Review Report

April 10, 2025
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
Applicant	Moderna Japan Co., Ltd.
Date of Application	June 28, 2024
Dosage Form/Strength	Suspension for injection: Each vial (2.5 mL) contains 0.25 mg of mRNA encoding the spike protein of SARS-CoV-2
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the booster dose of the vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant) or 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 6 months through 4 years of age, 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 condition.

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

A single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children 5 years ~~of age and older but younger than 12 years of age~~ <u>through 11 years of age</u>

A single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 months ~~of age and older but younger than 5 years of age~~ <u>through 4 years of age</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>For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.</u>

(Strikethrough denotes deletions and underline denotes additions or changes)

Approval Condition

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

Attachment

Review Report (1)

March 6, 2025

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

Product Submitted for Approval

Brand Name	Spikevax Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Moderna Japan Co., Ltd.
Date of Application	June 28, 2024
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 0.25 mg of mRNA encoding the spike protein of SARS-CoV-2

Proposed Indication

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

(No change)

Proposed 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

  A single dose (0.5 mL) of Spikevax is administered intramuscularly.

  Children 5 years of age and older but younger than 12 years of age

  A single dose (0.25 mL) of Spikevax is administered intramuscularly.

  Children 6 months of age and older but younger than 5 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.

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

(Underline denotes additions)

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List of Abbreviations

See Appendix.

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

Since January 2020, successive waves of the disease caused by SARS-CoV-2 infection (COVID-19) have occurred worldwide. On May 5, 2023, the World Health Organization (WHO) declared the end of the Public Health Emergency of International Concern for COVID-19.[1)] In Japan, on May 8, 2023, COVID-19 was reclassified as a "Class V infectious disease"[2)] under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (also referred to as Infectious Disease Control Act), though it had been previously classified as "novel and reemerging influenza infection" (equivalent to Class II infectious diseases). The special temporary SARS-CoV-2 vaccination program ended on March 31, 2024. However, SARS-CoV-2 variants with altered infectivity and transmissibility continue to emerge, resulting in the recurrence of sporadic outbreaks.

SARS-CoV-2 infections among children cause relatively mild symptoms and are less likely to lead to severe COVID-19 (COVID-19 disease in children and adolescents: Scientific brief. WHO; 29 September 2021[3)]). However, there have been reports of pediatric patients requiring hospitalization for treatment (*J Pediatric Infect Dis Soc*. 2021;10:1097-100). In Japan, acute encephalopathy and myocarditis were also reported in some children infected with SARS-CoV-2 (e.g., *Front Neurosci*. 2023;17:1085082).

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 initially approved in Japan in May 2021 for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)." By October 2023, in addition to the Spikevax monovalent (original strain) vaccines, other Spikevax vaccine products were approved for use as a primary series and as booster doses in individuals 6 years of age and older, as well as for the use as a primary series in children 6 months of age and older but younger than 6 years. Subsequently, in April 2024, the age classification for vaccination in children was changed in accordance with the "Modification in the Description of Dosage and Administration for SARS-CoV-2 Vaccines" (in Japanese) (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1, dated March 6, 2024). Following the amendment, the Dosage and Administration section for individuals 5 years of age and older primarily addresses use as a booster dose, while the Dosage and Administration section for children 6 months of age and older but younger than 5 years only addresses use as a primary series.

As of the end of January 2025, among vaccines approved in Japan for the prevention of disease caused by SARS-CoV-2 infection (COVID-19), Comirnaty Intramuscular Injection[4)] is the only vaccine that can be used as a booster dose in children 6 months through 4 years of age.

As of the end of February 2025, Spikevax Intramuscular Injection (a vaccine product adapted to the SARS-CoV-2 Omicron JN.1 variant, or a vaccine product adapted to the SARS-CoV-2 Omicron KP.2 variant) has

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 March 5, 2025)
2) "Ministerial Order Partially Amending the Regulations for Enforcement of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases" (Order of the Ministry of Health, Labour and Welfare No.74, dated April 28, 2023)
3) https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Children_and_adolescents-2021.1 (last accessed on March 5, 2025)
4) The brand name: "Comirnaty Intramuscular Injection for 6 months to 4 years old for three people"

been approved in ≥40 countries and regions. The use of Spikevax as a booster dose in children 6 months through 4 years of age or children 6 months through 5 years of age has been approved in ≥30 countries and regions. In the US, the bivalent (Original/BA.4-5) vaccine was granted Emergency Use Authorization (EUA) in December 2022 for the use as a booster dose (10 μg) in younger children (6 months through 5 years of age). In April 2023, the dosage for a booster dose in younger children was changed from 10 μg to 25 μg at the request of the Food and Drug Administration (FDA). Further, the age classification for vaccination in younger children was changed to 6 months through 4 years of age in accordance with the recommendation made by the Advisory Committee on Immunization Practices (ACIP) in September 2023. In Europe, a dose of 25 μg was approved as a booster dose for children 6 months through 4 years of age in August 2023.

The applicant has recently filed a partial change application to add the dosage for use as booster doses in children 6 months through 4 years of age based on the pivotal data from Study mRNA-1273-P204 (Study P204), a foreign phase II/III study of the monovalent (Original) vaccine in children 6 months through 5 years of age, and Study mRNA-1273-P306 (Study P306), a foreign phase III study of the bivalent (Original/BA.1) vaccine in children 6 months through 5 years of age.

2. Quality and Outline of the Review Conducted by PMDA

Because the intention of the present application is to obtain approval for a new dosage, no data relating to quality have been submitted.

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

Although the intention of the present application is to obtain approval for a new dosage, no new study data on non-clinical pharmacology have been submitted because non-clinical pharmacology data were evaluated during the review of the initial application.

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

Although the intention of the present application is to obtain approval for a new dosage, no new study data on non-clinical pharmacokinetics have been submitted because non-clinical pharmacokinetic data were evaluated during the review of the initial application.

5. Toxicology and Outline of the Review Conducted by PMDA

Because the intention of the present application is to obtain approval for a new dosage, no data relating to toxicology have been submitted.

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

No data from biopharmaceutic studies and associated analytical methods or clinical pharmacology studies have been submitted for the present application.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from studies presented in Table 1.

