeran, (c) Elasomeran and Davesomeran)
Applicant	Moderna Japan Co., Ltd.
Date of Application	May 25, 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 protein 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)
  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.
- 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 the primary series, Spikevax is administered intramuscularly as a series of 2 doses (1 mL each) at a recommended interval of 4 weeks.

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

Children 6 months of age and older but younger than 6 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.

(Underline denotes changes)

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List of Abbreviations

See Appendix.

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

A variety of measures including vaccine roll-out programs have been implemented to tackle the global pandemic of the disease caused by SARS-CoV-2 (COVID-19) starting in January 2020. However, the continued emergence of SARS-CoV-2 variants with varying infectivity, transmissibility, antigenicity, etc. has resulted in repeated waves of SARS-CoV-2 infection. While the World Health Organization (WHO) declared the end of the Public Health Emergency of International Concern for COVID-19 on May 5, 2023,[1)] it also stated that as measures to address the COVID-19 response, States Parties are recommended to continue to offer SARS-CoV-2 vaccination, to gather and report various data including epidemiological information, and to develop new vaccines and therapeutics for COVID-19.[2)]

In Japan, beginning on May 8, 2023, COVID-19 has been reclassified as the "Class V Infectious Disease" instead of "Novel Influenza Infection, etc." under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Disease Control Act). SARS-CoV-2 vaccines continue to be offered as a special temporary vaccination program under the Immunization Act. As of August 2023, approximately 80% of people in Japan have completed the primary SARS-CoV-2 vaccine series, and booster vaccination programs have also been implemented. However, the proportions of young children who completed the primary series remain as low as 23% for children aged 5 to 11 years and 3% for children aged 6 months to 4 years.[3)]

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)." By August 2023, the Spikevax monovalent (Original) vaccine was approved for use in the primary series and for use as booster doses, while the Spikevax bivalent (Original/Omicron BA.1) vaccine and the Spikevax bivalent (Original/Omicron BA.4-5) vaccine were approved for use as booster doses. Currently, however, the monovalent (Original) vaccine is no longer distributed in Japan, and available Spikevax vaccine products can only be used as booster doses in individuals aged 6 years and older.[4)] Among different vaccine products that are approved in Japan as of August 2023 for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)," "Comirnaty Intramuscular Injection for 6 months to 4 years old" is the only vaccine product for infants. In addition, the currently distributed Omicron-adapted SARS-CoV-2 vaccine that can be used for the primary series is confined to only 1 type[5)] for each age group. Outside Japan, the Omicron-adapted bivalent vaccine was granted emergency use authorization (EUA) in the US in April 2023 for the primary series of vaccination in all age groups 6 months and older based on the pivotal data from the foreign phase III study (Study mRNA-1273-P306 [hereinafter referred to as "Study P306"]), which assessed the immunogenicity 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 August 25, 2023)
2) https://cdn.who.int/media/docs/default-source/documents/ihr/covid-19_standing-recommendations_9-august-2023.pdf (last accessed on August 25, 2023)
3) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (last accessed on August 25, 2023)
4) The partial change application to add the dosage and administration for children aged 6 to 11 years was approved on August 2, 2023.
5) "Comirnaty RTU Intramuscular Injection" for individuals aged 12 years and older, "Comirnaty Intramuscular Injection for 5 to 11 years old" for children aged 5 to 11 years, and "Comirnaty Intramuscular Injection for 6 months to 4 years old" for children aged 6 months to 4 years.

safety of the Spikevax bivalent (Original/BA.1) vaccine for the primary series in children aged 6 months to 5 years.

The applicant has recently submitted a partial change application for use of the Omicron-adapted Spikevax bivalent vaccine for the primary series in individuals including children aged 6 months to 5 years based on the pivotal data from the foreign phase II/III study (Study mRNA-1273-P204 [hereinafter referred to as "Study P204"]), which was conducted to assess the monovalent (Original) vaccine in children aged 6 months to 5 years, and from the foreign phase III study (Study P306) mentioned above.

This report contains the results 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. 0613-1, dated on June 13, 2023).

2. Quality and Outline of the Review Conducted by PMDA

No new data relating to the quality of the drug substance or the drug product were submitted for the present application; however, data relating to the quality of novel excipients were submitted.

2.R Outline of the review conducted by PMDA

2.R.1 Novel excipients

The present application includes a vaccination regimen for a 1 mL dose of the vaccine product containing the active ingredient at a concentration of 0.1 mg/mL. The dose contains trometamol hydrochloride, SM-102, DSPC, and PEG2000-DMG in amounts greater than the maximum daily exposure of the respective substances that have been used in previously approved intramuscular formulations. Accordingly, these substances are defined as novel excipients.

From the data submitted for the present application and those for a marketing application for Spikevax Intramuscular Injection, PMDA concluded that there are no particular problems with the specifications for the excipients and their stability as well as the safety of the excipients contained in the vaccine product at the dosage regimen proposed in the present application. However, SM-102, DSPC, and PEG2000-DMG are excipients the use of which is permitted only in specified formulations in accordance with "Handling of excipients that are allowed to be used only in specific formulations or under specific conditions" (Administrative Notice dated on June 23, 2009, issued by the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare). Therefore, it was decided that the use of these excipients should not be deemed as a general precedent.

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 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 is intended for a new dosage, no new data were submitted under this section because the non-clinical pharmacokinetic data had 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.

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

The applicant submitted the efficacy and safety data, in the form of evaluation data from 2 studies (Table 1). While Study P204 was conducted in healthy children in different age groups (6 months to 1 year, 2 to 5 years, and 6 to 11 years), the data in the age range of 6 months to 5 years were submitted for the present application. Study P306, consisting of Parts 1 and 2, was conducted in children aged 6 months to 5 years. Although the study evaluated the primary series in Part 1 and booster doses in Part 2, only the results of the primary series from Part 1 were submitted for the present application.

Table 1. Overview of clinical studies (evaluation data)

Location	Study ID	Phase	Study population	Number of participants	Dosage regimen	Study objectives
Overseas	mRNA-1273 -P204	II/III	Healthy children aged 6 months to 5 years[a)]	Part 1: 6 months to 1 year: 150 2-5 years: 224	For the primary series, 2 intramuscular injections of the monovalent (Original) vaccine 25 μg or 50 μg[b)] administered 28 days apart	Safety Immunogenicity
			Healthy children aged 6 months to 5 years[a)]	Part 2: 6 months to 1 year: 2,355 2-5 years: 4,048	For the primary series, 2 intramuscular injections of the monovalent (Original) vaccine 25 μg[b)] or placebo[c)] administered 28 days apart	
Overseas	mRNA-1273 -P306	III	Healthy children aged 6 months to 5 years[a)]	Part 1: 179	For the primary series, 2 intramuscular injections of the bivalent (Original/BA.1) vaccine 25 μg administered 28 days apart	Safety Immunogenicity

a) Includes children with stable underlying disease
b) The vaccine product containing 100 μg of elasomeran per 0.5 mL was diluted to contain 25 μg or 50 μg of elasomeran per 0.5 mL for vaccination.
c) Physiological saline

7.1 Foreign phase II/III study (CTD 5.3.5.1.1, Study mRNA-1273-P204 [ongoing since March 2021, data cut-off on February 21, 2022])

An open-label, uncontrolled, dose-escalation study (Part 1) and a randomized, observer-blind, placebo-controlled, parallel-group study (Part 2) were conducted at 40 study centers in the US and 84 study centers in Canada, to evaluate the safety and immunogenicity of the monovalent (Original) vaccine in healthy children (including children with stable underlying disease) aged 6 months to 5 years (target sample size: Part 1, approximately 225 children aged 2 to 5 years and 150 children aged 6 months to 1 year; Part 2, maximum of

4,000 children [maximum of 3,000 children[6)] in the monovalent (Original) vaccine group and maximum of 1,000 children in the placebo group] each in children aged 2 to 5 years and in children aged 6 months to 1 year).

7.1.1 Part 1

Participants were to receive 2 intramuscular injections of the monovalent (Original) vaccine 25 μg or 50 μg[7)] 28 days apart. Safety data in children aged 2 to 5 years obtained at an earlier stage of the study were evaluated, and only the monovalent (Original) vaccine 25 μg was used in children aged 6 months to 1 year.

In the age group of 2 to 5 years, 224 participants (75 participants in the monovalent [Original] vaccine 25 μg group and 149 participants in the monovalent [Original] vaccine 50 μg group) who received at least 1 dose of the study vaccine were included in the full analysis set (FAS) and the safety analysis set. The safety analysis set comprised 69 and 155 subjects in the monovalent (Original) vaccine 25 μg and 50 μg groups, respectively, based on the actual dose administered. Of the participants included in the safety analysis set, 223 participants (69 participants [25 μg] and 154 participants [50 μg]) who provided any solicited adverse event data after study vaccination (i.e., had at least one post-dose solicited safety assessment) were included in the solicited adverse event analysis set. Of the participants included in the FAS, 123 participants who had documented evidence of SARS-CoV-2 status before the first study vaccination, and who had immunogenicity data before the first study vaccination and data from at least one antibody assessment after study vaccination (53 participants [25 μg] and 70 participants [50 μg])[8)] were included in the immunogenicity subset. Of the participants in the immunogenicity subset, 119 participants (50 participants [25 μg] and 69 participants [50 μg]), who had no major protocol deviations, etc., who had immunogenicity data at 28 days after the second study vaccination, and who had negative SARS-CoV-2 status at baseline, were included in the per protocol immunogenicity subset (PPIS). The PPIS was the primary analysis population for immunogenicity.

In the age group of 6 months to 1 year, 150 participants (monovalent [Original] vaccine 25 μg group) who had received at least 1 dose of the study vaccine were included in the FAS, safety analysis set, and solicited adverse event analysis set. Of the 150 participants, 102 participants were included in the immunogenicity subset. Of the 102 participants, 98 participants who had negative SARS-CoV-2 status before the first study vaccination were included in the PPIS.

In the SARS-CoV-2 test, reverse transcription polymerase chain reaction (RT-PCR) and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were performed. Participants who had negative results for both RT-PCR and antibody testing were considered SARS-CoV-2 negative, and those who had a positive result for either RT-PCR or antibody testing were considered SARS-CoV-2 positive.

[6)] The sample size was determined so that at least 1 adverse event could be detected with an incidence of 0.1%.
[7)] The vaccine product containing 100 μg of elasomeran per 0.5 mL was diluted to contain 25 μg or 50 μg of elasomeran per 0.5 mL for vaccination.
[8)] In Part 1, the first approximately 75 participants enrolled were assessed for immunogenicity.

The safety follow-up period was as follows:

- Solicited adverse events [9] (local events: pain, erythema/redness, swelling/induration, and lymphadenopathy[10]; and systemic events: fever, irritability/crying, sleepiness, and loss of appetite for the age groups of 6 months to 1 year and 2 years to 36 months and fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills for the age group of 37 months to 5 years): Reported through 7 days after each dose of the study vaccine (reported in the diary by 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,[11] adverse events of special interest (AESI),[12] and adverse events requiring treatment: Reported from the first dose of the study vaccine to completion of the study period

Table 2 and Table 3 show the incidence of solicited adverse events reported through 7 days after each dose of the study vaccine.

[9] The severity of adverse events was defined and evaluated using the Food and Drug Administration (FDA) Guidance (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials: September 2007) as reference.

[10] This was reported as axillary (or inguinal) swelling or tenderness ipsilateral to the injection site in the participant diary.

[11] In accordance with the definition of the US Centers for Disease Control and Prevention (CDC) (MMWR, *Morb Mortal Wkly Rep*. 2021;70:977-82), the protocol was amended concerning post-vaccination (against COVID-19) myocarditis and pericarditis before the start of Part 2 (Protocol Amendment 3 prepared on July [redacted], 2021). On and after July [redacted], 2021, in the safety telephone calls (safety follow-up calls during the 7 days after each dose of the vaccine or later), parents/guardians of participants were interviewed about whether the participants had the following symptoms: chest pain, chest pressure, chest discomfort, shortness of breath, tachypnoea at rest, pain when breathing, increased heart rate, cardiac flutter, or palpitations.

[12] 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 (including multisystem inflammatory syndrome in children [MIS-C]), 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 (children aged 2-5 years) (Study P204 Part 1, Solicited adverse event analysis set)

Event		First dose				Second dose			
		Monovalent (Original) 25 μg		Monovalent (Original) 50 μg		Monovalent (Original) 25 μg		Monovalent (Original) 50 μg	
		All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local	2 to 5 years	N = 69		N = 152		N = 69		N = 154	
	Any local adverse event	40 (58.0)	0	109 (71.7)	2 (1.3)	55 (79.7)	0	137 (89.0)	2 (1.3)
	Pain	39 (56.5)	0	104 (68.4)	1 (0.7)	54 (78.3)	0	136 (88.3)	1 (0.6)
	Erythema/redness	4 (5.8)	0	23 (15.1)	0	6 (8.7)	0	22 (14.3)	1 (0.6)
	Swelling/induration	4 (5.8)	0	17 (11.2)	1 (0.7)	6 (8.7)	0	18 (11.7)	0
	Lymphadenopathy[a)]	1 (1.4)	0	10 (6.6)	0	1 (1.4)	0	16 (10.4)	0
Systemic	2 years to 36 months	N = 9		N = 24		N = 9		N = 26	
	Any systemic adverse event	5 (55.6)	0	8 (33.3)	1 (4.2)	8 (88.9)	0	20 (76.9)	3 (11.5)
	Fever[b)]	1 (11.1)	0	2 (8.3)	1 (4.2)	0	0	9 (34.6)	3 (11.5)
	Irritability/crying	5 (55.6)	0	6 (26.1)[c)]	0	6 (66.7)	0	18 (69.2)	0
	Sleepiness	2 (22.2)	0	3 (13.0)[c)]	0	2 (22.2)	0	10 (38.5)	0
	Loss of appetite	1 (11.1)	0	0	0	2 (22.2)	0	7 (26.9)	2 (7.7)
	37 months to 5 years	N = 60		N = 128		N = 60		N = 128	
	Any systemic adverse event	16 (26.7)	0	54 (42.2)	2 (1.6)	29 (48.3)	1 (1.7)	85 (66.4)[d)]	11 (8.6)[d)]
	Fever[b)]	1 (1.7)	0	8 (6.3)	0	6 (10.0)	1 (1.7)	32 (25.0)	8 (6.3)
	Headache	5 (8.3)	0	13 (10.3)[d)]	0[d)]	11 (18.3)	0	33 (26.0)[e)]	1 (0.8)[e)]
	Fatigue	8 (13.3)	0	43 (34.1)[d)]	2 (1.6)[d)]	21 (35.0)	0	70 (55.1)[e)]	5 (3.9)[e)]
	Myalgia	4 (6.7)	0	12 (9.5)[d)]	1 (0.8)[d)]	9 (15.0)	0	24 (18.9)[e)]	1 (0.8)[e)]
	Arthralgia	2 (3.3)	0	5 (4.0)[d)]	1 (0.8)[d)]	3 (5.0)	0	11 (8.7)[e)]	0[e)]
	Nausea/vomiting	2 (3.3)	0	7 (5.6)[d)]	0[d)]	5 (8.3)	0	16 (12.6)[e)]	0[e)]
	Chills	0	0	4 (3.2)[d)]	0[d)]	3 (5.0)	0	20 (15.7)[e)]	0[e)]

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

a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site

b) For children aged 37 months to 5 years, Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C to 38.9°C, Grade 3 = 39.0°C to 40.0°C, and Grade 4 = >40.0°C. For children aged 2 years to 36 months, Grade 1 = 38.0°C to 38.4°C, Grade 2= 38.5°C to 39.5°C, Grade 3 = 39.6°C to 40.0°C, and Grade 4 = >40.0°C (oral temperature for children aged >4 years and tympanic membrane temperature for children aged ≤4 years).

c) N = 23; d) N = 126; e) N = 127

Table 3. The incidence of solicited adverse events reported through 7 days after each dose of the study vaccine (children aged 6 months to 1 year) (Study P204 Part 1, Solicited adverse event analysis set)