Table 1. Overview of clinical studies

Region	Study ID	Phase	Study population	Number of participants	Dosage regimen	Key endpoints
US and Canada	mRNA-1273-P204 (Part 2, primary series)	II/III	Healthy children 6 months through 5 years of age[a)]	6 months to 1 year: 2,665 2 to 5 years: 4,048	For the primary series, 2 doses of the monovalent (Original) vaccine 25 µg or placebo administered intramuscularly 28 days apart	Safety Immunogenicity
US and Canada	mRNA-1273-P204 (Part 1, booster dose)	II/III	Healthy children 6 months through 5 years of age[a)] who completed the primary series with the monovalent (Original) vaccine in Part 1	6 months to 1 year: 122 2 to 5 years: 137	At least 6 months after the second dose of the primary series, a single booster dose of monovalent (Original) vaccine[b)] was administered intramuscularly with the dosage below 6 months to 1 year: 10 µg 2 to 5 years: 10 µg or 25 µg	Safety Immunogenicity
US	mRNA-1273-P306 (Part 2)	III	Healthy children 6 months through 5 years of age[a)] who completed the primary series with the monovalent (Original) vaccine in Study P204	539	At least 4 months after the second dose of the primary series,[c)] a single booster dose of bivalent (Original/BA.1) vaccine 10 µg was administered intramuscularly	Safety Immunogenicity

a) Including children with stable underlying medical conditions
b) Initially, the applicant planned to use the monovalent (Original) vaccine. However, Protocol Amendment 9 specified that participants who had not yet received a booster dose would be offered, instead of the monovalent (Original) vaccine, an optional booster dose with the bivalent (Original/BA.1) vaccine (the same dosage).
c) Two doses of the monovalent (Original) vaccine 25 µg were administered intramuscularly, 4 weeks apart.

7.1 Foreign phase II/III study (CTD 5.3.5.1.2, Study mRNA-1273-P204, Part 2, primary series [ongoing since March 2021, data cut-off on September 7, 2022])

Study P204 Part 2 was a randomized, observer-blind, placebo-controlled, parallel-group study conducted at 85 study centers located in the US and Canada to evaluate the safety and immunogenicity of the monovalent (Original) vaccine in healthy children 6 months through 5 years of age (including children with stable underlying medical conditions) (target sample size, up to 4,000 participants each in the age groups 2 to 5 years of age and 6 months through 1 year of age [up to 3,000 participants in the monovalent (Original) vaccine group and up to 1,000 participants in the placebo group]).[5)]

In Part 2, for the primary series, participants in both age groups (6 months through 1 year of age and 2 years through 5 years of age) were to receive 2 doses of the monovalent (Original) vaccine 25 µg or placebo intramuscularly 28 days apart.[6)]

In children 6 months through 1 year of age, of the 2,665 randomized participants (1,995 participants in the monovalent [Original] vaccine 25 µg group and 670 participants in the placebo group; the same applies hereinafter for the order of the groups), 2,660 participants who had received at least 1 dose of the study vaccine

5) Although the participants in Study P204 were 6 months through 11 years of age, data for the age group of children 6 months through 5 years of age were submitted for the present application. Of the data from Part 2, safety data by the status of pre-primary series SARS-CoV-2 infection were used as pivotal data.
6) When the SARS-CoV-2 vaccine authorized under the EUA in the US became available, the trial was unblinded and participants who had received placebo were offered crossover vaccination with the monovalent (Original) vaccine. It was assumed that both age groups 6 months through 1 year of age and 2 years through 5 years of age had entered the unblinded period by June 30, 2022. There were 429 children 6 months through 1 year of age and 603 children 2 years through 5 years of age who had been assigned to placebo and then received the monovalent (Original) vaccine during the open-label period.

(1,993 and 667 participants) were included in the full analysis set (FAS) and the safety analysis set. Among these participants, 2,655 participants (1,990 and 665 participants) provided solicited adverse event data at least once after administration of the study vaccine (regardless of the dose number) and were included in the solicited adverse event analysis set. There were 2,642 participants (1,980 and 662 participants) in the solicited adverse event analysis set after the first dose, and 2,621 participants (1,974 and 647 participants) in the solicited adverse event analysis set after the second dose.

In children 2 years through 5 years of age, 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; the same applies hereinafter for the order of the groups), 4,038 participants who had received at least 1 dose of the study vaccine (3,031 and 1,007 participants) were included in the FAS and the safety analysis set. Among these participants, 4,012 participants (3,014 and 998 participants) were included in the solicited adverse event analysis set. There were 3,926 participants (2,955 and 971 participants) in the solicited adverse event analysis set after the first dose, and 3,949 participants (2,975 and 974 participants) in the solicited adverse event analysis set after the second dose.

For 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.

The safety follow-up periods were as follows:

- Solicited adverse events[7)] (local events: pain, erythema/redness, swelling/induration, lymphadenopathy[8)]; and systemic events: fever ≥38°C, irritability/crying, sleepiness, poor appetite [children 6 months through 1 year of age and children 2 years through 36 months of age]; fever ≥38°C, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills [children 37 months through 5 years of age]): through 7 days after study vaccination (reported in the participant diary by parents/guardians)
- Unsolicited adverse events (excluding solicited adverse events reported through 7 days after study vaccination): through 28 days after study vaccination
- Serious adverse events, acute myocarditis, or pericarditis,[9)] adverse events of special interest (AESI),[10)] and medically-attended adverse event (MAAE): after study vaccination throughout the entire study period

7) The severity of adverse events was defined and evaluated using the FDA's Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007) as a reference.

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

9) Regarding myocarditis and pericarditis reported after SARS-CoV-2 vaccination, the protocol was amended (Amendment 3) before the start of Part 2 in accordance with the definition of the US Centers for Disease Control and Prevention (CDC) (*MMWR Morb Mortal Wkly Rep.* 2021;70:977-82). On and after July [redacted], 2021, at the time of safety telephone calls (safety telephone calls made during the 7 days after vaccination and subsequently), participants were interviewed via the parents/guardians about the presence of the following symptoms: in addition to chest pain, chest pressure, or chest discomfort, shortness of breath, tachypnea at rest, or pain in respiration, increased heart rate, heart fluttering or pounding.

10) The AESI 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 of or worsening of neurologic disease, and anaphylaxis.

The incidences of solicited adverse events through 7 days after study vaccination for children 6 months through 1 year of age and children 2 years through 5 years of age are presented in Table 2 and Table 3, respectively.

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

First dose													
		Monovalent (Original) 25 µg						Placebo					
Pre-primary series SARS-CoV-2 status		Negative N = 1755			Positive N = 132			Negative N = 590			Positive N = 46		
			All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3
		N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)
Local	Any local adverse event	1754	770 (43.9)	10 (0.6)	132	53 (40.2)	1 (0.8)	590	193 (32.7)	2 (0.3)	46	20 (43.5)	0
	Pain	1753	644 (36.7)	0	132	48 (36.4)	0	590	173 (29.3)	0	46	17 (37.0)	0
	Erythema/redness	1754	149 (8.5)	5 (0.3)	131	12 (9.2)	1 (0.8)	590	23 (3.9)	2 (0.3)	46	2 (4.3)	0
	Swelling/induration	1753	145 (8.3)	6 (0.3)	132	11 (8.3)	0	590	18 (3.1)	0	46	2 (4.3)	0
	Lymphadenopathy [a)]	1753	102 (5.8)	0	131	9 (6.9)	0	590	27 (4.6)	0	46	4 (8.7)	0
Systemic	Any systemic adverse event	1754	1331 (75.9)	46 (2.6)	132	99 (75.0)	3 (2.3)	590	423 (71.7)	10 (1.7)	46	39 (84.8)	1 (2.2)
	Fever[b)]	1752	178 (10.2)	13 (0.7)	131	18 (13.7)	0	590	50 (8.5)	4 (0.7)	46	7 (15.2)	0
	Irritability/crying	1745	1175 (67.3)	23 (1.3)	131	93 (71.0)	2 (1.5)	588	361 (61.4)	6 (1.0)	46	34 (73.9)	1 (2.2)
	Sleepiness	1746	635 (36.4)	3 (0.2)	132	48 (36.4)	1 (0.8)	588	219 (37.2)	1 (0.2)	46	17 (37.0)	0
	Poor appetite	1745	517 (29.6)	13 (0.7)	131	38 (29.0)	0	588	158 (26.9)	1 (0.2)	46	15 (32.6)	0
Second dose													
		Monovalent (Original) 25 µg						Placebo					
Pre-primary series SARS-CoV-2 status		Negative N = 1751			Positive N = 131			Negative N = 579			Positive N = 43		
			All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3
		N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)
Local	Any local adverse event	1751	928 (53.0)	27 (1.5)	131	75 (57.3)	0	579	179 (30.9)	0	43	13 (30.2)	0
	Pain	1751	776 (44.3)	1 (<0.1)	131	67 (51.1)	0	579	152 (26.3)	0	43	11 (25.6)	0
	Erythema/redness	1751	239 (13.6)	15 (0.9)	131	15 (11.5)	0	579	25 (4.3)	0	43	1 (2.3)	0
	Swelling/induration	1751	263 (15.0)	17 (1.0)	131	16 (12.2)	0	579	14 (2.4)	0	43	2 (4.7)	0
	Lymphadenopathy[a)]	1751	157 (9.0)	0	131	12 (9.2)	0	579	26 (4.5)	0	43	4 (9.3)	0
Systemic	Any systemic adverse event	1751	1298 (74.1)	52 (3.0)	131	93 (71.0)	6 (4.6)	579	390 (67.4)	10 (1.7)	43	34 (79.1)	1 (2.3)
	Fever[b)]	1749	245 (14.0)	12 (0.7)	131	22 (16.8)	1 (0.8)	579	44 (7.6)	5 (0.9)	43	5 (11.6)	0
	Irritability/crying	1744	1129 (64.7)	29 (1.7)	131	84 (64.1)	3 (2.3)	578	338 (58.5)	4 (0.7)	43	32 (74.4)	0
	Sleepiness	1744	625 (35.8)	2 (0.1)	131	47 (35.9)	1 (0.8)	578	206 (35.6)	1 (0.2)	43	13 (30.2)	0
	Poor appetite	1744	559 (32.1)	15 (0.9)	131	37 (28.2)	2 (1.5)	578	151 (26.1)	1 (0.2)	43	15 (34.9)	1 (2.3)

N = number of participants evaluated; N1 = number of participants who provided the event data; n = number of participants who experienced the event

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

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

Table 3. Solicited adverse events through 7 days after each dose of the study vaccine (children 2 years through 5 years of age) (Study P204 Part 2: solicited adverse event analysis set)

First dose													
		Monovalent (Original) 25 µg						Placebo					
Pre-primary series SARS-CoV-2 status		Negative N = 2633			Positive N = 259			Negative N = 868			Positive N = 77		
			All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3
		N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)
Local	Any local adverse event	2632	1680 (63.8)	21 (0.8)	259	156 (60.2)	2 (0.8)	868	369 (42.5)	3 (0.3)	77	31 (40.3)	1 (1.3)
	Pain	2630	1632 (62.1)	3 (0.1)	259	146 (56.4)	1 (0.4)	868	347 (40.0)	0	77	29 (37.7)	0
	Erythema/redness	2631	147 (5.6)	11 (0.4)	259	10 (3.9)	1 (0.4)	868	12 (1.4)	2 (0.2)	77	2 (2.6)	1 (1.3)
	Swelling/induration	2631	126 (4.8)	10 (0.4)	259	9 (3.5)	0	868	16 (1.8)	2 (0.2)	77	0	0
	Lymphadenopathy [a)]	2630	172 (6.5)	0	259	29 (11.2)	0	868	52 (6.0)	0	77	2 (2.6)	0
Systemic	Any systemic adverse event	2632	1407 (53.5)	63 (2.4)	259	155 (59.8)	5 (1.9)	868	441 (50.8)	23 (2.6)	77	35 (45.5)	2 (2.6)
	Fever[b)]	2632	224 (8.5)	28 (1.1)	259	34 (13.1)	2 (0.8)	868	53 (6.1)	9 (1.0)	77	4 (5.2)	0
	Headache	1803	207 (11.5)	5 (0.3)	170	22 (12.9)	0	581	67 (11.5)	2 (0.3)	50	9 (18.0)	0
	Fatigue	1803	728 (40.4)	19 (1.1)	170	67 (39.4)	2 (1.2)	581	214 (36.8)	9 (1.5)	50	18 (36.0)	2 (4.0)
	Myalgia	1803	178 (9.9)	5 (0.3)	170	19 (11.2)	0	581	56 (9.6)	2 (0.3)	50	1 (2.0)	0
	Arthralgia	1803	111 (6.2)	2 (0.1)	170	11 (6.5)	0	581	32 (5.5)	1 (0.2)	50	0	0
	Nausea/vomiting	1803	118 (6.5)	5 (0.3)	170	16 (9.4)	2 (1.2)	581	46 (7.9)	1 (0.2)	50	3 (6.0)	1 (2.0)
	Chills	1803	111 (6.2)	1 (<0.1)	170	15 (8.8)	0	581	34 (5.9)	0	50	5 (10.0)	0
	Irritability/crying	827	442 (53.4)	9 (1.1)	88	54 (61.4)	2 (2.3)	284	146 (51.4)	4 (1.4)	27	13 (48.1)	0
	Sleepiness	827	249 (30.1)	2 (0.2)	88	31 (35.2)	0	284	85 (29.9)	0	27	4 (14.8)	0
	Poor appetite	828	199 (24.0)	5 (0.6)	88	22 (25.0)	1 (1.1)	284	62 (21.8)	2 (0.7)	27	4 (14.8)	0
Second dose													
		Monovalent (Original) 25 µg						Placebo					
Pre-primary series SARS-CoV-2 status		Negative N = 2650			Positive N = 262			Negative N = 870			Positive N = 77		
			All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3		All Grades	Grade ≥3
		N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)	N1	n (%)	n (%)
Local	Any local adverse event	2650	1955 (73.8)	33 (1.2)	262	183 (69.8)	0	870	378 (43.4)	0	76	23 (30.3)	0
	Pain	2650	1898 (71.6)	10 (0.4)	262	182 (69.5)	0	870	369 (42.4)	0	76	23 (30.3)	0
	Erythema/redness	2650	241 (9.1)	13 (0.5)	262	13 (5.0)	0	870	16 (1.8)	0	76	1 (1.3)	0
	Swelling/induration	2650	223 (8.4)	13 (0.5)	262	13 (5.0)	0	870	12 (1.4)	0	76	1 (1.3)	0
	Lymphadenopathy [a)]	2650	245 (9.2)	1 (<0.1)	262	19 (7.3)	0	870	32 (3.7)	0	76	1 (1.3)	0
Systemic	Any systemic adverse event	2650	1636 (61.7)	116 (4.4)	262	161 (61.5)	18 (6.9)	870	395 (45.4)	14 (1.6)	77	32 (41.6)	1 (1.3)
	Fever[b)]	2649	441 (16.6)	63 (2.4)	262	53 (20.2)	14 (5.3)	869	53 (6.1)	2 (0.2)	77	9 (11.7)	0
	Headache	1796	284 (15.8)	8 (0.4)	169	20 (11.8)	0	572	48 (8.4)	1 (0.2)	46	3 (6.5)	0
	Fatigue	1796	882 (49.1)	40 (2.2)	169	63 (37.3)	3 (1.8)	572	173 (30.2)	8 (1.4)	46	11 (23.9)	1 (2.2)
	Myalgia	1796	285 (15.9)	8 (0.4)	169	22 (13.0)	1 (0.6)	572	47 (8.2)	3 (0.5)	46	1 (2.2)	0
	Arthralgia	1796	154 (8.6)	3 (0.2)	169	13 (7.7)	0	572	27 (4.7)	0	46	1 (2.2)	0
	Nausea/vomiting	1796	171 (9.5)	7 (0.4)	169	19 (11.2)	0	572	29 (5.1)	0	46	2 (4.3)	0
	Chills	1796	225 (12.5)	4 (0.2)	169	15 (8.9)	0	572	28 (4.9)	2 (0.3)	46	1 (2.2)	0