Event		First dose		Second dose	
		Monovalent (Original) 25 μg N = 149		Monovalent (Original) 25 μg N = 150	
		All Grades	Grade ≥3	All Grades	Grade ≥3
		n (%)	n (%)	n (%)	n (%)
Local	Any local adverse event	60 (40.3)	0	71 (47.3)	3 (2.0)
	Pain	48 (32.2)	0	58 (38.7)	0
	Erythema/redness	11 (7.4)	0	20 (13.3)	1 (0.7)
	Swelling/induration	14 (9.4)	0	18 (12.0)	2 (1.3)
	Lymphadenopathy[a)]	15 (10.1)	0	11 (7.3)	0
Systemic	Any systemic adverse event	107 (71.8)	1 (0.7)	104 (69.3)	3 (2.0)
	Fever[b)]	11 (7.4)	0	17 (11.3)	1 (0.7)
	Irritability/crying	94 (63.1)	0	94 (62.7)	0
	Sleepiness	39 (26.2)	1 (0.7)	42 (28.0)	0
	Loss of appetite	28 (18.8)	0	38 (25.3)	2 (1.3)

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

a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site

b) Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C to 39.5°C, Grade 3 = 39.6°C to 40.0°C, and Grade 4 = >40.0°C (tympanic membrane temperature)

The incidence of unsolicited adverse events reported through 28 days after the first or second dose of the study vaccine and that of the events classified as adverse reactions were as follows: for children aged 2 to 5 years, 23.2% (16 of 69 participants) (adverse reaction, 7.2% [5 of 69 participants]) in the monovalent (Original) vaccine 25 μg group and 36.1% (56 of 155 participants) (adverse reaction, 11.0% [17 of 155 participants]) in the monovalent (Original) vaccine 50 μg group; and for children aged 6 months to 1 year, 53.3% (80 of 150

participants) (adverse reaction, 15.3% [23 of 150 participants]) in the monovalent (Original) vaccine 25 μg group. Unsolicited adverse events occurring in >2% of participants aged 2 to 5 years in the monovalent (Original) vaccine 25 μg group were cough (5.8%, 4 of 69 participants), nasal congestion (5.8%, 4 of 69 participants), injection site erythema (4.3%, 3 of 69 participants), abdominal pain (2.9%, 2 of 69 participants), and fever (2.9%, 2 of 69 participants). Among these events, a causal relationship could not be ruled out for injection site erythema (3 participants). Unsolicited adverse events occurring in >2% of participants aged 2 to 5 years in the monovalent (Original) vaccine 50 μg group were upper respiratory tract infection (7.7%, 12 of 155 participants), fever (7.7%, 12 of 155 participants), injection site erythema (4.5%, 7 of 155 participants), cough (3.9%, 6 of 155 participants), and rhinorrhoea (3.9%, 6 of 155 participants). Among these events, a causal relationship to the study vaccine could not be ruled out for injection site erythema (7 participants) and fever (3 participants). Unsolicited adverse events occurring in >2% of participants aged 6 months to 1 year in the monovalent (Original) vaccine 25 μg group are fever (9.3%, 14 of 150 participants), upper respiratory tract infection (8.7%, 13 of 150 participants), irritability (8.0%, 12 of 150 participants), teething (7.3%, 11 of 150 participants), otitis media (6.0%, 9 of 150 participants), decreased appetite (6.0%, 9 of 150 participants), rhinorrhoea (6.0%, 9 of 150 participants), otitis media acute (4.7%, 7 of 150 participants), hand-foot-and-mouth disease (4.0%, 6 of 150 participants), cough (3.3%, 5 of 150 participants), somnolence (2.7%, 4 of 150 participants), wheezing (2.7%, 4 of 150 participants), diarrhoea (2.7%, 4 of 150 participants), and injection site lymphadenopathy (2.7%, 4 of 150 participants). Among these events, a causal relationship to the study vaccine could not be ruled out for irritability (11 participants), decreased appetite (7 participants), somnolence (4 participants), injection site lymphadenopathy (4 participants), fever (2 participants), and diarrhoea (2 participants).

Up to the data cut-off on February 21, 2022, there were no reports of death, nor did any adverse event lead to study discontinuation in any age group.

Up to the data cut-off on February 21, 2022, no serious adverse events occurred in children aged 2 to 5 years, while serious adverse events occurred in 3 children aged 6 months to 1 year in the monovalent (Original) vaccine 25 μg group (cough/wheezing/urticaria in 1 participant, febrile convulsion in 1 participant, and rhinovirus infection in 1 participant). A causal relationship to the study vaccine was ruled out for all these events and their outcome was reported as resolved.

Table 4 shows the neutralizing antibody titers against the original strain as measured by pseudovirus neutralization assay (PsVNA) (50% inhibitory dilution) at 28 days after the second dose of the study vaccine in each group, and the comparison of the data from Study P204 with the immunogenicity data from Study mRNA-1272-P301 (hereinafter referred to as “Study P301”) in participants aged 18 to 25 years.

Table 4. Comparison of serum neutralizing antibody GMT against the original strain (50% inhibitory dilution) and seroresponse rates (Study P204 Part 1 and Study P301 [participants aged 18-25 years], PPIS)

			P204 (2-5 years)		P204 (6 months to 1 year)	P301 (18-25 years)
			Monovalent (Original) 25 μg (N = 50)	Monovalent (Original) 50 μg (N = 69)	Monovalent (Original) 25 μg (N = 98)	Monovalent (Original) 100 μg (N = 295)
GMT						
Pre-first dose	n		50	69	96	295
	GMT [two-sided 95% CI][a)]		9.250 [NE, NE]	9.250 [NE, NE]	9.565 [9.255, 9.886]	9.285 [9.216, 9.355]
28 days post-second dose	n		50	69	97	295
	GMT [two-sided 95% CI][a)]		1013.766 [846.185, 1214.535]	1844.127 [1602.336, 2122.404]	1782.603 [1542.045, 2060.688]	1299.855 [1170.622, 1443.354]
	GMFR [two-sided 95% CI][a)*]		109.596 [91.479, 131.301]	199.365 [173.226, 229.449]	188.484 [161.932, 219.389]	139.990 [126.103, 155.405]
	GLSM [two-sided 95% CI][b)]	6 months to 1 year			1782.603 [1498.398, 2120.713]	1299.855 [1176.638, 1435.974]
		2-5 years	1013.766 [803.087, 1279.714]	1844.127 [1512.393, 2248.625]		1299.855 [1180.977, 1430.698]
	GMR (P204/P301) [two-sided 95% CI][b)]		0.780 [0.606, 1.003]	1.419 [1.138, 1.768]	1.371 [1.123, 1.675]	–
Seroresponse rate						
n[c)]/N1			50/50	69/69	96/96	292/295
Seroresponse rate [two-sided 95% CI] (%)[d)]			100 [92.9, 100.0]	100 [94.8, 100.0]	100 [96.2,100.0]	99.0 [97.1, 99.8]
Difference in seroresponse rate (P204 − P301) [two-sided 95% CI][e)]			1.0 [−6.1, 3.0]	1.0 [−4.3, 3.0]	1.0 [−2.8, 3.0]	–

Antibody titer 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 to ULOQ]: 18.5-45118)

N = number of participants analyzed; 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

* N1 is the number of participants analyzed.

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 presentation.

b) An analysis of covariance model with the antibody titer at 28 days post-second dose in Studies P204 and P301 as the dependent variables, and the group variable (children aged 6 months to 1 year or 2-5 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 titers 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 stratified Miettinen-Nurminen method adjusted for age group.

7.1.2 Part 2

Participants in both age groups (6 months to 1 year and 2 to 5 years) were to receive 2 intramuscular injections of the monovalent (Original) vaccine 25 μg or placebo 28 days apart.

In the age group of 6 months to 1 year, of the 2,355 randomized participants (1,762 participants in the monovalent [Original] vaccine 25 μg group and 593 participants in the placebo group), 2,350 participants who had received at least 1 dose of the study vaccine were included in the FAS (1,760 participants [25 μg] and 590 [placebo]). The safety analysis set comprised 1,761 participants in the monovalent (Original) vaccine 25 μg group and 589 participants in the placebo group, based on the actual dose administered. Of the participants in the safety analysis set, 1,758 participants in the monovalent (Original) vaccine 25 μg group and 585 participants in the placebo group were included in the solicited adverse event analysis set. Of the participants included in the FAS, the first 274 participants in the monovalent (Original) vaccine 25 μg group were included in the immunogenicity subset, of which, 230 participants who had no major protocol deviations, etc., who had immunogenicity data at 28 days after the second dose of the study vaccine, and who had negative SARS-CoV-2 status at baseline were included in the PPIS. The per protocol set for efficacy (PPES) consisted of FAS participants who had negative SARS-CoV-2 status at baseline, who had no major protocol deviations, and who

received 2 doses of the study vaccine as planned. A total of 2,024 participants (1,511 participants [25 μg] and 513 participants [placebo]) were included in the PPES.

In the age group of 2 to 5 years, of the 4,048 randomized participants (3,040 participants in the monovalent [Original] vaccine 25 μg group and 1,008 participants in the placebo group), 4,038 participants (3,031 participants [25 μg] and 1,007 participants [placebo]) who had received at least 1 dose of the study drug were included in the FAS and the safety analysis set. Of the participants in the safety analysis set, 4,013 participants (3,016 participants [25 μg] and 997 participants [placebo]) who provided any solicited adverse event data after study vaccination (i.e., had at least one post-dose solicited safety assessment) were included in the solicited adverse event analysis set. Of the participants included in the FAS, the first 302 subjects in the monovalent (Original) vaccine 25 μg group were included in the immunogenicity subset. In the immunogenicity subset, the PPIS[13)] consisted of 264 participants who had no major protocol deviations, etc., who had immunogenicity data at 28 days after the second dose of the study vaccine, and who had negative SARS-CoV-2 status at baseline. The PPIS was the primary analysis population for immunogenicity. The PPES consisted of FAS participants who had negative SARS-CoV-2 status at baseline, who had no major protocol deviations, and who received 2 doses of the study vaccine as planned. A total of 3,452 participants (2,594 participants [25 μg] and 858 participants [placebo]) were included in the PPES.

In the SARS-CoV-2 test, RT-PCR and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were performed. Participants who had negative results for both RT-PCR and antibody testing were considered SARS-CoV-2 negative, and those who had a positive result for either RT-PCR or antibody testing were considered SARS-CoV-2 positive.

The primary immunogenicity endpoints were the geometric mean titer (GMT) of neutralizing antibodies (as measured by PsVNA, 50% inhibitory dilution) against SARS-CoV-2 and seroresponse rate at 28 days after the second dose of the study vaccine. The ratio of geometric mean titers (GMR) of neutralizing antibodies and seroresponse rate difference were obtained, and the non-inferiority of the results in participants aged 6 months to 1 year and participants aged 2 to 5 years in this study to the results in participants aged 18 to 25 years in Study P301 was evaluated to determine whether the results met the criteria for immunobridging. Seroresponse was defined as a ≥4-fold rise in neutralizing antibody titers from pre-first dose (if the neutralizing antibody titer pre-first dose reported was below the lower limit of quantification [LLOQ], a ≥4-fold rise from the LLOQ). The success criteria for non-inferiority are shown below. Non-inferiority was considered to be demonstrated if

13) The number of participants required for immunogenicity analysis in Part 2 was determined based on the following assumptions. In the comparison of the PPIS for each age group in Study P204 with the PPIS for participants aged 18 to 25 years in Study P301, assuming a ratio of geometric mean titers (GMR) of 1, a non-inferiority margin of 0.67, a GMR point estimate minimum threshold of 0.8, and a standard deviation of the natural log-transformed level of 1.5, with approximately 289 participants who received the monovalent (Original) vaccine in the PPIS for each age group, there would be 90% power to demonstrate the non-inferiority of the immune response as measured by the antibody geometric mean (GM) in the pediatric population at a two-sided α of 0.05, compared to that in participants aged 18 to 25 years in Study P301. With approximately 289 participants who received the monovalent (Original) vaccine in the PPIS for each age group, assuming a seroresponse rate of ≥95% (seroresponse rate difference between Study P204 and P301 ≤4%), a non-inferiority margin of 10%, a point estimate minimum threshold of −5% for seroresponse rate difference in both age groups of Study P204 and in participants aged 18 to 25 years in Study P301, there would be at least 90% power to demonstrate the non-inferiority of the seroresponse rate of the pediatric population at a two-sided α of 0.05, compared to that in participants aged 18 to 25 years who received mRNA-1273 in Study P301. Assuming a PPIS exclusion rate of 25%, a maximum of 396 participants in the monovalent (Original) vaccine 25 μg group were to be included in the immunogenicity subset.

both of the following criteria for the primary endpoints were met. To address multiplicity issues, the fixed sequence procedure (in order from the older to the younger age groups in Study P204) was used to evaluate non-inferiority.

- GMR: the lower bound of the two-sided 95% confidence interval of the GMR of SARS-CoV-2 neutralizing antibody titers in Study P204 (children aged 6 months to 1 year or those aged 2 to 5 years) to that in Study P301 (participants aged 18 to 25 years) is >0.67 and the GMR point estimate is ≥0.8.
- Difference in seroresponse rate: the lower bound of the two-sided 95% confidence interval of the seroresponse rate difference (Study P204 [children aged 6 months to 1 year or those aged 2 to 5 years] minus Study P301 [participants aged 18 to 25 years, PPIS]) is >−10% and the seroresponse rate difference point estimate is >−5%.

Table 5 shows the results for the primary immunogenicity endpoints at 28 days after study vaccination. The immunogenicity data in the age groups of 2 to 5 years and 6 months to 1 year were compared to the results from Study P301 (participants aged 18 to 25 years). Both the lower bound of the two-sided 95% confidence interval of the GMR of neutralizing antibodies against the original strain and the lower bound of the two-sided 95% confidence interval of the difference in seroresponse rate were greater than the non-inferiority margins, while the GMR point estimate was ≥0.8 and the seroresponse rate difference point estimate was >−5%. Therefore, the results in both age groups met the prespecified success criteria for non-inferiority.

Table 5. Comparison of serum neutralizing antibody titers (50% inhibitory dilution) against the original strain (Study P204 Part 2, PPIS)

			P204		P301 (18-25 years)
			6 months to 1 year Monovalent (Original) 25 μg N = 230	2-5 years Monovalent (Original) 25 μg N = 264	Monovalent (Original) 100 μg N = 295
GMT					
Pre-first dose	n		230	264	294
	GMT [two-sided 95% CI][a)]		7.9 [7.38, 8.47]	7.7 [7.24, 8.17]	11.1 [10.55, 11.68]
28 days post-second dose	n		230	264	291
	GMT [two-sided 95% CI][a)]		1780.7 [1616.18, 1961.88]	1410.0 [1272.02, 1562.98]	1390.8 [1263.49, 1530.89]
	GMFR [two-sided 95% CI][a)*]		225.3 [200.40, 253.27]	183.3 [164.03, 204.91]	125.8 [112.99, 139.96]
	GLSM [two-sided 95% CI][b)]	6 months to 1 year	1780.658 [1606.375, 1973.849]		1390.781 [1269.081, 1524.152]
		2-5 years		1410.015 [1273.782, 1560.820]	1390.781 [1262.487, 1532.113]
	GMR (P204/P301) [two-sided 95% CI][b)]		1.280 [1.115, 1.470]	1.014 [0.881, 1.167]	–
Seroresponse rate					
n[c)]/N1			230/230	261/264	289/291
Seroresponse rate [two-sided 95% CI][d)] (%)			100 [98.4, 100.0]	98.9 [96.7, 99.8]	99.3 [97.5, 99.9]
Difference in seroresponse rate (P204 − P301) [two-sided 95% CI][e)]			0.7 [−1.0, 2.5]	−0.4 [−2.7, 1.5]	–

Antibody titer 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 to ULOQ]: 10-281600)
N = number of participants analyzed; 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
* N1 is the number of participants analyzed.
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 presentation.
b) An analysis of covariance model with the antibody titer at 28 days post-second dose in Studies P204 and P301 as the dependent variables, and the group variable (children aged 6 months to 1 year or 2-5 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 titers 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 stratified Miettinen-Nurminen method adjusted for age group

The grading scale used for the assessment of the severity of adverse events and the safety follow-up period were the same as those employed in Part 1.

Solicited adverse events reported through 7 days after study vaccination in children aged 6 months to 1 year and those aged 2 to 5 years are shown in Table 6 and Table 7, respectively.