	Irritability/crying	854	466 (54.6)	8 (0.9)	93	54 (58.1)	2 (2.2)	297	137 (46.1)	3 (1.0)	30	14 (46.7)	0
	Sleepiness	854	300 (35.1)	1 (0.1)	93	43 (46.2)	0	297	75 (25.3)	0	30	12 (40.0)	0
	Poor appetite	854	252 (29.5)	7 (0.8)	93	38 (40.9)	1 (1.1)	297	59 (19.9)	0	30	8 (26.7)	0

N = number of participants evaluated; N1 = number of participants who provided the event data; n = number of participants who experienced the event

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

b) For children 2 years through 36 months of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-39.5°C; Grade 3, 39.6°C-40.0°C; Grade 4, >40.0°C; For children 37 months through 5 years of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-38.9°C; Grade 3, 39.0°C-40.0°C; Grade 4, >40.0°C (oral temperature for children >4 years of age; tympanic temperature for children ≤4 years of age)

The incidence of unsolicited adverse events occurring in ≥2% of participants in either group through 28 days after study vaccination in children in the age groups 6 months through 1 year of age and 2 years through 5 years of age is shown in Table 4 and Table 5, respectively. Among children 6 months through 1 year of age, Grade ≥3 unsolicited adverse events occurred in 25 of 1,767 participants (1.4%) and 1 of 133 participants (0.8%) in the pre-primary series SARS-CoV-2 negative group and positive group, respectively (the same applies hereinafter for the order of the groups). Among children 2 years through 5 years of age, Grade ≥3 unsolicited adverse events occurred in 20 of 2,697 participants (0.7%) and 2 of 267 participants (0.7%). The incidence of unsolicited adverse reactions was 17.5% (310 of 1,767 participants) and 15.0% (20 of 133 participants) in children 6 months through 1 year of age, and 9.8% (264 of 2,697 participants) and 6.7% (18 of 267 participants) in children 2 years through 5 years of age. Grade ≥3 unsolicited adverse reactions occurred in 13 of 1,767 participants (0.7%) and 1 of 133 participants (0.8%) in children 6 months through 1 year of age, and 17 of 2,697 participants (0.6%) and 1 of 267 participants (0.4%) in children 2 years through 5 years of age.

Table 4. Unsolicited adverse events occurring in ≥2% of participants through 28 days after study vaccination (the first dose or second dose) (children 6 months through 1 year of age) (Study P204 Part 2, safety analysis set)

Pre-primary series SARS-CoV-2 negative			Pre-primary series SARS-CoV-2 positive		
	Monovalent (Original) 25 µg N = 1767	Placebo N = 594		Monovalent (Original) 25 µg N = 133	Placebo N = 47
	n (%)	n (%)		n (%)	n (%)
Any adverse event	941 (53.3)	306 (51.5)	Any adverse event	69 (51.9)	22 (46.8)
Upper respiratory tract infection	208 (11.8)	79 (13.3)	Upper respiratory tract infection	17 (12.8)	9 (19.1)
Irritability	161 (9.1)	55 (9.3)	Irritability	13 (9.8)	3 (6.4)
Teething	94 (5.3)	33 (5.6)	Cough	9 (6.8)	1 (2.1)
Fever	88 (5.0)	36 (6.1)	Rhinorrhoea	8 (6.0)	1 (2.1)
Rhinorrhoea	81 (4.6)	31 (5.2)	Fever	7 (5.3)	4 (8.5)
Decreased appetite	77 (4.4)	33 (5.6)	Ear infection	5 (3.8)	4 (8.5)
Ear infection	67 (3.8)	18 (3.0)	Nasal congestion	5 (3.8)	0
Cough	67 (3.8)	21 (3.5)	Vomiting	5 (3.8)	0
COVID-19	66 (3.7)	33 (5.6)	Diarrhoea	4 (3.0)	1 (2.1)
Diarrhoea	56 (3.2)	13 (2.2)	Otitis media	4 (3.0)	0
Otitis media	52 (2.9)	21 (3.5)	Decreased appetite	3 (2.3)	2 (4.3)
Vomiting	37 (2.1)	17 (2.9)	Gastroenteritis	3 (2.3)	0
Nasal congestion	36 (2.0)	16 (2.7)	Somnolence	3 (2.3)	0
Somnolence	35 (2.0)	16 (2.7)	COVID-19	2 (1.5)	2 (4.3)
Viral upper respiratory tract infection	34 (1.9)	13 (2.2)	Teething	2 (1.5)	2 (4.3)
			Otitis media acute	1 (0.8)	1 (2.1)
			Seasonal allergy	1 (0.8)	1 (2.1)
			Adenovirus infection	0	1 (2.1)
			Bacterial infection	0	1 (2.1)
			Conjunctivitis	0	1 (2.1)
			Iron deficiency anaemia	0	1 (2.1)
			Eye swelling	0	1 (2.1)
			Eczema	0	1 (2.1)
			Rash maculo-papular	0	1 (2.1)
			Urticaria	0	1 (2.1)
			Swelling face	0	1 (2.1)
			Arthropod bite	0	1 (2.1)
			Radial head dislocation	0	1 (2.1)
			Skin laceration	0	1 (2.1)

N = number of participants evaluated;
n = number of participants who experienced the event

Table 5. Unsolicited adverse events occurring in ≥2% of participants through 28 days after study vaccination (the first dose or second dose) (children 2 years through 5 years of age) (Study P204 Part 2, safety analysis set)

Pre-primary series SARS-CoV-2 negative			Pre-primary series SARS-CoV-2 positive		
	Monovalent (Original) 25 µg N = 2697	Placebo N = 897		Monovalent (Original) 25 µg N = 267	Placebo N = 82
	n (%)	n (%)		n (%)	n (%)
Any adverse event	1121 (41.6)	358 (39.9)	Any adverse event	102 (38.2)	31 (37.8)
Upper respiratory tract infection	231 (8.6)	90 (10.0)	Upper respiratory tract infection	21 (7.9)	9 (11.0)
Rhinorrhoea	114 (4.2)	33 (3.7)	Nasopharyngitis	10 (3.7)	1 (1.2)
Cough	105 (3.9)	38 (4.2)	Fever	8 (3.0)	6 (7.3)
COVID-19	94 (3.5)	54 (6.0)	Fatigue	8 (3.0)	2 (2.4)
Fever	85 (3.2)	28 (3.1)	Rhinorrhoea	7 (2.6)	7 (8.5)
Viral upper respiratory tract infection	57 (2.1)	12 (1.3)	COVID-19	7 (2.6)	1 (1.2)
Fatigue	57 (2.1)	20 (2.2)	Cough	6 (2.2)	5 (6.1)
Nasal congestion	56 (2.1)	18 (2.0)	Irritability	6 (2.2)	2 (2.4)
Vomiting	55 (2.0)	14 (1.6)	Viral upper respiratory tract infection	3 (1.1)	3 (3.7)
Ear infection	43 (1.6)	22 (2.5)	Ear infection	3 (1.1)	2 (2.4)
			Decreased appetite	3 (1.1)	2 (2.4)
			Diarrhoea	3 (1.1)	2 (2.4)
			Nasal congestion	2 (0.7)	2 (2.4)
			Gastrointestinal viral infection	1 (0.4)	2 (2.4)
			Rash	0	2 (2.4)

N = number of participants evaluated;
n = number of participants who experienced the event

According to the analysis of data collected through 28 days after study vaccination (the first dose or second dose) and over the period of the blinded phase[11] (hereinafter "over the blinded period"), there were no reports of death in either age group (data cut-off date, September 7, 2022). Adverse events leading to study discontinuation within 28 days of study vaccination occurred in 1 participant (urticaria) in the monovalent (Original) 25 µg group and 1 participant (COVID-19) in the placebo group among children 6 months through 1 year of age, and 1 participant (urticaria) in the monovalent (Original) 25 µg group among children 2 years through 5 years of age. All these events were reported after the first dose of study vaccination. The second dose was not administered. Among these events, the 2 cases of urticaria were considered possibly causally related to the study vaccine, and both events were mild in severity and the outcomes were reported as "resolved."

In children 6 months through 1 year of age, within 28 days of study vaccination (the first dose or second dose), serious adverse events occurred in 13 of 1,993 participants (0.7%) in the monovalent (Original) 25 µg group (bronchiolitis, gastroenteritis salmonella, mastoiditis, metapneumovirus infection, respiratory syncytial virus infection, rhinovirus infection, bone marrow failure, electrolyte imbalance, febrile convulsion, seizure, fever/ febrile convulsion, foreign body in respiratory tract, tibia fracture [1 participant each]) and no serious adverse events occurred in the placebo group. Among these events, fever and febrile convulsion[12] reported in 1 participant were considered related to the study vaccine, and the outcome was reported as "resolved." Over the blinded period, serious adverse events occurred in 31of 1,993 participants (1.6%) in the monovalent (Original) 25 µg group (bronchiolitis [4 participants]; febrile convulsion [3 participants]; croup infectious, rhinovirus infection, adenovirus infection, pneumonia, asthma [2 participants each]; gastroenteritis salmonella, gastroenteritis viral, mastoiditis, metapneumovirus infection, respiratory syncytial virus infection, bone marrow failure, lymphadenitis, diabetic ketoacidosis, electrolyte imbalance, type 1 diabetes mellitus, seizure, bronchospasm, dyspnoea, erythema multiforme, branchial cyst, fever, foreign body in respiratory tract, tibia fracture [1 participant each; some participants had more than 1 event]) and 6 of 667 participants (0.9%) in the placebo group (bronchiolitis [3 participants]; acute respiratory failure [2 participants]; croup infectious, rhinovirus infection, hypoxia [1 participant each]) (data cut-off date, September 7, 2022). Among these events, diabetic ketoacidosis and type 1 diabetes mellitus[13] reported in 1 participant in the monovalent (Original) 25 µg group were considered related to the study vaccine. The outcome of diabetic ketoacidosis was reported as "resolved," while the case of type 1 diabetes mellitus required continued treatment. Among participants who experienced serious adverse events, only 1 participant (bronchiolitis, in the monovalent [Original] 25 µg group) had tested positive for pre-primary series SARS-CoV-2; all other participants had either tested negative for pre-primary series SARS-CoV-2 or had an unknown status.

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11) Although Study P204 Part 2 was initiated as an observer-blind study, all participants were unblinded when the SARS-CoV-2 vaccine authorized under the EUA in the US became available. At that time, those who had received placebo were offered the option of continuing the study by switching over to vaccination with the monovalent (Original) vaccine, or discontinuing the study to receive the authorized vaccine. It was assumed that in either case, all participants had entered the unblinded period by [redacted], 20[redacted].

12) A girl aged [redacted] years, who developed a severe fever on the day of the first dose, experienced febrile convulsions on the following day (Day 2). This participant had recovered by Day 3.

13) A girl aged [redacted] years, who was diagnosed as having diabetic ketoacidosis and type 1 diabetes mellitus on the 13th day after the second dose of the study vaccine (Day 66), was hospitalized. The symptoms improved 1 week later and the participant was discharged from the hospital. The outcome was reported as "resolved." The investigator considered that a causal relationship to the study vaccine could not be ruled out; however, the investigator also reported that a viral upper respiratory infection was more likely to have triggered the events because this participant had a genetic predisposition to borderline diabetes due to a family history of type I diabetes mellitus.