Table 6. Solicited adverse events reported through 7 days after each dose of study vaccine (children aged 6 months to 1 year) (Study P204 Part 2, Solicited adverse event analysis set)

First dose							
Event		Monovalent (Original) 25 μg N = 1746			Placebo N = 582		
		N1	All Grades n (%)	Grade ≥3 n (%)	N1	All Grades n (%)	Grade ≥3 n (%)
Local	Any local adverse event	1745	775 (44.4)	9 (0.5)	582	193 (33.2)	2 (0.3)
	Pain	1744	652 (37.4)	0	582	175 (30.1)	0
	Erythema/redness	1744	150 (8.6)	5 (0.3)	582	24 (4.1)	2 (0.3)
	Swelling/induration	1744	146 (8.4)	5 (0.3)	582	15 (2.6)	0
	Lymphadenopathy[a)]	1743	102 (5.9)	0	582	26 (4.5)	0
Systemic	Any systemic adverse event	1745	1334 (76.4)	46 (2.6)	582	421 (72.3)	11 (1.9)
	Fever[b)]	1743	191 (11.0)	12 (0.7)	582	49 (8.4)	4 (0.7)
	Irritability/crying	1737	1175 (67.6)	24 (1.4)	581	361 (62.1)	6 (1.0)
	Sleepiness	1739	645 (37.1)	4 (0.2)	581	217 (37.3)	1 (0.2)
	Loss of appetite	1737	524 (30.2)	10 (0.6)	581	152 (26.2)	1 (0.2)
Second dose							
Event		Monovalent (Original) 25 μg N = 1596			Placebo N = 526		
		N1	All Grades n (%)	Grade ≥3 n (%)	N1	All Grades n (%)	Grade ≥3 n (%)
Local	Any local adverse event	1596	868 (54.4)	22 (1.4)	526	159 (30.2)	0
	Pain	1596	738 (46.2)	0	526	135 (25.7)	0
	Erythema/redness	1596	215 (13.5)	13 (0.8)	526	20 (3.8)	0
	Swelling/induration	1596	243 (15.2)	14 (0.9)	526	11 (2.1)	0
	Lymphadenopathy[a)]	1596	148 (9.3)	0	526	28 (5.3)	0
Systemic	Any systemic adverse event	1596	1174 (73.6)	47 (2.9)	526	350 (66.5)	12 (2.3)
	Fever[b)]	1594	232 (14.6)	10 (0.6)	526	44 (8.4)	6 (1.1)
	Irritability/crying	1589	1021 (64.3)	25 (1.6)	525	307 (58.5)	5 (1.0)
	Sleepiness	1589	558 (35.1)	1 (<0.1)	525	175 (33.3)	1 (0.2)
	Loss of appetite	1589	510 (32.1)	16 (1.0)	525	132 (25.1)	2 (0.4)

N = number of participants analyzed; N1 = number of participants who provided adverse event data; n = number of participants with the event

a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site

b) Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C to 39.5°C, Grade 3 = 39.6°C to 40.0°C, Grade 4 = >40.0°C (tympanic membrane temperature)

Table 7. Solicited adverse events reported through 7 days after each dose of study vaccine (children aged 2 to 5 years) (Study P204 Part 2, Solicited adverse event analysis set)

First dose							
Event		Monovalent (Original) 25 μg N = 2957			Placebo N = 970		
		N1	All Grades n (%)	Grade ≥3 n (%)	N1	All Grades n (%)	Grade ≥3 n (%)
Local	Any local adverse event	2956	1874 (63.4)	23 (0.8)	970	407 (42.0)	4 (0.4)
	Pain	2954	1813 (61.4)	4 (0.1)	970	382 (39.4)	0
	Erythema/redness	2955	164 (5.5)	12 (0.4)	970	14 (1.4)	3 (0.3)
	Swelling/induration	2955	134 (4.5)	10 (0.3)	970	17 (1.8)	2 (0.2)
	Lymphadenopathy[a)]	2954	205 (6.9)	0	970	56 (5.8)	0
Systemic	2 years to 36 months	N = 944			N = 320		
	Any systemic adverse event	944	612 (65.0)	21 (2.2)	320	198 (61.9)	10 (3.1)
	Fever[b)]	942	106 (11.3)	6 (0.6)	320	25 (7.8)	4 (1.3)
	Irritability/crying	941	513 (54.5)	12 (1.3)	319	163 (51.1)	6 (1.9)
	Sleepiness	941	285 (30.3)	2 (0.2)	319	92 (28.8)	0
	Loss of appetite	941	225 (23.9)	7 (0.7)	319	71 (22.3)	1 (0.3)
	37 months to 5 years	N = 2013			N = 650		
	Any systemic adverse event	2013	983 (48.8)	48 (2.4)	650	290 (44.6)	15 (2.3)
	Fever[b)]	2013	155 (7.7)	24 (1.2)	650	33 (5.1)	5 (0.8)
	Headache	2013	232 (11.5)	5 (0.2)	650	78 (12.0)	2 (0.3)
	Fatigue	2013	807 (40.1)	21 (1.0)	650	236 (36.3)	11 (1.7)
	Myalgia	2013	200 (9.9)	5 (0.2)	650	60 (9.2)	2 (0.3)
	Arthralgia	2013	124 (6.2)	2 (<0.1)	650	32 (4.9)	1 (0.2)
	Nausea/vomiting	2013	137 (6.8)	7 (0.3)	650	50 (7.7)	2 (0.3)
	Chills	2013	129 (6.4)	1 (<0.1)	650	40 (6.2)	0
Second dose							
Event		Monovalent (Original) 25 μg N = 2938			Placebo N = 959		
		N1	All Grades n (%)	Grade ≥3 n (%)	N1	All Grades n (%)	Grade ≥3 n (%)
Local	Any local adverse event	2938	2157 (73.4)	34 (1.2)	959	404 (42.1)	0
	Pain	2938	2099 (71.4)	11 (0.4)	959	395 (41.2)	0
	Erythema/redness	2938	259 (8.8)	12 (0.4)	959	15 (1.6)	0
	Swelling/induration	2938	240 (8.2)	13 (0.4)	959	11 (1.1)	0
	Lymphadenopathy[a)]	2938	267 (9.1)	1 (<0.1)	959	31 (3.2)	0
Systemic	2 years to 36 months	N = 963			N = 330		
	Any systemic adverse event	963	651 (67.6)	31 (3.2)	330	194 (58.8)	2 (0.6)
	Fever[b)]	962	182 (18.9)	15 (1.6)	330	35 (10.6)	0
	Irritability/crying	963	523 (54.3)	10 (1.0)	330	148 (44.8)	2 (0.6)
	Sleepiness	963	347 (36.0)	1 (0.1)	330	89 (27.0)	0
	Loss of appetite	963	294 (30.5)	8 (0.8)	330	69 (20.9)	0
	37 months to 5 years	N = 1975			N = 629		
	Any systemic adverse event	1975	1163 (58.9)	104 (5.3)	629	234 (37.2)	11 (1.7)
	Fever[b)]	1974	316 (16.0)	62 (3.1)	627	28 (4.5)	2 (0.3)
	Headache	1975	310 (15.7)	8 (0.4)	629	51 (8.1)	1 (0.2)
	Fatigue	1975	956 (48.4)	45 (2.3)	629	185 (29.4)	8 (1.3)
	Myalgia	1975	310 (15.7)	9 (0.5)	629	47 (7.5)	3 (0.5)
	Arthralgia	1975	168 (8.5)	3 (0.2)	629	28 (4.5)	0
	Nausea/vomiting	1975	194 (9.8)	6 (0.3)	629	30 (4.8)	0
	Chills	1975	245 (12.4)	10 (1.0)	629	31 (4.9)	2 (0.3)

N = number of participants analyzed; N1 = number of participants who provided adverse event data; n = number of participants with the event

a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site

b) For children aged 2 years to 36 months, Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C to 39.5°C, Grade 3 = 39.6°C to 40°C, Grade 4 = >40.0°C; For children aged 37 months to 5 years, Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C = 38.9°C, Grade 3 = 39.0°C to 40.0°C, Grade 4 = >40.0°C (oral temperature for children aged >4 years and tympanic membrane temperature for children aged ≤4 years).

Table 8 shows the incidences of unsolicited adverse events reported through 28 days after the first or second dose of the study vaccine and those classified as adverse reactions (unsolicited adverse events occurring in ≥2% of participants in either group).

Table 8. Adverse events reported through 28 days after the final dose of the study vaccine in ≥2% of participants in either group, and those classified as adverse reactions (Study P204 Part 2, Safety analysis set)

	Monovalent (Original) 25 μg		Placebo	
6 months to 1 year	N = 1761		N = 589	
	Unsolicited adverse event	Adverse reaction	Unsolicited adverse event	Adverse reaction
	n (%)	n (%)	n (%)	n (%)
Any event reported	869 (49.3)	292 (16.6)	284 (48.2)	71 (12.1)
Upper respiratory tract infection	182 (10.3)	1 (<0.1)	72 (12.2)	0
Irritability	151 (8.6)	146 (8.3)	47 (8.0)	46 (7.8)
Pyrexia	90 (5.1)	27 (1.5)	31 (5.3)	4 (0.7)
Teething	83 (4.7)	0	31 (5.3)	0
Rhinorrhoea	76 (4.3)	3 (0.2)	27 (4.6)	0
Cough	74 (4.2)	1 (<0.1)	21 (3.6)	1 (0.2)
Decreased appetite	68 (3.9)	65 (3.7)	26 (4.4)	25 (4.2)
Ear infection	66 (3.7)	0	18 (3.1)	0
COVID-19	62 (3.5)	0	29 (4.9)	0
Diarrhoea	57 (3.2)	12 (0.7)	13 (2.2)	0
Otitis media	46 (2.6)	0	22 (3.7)	0
Nasal congestion	37 (2.1)	1 (<0.1)	14 (2.4)	0
Somnolence	33 (1.9)	32 (1.8)	15 (2.5)	14 (2.4)
Vomiting	33 (1.9)	6 (0.3)	13 (2.2)	4 (0.7)
2–5 years	N = 3031		N = 1007	
	Unsolicited adverse event	Adverse reaction	Unsolicited adverse event	Adverse reaction
	n (%)	n (%)	n (%)	n (%)
Any event reported	1212 (40.0)	286 (9.4)	378 (37.5)	80 (7.9)
Upper respiratory tract infection	244 (8.1)	1 (<0.1)	93 (9.2)	0
Rhinorrhoea	119 (3.9)	3 (<0.1)	42 (4.2)	0
Cough	110 (3.6)	1 (<0.1)	44 (4.4)	0
COVID-19	93 (3.1)	0	55 (5.5)	0
Pyrexia	95 (3.1)	35 (1.2)	36 (3.6)	15 (1.5)
Nasal congestion	60 (2.0)	3 (<0.1)	23 (2.3)	0
Fatigue	58 (1.9)	46 (1.5)	23 (2.3)	21 (2.1)
Ear infection	45 (1.5)	0	20 (2.0)	0

N = number of participants analyzed; n = number of participants with the event; MedDRA/J ver.23.0

Up to the data cut-off on February 21, 2022, in children aged 6 months to 1 year, adverse events led to study discontinuation in 1 participant (urticaria) in the monovalent (Original) vaccine 25 μg group and 1 participant (COVID-19) in the placebo group. In children aged 2 to 5 years, an adverse event (urticaria) led to study discontinuation in 1 participant in the monovalent (Original) vaccine 25 μg group. While a causal relationship between urticaria and the study vaccine could not be ruled out in either of the two age groups in the monovalent (Original) vaccine 25 μg group, the event was mild in severity in both age groups. The outcome was reported as resolved.

Up to the data cut-off on February 21, 2022, in children aged 6 months to 1 year, serious adverse events occurred in 15 participants in the monovalent (Original) vaccine 25 μg group (febrile convulsion [2 participants], bronchiolitis [1 participant], mastoiditis [1 participant], metapneumovirus infection [1 participant], rhinovirus infection [1 participant], electrolyte imbalance [1 participant], pyrexia/febrile convulsion [1 participant], foreign body in respiratory tract [1 participant], asthma [1 participant], adenovirus infection [1 participant], erythema multiforme [1 participant], croup infectious [1 participant], gastroenteritis viral [1 participant], and diabetic ketoacidosis/type 1 diabetes mellitus [1 participant]), while serious adverse events occurred in 1 participant in the placebo group (bronchiolitis/rhinovirus infection/acute respiratory failure). While a causal relationship to the study vaccine could not be ruled out for pyrexia/febrile convulsion

in 1 participant[14] and diabetic ketoacidosis/type 1 diabetes mellitus in 1 participant,[15] their outcomes were reported as resolved. In children aged 2 to 5 years, serious adverse events occurred in 9 participants in the monovalent (Original) vaccine 25 μg group (metapneumovirus infection [1 participant], pneumonia viral/bronchial hyperreactivity/respiratory distress [1 participant], adenovirus infection [1 participant], seizure [1 participant], rhinovirus infection [1 participant], Epstein-Barr virus infection [1 participant], urinary tract infection [1 participant], humerus fracture [1 participant], and bronchial hyperreactivity [1 participant]), while serious adverse events occurred in 2 participants in the placebo group (abdominal wall abscess [1 participant] and rhinovirus infection/asthma [1 participant]). The outcomes of the events were reported as resolved, and a causal relationship to the study vaccine was ruled out for all these events. There were no reports of death.

7.2 Foreign phase III study (CTD 5.3.5.1.2, Study mRNA-1273-P306 [ongoing since June 2022, data cut-off on December 5, 2022 for interim analysis [Part 1])

Study P306 is an uncontrolled study to assess the safety and immunogenicity of the bivalent (Original/BA.1) vaccine in children aged 6 months to 5 years. The study consisted of Part 1, which evaluated the primary series, and Part 2,[16] which evaluated booster doses. Only the data from Part 1 were submitted for the present application.

In Part 1, the safety and immunogenicity of the bivalent (Original/BA.1) vaccine were evaluated in healthy children (including children with stable underlying disease) aged 6 months to 5 years not vaccinated with any COVID-19 vaccine (target sample size, approximately 480 participants[17]) at 24 study centers in the US. The timing of an interim analysis in Part 1 was not specified in advance. However, in order to acquire information on the bivalent (Original/BA.1) vaccine for the primary series at an earlier timing, an interim analysis was performed with a cut-off on December 5, 2022,[18] which was selected as a timepoint that would allow acquisition of immunogenicity data from approximately 80 participants.

Participants were to receive 2 intramuscular injections of the bivalent (Original/BA.1) vaccine 25 μg 28 days apart.

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[14] A girl, aged [redacted] years, developed a severe fever on the day of the first dose of the study vaccine, had febrile convulsions on the next day (Day 2), and recovered on Day 3. As of the data cut-off date, the study was ongoing.

[15] A girl, aged [redacted] years, was diagnosed with diabetic ketoacidosis and type 1 diabetes mellitus on the 13th day after the second dose of the study vaccine (Day 66) and was hospitalized. One week later, the girl was discharged from the hospital with improvement. The outcome was reported as resolved. Although the investigator considered that a causal relationship to the study vaccine could not be ruled out, the investigator also reported that a viral upper respiratory infection may have triggered the events because the girl had a genetic predisposition for borderline diabetes due to a family history of type 1 diabetes mellitus.

[16] Part 2 of the study was conducted to evaluate the safety and immunogenicity of the bivalent (Original/BA.1) vaccine as a booster dose in participants who had completed the 2-dose series of the monovalent (Original) vaccine.

[17] Assuming a GMR against the Omicron BA.1 lineage (GM value after the primary series of the bivalent [Original/BA.1] vaccine 25 μg in Study P306 divided by the GM value after the primary series of the monovalent [Original] vaccine 25 μg in the same age group [6 months to 5 years of age] from Study P204) of 1.5, a standard deviation of the natural log-transformed level of 1.8, with approximately 416 participants in the PPIS, there would be 90% power to demonstrate the superiority of the GM value of the bivalent (Original/BA.1) vaccine to that of the monovalent (Original) vaccine at a one-sided α of 0.025. Taking into account of participants who would be excluded from the PPIS, approximately 480 participants were to be enrolled in the study.

[18] On November [redacted], 2022, FDA asked Moderna to provide data on the primary series with the bivalent vaccine for the purpose of a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting (held on January 26, 2023), and agreed that immunogenicity data of 75 to 85 participants and safety data of approximately 130 participants (reported through 7 days after the second dose) from ongoing Study P306 were to be presented for the VRBPAC meeting and to be the basis for an EUA for the bivalent vaccine as the primary series in children aged 6 months to 5 years. In response to the request, an interim analysis involving hypothesis testing was performed with a data cut-off on December 5, 2022, albeit not prespecified. Since no hypothesis tests for superiority or non-inferiority were planned for the primary immunogenicity endpoint, which would become available after the interim analysis, the Type I error rate was not adjusted.

All 179 participants (48 participants [aged 6 months to 1 year] and 131 participants [aged 2 to 5 years]) who had received at least 1 dose of the study vaccine were included in the FAS and the safety analysis set. Of the participants included in the safety analysis set, all participants who had provided solicited adverse event data were included in the solicited adverse event analysis set. Of the FAS, 71 participants (17 participants [aged 6 months to 1 year] and 54 participants [aged 2 to 5 years]) who were compliant with the protocol, who had documented evidence of SARS-CoV-2 status before the first dose of the study vaccine, and who had immunogenicity data at 28 days after the second dose were included in the PPIS. Of the 71 participants, 45 participants (9 participants [aged 6 months to 1 year] and 36 participants [aged 2 to 5 years]) who had positive SARS-CoV-2 status before the first dose of the study vaccine were excluded, and the remaining 26 participants (8 participants [aged 6 months to 1 year] and 18 participants [aged 2 to 5 years]) were included in the PPIS-Neg. The PPIS was the primary analysis population for immunogenicity.

In the SARS-CoV-2 test, RT-PCR and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were used. Participants who had negative results for both RT-PCR and antibody testing were considered SARS-CoV-2 negative.

The primary immunogenicity endpoints were the GM values of neutralizing antibodies (as measured by PsVNA, 50% inhibitory dilution) against the Omicron BA.1 lineage at 28 days after the second dose of the study vaccine and the GM values of neutralizing antibodies (as measured by PsVNA at 50% inhibitory dilution) against the original strain at 28 days after the second dose of the study vaccine. The results of the primary endpoints were compared with the GM values[19)] after the primary series of the monovalent (Original) vaccine 25 μg (28 days after the second dose) in the same age group (6 months to 5 years) from Study P204 to evaluate the superiority of the bivalent (Original/BA.1) vaccine to the monovalent (Original) vaccine in terms of the seroresponse against the Omicron BA.1 lineage and the non-inferiority of the bivalent (Original/BA.1) vaccine to the monovalent (Original) vaccine in terms of the seroresponse against the original strain. The success criteria for superiority and non-inferiority are as shown below. Vaccine efficacy was considered to be demonstrated when both criteria were met.

- As for the GM of neutralizing antibody titers against the Omicron BA.1 lineage, the lower bound of the two-sided 95% confidence interval of the GMR of Study P306 (6 months to 5 years) to Study P204 (6 months to 5 years) is >1.
- As for the GM of neutralizing antibody titers against the original strain, the lower bound of the two-sided 95% confidence interval of the GMR of Study P306 (6 months to 5 years) to Study P204 (6 months to 5 years) is >0.667 based on the non-inferiority margin of 1.5.

Table 9 shows the results of the primary immunogenicity endpoints. Both the lower bound of the two-sided 95% confidence interval of the neutralizing antibody GMR against the Omicron BA.1 lineage and that against

[19)] Evaluated in participants in the PPIS regardless of prior SARS-CoV-2 infection status.

the original strain were greater than the superiority and non-inferiority margins, respectively, and therefore the results met the prespecified success criteria.

Table 9. Comparison of serum neutralizing antibody titers (50% inhibitory dilution) against the Omicron BA.1 lineage and against the original strain (Study P306, PPIS)

	Omicron BA.1		Original strain	
	P306	P204	P306	P204
	Bivalent (Original/BA.1) 25 μg N = 71	Monovalent (Original) 25 μg N = 632	Bivalent (Original/BA.1) 25 μg N = 71	Monovalent (Original) 25 μg N = 632
Pre-first dose				
n	69	369	68	617
GMC [two-sided 95% CI][a)]	49.2 [30.4, 79.6]	5.9 [5.5, 6.2]	35.6 [24.0, 52.7]	9.6 [8.9, 10.4]
28 days post-second dose				
n	58	402	66	594
N1	56	257	66	585
GMC [two-sided 95% CI][a)]	1889.7 [1430.0, 2497.2]	74.3 [67.7, 81.7]	1432.9 [1054.5, 1947.0]	1732.5 [1611.5, 1862.5]
GMFR [two-sided 95% CI][a)*]	48.2 [28.6, 81.2]	13.0 [11.6, 14.5]	41.8 [30.1, 58.0]	183.8 [170.1, 198.7]
GLSM [two-sided 95% CI][b)]	1889.7 [1520.4, 2348.7]	74.3 [68.5, 80.8]	1432.9 [1173.4, 1749.7]	1732.5 [1620.9, 1851.8]
GMR [two-sided 95% CI][b)] (P306/P204)	25.4 [20.1, 32.1]		0.83 [0.67, 1.02]	

Antibody titer 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 to ULOQ]: 8-41984 for Omicron BA.1 and 10-4505600 for original strain)

N = number of participants analyzed; 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

* N1 is the number of participants analyzed.

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 presentation.

b) An analysis of covariance model with the antibody titer at 28 days post-second dose in Studies P306 and P204 as the dependent variables, and the group variable (bivalent vaccine or monovalent vaccine) as the fixed effect, adjusted for the age group and pre-first dose SARS-CoV-2 status.

The safety follow-up period was as follows:

- Solicited adverse events[9)] (local events: pain, erythema/redness, swelling/induration, and lymphadenopathy[10)]; and systemic events: fever, irritability/crying, sleepiness, loss of appetite [6 to 36 months]; fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills [37 months to 5 years]): Reported through 7 days after study vaccination (reported in the diary by parents/guardians)
- 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, AESI,[12)] and adverse events requiring treatment: Reported from the first dose of the study vaccine until completion of the study period

Table 10 shows solicited adverse events reported through 7 days after each dose of the study vaccine.

Table 10. Solicited adverse events reported through 7 days after each dose of study vaccine (Study P306, Solicited adverse event analysis set)

Event		Bivalent (Original/BA.1) 25 μg (N = 179)					
		First dose			Second dose		
		N1	All Grades	Grade ≥3	N1	All Grades	Grade ≥3
			n (%)	n (%)		n (%)	n (%)
Local	Any local adverse event	179	67 (37.4)	1 (0.6)	141	64 (45.4)	0
	Pain	179	61 (34.1)	0	141	62 (44.0)	0
	Erythema/redness	179	3 (1.7)	1 (0.6)	141	5 (3.5)	0
	Swelling/induration	179	2 (1.1)	0	141	3 (2.1)	0
	Lymphadenopathy[a)]	179	11 (6.1)	0	141	5 (3.5)	0
Systemic	Any systemic adverse event	179	80 (44.7)	2 (1.1)	141	69 (48.9)	4 (2.8)
	Fever[b)]	179	16 (8.9)	2 (1.1)	141	19 (13.5)	2 (1.4)
	Headache	90	10 (11.1)	0	71	8 (11.3)	0
	Fatigue	90	23 (25.6)	1 (1.1)	71	24 (33.8)	0
	Myalgia	90	11 (12.2)	0	71	11 (15.5)	0
	Arthralgia	90	7 (7.8)	0	71	9 (12.7)	0
	Nausea/vomiting	90	5 (5.6)	0	71	5 (7.0)	0
	Chills	90	4 (4.4)	0	71	6 (8.5)	0
	Irritability/crying	79	35 (44.3)	0	70	29 (41.4)	1 (1.4)
	Sleepiness	79	24 (30.4)	0	70	22 (31.4)	0
	Loss of appetite	79	20 (25.3)	0	70	19 (27.1)	1 (1.4)

N = number of participants analyzed; N1 = number of participants who provided adverse event data; n= number of participants with the event

a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site

b) For children aged 6 to 36 months, Grade 1 = 38.0°C to 38.4°C, Grade 2: 38.5°C to 39.5°C, Grade 3, 39.6°C to 40.0°C, Grade 4, >40.0°C (tympanic membrane temperature). For children aged 37 months to 5 years, Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C to 38.9°C, Grade 3 = 39.0°C to 40.0°C, Grade 4 = >40.0°C.

The incidences of unsolicited adverse events reported through 28 days after the first or second dose of the study vaccine and those classified as adverse reactions were 30.7% (55 of 179 participants) and 1.1% (2 of 179 participants), respectively. Unsolicited adverse events occurring in ≥2% of participants were upper respiratory tract infection (8.9%, 16 participants), rhinorrhoea (2.8%, 5 participants), and ear infection (2.2%, 4 participants). Diarrhoea (1 participant) and croup (1 participant) were classified as adverse reactions.

There were no reports of death, nor did any adverse event lead to study discontinuation. A serious adverse event (exacerbation of asthma) was reported in 1 participant. A causal relationship to the study vaccine was ruled out, and the outcome was reported as resolved.

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 the use of the Omicron-adapted bivalent vaccine for the primary series in individuals including children aged 6 months to 5 years:

The development of Spikevax has been accelerated to address the global public health emergency caused by the COVID-19 pandemic. In the development program for pediatric use, the FDA guidance documents on COVID-19 vaccine development[20)21)] were used as references, and an immunobridging approach was adopted to infer the efficacy of Spikevax based on the similarity of the immunogenicity of the vaccine product in a target population to that in another population in which the efficacy of the vaccine product (vaccine efficacy in preventing COVID-19) has already been demonstrated by clinical studies. This approach has been addressed in "Consideration for Evaluation of SARS-CoV-2 Vaccine (Appendix 3): Consideration for Evaluation of

[20)] Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19: https://www.fda.gov/media/139638/download (last accessed on August 25, 2023)

[21)] Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19: https://www.fda.gov/media/142749/download (last accessed on August 25, 2023)

SARS-CoV-2 Vaccine Based on Immunogenicity" (October 22, 2021, Office of Vaccines and Blood Products, PMDA) (hereinafter referred to as "Appendix 3"). The monovalent (Original) vaccine was approved for the primary series in individuals aged 6 to 11 years and those aged 12 to 17 years based on the results of analyses in which the efficacy of the vaccine product was evaluated in a similar manner (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on July 12, 2023, and the Package Insert revised on July 26, 2021).

In the development program for use of Spikevax in children aged 6 months to 5 years, the immunogenicity and safety of the monovalent (Original) vaccine in children aged 6 months to 5 years were evaluated in Study P204, a foreign phase II/III study which evaluated the monovalent (Original) vaccine in children aged 6 months to 11 years. After Study P204 Part 1 as a dose-finding study, the dose of 25 μg was selected for both age groups of 6 months to 1 year and 2 to 5 years, in view of the safety and immunogenicity results after the second dose of Spikevax [see Section 7.1.1]. Subsequently, immunogenicity data for the age groups of 6 months to 1 year and 2 to 5 years from Study P204 Part 2 were compared to those for the age group of 18 to 25 years from Study P301. In Study P204 Part 2, the success criteria for immunobridging were met for both age groups of children, suggesting that the monovalent (Original) vaccine for the primary series in children aged 6 months to 5 years is expected to have efficacy [see Sections 7.1 and 7.R.2]. In either age group, safety data indicated no significant concerns and the results demonstrated the acceptable tolerability of the vaccine product [see Section 7.R.3].

Reduced efficacy of the monovalent (Original) vaccine has been reported since the Omicron variant became predominant (*N Engl J Med.* 2022;386:1532-46). In Study P204, which was conducted during the Omicron surge, the vaccine efficacy (VE) of the monovalent (Original) vaccine against COVID-19 in children aged 6 months to 5 years was low [see Section 7.R.2]. In this context, Study P306 was conducted in children aged 6 months to 5 years using the bivalent (Original/BA.1) vaccine for the primary series to evaluate the safety and efficacy (immunogenicity) of the Omicron-adapted bivalent vaccine, which was confirmed to elicit a stronger immune response to the Omicron variant compared to the monovalent (Original) vaccine. In Study P306, based on a concept similar to that of the evaluation in Study P205 (Part G and Part H), which evaluated the efficacy of the bivalent vaccine in individuals aged ≥18 years (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated September 7, 2022 and Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated July 12, 2023), the applicant evaluated the efficacy of the bivalent (Original/BA.1) vaccine by comparing the data on the immunogenicity of the bivalent (Original/BA.1) vaccine in children aged 6 months to 5 years to the data on that of the monovalent (Original) vaccine in the same age group, using the neutralizing antibody titers against the Omicron BA.1 lineage as a measure.

Analyses comparing the immunogenicity of the bivalent (Original/BA.1) vaccine for the primary series (Study P306) with that of the monovalent (Original) vaccine for the primary series (Study P204) in children aged 6 months to 5 years [see Section 7.2] suggest that the bivalent (Original/BA.1) vaccine for the primary series elicits a potent immune response against the Omicron BA.1 lineage. The bivalent vaccine is expected to have efficacy against the Omicron variant.

Although the only available clinical study data on the primary series with the bivalent vaccine are those from Study P306 in children aged 6 months to 5 years, it is beneficial to use the bivalent vaccine for the primary series not only in children aged 6 months to 5 years but also in individuals aged ≥6 years because changing the target antigen of the primary series vaccine to the predominant circulating variant will increase vaccine efficacy for the following reasons: (1) The results from Study P306 suggest that the clinical usefulness of the primary series with the bivalent (Original/BA.1) vaccine is expected to be greater than that of the primary series with the monovalent (Original) vaccine in terms of vaccine efficacy against the Omicron variant; (2) the immunobridging criteria were met in both age groups (6 months to 5 years and 6 to 11 years) assessed in Study P204, when the data were compared to the data from Study P301 which evaluated the vaccine efficacy (in participants aged ≥18 years), and the primary series with Spikevax is expected to have efficacy in individuals aged ≥6 months [see Section 7.2] (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on July 12, 2023); and (3) a booster dose with the bivalent vaccine is expected to elicit greater immune responses (efficacy) against the Omicron variant in individuals aged ≥6 years than a booster dose with the monovalent (Original) vaccine (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on July 12, 2023). The use of the bivalent vaccines for the primary series is recommended by the VRBPAC[22)] and the European Medicines Agency (EMA) Emergency Task Force.[23)]

Based on the above, the present application was filed on the basis of immunogenicity and safety results from Study P204 and Study P306 Part 1 to obtain approval for the dosage and administration of the primary series of the bivalent vaccine in individuals aged ≥6 months.

PMDA's view:

As stated in the FDA's "Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19 for Use in Pediatric Populations,"[24)] the generally lower incidence of COVID-19 and its milder disease course in children may make it infeasible to conduct an adequately powered clinical study to demonstrate the efficacy of a SARS-CoV-2 vaccine in a pediatric population; however, it has been shown that neutralizing antibody titer can be used as a biomarker to infer the efficacy of a SARS-CoV-2 vaccine (*Nat Med.* 2021;27:1205-11). If the efficacy of a vaccine has been demonstrated in any other population, such as adults, an immunobridging approach using the neutralizing antibody GMTs and seroresponse rates can be employed to infer its efficacy in a pediatric population. It has become gradually clear that there is a correlation between the neutralizing antibody titer after SARS-CoV-2 vaccination and vaccine efficacy in preventing COVID-19 (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11). In Japan, against this background, Appendix 3 shows that for the development of a novel SARS-CoV-2 vaccine, an immunobridging approach can be employed to evaluate the efficacy of the vaccine based on an immunogenicity measure, using an approved SARS-CoV-2 vaccine

22) https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-january-26-2023-meeting-announcement (last accessed on August 25, 2023)
23) https://www.ema.europa.eu/en/documents/other/etf-statement-use-ema-approved-bivalent-original/omicron-ba4-5-mrna-vaccines-primary-series_en.pdf (last accessed on August 25, 2023)
24) https://www.fda.gov/media/149935/download (last accessed on August 25, 2023)

with demonstrated efficacy in preventing COVID-19 as the control. In addition, Appendix 3 suggests the possibility of conducting an efficacy evaluation using an immunobridging approach based on data from a study in which the efficacy has been evaluated in different age groups.

In view of the above rationale, PMDA concluded that the following evaluation policies could be taken in the development of Spikevax for use in children aged 6 months to 5 years, as stated by the applicant: For the evaluation of the monovalent (Original) vaccine, the neutralizing antibody titers in children aged 6 months to 5 years are assessed in a clinical study, and the efficacy of the primary series in children aged 6 months to 5 years is determined by comparing the data from the age group of 6 months to 5 years with the data from another age group in which the efficacy has already been demonstrated. For the bivalent (Original/BA.1) vaccine, the efficacy of the primary series can be evaluated according to the prespecified immunobridging success criteria.