In children 2 years through 5 years of age, within 28 days of study vaccination (the first dose or second dose), serious adverse events occurred in 4 of 3,031 participants (0.1%) in the monovalent (Original) 25 µg group (adenovirus infection, metapneumovirus infection, pneumonia viral, and seizure [1 participant each]), and 1 of 1,007 participants (<0.1%) (abdominal wall abscess) in the placebo group. Over the blinded period, serious adverse events occurred in 19 of 3,031 participants (0.6%) in the monovalent (Original) 25 µg group (metapneumovirus infection [2 participants]; rhinovirus infection, adenovirus infection, croup infectious, Epstein-Barr virus infection, gastroenteritis, pneumonia respiratory syncytial viral, pneumonia viral, respiratory syncytial virus bronchiolitis, respiratory syncytial virus infection, urinary tract infection, seizure, Kawasaki's disease, asthma, bronchial hyperreactivity, constipation, hepatitis acute, dermatomyositis, fever, humerus fracture [1 participant each; some participants had more than 1 event]) and 3 of 1,007 participants (0.3%) in the placebo group (rhinovirus infection, abdominal wall abscess, asthma, systemic inflammatory response syndrome [1 participant each; some participants had more than 1 event]). All of these events were considered unrelated to the study vaccine (data cut-off date, September 7, 2022). Of participants who experienced serious adverse events, 2 participants in the monovalent (Original) 25 µg group had tested positive for pre-primary series SARS-CoV-2 test (pneumonia viral, constipation [1 participant each]); all other participants had either tested negative for pre-primary series SARS-CoV-2 or had an unknown status.

7.2 Foreign phase II/III study (CTD 5.3.5.1.3, Study mRNA-1273-P204, Part 1, booster dose phase [ongoing since March 2021, data cut-off on June 1, 2023])

An open-label, uncontrolled study was conducted at 61 study centers located in the US and Canada to evaluate the safety and immunogenicity of the monovalent (Original) vaccine as a booster dose.[14)] This booster dose phase of the study enrolled healthy children 6 months through 5 years of age who had received 2 doses of the monovalent (Original) vaccine (50 µg or 25 µg) for the primary series in Study P204 Part 1 (including children with stable underlying medical conditions).

Participants of both age groups (6 months through 1 year of age and 2 years through 5 years of age) were to receive a single dose of the monovalent (Original) vaccine 10 µg intramuscularly at least 6 months after the second dose of the primary series. Participants who were in the age group 2 years through 5 years at enrollment (primary series) but turned 6 years of age prior to the booster dose were to receive a single intramuscular dose of 25 µg. This section only describes the results from the group of participants who received 2 doses of the monovalent (Original) vaccine 25 µg for the primary series and the monovalent (Original) vaccine 10 µg as a booster dose, which were the pivotal data for the present application.

[14)] Although the population of Study P204 was 6 months through 11 years of age, clinical results data for participants 6 months through 5 years of age were submitted for the present application.

A total of 153 participants (122 participants 6 months through 1 year of age and 31 participants 2 years through 5 years of age),[15)] who received the monovalent (Original) vaccine 25 µg for the primary series and the monovalent (Original) vaccine 10 µg as a booster dose, were included in the FAS and the safety analysis set. All the 153 participants in the safety analysis set provided solicited adverse event data at least once after administration of a booster dose, and all these participants were included in the solicited adverse event analysis set. Of the FAS, participants whose immunogenicity data after a booster dose were available, who had no major protocol violations, and were not receiving highly active anti-retroviral therapy (HAART) if diagnosed as having human immunodeficiency virus (HIV) were included in the per protocol immunogenicity subset (PPIS) (103 participants in total; 84 participants 6 months through 1 year of age and 19 participants 2 years through 5 years of age). Participants in the PPIS whose status was pre-booster SARS-CoV-2 negative were included in the PPIS-Neg (76 participants in total; 60 participants 6 months through 1 year of age and 16 participants 2 years through 5 years of age). The primary analysis population for immunogenicity was the PPIS-Neg.

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 co-primary immunogenicity endpoints were the geometric mean (GM) value of neutralizing antibodies against SARS-CoV-2 (original strain) (pseudovirus neutralization assay [PsVNA], 50% inhibitory dilution) and the seroresponse rate at 28 days post-booster dose. For each co-primary endpoint, non-inferiority of the results in participants 6 months through 5 years of age to the results in participants 18 through 25 years of age at Day 57 (28 days post-second dose of the primary series) in Study P301, which evaluated the efficacy in the prevention of COVID-19 in participants ≥18 years of age, 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 the pre-first primary series dose (if neutralizing antibody pre-first primary series dose reported was below the lower limit of quantification [LLOQ], a ≥4-fold rise from the LLOQ). When both of the following success criteria for the co-primary endpoints were met, non-inferiority was considered to be demonstrated.

- GM value: the lower bound of the two-sided 95% confidence interval (CI) of the ratio of GM titers (GMR) in Study P204 (6 months through 5 years of age, at 28 days post-booster dose) to that in Study P301 (18 through 25 years of age, Day 57 [28 days post-second dose of the primary series]) is >0.67.
- Seroresponse rate: the lower bound of the two-sided 95% CI of seroresponse rate difference (Study P204 [6 months through 5 years of age, at 28 days post-booster dose] minus Study P301 [18 through 25 years of age, Day 57 (28 days post-second dose of the primary series)]) is >−10%.

[15)] With 289 participants each in the PPIS-Neg in Studies P204 and P301 (control), there will be ≥90% power in each of the following tests.
- Assuming a GMR (Study P204/P301) of 1.0 based on neutralizing antibody GM values against the original strain, non-inferiority is evaluated.
- Assuming that the neutralizing antibody seroresponse rate against the original strain in Study P204 is ≥95% with a difference of 4% between Studies P204 and P301, non-inferiority is evaluated for the difference in seroresponse rate.

The vaccine product used as a booster dose was changed to the bivalent (Original/BA.1) vaccine from the monovalent (Original) vaccine during the period of Study P204. As a result, 153 participants received the monovalent (Original) vaccine 25 µg for the primary series and the monovalent (Original) vaccine 10 µg as a booster dose in the booster dose phase in Study P204 Part 1.

Table 6 shows the results for the co-primary immunogenicity endpoints at 28 days post-booster dose. The results for immune response at 28 days post-booster dose were compared with those in Study P301 (participants 18 through 25 years of age, at Day 57 [28 days post-second dose of the primary series]). The lower bound of the two-sided 95% CI of the neutralizing antibody GMR against the original strain, and the lower bound of the two-sided 95% CI of seroresponse rate difference were both greater than the non-inferiority margins, indicating that the results met the prespecified success criteria for non-inferiority. The median interval [range] between the second dose of the primary series and the booster dose was 301.0 days [236, 376].