The present application is intended to allow the bivalent vaccine to be used for the primary series in individuals aged ≥6 months. However, the Study P306 data submitted by the applicant only include the data on the safety and immunogenicity of the bivalent (Original/BA.1) vaccine in children aged 6 months to 5 years, and the results for the primary series of the bivalent vaccine in individuals aged ≥6 years have not been presented. The applicant explained that the efficacy of the primary series of Spikevax in all age groups could be supported by the results of clinical studies that were previously conducted in various age groups to assess the primary series with the monovalent (Original) vaccine; and that Study P205 (Part G and Part H), which assessed the safety and efficacy of the bivalent vaccine, albeit as a booster dose, in individuals aged ≥18 years, has demonstrated that the bivalent vaccine elicits an immune response against the Omicron variant. Given these and other factors, it is reasonable to assume that the immune response shown after the primary series of the bivalent (Original/BA.1) vaccine in Study P306 will also be elicited in individuals aged ≥6 years. In addition, because of widely implemented SARS-CoV-2 vaccine roll-out programs and of the growing number of people infected due to repeated waves of SARS-CoV-2 infection, there are fewer people unvaccinated with any SARS-CoV-2 vaccine or SARS-CoV-2 infection-naïve individuals today. In this situation, it is difficult to conduct a study that evaluates the efficacy of the primary series of a SARS-CoV-2 vaccine in all age groups. Accordingly, PMDA decided to evaluate the safety and efficacy of Spikevax in children aged 6 months to 5 years, as well as the safety and efficacy of the primary series of the bivalent vaccine in all age groups including the age group of 6 months to 5 years based on the submitted data.

When the review of the present application was underway, the regulatory authorities of countries including Japan issued a recommendation on changing the antigenic composition of approvedSARS-CoV-2 vaccines to the Omicron XBB.1 lineage, so as to provide protection against SARS-CoV-2 variants circulating in or after the fall of 2023. The Japanese regulatory authority announced its plan to use monovalent vaccines targeting the Omicron sublineage, XBB.1.5, as the main SARS-CoV-2 vaccines for vaccination starting in the fall of 2023.[25)] The applicant filed an application for a monovalent (XBB.1.5) vaccine containing an mRNA encoding the spike protein of the Omicron XBB.1.5 lineage, currently designated as a variant of interest (VOI) by the

[25)] The materials from the 47th and 49th meetings of the Subcommittee on Immunization and Vaccines of the Health Sciences Council: https://www.mhlw.go.jp/stf/shingi/shingi-kousei_127713.html (last accessed on August 25, 2023)

WHO; however, the current application for the monovalent (XBB.1.5) vaccine involves the addition of a booster regimen only, which has already been approved for the bivalent vaccines. In the present application, therefore, PMDA decided to review whether the bivalent (Original/BA.1) and (Original/BA.4-5) vaccines can be approved for the primary series, which was originally intended for in the application; and whether the monovalent (XBB.1.5) vaccine can also be added as an Omicron-adapted SARS-CoV-2 vaccine for the primary series.

7.R.2 Efficacy

7.R.2.1 Efficacy of Spikevax in children aged 6 months to 5 years

The applicant's explanation about the efficacy of Spikevax in children aged 6 months to 5 years:
To evaluate the efficacy (immunogenicity) of the primary series of Spikevax in children aged 6 months to 1 year and those aged 2 to 5 years, Studies P204 and P306 were conducted using the monovalent (Original) vaccine and the bivalent (Original/BA.1) vaccine, respectively.

Study P204 Part 2 was designed to evaluate the GMTs of neutralizing antibodies against the original strain at 28 days after the second dose of the monovalent (Original) vaccine 25 μg and seroresponse rates, the primary endpoints, and to compare the results to the immunogenicity results of Study P301 (data from a randomly extracted population from participants aged 18 to 25 years), a study which evaluated the efficacy of the primary series of the monovalent (Original) vaccine 100 μg in the prevention of COVID-19 in participants aged ≥18 years. The GMR of the neutralizing antibodies against the original strain and the difference in neutralizing antibody seroresponse rate met the prespecified criteria for non-inferiority in both age groups of 2 to 5 years and 6 months to 1 year [see Section 7.1.2].

Table 11 shows the demographics and baseline characteristics of participants (PPIS) in Study P204 Part 2 and Study P301 (control). The demographics and baseline characteristics of participants in each age group of Study P204 were similar to those in the population in Study P301, except for body weight.

Table 11. Comparison of demographic characteristics (Study P204 Part 2, PPIS)

		P204		P301
		6 months to 1 year	2-5 years	(18-25 years)
		Monovalent (Original) 25 μg N = 230	Monovalent (Original) 25 μg N = 264	Monovalent (Original) 100 μg N = 295
		n (%)	n (%)	n (%)
Sex	Male	110 (47.8)	141 (53.4)	142 (48.1)
	Female	120 (52.2)	123 (46.6)	153 (51.9)
Race	White	173 (75.2)	188 (71.2)	206 (69.8)
	African American	12 (5.2)	20 (7.6)	29 (9.8)
	Asian	12 (5.2)	16 (6.1)	30 (10.2)
	Multiracial	24 (10.4)	34 (12.9)	14 (4.7)
	Other[a)]/unknown	9 (3.9)	6 (2.2)	16 (5.4)
Ethnicity	Hispanic or Latino	39 (17.0)	47 (17.8)	78 (26.4)
	Not Hispanic or Latino	189 (82.2)	217 (82.2)	215 (72.9)
	Unknown	2 (0.9)	0	2 (0.7)
Body weight (kg)	Median (Min, Max)	11.00 (7.0, 29.3)	16.09 (10.7, 34.8)	73.62 (44.0, 158.2)

N = Number of participants analyzed; n = Number of participants applicable
a) American Indian, Alaska native, Native Hawaiian, or other races

The incidence rate of COVID-19 and the SARS-CoV-2 infection rate, the secondary endpoints of Study P204 Part 2, were evaluated. Table 12 shows the results of an assessment of vaccine efficacy in the prevention of COVID-19 and SARS-CoV-2 infection starting 14 days after the second dose of the study vaccine. Study P204 Part 2 was conducted during the surge of Omicron variant cases, which led to an increase in the number of participants who were affected by hospital visit restrictions, and who were tested only at home after virus exposure or after the onset of COVID-19 symptoms (i.e., participants not tested by RT-PCR). Accordingly, a sensitivity analysis was performed to assess VE and its 95% confidence interval (CI) in confirmed COVID-19 cases including not only cases confirmed by RT-PCR but also those determined by any other testing methods (i.e., cases confirmed by RT-PCR, cases determined only by home testing, and cases identified by unspecified testing methods). The values of VE with its 95% CI in children aged 2 to 5 years and those aged 6 months to 1 year were 37.5% [11.8%, 55.3%] and 43.7% [8.5%, 64.8%], respectively, according to the case definition of Study P301; and 28.5% [5.9%, 45.3%] and 53.5% [32.4%, 67.8%], respectively, according to the definition of the Centers for Disease Control and Prevention in the US (CDC). These results did not differ significantly from the VE calculated using the confirmed COVID-19 cases by RT-PCR, which support the results of VE evaluated according to the case definition specified in the protocol. The values of VE in Study P204 Part 2 were lower than those in Study P301 in participants aged ≥18 years, but were similar to the estimated vaccine efficacy in adults during the surge of COVID-19 due to the Omicron variant (*Nat Med.* 2022;28:1063-71, *N Engl J Med.* 2022;386:1532-46).

Table 12. Incidence rate of COVID-19 and SARS-CoV-2 infection rate starting 14 days after the second dose of the study vaccine (Study P204 Part 2, PPES, children aged 2 to 5 years and those aged 6 months to 1 year)

	2-5 years		6 months to 1 year	
	Monovalent (Original) N = 2594	Placebo N = 858	Monovalent (Original) N = 1511	Placebo N = 513
COVID-19 according to the case definition in Study P301[a)]				
Confirmed COVID-19 cases	71	43	37	18
Incidence rate [two-sided 95% CI][b)] (per 1000 person-years)	103.761 [81.038, 130.880]	193.528 [140.057, 260.681]	99.981 [70.396, 137.811]	146.042 [86.553, 230.809]
VE [two-sided 95% CI][c)] (%)	46.4 [19.8, 63.8]		31.5 [−27.7, 62.0]	
COVID-19 according to the CDC case definition[d)]				
Confirmed COVID-19 cases	119	61	51	34
Incidence rate [two-sided 95% CI][b)] (per 1000 person-years)	175.023 [144.992, 209.441]	276.980 [211.868, 355.792]	138.239 [102.928, 181.759]	279.822 [193.785, 391.023]
VE [two-sided 95% CI][c)] (%)	36.8 [12.5, 54.0]		50.6 [21.4, 68.6]	
SARS-CoV-2 infection (regardless of symptoms)[e)]				
Confirmed SARS-CoV-2 infection cases	198	93	81	45
Infection rate [two-sided 95% CI][b)] (per 1000 person-years)	296.924 [257.004, 341.288]	433.362 [349.779, 530.898]	222.821 [176.952, 276.946]	374.376 [273.073, 500.945]
VE [two-sided 95% CI][c)] (%)	31.5 [11.4, 46.7]		40.5 [12.3, 59.2]	

N = number of participants analyzed; VE = 1 minus the monovalent (Original) vaccine-to-placebo ratio of incidence rate or infection rate

a) Cases with a positive RT-PCR test result after the first dose of the study vaccine, AND the following eligible symptoms:
At least 2 systemic symptoms: fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder; OR
At least 1 of the following respiratory signs/symptoms: cough, shortness of breath, or difficulty breathing; OR clinical or radiographical evidence of pneumonia

b) The incidence rate for each group was defined as the number of participants as confirmed cases for each event divided by the number of participants at risk and adjusted for person-years (total time at risk) in each group. The two-sided 95% CI was calculated using the exact method (Poisson distribution).

c) The two-sided 95% CI was calculated using the exact method.

d) Cases with at least 1 positive RT-PCR result for SARS-CoV-2, AND at least 1 of the following prespecified COVID-19 symptoms that were derived from the CDC case definitions:
Systemic symptoms: fever (body temperature ≥38°C) or chills (of any duration, including ≤48 hours), fatigue, headache, myalgia, nasal congestion, rhinorrhoea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea or vomiting, poor appetite/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)

e) Had a negative antibody test result based on binding antibodies specific to SARS-CoV-2 nucleocapsid before the first dose of the study vaccine that became positive after the first dose, OR a positive RT-PCR test result after the first dose.

Study P306 was designed to evaluate the geometric mean concentration (GMC) of neutralizing antibodies against the Omicron BA.1 lineage and the original strain after the second dose of the bivalent (Original/BA.1) vaccine 25 μg, a primary endpoint, and to compare the results to the immunogenicity results of Study P204. The GMR calculated from the neutralizing antibody GMC against the Omicron BA.1 lineage and that from the neutralizing antibody GMC against the original strain both met the prespecified success criteria for superiority and non-inferiority, respectively [see Section 7.2].

Table 13 shows the demographics and baseline characteristics of the PPIS in Study P306 and its control, Study P204. The results were similar, except for the SARS-CoV-2 status before the first dose of the study vaccine.

Table 13. Comparison of demographics and baseline characteristics (Study P306, PPIS, 6 months to 5 years)

		P306 Part 1 Bivalent (Original/BA.1) 25 μg N = 71	P204 Monovalent (Original) 25 μg N = 632
		n (%)	n (%)
Sex	Male	43 (60.6)	325 (51.4)
	Female	28 (39.4)	307 (48.6)
Race	White	49 (69.0)	462 (73.1)
	African American	12 (16.9)	43 (6.8)
	Asian	4 (5.6)	34 (5.4)
	Multiracial	4 (5.6)	72 (11.4)
	Other[a)]/unknown	2 (2.8)	21 (3.3)
Ethnicity	Hispanic or Latino	6 (8.5)	115 (18.2)
	Not Hispanic or Latino	65 (91.5)	513 (81.2)
	Unknown	0	4 (0.6)
Body weight (kg)	Median (Min, Max)	15.18 (7.0, 28.9)	13.30 (7.0, 34.8)
Age (years)	Median (Min, Max)	3.00 (0.5, 5.0)	2.00 (0.5, 5.0)
Pre-first dose SARS-CoV-2 test result	Negative	26 (36.6)	590 (93.4)
	Positive	45 (63.4)	42 (6.6)

N = number of participants analyzed; n = number of participants applicable
a) American Indian, Alaska native, Native Hawaiian, and other races

The proportion of participants with positive SARS-CoV-2 status before the first study dose was higher in the Study P306 population than in the Study P204 population. This may be attributable to the timing of participant enrollment, which differed between the studies. Study P306 started to enroll participants after the surge of Omicron BA.1 infections in the US, where the study was conducted.

In the hypothesis tests for the primary endpoint in Study P306 Part 1, the analyses were conducted, regardless of the SARS-CoV-2 status before the first dose of the study vaccine, in order to incorporate the immunological condition of the PPIS as the analysis population. Table 14 shows the results of analysis by the SARS-CoV-2 status. In the subgroup of participants with negative SARS-CoV-2 status, the neutralizing antibody GMC against Omicron BA.1 after the primary series of the bivalent (Original/BA.1) vaccine was higher than that after the primary series of the monovalent (Original) vaccine (Study P204). These results were consistent with those in the subgroup of participants with positive SARS-CoV-2 status. Taken together, even if there are differences in the proportion of participants with positive SARS-CoV-2 status between the 2 studies, it is reasonably assumed that the bivalent (Original/BA.1) vaccine used as the primary series can elicit a stronger immune response against Omicron BA.1 than the monovalent (Original) vaccine. This assumption is supported by the analysis by the SARS-CoV-2 status.

Conversely, the neutralizing antibody titers against the original strain after the second dose of the bivalent (Original/BA.1) vaccine were lower than the immunology data from Study P204 as the comparator study, regardless of the pre-first dose SARS-CoV-2 status (Table 14). These results are considered attributable to the amount of the active ingredient (mRNA of the original strain) contained in the bivalent (Original/BA.1) vaccine, which is half that contained in the monovalent (Original) vaccine. However, the neutralizing antibody titer in each subgroup is effective enough to prevent COVID-19, according to the study on the correlation between the immunogenicity of the monovalent (Original) vaccine and its efficacy in preventing COVID-19 (*Science*. 2022;375:43-50). The results demonstrated that the primary series of the bivalent vaccine elicits a seroresponse against the original strain in addition to eliciting an immune response to variants.

Table 14. Neutralizing antibody titers (50% inhibitory dilution) against the Omicron BA.1 lineage and the original strain by SARS-CoV-2 status (Study P306, PPIS, children aged 6 months to 5 years)

	Omicron BA.1		Original strain	
	P306	P204	P306	P204
	Bivalent (Original/BA.1) 25 μg	Monovalent (Original) 25 μg	Bivalent (Original/BA.1) 25 μg	Monovalent (Original) 25 μg
Overall				
	N = 71	N = 632	N = 71	N = 632
Pre-first dose	n = 69	n = 369	n = 68	n = 617
GMC [two-sided 95% CI][a)]	49.2 [30.4, 79.6]	5.9 [5.5, 6.2]	35.6 [24.0, 52.7]	9.6 [8.9, 10.4]
28 days post-second dose	n = 58	n = 402	n = 66	n = 594
GMC [two-sided 95% CI][a)]	1889.7 [1430.0, 2497.2]	74.3 [67.7, 81.7]	1432.9 [1054.5, 1947.0]	1732.5 [1611.5, 1862.5]
GMFR [two-sided 95% CI][a)*]	48.2 [28.6, 81.2]	13.0 [11.6, 14.5]	41.8 [30.1, 58.0]	183.8 [170.1, 198.7]
GLSM [two-sided 95% CI][b)]	1889.7 [1520.4, 2348.7]	74.3 [68.5, 80.8]	1432.9 [1173.4, 1749.7]	1732.5 [1620.9, 1851.8]
GMR [two-sided 95% CI][b)]	25.4 [20.1, 32.1]		0.83 [0.67, 1.02]	
Seroresponse rate				
Seroresponse rate (n1/N1) [two-sided 95% CI][c)] (%)	83.9 (47/56) [71.7, 92.4]	86.8 (223/257) [82.0, 90.7]	92.4 (61/66) [83.2, 97.5]	99.5 (582/585) [98.5, 99.9]
Difference [two-sided 95% CI][d)]	−2.8 [−15.2, 6.0]		−7.1 [−16.0, −2.7]	
Negative SARS-CoV-2 status				
	N = 26	N = 590	N = 26	N = 590
Pre-first dose	n = 25	n = 347	n = 25	n = 575
GMC [two-sided 95% CI][a)]	8.1 [4.8, 13.8]	5.4 [5.1, 5.7]	12.5 [8.4, 18.6]	7.7 [7.4, 8.0]
28 days post-second dose	n = 24	n = 380	n = 25	n = 557
GMC [two-sided 95% CI][a)]	1037.9 [786.5, 1369.7]	65.7 [60.6, 71.3]	612.5 [448.2, 836.9]	1559.4 [1459.2, 1666.6]
GMFR [two-sided 95% CI][a)*]	155.2 [89.6, 268.9]	12.2 [11.0, 13.7]	49.0 [28.7, 83.6]	202.8 [188.3, 218.4]
GLSM [two-sided 95% CI][b)]	1037.9 [754.4, 1427.9]	65.7 [60.7, 71.2]	612.5 [448.8, 835.8]	1559.4 [1460.0, 1665.6]
GMR [two-sided 95% CI][b)]	15.8 [11.4, 21.9]		0.39 [0.29, 0.54]	
Seroresponse rate				
Seroresponse rate (n1/N1) [two-sided 95% CI][c)] (%)	95.7 (22/23) [78.1, 99.9]	86.1 (210/244) [81.1, 90.2]	92.0 (23/25) [74.0, 99.0]	99.5 (545/548) [98.4, 99.9]
Difference [two-sided 95% CI][d)]	9.6 [−7.4, 16.2]		−7.5 [−24.4, −1.6]	
Positive SARS-CoV-2 status				

	N = 45	N = 42	N = 45	N = 42
Pre-first dose	n = 44	n = 22	n = 43	n = 42
GMC [two-sided 95% CI][a)]	137.2 [85.4, 220.5]	21.6 [15.4, 30.3]	65.4 [39.7, 107.8]	185.8 [135.5, 254.8]
28 days post-second dose	n = 34	n = 22	n = 41	n = 37
GMC [two-sided 95% CI][a)]	2884.6 [1969.9, 4224.1]	625.3 [421.3, 928.2]	2405.9 [1643.4, 3522.2]	8445.1 [6397.6, 11147.8]
GMFR [two-sided 95% CI][a)*]	21.3 [10.7, 42.4]	38.8 [29.7, 50.6]	37.9 [24.6, 58.3]	42.9 [33.1, 55.6]
GLSM [two-sided 95% CI][b)]	2884.6 [2028.8, 4101.4]	625.3 [403.7, 968.6]	2405.9 [1734.1, 3338.0]	8445.1 [5982.7, 11920.9]
GMR [two-sided 95% CI][b)]	4.6 [2.6, 8.1]		0.29 [0.18, 0.46]	
Seroresponse rate				
Seroresponse rate (n1/N1) [two-sided 95% CI][c)] (%)	75.8 (25/33) [57.7, 88.9]	100 (13/13) [75.3, 100.0]	92.7 (38/41) [80.1, 98.5]	100 (37/37) [90.5, 100.0]
Difference [two-sided 95% CI][d)]	−24.2 [−41.2, 0.6]		−7.3 [−19.5, 2.5]	

Antibody titer 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 to ULOQ]: 8-41984 [Omicron BA.1])
N = number of participants analyzed; 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;
n1 = number of participants who met the definition of seroresponse rate, 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)
* N1 is the number of participants analyzed.
GMR = P306/P204; Difference in seroresponse rate = P306 − P204
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
b) An analysis of covariance model with the antibody titer at the timepoint after the second dose as the dependent variable, and the group variable (bivalent or monovalent) as the fixed effect, adjusted for the age group and pre-first dose SARS-CoV-2 status
c) Two-sided 95% CI was calculated using the Clopper-Pearson method.
d) Two-sided 95% CI was calculated using the Miettinen-Nurminen method.

The analysis comparing the immunogenicity data for the primary series of the monovalent (Original) vaccine in Study P204 to the data from participants aged 18 to 25 years in Study P301, and the analysis comparing the immunogenicity data for the primary series of the bivalent (Original/BA.1) vaccine in Study P306 to the data for the primary series of the monovalent (Original) vaccine, met the immunobridging success criteria; therefore, the primary series of the bivalent (Original/BA.1) vaccine is expected to have efficacy in children aged 6 months to 5 years.

PMDA's view:

Given that the characteristics of participants aged 6 months to 5 years in Study P204 Part 2 were similar to the characteristics of those aged 18 to 25 years in Study P301, except for body weight which is different because of the age difference (Table 11), and that the high efficacy of the vaccine in preventing COVID-19 was demonstrated in Study P301 regardless of the demographics and baseline characteristics (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), the immunogenicity data from the two groups can be used for comparison. When the immunogenicity data from Study P204 Part 2 were compared to the immunogenicity data in participants aged 18 to 25 years from Study P301 (control) in terms of the neutralizing antibody GMR and the difference in seroresponse rates at 28 days after the second dose of the monovalent (Original) vaccine, the immunobridging success criteria were met [see Section 7.1.2]. The results could support the efficacy of the monovalent (Original) vaccine in children aged 6 months to 5 years. The vaccine efficacy in preventing COVID-19, a secondary endpoint of Study P204, was lower than that in Study P301. However, this outcome was probably affected by the difference in circulating SARS-CoV-2 variants during the evaluation period of the studies; therefore, the applicant's assertion that the results are consistent with the estimated vaccine efficacy in adults evaluated at the same time as participants in Study P204 is reasonable.

The proportion of participants with a positive pre-first dose SARS-CoV-2 status for the primary series of the

bivalent (Original/BA.1) vaccine in Study P306 differed significantly from the proportion of participants with a positive pre-first dose SARS-CoV-2 status in each analysis set in Study P204 (control), and GMC by SARS-CoV-2 status also differed significantly. Therefore, it is difficult to evaluate efficacy solely based on the outcome of immunogenicity in the PPIS regardless of SARS-CoV-2 status, the primary immunogenicity subset. However, according to the data on the neutralizing antibody titers against the original strain, the GMC at 28 days after the second dose of the bivalent (Original/BA.1) vaccine (Study P306) was lower than that for the monovalent (Original) vaccine (Study P204) regardless of SARS-CoV-2 status, while there was a certain level of increase in neutralizing activity compared to the neutralizing antibody titers at baseline. According to the data on the neutralizing antibody titers against the Omicron BA.1 lineage, the GMC at 28 days after the second dose of the bivalent (Original/BA.1) vaccine (Study P306) was higher than that for the monovalent (Original) vaccine (Study P204) regardless of SARS-CoV-2 status. The above results support the efficacy of the primary series of the bivalent (Original/BA.1) vaccine in children aged 6 months to 5 years, and therefore, the bivalent (Original/BA.1) vaccine is expected to be more effective against the Omicron BA.1 lineage, compared to the monovalent (Original) vaccine.

7.R.2.2 Efficacy of the primary series of Omicron-adapted vaccines

The applicant's explanation about the efficacy of the primary series of the Omicron-adapted Spikevax vaccines in individuals including those aged ≥6 years:

Study P306, which evaluated the primary series of the bivalent (Original/BA.1) vaccine in children aged 6 months to 5 years, demonstrated that the immune response against the Omicron BA.1 lineage after the primary series of the bivalent (Original/BA.1) vaccine is higher than that after the primary series of the monovalent (Original) vaccine [see Sections 7.2 and 7.R.2.1].

Although no clinical studies have been conducted to evaluate the bivalent vaccine in individuals aged ≥6 years, the results of Study P306 conducted in children aged 6 months to 5 years can be extrapolated to age range ≥6 years, in which the monovalent (Original) vaccine has been approved for the primary series, and the immune response against the Omicron BA.1 lineage, which was reported to be high in children aged 6 months to 5 years, is expected to be high in individuals aged ≥6 years as well, given the following factors: (1) 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) states that, in general, the results of a clinical study conducted in a single age group can be extrapolated to other age groups in which the ancestral vaccine has already been approved; and (2) the evaluation using an immunobridging approach resulted in the conclusion that vaccine efficacy in preventing COVID-19 after the primary series of the monovalent (Original) vaccine in the age groups of 6 to 11 years and 12 to 17 years could be inferred from that in participants aged ≥18 years in Study P301, and the regimens for these age groups have been approved.

The analysis comparing the immunogenicity of the bivalent (Original/BA.4-5) vaccine to that of the monovalent (Original) vaccine in Study P205 in participants aged ≥18 years met the success criteria for immunobridging (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on

July 12, 2023), albeit the evaluation of the booster regimen. The analysis comparing the immunogenicity of the bivalent (Original/BA.1) vaccine to that of the monovalent (Original) vaccine in Study P205 also met the success criteria for immunobridging (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on September 7, 2022). Because the amount of mRNA contained in an approved booster dose is the same for all Spikevax vaccines (the monovalent [Original], bivalent [Original/BA.1], and bivalent [Original/BA.4-5] vaccines), the primary series of the bivalent (Original/BA.4-5) vaccine is expected to have similar efficacy to that of the bivalent (Original/BA.1) vaccine.

Study P205 Part J was conducted to evaluate the safety and immunogenicity of the monovalent (XBB.1.5) vaccine as the third booster dose in individuals aged ≥18 years who had completed the primary series and 2 booster doses and for whom it had been at least 3 months since their previous dose (target sample size, 50 participants[26)]). Data from the study became available (data cut-off on May 16, 2023). The neutralizing antibody GMT [95% CI] against the Omicron XBB.1.5 lineage was 154.7 [106.8, 224.1] before vaccination and 2579.0 [1809.1, 3676.7] at 14 days after the booster dose of the monovalent (XBB.1.5) vaccine, indicating a strong neutralizing antibody response. There are reports of strong neutralizing antibody responses against Omicron sublineages other than XBB.1.5 (i.e., XBB.1.16, BA.4-5, and BQ.1.1) as well as the original strain, suggesting that the monovalent (XBB.1.5) vaccine will elicit an immune response against variants of current concern. In previous studies, Spikevax vaccines, whether monovalent or bivalent, or regardless of variants to be targeted, induced a strong neutralizing antibody response against the original strain as well as variants when administered as a booster dose or for the primary series in an appropriate dose according to age. Accordingly, based on the results of Study P205 Part J, the monovalent (XBB.1.5) vaccine is also expected to elicit an immune response against currently circulating variants and those of global interest and to be effective when administered for the primary series.

In view of the above, the primary series of the Omicron-adapted vaccines, i.e., the bivalent (Original/BA.1), bivalent (Original/BA.4-5), and monovalent (XBB.1.5) vaccines, is expected to have efficacy in individuals aged ≥6 months.

PMDA's view:
According to the applicant, vaccination with the bivalent (Original/BA.1) vaccine in individuals aged ≥6 years is expected to yield efficacy results similar to those in Study P306 which evaluated the primary series of the bivalent (Original/BA.1) vaccine in children aged 6 months to 5 years, in view of the fact that the efficacy of the bivalent (Original/BA.1) vaccine was inferred based on the non-inferiority of immune response data from the clinical study on the primary series of the monovalent (Original) vaccine in different age groups to those from the clinical study that demonstrated the efficacy of the monovalent (Original) vaccine to prevent COVID-19 in participants aged ≥18 years, and that this conclusion was made for all age groups (e.g., Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated on May 17, 2021; Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on July 12, 2023). The

[26)] Individuals who had received the primary series of the monovalent (Original) vaccine, a booster dose of the monovalent (Original) vaccine, and a booster dose of the bivalent (Original/BA.4-5) vaccine

applicant's reasoning above is acceptable. Based on data including the results from the clinical studies of the bivalent (Original/BA.1) vaccine and the bivalent (Original/BA.4-5) vaccine (Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on September 7, 2022, and Report on Special Approval for Emergency of Spikevax Intramuscular Injection, dated on July 12, 2023), it is reasonable to assume that the efficacy of the bivalent (Original/BA.4-5) vaccine will be similar to that of the bivalent (Original/BA.1) vaccine. Although there have been no available data from clinical studies where the monovalent (XBB.1.5) vaccine was administered for the primary series, it has been demonstrated that neutralizing antibodies against Omicron XBB.1.5 and other sublineages were elicited in participants who received the monovalent (XBB.1.5) vaccine as a booster dose; therefore, it is reasonable to assume that an immune response equivalent to that following a booster dose will be elicited in recipients of the vaccine for the primary series.

Based on the above, the primary series of the Omicron-adapted vaccines, including the bivalent (Original/BA.1) vaccine and the bivalent (Original/BA.4-5) vaccine, as well as the monovalent (XBB.1.5) vaccine, a new vaccine product developed by the applicant, is expected to have efficacy.

Vaccine efficacy wanes over time after vaccination, and the monovalent vaccine targeting the original strain does not provide sufficient protection against Omicron variants (e.g., *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). Circulating SARS-CoV-2 variants continue to evolve, and another Omicron sublineage or new variants are likely to emerge. For these reasons, the applicant should gather data and reports accrued in Japan and other countries concerning epidemiological information such as the emergence and circulation of variants as well as vaccine efficacy, and should consider necessary actions based on the data so obtained.

7.R.3 Safety

The applicant's explanation about the safety of the primary series of Omicron-adapted vaccines in individuals aged ≥6 months:

(1) Adverse events reported in clinical studies

In Study P204 Part 2, regardless of age group, the incidences of local and systemic solicited adverse events were higher in the monovalent (Original) vaccine 25 μg group than in the placebo group, and the adverse events occurred more frequently after the second dose than after the first dose (see Table 6 and Table 7). Most of reported local and systemic solicited adverse events were classified as Grade 1 or 2 in severity (see Table 6 and Table 7), which disappeared shortly after the onset of symptoms, with a median duration of 1.0 to 3.0 days.

The incidence of unsolicited adverse events was low, most of which were classified as Grade 1 or 2 in severity. All the serious adverse events for which a causal relationship to the monovalent (Original) vaccine could not be ruled out resolved [see Section 7.1]. Based on these and other factors, no significant safety concerns have been currently identified with the use of the monovalent (Original) vaccine in children aged 6 months to 5 years.

Table 10 shows the incidence of solicited adverse events after the primary series of the bivalent (Original/BA.1) vaccine 25 μg in Study P306 Part 1. The results are consistent with those after the primary series of the monovalent (Original) vaccine 25 μg in the same age group in Study P204. There were no Grade ≥3 events occurring more frequently in Study P306 than in Study P204 (Table 15). The solicited adverse events disappeared shortly after the onset of symptoms, with a median duration of 1.0 to 2.0 days. The incidence of unsolicited adverse events was low, most of which were classified as Grade 1 or 2 in severity. There were no reports of serious adverse events for which a causal relationship to the bivalent (Original/BA.1) vaccine could not be ruled out [see Section 7.2].

Table 15. Solicited adverse events reported through 7 days after administration of the bivalent (Original/BA.1) vaccine (P306) or the monovalent (Original) vaccine (P204) (Solicited adverse event analysis set, children aged 6 months to 5 years)

Event		P306 (6 months to 5 years) Bivalent (Original/BA.1) 25 μg N = 179			P204 (6 months to 5 years) Monovalent (Original) 25 μg N = 4774		
		N1	All Grades	Grade ≥3	N1	All Grades	Grade ≥3
			n (%)	n (%)		n (%)	n (%)
Local	Any local adverse event	179	97 (54.2)	1 (0.6)	4773	3666 (76.8)	84 (1.8)
	Pain	179	92 (51.4)	0	4772	3445 (72.2)	15 (0.3)
	Erythema (redness)	179	8 (4.5)	1 (0.6)	4772	683 (14.3)	39 (0.8)
	Swelling/induration	179	5 (2.8)	1 (0.6)	4773	646 (13.5)	41 (0.9)
	Lymphadenopathy[a)]	179	15 (8.4)	0	4772	618 (13.0)	1 (<0.1)
Systemic	Any systemic adverse event	179	113 (63.1)	6 (3.4)	4773	3855 (80.8)	288 (6.0)
	Fever[b)]	179	34 (19.0)	4 (2.2)	4773	1065 (22.3)	125 (2.6)
	Headache	91	16 (17.6)	0	2037	466 (22.9)	13 (0.6)
	Fatigue	91	38 (41.8)	1 (1.1)	2037	1261 (61.9)	64 (3.1)
	Myalgia	91	20 (22.0)	0	2037	451 (22.1)	14 (0.7)
	Arthralgia	91	15 (16.5)	0	2037	260 (12.8)	5 (0.2)
	Nausea/vomiting	91	9 (9.9)	0	2037	309 (15.2)	13 (0.6)
	Chills	91	10 (11.0)	0	2037	342 (16.8)	5 (0.2)
	Irritability/crying	87	48 (55.2)	1 (1.1)	2735	2126 (77.7)	70 (2.6)
	Sleepiness	87	38 (43.7)	0	2735	1383 (50.6)	8 (0.3)
	Loss of appetite	87	32 (36.8)	1 (1.1)	2735	1218 (44.5)	40 (1.5)

N = number of participants analyzed; N1 = number of participants who provided adverse event data; n = number of participants with the event

a) Axillary swelling or tenderness ipsilateral to the injection site

b) For children aged 6-36 months, Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C to 39.5°C, Grade 3 = 39.6°C to 40°C, and Grade 4 = >40.0°C. For children aged 37 months to 5 years, Grade 1 = 38.0°C to 38.4°C, Grade 2 = 38.5°C to 38.9°C, Grade 3 = 39.0°C to 40.0°C, Grade 4 = >40.0°C (tympanic membrane temperature in Study P306; in Study P204, oral temperature for children aged >4 years and tympanic membrane temperature for children aged ≤4 years).