Table 6. Comparison of serum neutralizing antibody titers against the original strain and seroresponse rate (Study P204 Part 1, PPIS-Neg)

		P204 (6 months through 5 years of age)	P301 (18 through 25 years of age)
		Monovalent (Original) vaccine Primary series 25 µg + booster 10 µg N = 76	Monovalent (Original) vaccine Primary series 100 µg N = 296
GMC			
Pre-primary series	n	72	295
	GMC [two-sided 95% CI][a)]	9.8 [8.8, 10.9]	11.1 [10.5, 11.6]
Study P204: 28 days post-booster dose Study P301: Day 57 (28 days after the second dose of the primary series)	n	76	294
	GMC [two-sided 95% CI][a)]	5457.2 [4525.7, 6580.3]	1400.4 [1272.7, 1541.0]
	N1	72	294
	GMFR [two-sided 95% CI][a)]	555.7 [440.2, 701.5]	126.6 [113.8, 140.9]
	GLSM [two-sided 95% CI][b)]	5457.2 [4525.0, 6581.3]	1400.4 [1273.2, 1540.3]
	GMR (P204/P301) [two-sided 95% CI][b)]	3.897 [3.158, 4.808]	
Seroresponse rate			
n1/N1		72/72	292/294
Seroresponse rate [two-sided 95% CI][c)] (%)		100 [95.0, 100.0]	99.3 [97.6, >99.9]
Seroresponse rate difference (P204−P301) [two-sided 95% CI][d)] (%)		0.7 [-4.4, 2.4]	

Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the upper limit of quantification (ULOQ) were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 10-111433

N = number of participants evaluated; N1 = number of participants with non-missing data before the primary series and at the time point of evaluation; n = number of participants with non-missing data at the time point of evaluation

n1 = number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ)

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or log-transformed values for the fold rise in antibody titer
b) An analysis of covariance model with the antibody titer at 28 days post-booster dose in Study P204 or at Day 57 in Study P301 as a dependent variable, and the group variable (6 months through 5 years of age in Study P204 vs 18 years through 25 years of age in Study P301) as the fixed effect
c) Two-sided 95% CI was calculated using the Clopper-Pearson method
d) Two-sided 95% CI was calculated using the stratified Miettinen-Nurminen method with adjustment for age group

The safety follow-up periods were as follows:

- Solicited adverse events[7)] (local events [pain, erythema/redness, swelling/induration, lymphadenopathy[8)]] and systemic events [fever ≥38°C, irritability/crying, sleepiness, and poor appetite for children 6 months through 1 year of age and children 2 years through 36 months of age; fever ≥38°C, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills for children 37 months through 5 years of age]): through 7 days after study vaccination (reported in the participant diary by parents/guardians)
- Unsolicited adverse events (excluding solicited adverse events reported through 7 days after study vaccination): through 28 days after study vaccination
- Serious adverse events, acute myocarditis, or pericarditis,[9)] AESI,[10)] MAAE: after study vaccination throughout the entire study period

The incidences of solicited adverse events through 7 days after study vaccination for children 6 months through 1 year of age and children 2 years through 5 years of age are presented in Table 7 and Table 8, respectively. Table 9 shows the incidence of unsolicited adverse events occurring in ≥2 participants in either group through 28 days after study vaccination and those classified as adverse reactions. None of the events were classified as Grade ≥3.

Table 7. Incidence of solicited adverse events through 7 days after study vaccination (children 6 months through 1 year of age) (Study P204 Part 1, solicited adverse event analysis set)

Event		6 months through 1 year of age N = 122	
		All Grades	Grade ≥3
		n (%)	n (%)
Local	Any local adverse event	56 (45.9)	2 (1.6)
	Pain	48 (39.3)	0
	Erythema/redness	14 (11.5)	2 (1.6)
	Swelling/induration	15 (12.3)	1 (0.8)
	Lymphadenopathy[a)]	6 (4.9)	0
Systemic	Any systemic adverse event	81 (66.4)	4 (3.3)
	Fever[b) c)]	13 (10.7)	3 (2.5)
	Irritability/crying	64 (52.5)	0
	Sleepiness	34 (27.9)	1 (0.8)
	Poor appetite	32 (26.2)	0

N = number of participants evaluated; n = number of participants who experienced the event

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

b) The number of participants included in the analysis of incidence (the number of participants who provided the event data) was 121

c) Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-39.5°C; Grade 3, 39.6°C-40.0°C; Grade 4, >40.0°C (tympanic temperature)

Table 8. Incidence of solicited adverse events through 7 days after study vaccination (children 2 years through 5 years of age) (Study P204 Part 1, solicited adverse event analysis set)

Event		All Grades		Grade ≥3
		n (%)		n (%)
Local	2 years through 5 years of age		N = 31	
	Any local adverse event	19 (61.3)		0
	Pain	18 (58.1)		0
	Erythema/redness	1 (3.2)		0
	Swelling/induration	3 (9.7)		0
	Lymphadenopathy[a)]	1 (3.2)		0
Systemic	2 years through 36 months of age		N = 6	
	Any systemic adverse event	4 (66.7)		0
	Fever[b)]	0		0
	Irritability/crying	4 (66.7)		0
	Sleepiness	2 (33.3)		0
	Poor appetite	1 (16.7)		0
	37 months through 5 years of age		N = 25	
	Any systemic adverse event	12 (48.0)		1 (4.0)
	Fever[b)]	1 (4.0)		1 (4.0)
	Headache	5 (20.0)		0
	Fatigue	8 (32.0)		0
	Myalgia	3 (12.0)		0
	Arthralgia	2 (8.0)		0
	Nausea/vomiting	1 (4.0)		0
	Chills	2 (8.0)		0

N = number of participants evaluated; n = number of participants who experienced the event

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

b) For children 37 months through 5 years of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-38.9°C; Grade 3, 39.0°C-40.0°C; Grade 4, >40.0°C;
For children 2 years through 36 months of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-39.5°C; Grade 3, 39.6°C-40.0°C; Grade 4, >40.0°C (oral temperature for children >4 years of age; tympanic temperature for children ≤4 years of age)

Table 9. Incidence of unsolicited adverse events occurring in ≥2 participants in either age group and the incidence of adverse reactions through 28 days after study vaccination (Study P204 Part 1, safety analysis set)

	6 months through 1 year of age N = 122		2 years through 5 years of age N = 31	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions
	n (%)	n (%)	n (%)	n (%)
Any adverse event	31 (25.4)	3 (2.5)	8 (25.8)	2 (6.5)
Upper respiratory tract infection	8 (6.6)	0	2 (6.5)	0
Asymptomatic COVID-19	4 (3.3)	0	1 (3.2)	0
Otitis media	3 (2.5)	0	0	0
COVID-19	3 (2.5)	0	0	0
Rhinorrhoea	3 (2.5)	0	0	0
Cough	2 (1.6)	0	1 (3.2)	0
Nasal congestion	2 (1.6)	0	0	0
Injection site induration	2 (1.6)	1 (0.8)	0	0
Fever	2 (1.6)	0	0	0

N = number of participants evaluated; n = number of participants who experienced the event

Up to the data cut-off date (June 1, 2023), there were no deaths or adverse events leading to study discontinuation in either age group.

No serious adverse events occurred in either age group within 28 days after the booster dose. Beyond 28 days post-booster dose up to the data cut-off date (June 1, 2023), no serious adverse events occurred in the age group of children 2 years through 5 years of age. Serious adverse events occurred in 1 participant in the age group of children 6 months through 1 year of age (pharyngeal abscess/streptococcal infection), and both events were considered unrelated to the study vaccine. Their outcomes were reported as “resolved.”