The risk of myocarditis/pericarditis and multisystem inflammatory syndrome in children (MIS-C), adverse events of special interest, was evaluated in both studies. There were no reports of adverse events coded to myocarditis/pericarditis or MIS-C.

Studies P204 and P306 allowed enrollment of children with stable underlying disease. Safety analyses were performed based on the presence or absence of underlying disease[27)] as risk factors for severe COVID-19. Although the unbalanced number of participants in each subgroup precluded a stringent comparison, there were no differences in safety profiles in children aged 6 months to 5 years regardless of the presence or absence of underlying disease.

(2) Post-marketing safety information

The post-marketing safety data for Spikevax vaccines were collected from the latest Monthly Summary Safety Report (survey period, May [redacted], 2023 to June [redacted], 2023). As of June [redacted], 2023, an estimated 780 million or more doses of the monovalent (Original) vaccine and 70 million or more doses of the bivalent (Original/BA.1) vaccine, and 119 million or more doses of the bivalent (Original/BA.4-5) vaccine have been administered. The following number of adverse events in all age groups were reported in the post-market setting: 2,647,509 adverse events in 683,169 recipients of the monovalent (Original) vaccine (including 431,787 serious adverse events in 139,445 recipients), 39,702 adverse events in 11,604 recipients of the bivalent (Original/BA.1) vaccine (including 12,155 serious adverse events in 4,290 recipients); and 16,476 adverse events in 6,336 recipients of the bivalent (Original/BA.4-5) vaccine (including 760 serious adverse events in 457 recipients).

27) Data are based on the medical history reported by each participant. Participants with increased risk factors (e.g., obesity, asthma, chronic pulmonary disease, and cardiac disease) for severe COVID-19 accounted for 17.4% (870 of 5,011 participants) in Study P204 and 20.7% (37 of 179 participants) in Study P306 Part 1.

Commonly reported adverse events (excluding those related to vaccine administration errors or other inappropriate use of vaccines) include headache, fatigue, and fever, which were consistent among monovalent (Original), bivalent (Original/BA.1), and bivalent (Original/BA.4-5) vaccine recipients. The summary of adverse events reported in children aged 6 months to 5 years[28)] was as follows: 2,739 adverse events in 1,056 recipients of the monovalent (Original) vaccine (including 204 serious adverse events in 86 recipients); 21 adverse events in 8 recipients of the bivalent (Original/BA.1) vaccine (including 9 serious adverse events in 4 recipients); and 356 adverse events in 154 recipients of the bivalent (Original/BA.4-5) vaccine (including 2 serious adverse events in 2 recipients). The majority of the events were classified as non-serious. Commonly reported serious adverse events after vaccination with the monovalent (Original) vaccine were fever and febrile convulsion. Although there is only limited information on the bivalent vaccines used in children aged 6 months to 5 years, serious adverse events reported in this age group after vaccination with the bivalent vaccines were hypertension, palpitations, swelling, and pain in 1 recipient each for the bivalent (Original/BA.1) vaccine and sudden death and death in 1 recipient each[29)] for the bivalent (Original/BA.4-5) vaccine. Reported data including these serious adverse events are evaluated on a regular basis. Current data have indicated no risks requiring additional cautionary statements for use in children including those aged 6 months to 5 years. The assessment of incidence of adverse reactions and other events in each survey period and the comprehensive evaluation based on accrued Spikevax safety data confirmed that the safety of Spikevax vaccines, including Omicron-adapted bivalent vaccines, was consistent with the safety profile of the monovalent (Original) vaccine in all age groups. No new concerns have been identified for any of the vaccine products. Safety issues including myocarditis/pericarditis and other identified risks associated with Spikevax will continue to be monitored.

As describe above, there are no serious safety concerns associated with either the monovalent (Original) vaccine or the Omicron-adapted bivalent vaccines when used for the primary series in children aged 6 months to 5 years. Additionally, given that Studies P204 and P306 confirmed that the safety profiles in children aged 6 months to 5 years were consistent regardless of vaccine products used, the safety profile is consistent across the vaccine products used for the primary series in individuals aged ≥6 years. In view of the above findings, the safety of the bivalent vaccines for the primary series is tolerable in all age groups 6 months and older.

In Study P205 Part J (data cut-off on May 16, 2023; 50 participants for safety analysis), the incidences of local and systemic solicited adverse events reported through 7 days after the administration of the monovalent (XBB.1.5) vaccine were 68.0% (34 of 50 participants) and 58.0% (29 of 50 participants), respectively. The most common local solicited adverse events were pain and lymphadenopathy, while the most common systemic solicited adverse events were fatigue, myalgia, and headache. Unsolicited adverse events (data cut-off on May 16, 2023, median follow-up of 20 days, ranging from 20 to 22 days) occurred in 5 of 50 participants (10%) receiving the monovalent (XBB.1.5) vaccine (respiratory tract infection viral, viral infection, seasonal allergy, rash pruritic, pain in extremity, and tooth fracture). A causal relationship to the study vaccine could not

[28)] This includes reports of adverse events occurring in children (6 months to 5 years) born to mothers who had received Spikevax during pregnancy.
[29)] Both of the reported adverse events lack information including the status of vaccination with Spikevax, characteristics of the children, and the clinical course from vaccination to death.

be ruled out for rash pruritic and pain in extremity. There were no reports of death or serious adverse events. The results from the study showed that the safety profiles were similar to those in the clinical studies of the monovalent (Original) vaccine and Omicron-adapted bivalent vaccines. Since Study P205 Part J showed that the safety profiles obtained were consistent regardless of the target antigen of the vaccine product, albeit evaluation of the vaccine as a booster dose, the safety profiles of the monovalent (XBB.1.5) vaccine for the primary series is also expected to be similar to those of the monovalent (Original) vaccine which has been administered to a large number of people. Therefore, the applicant considers that the primary series of the monovalent (XBB.1.5) vaccine will be well tolerated in all age groups 6 months and older, as with the monovalent (Original) vaccine and the bivalent vaccines.

PMDA's view:
In Study P204 which was conducted in children aged 6 months to 5 years, local and systemic solicited adverse events occurred in many of the participants in the monovalent (Original) vaccine group, most of which were classified as Grade 1 or 2 in severity and were reversible. The majority of unsolicited adverse events reported in Study P204 were events anticipated from the safety information that has previously been reported in those aged ≥6 years, and were classified as Grade 1 or 2 in severity. The results of Study P306 showed that the safety profiles of the bivalent (Original/BA.1) vaccine for the primary series in children aged 6 months to 5 years were similar to those of the monovalent (Original) vaccine for the primary series in Study P204. In addition to the above results, currently available data from the clinical studies of Spikevax, including those of Study P205 Part J that investigated the use of the monovalent (XBB.1.5) vaccine (for which the data were submitted during the review of the present application), did not indicate a clear difference in the safety arising from the difference in the vaccine product. Furthermore, foreign post-marketing data, albeit limited in availability, have indicated no safety concerns in children aged 6 months to 5 years. The above and other data indicate that the Omicron-adapted vaccines for the primary series in children aged 6 months to 5 years have acceptable safety.

Although no clinical studies have been conducted to evaluate the Omicron-adapted vaccines for the primary series in individuals aged ≥6 years, the development of the vaccines was underway during the roll-out of the primary series vaccination programs for monovalent (Original) vaccines including those of other manufacturers. Under such circumstances, there would have been no choice but to plan to evaluate the primary series of the Omicron-adapted vaccine in children aged 6 months to 5 years, an age group in which SARS-CoV-2 unvaccinated individuals were easily recruited and which was regarded as highly in need of the primary series. In view of the results from Study P306 and Study P205 Part J as well as previously obtained data on Spikevax vaccination, the applicant's explanation that the primary series of the Omicron-adapted vaccines in individuals ≥6 years currently raises no particular safety concerns is reasonable. The Omicron-adapted vaccines have acceptable safety in individuals ≥6 years, as well.

However, the monovalent (Original) vaccine for the primary series has not been given to children aged 6 months to 11 years in Japan, and there is only limited safety information on the use of Omicron-adapted vaccines for the primary series in foreign countries. The applicant should therefore continue to gather safety information, promptly evaluate data so obtained, provide information to healthcare professionals, and take

other appropriate actions. Furthermore, healthcare professionals, vaccine recipients, and their parents/guardians should be appropriately informed of the time to onset and duration of potential adverse events as well as the importance of early detection of adverse reactions, because (i) solicited adverse events (local and systemic) occurred in many study participants; (ii) in particular, the incidence of adverse events after the second dose was higher than that after the first dose; and (iii) myocarditis and pericarditis could occur in all age groups. In particular, a cautionary statement regarding the need for immediate medical attention in case of the onset of myocarditis and pericarditis remains in effect ("Reminder: Action to be Taken for Vaccine Recipients Developing Symptoms Suspected of Adverse Reactions Associated with SARS-CoV-2 Vaccine [Administrative Notice dated July 28, 2023, issued by the Office of Counselor in charge of Vaccination, Health Service Bureau, Ministry of Health, Labour and Welfare, and the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare]). The applicant should appropriately provide information through the package insert and other materials. Additionally, the applicant should remain vigilant for myocarditis and pericarditis, as well as gather information on the monovalent (XBB.1.5) vaccine, for which data on its use in clinical practice are still limited.

7.R.4 Clinical positioning

PMDA's conclusion on the clinical positioning of Spikevax:

The WHO declared the end of the Public Health Emergency of International Concern for COVID-19 on May 5, 2023.[1)] In Japan, on May 8, 2023, COVID-19 was reclassified as the Class V Infectious Disease instead of "Novel Influenza Infection, etc." under the Infectious Disease Control Act. SARS-CoV-2 vaccines continue to be offered as part of a special temporary vaccination program under the Immunization Act. Although a booster dose with monovalent vaccines targeting the original strain showed some efficacy against the Omicron variant which has been predominant worldwide since 2022, the vaccine efficacy was lower than that against a previously circulating variant (Delta variant) and its durability decreased (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). In this context, Omicron-adapted vaccines used as booster doses were developed by modifying the monovalent vaccines targeting the original strain. In March 2023, the Strategic Advisory Group of Experts (SAGE) of the WHO issued a recommendation for the use of bivalent mRNA vaccines containing the BA.5 strain for the primary series (WHO.SAGE updates COVID-19 vaccination guidance.[30)]). In the US, the use of bivalent (Original/BA.4-5) vaccines for the primary series is recommended in all age groups 6 months and older, while in Europe, a statement has been issued to allow the use of bivalent (Original/BA.4-5) vaccines for the primary series.[23)] As of August 2023, Omicron-adapted vaccines marketed in Japan are available for both the primary series and booster doses in individuals aged ≥6 months, while Omicron-adapted Spikevax vaccines can be used only as a booster dose in individuals aged ≥6 years.

Based on the submitted data for the present application (the results of Studies P204 and P306) and currently available data on the use of Spikevax for the primary series and as a booster dose, the Omicron-adapted vaccines for the primary series are expected to have efficacy in individuals aged ≥6 months [see Section 7.R.2]

[30)] https://www.who.int/news/item/28-03-2023-sage-updates-covid-19-vaccination-guidance (last accessed on August 25, 2023)

and have acceptable safety [see Section 7.R.3]. As discussed earlier, given the international consensus on SARS-CoV-2 vaccines and trends in other regulatory authorities, it is reasonable to recommend the use of Omicron-adapted SARS-CoV-2 vaccines for the primary series in all age groups in Japan.

As the total number of people infected with SARS-CoV-2 increased during the predominance of the Omicron variant, the number of children with severe COVID-19 and fatal cases also increased in Japan.[31)] There have been reports on MIS-C, a complication of COVID-19 presenting with fever and multiorgan disorder (Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children [MIS-C] in the United States[32)]), long COVID symptoms, such as fatigue, headache, and shortness of breath, which are persistent after SARS-CoV-2 infection (*Lancet Child Adolesc Health*. 2022;6:240-8), and acute encephalopathy (*Front Neurosci.* 2023;17:1085082 doi: 10.3389/fnins.2023.1085082). SARS-CoV-2 vaccination rates in children aged 6 months to 11 years remain low as of August 2023 [see Section 1]. The number of children with severe COVID-19 will increase with a rise in the number of persons infected with SARS-CoV-2 due to the future spread of SARS-CoV-2 variants. Therefore, vaccination is an important measure to prevent COVID-19 in children. The Japan Pediatric Society recommends that SARS-CoV-2 vaccination should be continued in all children aged 6 months to 17 years since COVID-19 remains a threat to children in Japan ("Novel Coronavirus Vaccination in Children: 2023.6 Supplement," dated June 9, 2023 by the Committee on Immunization and Prevention of Infectious Diseases, Japan Pediatric Society [in Japanese] [33)]). While the SARS-CoV-2 vaccination program campaign starting in the fall of 2023 will mainly cover the elderly and people at increased risk of severe COVID-19, vaccination opportunities will also be available to individuals aged ≥6 months;[25)] therefore, populations ranging from infants to the elderly will receive the vaccine considering individual risks and benefits. Given the current situation in Japan, where only a single type of Omicron-adapted SARS-CoV-2 vaccine that can be used for the primary series is available,[5)] it is clinically significant to increase the number of vaccine options by introducing the Omicron-adapted Spikevax vaccines, which can be used for the primary series in a wide range of age groups including infants and young children.

In May 2023, the WHO's Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) issued a statement which recommends the use of monovalent vaccines targeting Omicron XBB.1 (including the XBB.1.5 sublineage) for the SARS-CoV-2 vaccination roll-out programs in or after fall 2023.[34)] In Japan, Omicron XBB.1.5-adapted monovalent vaccines will be used for the vaccination roll-out programs starting in the fall of 2023.[25)] The data from Study P205 Part J presented in the review of the present application and the results from clinical studies of Omicron-adapted vaccines other than those for the monovalent (Original) vaccine have demonstrated that Omicron-adapted vaccines elicit a strong immune response against the targeted virus strain, and that their safety profiles are consistent across the vaccine products; therefore, the monovalent (XBB.1.5) vaccine can also be used for the primary series in individuals aged ≥6 months, which will serve as a measure to address an ongoing increase in the number of COVID-19 cases.

31) https://covid19.mhlw.go.jp/ (last accessed on August 25, 2023)
32) https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (last accessed on August 25, 2023)
33) http://www.jpeds.or.jp/uploads/files/20230609_vaccine_hoi.pdf (last accessed on August 25, 2023)
34) https://www.who.int/news/item/18-05-2023-statement-on-the-antigen-composition-of-covid-19-vaccines (last accessed on August 25, 2023)

7.R.5 Dosage and administration

A partial change application for the dosage regimen of the Spikevax vaccine in children aged 6 to 11 years was approved on August 2, 2023. After filing the present application, the applicant filed a partial change application to add the manufacturing process of the monovalent (XBB.1.5) vaccine. Based on the discussions on the efficacy and safety of the monovalent (XBB.1.5) vaccine in Sections 7.R.2 and 7.R.3, respectively, the applicant plans to include the dosage regimen for the primary series of the monovalent (XBB.1.5) vaccine in the present application, so that the Omicron-adapted monovalent vaccine will also be available for the primary series. The proposed dosage and administration presented during the review are as shown below (Underline denotes changes proposed at the time of submission of the application; double underline denotes modifications associated with changes to the partial change application).

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

  Individuals 12 years of age and older

  For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (1 mL each) at a recommended interval of 4 weeks.

  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 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 months of age and older but younger than 6 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.

The applicant's explanation about the rationale for dose selection:

In Study P204 Part 1, prior to the evaluation in children aged 6 months to 1 year, a dose-finding study was performed in children aged 2 to 5 years. The monovalent (Original) vaccine 50 μg was first evaluated in children aged 2 to 5 years. Given the similarity in the incidence of fever at the 50 μg dose to that after administration of the 100 μg dose in children aged 6 to 11 years, and the incidence of solicited adverse events/reactions in children aged 2 to 5 years receiving the 50 μg dose and children 6 to 11 years receiving the 100 μg dose, the applicant decided to use a lower dose, the 25 μg dose, instead of using the 100 μg dose in

children aged 2 to 5 years. In view of the safety profile in children aged 2 to 5 years receiving the 50 μg dose, only the 25 μg dose was used for the evaluation in children aged 6 months to 1 year. The results for each dose group in children aged 2 to 5 years and those aged 6 months to 1 year were compared to the results in participants aged 18 to 25 years from Study P301 in terms of the GMR of neutralizing antibodies against the original strain at 28 days after the second dose as well as the seroresponse rate. There were no significant differences between children aged 2 to 5 years or those aged 6 months to 1 year and participants aged 18 to 25 years [see Section 7.1.1]. The safety results showed that the incidences of local and systemic solicited adverse events and the severity in children aged 2 to 5 years were higher in the 50 μg group than in the 25 μg group. The results demonstrated that the 25 μg dose has acceptable tolerability in children aged 6 months to 1 year. Based on the above results, the 25 μg dose was selected for both age groups in Study P204 Part 2. The immune response shown in Study P204 Part 2 indicated that the monovalent (Original) vaccine has efficacy in children aged 6 months to 5 years [see Section 7.R.2]. The results indicated the acceptable safety of the vaccine [see Section 7.R.3].

In Study P306, the dose of the bivalent (Original/BA.1) vaccine was set at the same level as that of the monovalent (Original) vaccine, as with the regimen used for other age groups. The study evaluated the primary series of the bivalent (Original/BA.1) vaccine at a dose of 25 μg, which was selected for Study P204 Part 2. Consequently, the immunogenicity data at that dose met the prespecified success criteria [see Section 7.2], and no significant safety concerns have been identified [see Section 7.R.3].

Based on the results of Study P306, and considering that the dosage regimens for the Omicron-adapted bivalent vaccines are identical regardless of their active ingredients, 0.25 mL per dose (corresponding to 25 μg) was selected as the proposed dosage and administration for the bivalent vaccine for the primary series in children aged 6 months to 5 years: “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.”

Although there are no results from clinical studies of bivalent vaccines for the primary dose in individuals aged ≥6 years, given the dosage regimen selected for children aged 6 months to 5 years and previously acquired data on Spikevax vaccination, the bivalent vaccine for the primary series is expected to have efficacy by administering the same amount of mRNA per dose as that of the monovalent (Original) vaccine, while the safety profile is similar to that reported previously.

The concentration of the active ingredient (mRNA) in the monovalent (Original) vaccine product is twice that of the bivalent vaccines (0.2 mg/mL); therefore, the dose (injection volume) of the bivalent vaccine for the primary series (1.0 mL for individuals ≥12 years of age and 0.5 mL for children ≥6 years of age but <12 years of age) is double the volume of the monovalent (Original) vaccine (0.5 mL for individuals ≥12 years of age and 0.25 mL for children ≥6 years of age but <12 years of age). Study CoVPN3008,[35)] an ongoing study conducted by the US National Institutes of Health (NIH) in individuals aged ≥18 years, is evaluating the 1 mL

[35)] https://classic.clinicaltrials.gov/ct2/show/NCT05168813 (last accessed on August 25, 2023)

(100 μg) dose of the bivalent (Original/BA.4-5) vaccine. The results show that the safety profile is similar to the known safety profile, and no new concerns have been identified. Accordingly, doses of 1 mL (containing 100 μg of mRNA) and 0.5 mL (containing 50 μg of mRNA) were selected as the dosage and administration of the bivalent vaccine for the primary series in individuals aged ≥12 years and children aged 6 to 11 years, respectively.

In view of the accrued data including clinical study results for Spikevax vaccine products, the dose level (as mRNA) equivalent to that of other Spikevax vaccine products can be selected for the primary series of the monovalent (XBB.1.5) vaccine (active ingredient [mRNA] concentration of 0.1 mg/mL) in both age groups to ensure the safety and efficacy of Spikevax that have already been demonstrated with the vaccine products.

PMDA's conclusion on the dosage and administration of Spikevax:
Based on the applicant's explanation and the submitted clinical study data, the dosage regimen evaluated in Study P204 Part 2 and Study P306 in children aged 6 months to 5 years can be recommended as the dosage regimen for the primary series of the Omicron-adapted vaccines. In addition, based on the applicant's explanation, the amounts of mRNA per dose of an Omicron-adapted vaccine used for the primary series in children aged ≥6 years and in adults can be equal regardless of vaccine type (50 μg for children aged 6 to 11 years and 100 μg for individuals aged ≥12 years), and 2 doses should be administered at the same dosing interval as that of the monovalent (Original) vaccine. While the injection volume of the Omicron-adapted vaccines for the primary series is twice that of the monovalent (Original) vaccine for the primary series, the applicant's information did not raise any particular safety concerns.

Although the partial change application to add the manufacturing process of the monovalent (XBB.1.5) vaccine has not been approved, upon the approval of the application, the dosage regimen for the primary series of the Omicron-adapted vaccines can be applied to not only the bivalent vaccines but also the monovalent (XBB.1.5) vaccine, as proposed by the applicant. However, given that the dosing regimen and injection volume differ from those for the primary series of the monovalent (Original) vaccine in individuals aged ≥12 years in the special temporary vaccination program, the applicant should provide information on the dosing regimens newly added for each age group as well as other information on the proper use of Spikevax.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance of Spikevax:
In Studies P204 and P306, no significant safety concerns have been identified after the administration of the monovalent (Original) vaccine or bivalent (Original/BA.1) vaccine in children aged 6 months to 5 years. However, there are no data on the safety of Spikevax in Japanese children aged 6 months to 5 years. Data should therefore be gathered proactively to evaluate the safety of Spikevax in clinical practice. Accordingly, the applicant plans to conduct a post-marketing specified use-results survey (target sample size, 30 participants) to collect safety data, including the incidence of adverse events reported after the primary series of Spikevax in children aged 6 months to 5 years, as well as information on proper use such as vaccine administration errors. Although the sample size is small from a feasibility perspective, the survey will include the incidence of

COVID-19. The survey will investigate the doses of Spikevax in clinical practice; therefore, the study population will be the recipients of one of the Spikevax vaccine products distributed during the survey period.

PMDA's view:

Based on the analysis in Section 7.R.3, the results of clinical studies in children aged 6 months to 5 years and overseas post-marketing data on Spikevax showed that the primary series of Spikevax in children aged 6 months to 5 years has acceptable safety. In addition, based on the clinical study results of Spikevax and past vaccination data from in and outside of Japan in individuals aged ≥6 years, the safety profile of the Omicron-adapted vaccines used for the primary series is inferred to be similar to that of the monovalent (Original) vaccine. As long as adequate risk management is implemented, there should be no problems with the tolerability of the vaccine in all age groups 6 months and older. As of August 2023, the available safety information on the primary series of Spikevax in Japanese vaccine recipients is confined to monovalent (Original) vaccine recipients aged ≥12 years. Given the proportion of people who completed the primary series in Japan [see Section 1], the majority of individuals eligible for the primary series of SARS-CoV-2 vaccines are likely to be children aged <12 years; therefore, it is essential to collect safety information on the primary series of Spikevax in Japanese children aged 6 months to 11 years, an age group in which Spikevax vaccines have not been used. The applicant should gather such information proactively to evaluate the safety of Spikevax vaccines in clinical practice. The applicant needs to develop a specific plan for the specified use-results survey after reconsidering the age range of the study population while taking into account the Government's policy on SARS-CoV-2 vaccination and the vaccine products distributed during the survey period. In addition, the applicant should remain vigilant for the risk of rare events such as shock, anaphylaxis, myocarditis, and pericarditis, by gathering spontaneous adverse event reports in and outside of Japan.

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

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

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

The 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 5.3.5.1.2) 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 Review Report (1)

On the basis of the data submitted and the currently available knowledge, PMDA considers that the primary series of Spikevax (herein defined as mRNA vaccine products containing mRNA encoding the spike protein of SARS-CoV-2 Omicron variant) has a certain level of efficacy in preventing disease caused by SARS-CoV-2 infection (COVID-19) in all age groups 6 months and older, and that the vaccines have acceptable safety with no significant safety concerns. Making the vaccine products other than the monovalent (Original) vaccine available for use as the primary series has clinical significance, based on the assessment of its benefit-risk balance taking into account the status of SARS-CoV-2 outbreaks and individual risk factors.

PMDA concluded that Spikevax 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)

October 5, 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	May 25, 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.2 Efficacy," "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).

A partial change application filed for adding the manufacturing process for the monovalent (XBB.1.5) vaccine, which is a vaccine product targeting SARS-CoV-2 Omicron XBB.1.5, was approved on September 12, 2023. This allows the use of the monovalent (XBB.1.5) vaccine as a booster dose in individuals aged ≥6 years. When the partial change application was approved, the Indication section was modified.[36)]

[36)] The details of the "Indication" included in the partial change application that was approved on September 12, 2023 are as follows (strikethroughs indicate deletion):

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)~~

1.1 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Section "7.R.6 Post-marketing investigations" in the Report on Special Approval for Emergency (1), while raising the following comments:

- There is limited past clinical experience of Spikevax in pediatrics, and no information on its use in Japanese children. In addition, there is only limited information on the safety of Omicron-adapted vaccine products. For these and other reasons, the applicant should remain vigilant for the risk of myocarditis/pericarditis, which is more likely to be reported in younger people.
- To plan post-marketing surveillance, its details should be discussed, including the appropriateness of the sample size (30 for the survey of the primary series in children aged 6 months to 5 years)
- Since circulating SARS-CoV-2 variants constantly change, vaccine efficacy should be continuously monitored.

PMDA asked the applicant to reexamine the proposed study population for the specified use-results survey and reconsider the target sample size based on the latest information.

The applicant responded as follows:
Given the current SARS-CoV-2 vaccination status in children aged ≥6 months, data on vaccination with Spikevax in children aged 6 to 11 years, and the period of the vaccination roll-out program starting in the fall of 2023 (until March 31, 2024), the applicant plans to conduct the survey with the maximum feasible sample size, assuming that the number of vaccinations with Spikevax in children aged 6 months to 11 years will remain low for the time being.

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 16, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 17 and Table 18. Although individuals aged ≥6 months are allowed to receive SARS-CoV-2 vaccines, the target sample size proposed by the applicant in the plan for the specified use-results survey (including the change in the number of children aged 6 to 11 years for a booster dose) is reasonable because the provisions of "Recommendations for Vaccination" and "Duty to endeavor to receive vaccination" specified in the Immunization Act primarily apply to the elderly as well as people at increased risk of severe COVID-19.Given the sample size, survey period, and other factors, information that can be obtained from the survey may be limited. Even so, the applicant should evaluate the safety of Spikevax based on data from the survey as well as from other sources, and take safety measures as necessary in a timely manner.

Table 16. 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 17. 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 (a booster dose in pediatric recipients aged 6 to 11 years) ・ Early post-marketing phase vigilance (primary series in individuals aged ≥6 months) (Spikevax Intramuscular Injection [Monovalent: Omicron XBB.1.5]) ・ General use-results survey (a follow-up of participants in the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan) (Spikevax Intramuscular Injection [Monovalent: original strain]) ・ Specified use-results survey (pediatric recipients aged 6 months to 11 years) (Spikevax Intramuscular Injection [Monovalent: Omicron XBB.1.5]) ・ Post-marketing database survey: shock, anaphylaxis (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) (Spikevax Intramuscular Injection [Monovalent: original strain]) ・ Post-marketing database survey: acute phase solicited adverse events (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) (Spikevax Intramuscular Injection [Monovalent: original strain]) ・ 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) (Spikevax Intramuscular Injection [Monovalent: original strain]) ・ Foreign phase III study (Study mRNA-1273-P301 [primary series]) (Spikevax Intramuscular Injection [Monovalent: original strain])	・ Disseminate data gathered during early post-marketing phase vigilance (a booster dose in pediatric recipients aged 6 to 11 years) ・ Disseminate data gathered during early post-marketing phase vigilance (primary series in individuals aged ≥6 months) (Spikevax Intramuscular Injection [Monovalent: Omicron XBB.1.5]) ・ Develop and disseminate information for healthcare professionals (guide for proper use) ・ Develop and disseminate information materials for vaccine recipients (For anyone receiving the Spikevax Intramuscular Injection) ・ Develop and disseminate information materials for vaccine recipients (For children receiving the Spikevax Intramuscular Injection and their parents or guardians) ・ Publish information on reported adverse reactions periodically (a booster dose in pediatric recipients aged 6 to 11 years) ・ Publish information on reported adverse reactions periodically (primary series in individuals aged ≥6 months) (Spikevax Intramuscular Injection [Monovalent: Omicron XBB.1.5]

(Underline denotes changes for the present application)

Table 18. Outline of specified use-results survey (draft)

Objective	Safety of Spikevax, vaccine administration errors, and the incidence of COVID-19 in children aged 6 months to 11 years in clinical practice
Survey method	Central registry
Population	(1) Children aged 6 to 11 years who received Spikevax as a booster dose (2) Infants and young children aged 6 months to 5 years who received Spikevax for the primary series (3) Children aged 6 to 11 years who received Spikevax for the primary series
Observation period	(1) Until 28 days after Spikevax vaccination (2) and (3) From the day of first dose of Spikevax to 28 days after the second dose of Spikevax
Planned sample size	(1) 120 recipients (2) 120 recipients (3) 20 recipients
Main survey items	Characteristics of vaccine recipients, Spikevax vaccination status, concomitant drugs, presence/absence and details of adverse events, status of SARS-CoV-2 infection or onset of COVID-19, local and systemic solicited adverse events reported through 7 days after Spikevax vaccination that were reported in the patient diary

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

Indication

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

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

  Individuals 12 years of age and older

  For the primary series, Spikevax is administered intramuscularly as a series of 2 doses (1 mL each) at a recommended interval of 4 weeks.

  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 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 months of age and older but younger than 6 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.

(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 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 the cases 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.

Appendix

List of Abbreviations

AESI	Adverse events of special interest
Bivalent (Original/BA.1) vaccine	Bivalent vaccine containing elasomeran and imelasomeran at a mass ratio of 1:1
Bivalent (Original/BA.4-5) vaccine	Bivalent vaccine containing elasomeran and davesomeran at a mass ratio of 1:1
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLSM	Geometric least squares mean
GM	Geometric mean
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMR	Ratio of Geometric mean titers
GMT	Geometric mean titer
LLOQ	Lower limit of quantification
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MIS-C	Multisystem inflammatory syndrome in children
Monovalent (Original) vaccine	Monovalent vaccine containing elasomeran
Monovalent (XBB.1.5) vaccine	Monovalent vaccine containing andusomeran
mRNA	Messenger RNA
Original strain	SARS-CoV-2 Wuhan-Hu-1 strain (D614G)
PEG2000-DMG	1,2-Dimyristoyl-rac-glycero-3-methylpolyoxyethylene
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 set for efficacy
PPIS	Per protocol immunogenicity subset
PPIS-Neg	Per protocol immunogenicity subset - negative
PsVNA	Pseudovirus neutralization assay
RNA	Ribonucleic acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SM-102	Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
Spikevax	Spikevax Intramuscular Injection
Study P204	Study mRNA-1273-P204
Study P205	Study mRNA-1273-P205
Study P301	Study mRNA-1273-P301
Study P306	Study mRNA-1273-P306
ULOQ	Upper limit of quantification
VE	Vaccine efficacy
VOI	Variants of interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee

WHO	World Health Organization