7.3 Foreign phase III study (CTD 5.3.5.1.1, Study mRNA-1273-P306, Part 2 [ongoing since June 2022; data cut-off on March 21, 2023])

Study P306 was an open-label, uncontrolled study to evaluate the safety and immunogenicity of the bivalent (Original/BA.1) vaccine in children 6 months through 5 years of age. The study consisted of Part 1 and Part 2, which evaluated the primary series and booster doses, respectively. Data from Part 2that evaluated the booster dose were submitted in the support of the present application.

Study P306 Part 2 was conducted at 16 study centers in the US to assess the safety and immunogenicity of the bivalent (Original/BA.1) vaccine as a booster dose in participants who had received 2 doses of the monovalent (Original) vaccine 25 µg for the primary series in Study P204 (target sample size, 480 participants).[16)]

Participants were to receive a single intramuscular dose of the bivalent (Original/BA.1) vaccine 10 µg at least 4 months after the second dose of the primary series.

A total of 539 participants who received the study vaccine as a booster dose (114 participants 6 months through 1 year of age and 425 participants 2 years through 5 years of age) were included in the FAS and the safety analysis set. All 539 participants in the safety analysis set provided solicited adverse event data at least once

16) With 289 participants each in the PPIS-Neg in Study P306 Part 2 and Study P204 (control), there will be ≥90% power in each of the following testing. A sample size of 480 participants was selected for Study P306 Part 2 assuming 40% to be excluded from the PPIS-Neg.
- Assuming a GMR (Study P306/P204) of 1.5 based on neutralizing antibody GM values against Omicron BA.1, superiority is evaluated.
- Assuming that the neutralizing antibody seroresponse rate against Omicron BA.1 is 90% in Study P306 and 80% in Study P204, non-inferiority is evaluated the difference in seroresponse rate.

after study vaccination, and these participants were included in the solicited adverse event analysis set. Of the FAS, participants whose immunogenicity data after a booster dose were available and who had no major protocol violations and were not receiving HAART if diagnosed as having HIV were included in the PPIS (467 participants in total; 99 participants 6 months through 1 year of age and 368 participants 2 years through 5 years of age). Participants in the PPIS who had negative pre-booster SARS-CoV-2 status were included in the PPIS-Neg (319 participants in total; 71 participants 6 months through 1 year of age and 248 participants 2 years through 5 years of age). The primary analysis population for immunogenicity was the PPIS-Neg.

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 co-primary immunogenicity endpoints were the GM value of neutralizing antibodies against Omicron BA.1 (PsVNA, 50% inhibitory dilution) and the seroresponse rate at 28 days post-booster dose, as well as the GM value of neutralizing antibodies against the original strain (PsVNA, 50% inhibitory dilution) and the seroresponse rate at 28 days post-booster dose. For the co-primary endpoints, superiority or non-inferiority of the results at 28 days post-booster dose to the results[17)] for the primary series with the monovalent (Original) vaccine 25 µg at Day 57 (28 days post-second dose) in the same age group (6 months through 5 years of age) in Study P204 was evaluated. Seroresponse was defined as a ≥4-fold rise in neutralizing antibody titers from the pre-first primary series dose (if neutralizing antibody pre-first primary series dose was below the LLOQ, a ≥4-fold rise from LLOQ). The criteria for establishing superiority and non-inferiority are as presented below. When all 4 criteria were met, efficacy was to be demonstrated.

- The lower bound of the two-sided 95% CI for GMR (Study P306 [28 days post-booster dose, 6 months through 5 years of age] / P204 [Day 57 (28 days post-second dose of the primary series), 6 months through 5 years of age]) based on neutralizing antibody GM values against Omicron BA.1 was >1.0 (superiority)
- The lower bound of the two-sided 95% CI for the difference in neutralizing antibody seroresponse against Omicron BA.1 (Study P306 [28 days post-booster dose, 6 months through 5 years of age] minus Study P204 [Day 57 (28 days post-second dose of the primary series), 6 months through 5 years of age]) was >−5% (non-inferiority)
- The lower bound of the two-sided 95% CI for GMR (Study P306 [28 days post-booster dose, 6 months through 5 years of age] / Study P204 [Day 57 (28 days post-second dose of the primary series), 6 months through 5 years of age] based on neutralizing antibody GM values against the original strain was >0.667 (non-inferiority)
- The lower bound of the two-sided 95% CI for the difference in neutralizing antibody seroresponse against the original strain (Study P306 [28 days post-booster dose, 6 months through 5 years of age] minus Study P204 [Day 57 (28 days post-second dose of the primary series), 6 months through 5 years of age] was >−10% (non-inferiority)

17) Of the PPIS, those who were pre-first primary series dose SARS-CoV-2 negative (PPIS-Neg) were used for analysis.

Table 10 shows the results for the primary immunogenicity endpoints. The lower bound for the two-sided 95% CI of the neutralizing antibody GMR against the original strain and that against Omicron BA.1, and the lower bound for the two-sided 95% CI of the difference in neutralizing antibody seroresponse rate against the original strain or Omicron BA.1 were all greater than the respective superiority or non-inferiority margin, indicating that the results met the prespecified success criteria. The median interval [range] between the second dose of the primary series and the booster dose was 7.85 months [4.0, 12.1].

Table 10. Serum neutralizing antibody titers and seroresponse rates against Omicron BA.1 and against the original strain (Study P306 Part 2, PPIS-Neg)

		Omicron BA.1		Original strain	
		P306	P204	P306	P204
		Monovalent (Original) Primary series 25 µg + Bivalent (Original/BA.1) Booster 10 µg N = 319	Monovalent (Original) Primary series 25 µg N = 590	Monovalent (Original) Primary series 25 µg + Bivalent (Original/BA.1) Booster 10 µg N = 319	Monovalent (Original) Primary series 25 µg N = 590
GMC					
Pre-first primary series	n	309	347	311	575
	GMC [two-sided 95% CI][b)]	4.1 [4.1, 4.2]	5.4 [5.1, 5.7]	5.3 [5.2, 5.4]	7.7 [7.4, 8.0]
28 days post-study dose[a)]	n	309	380	311	557
	GMC [two-sided 95% CI][b)]	788.4 [704.0, 883.0]	65.7 [60.6, 71.3]	4729.1 [4299.6, 5201.6]	1559.4 [1459.2, 1666.6]
	N1	309	244	311	548
	GMFR from pre-primary series [two-sided 95% CI][b)]	191.0 [170.5, 213.9]	12.2 [11.0, 13.7]	891.7 [808.9, 983.0]	202.8 [188.3, 218.4]
Pre-booster dose	n	311		318	
	GMC [two-sided 95% CI][b)]	36.3 [33.1, 39.8]		354.6 [328.4, 382.8]	
28 days post-study dose[a)]	n	313	380	315	557
	GMC [two-sided 95% CI][b)]	792.1 [708.1, 886.1]	65.7 [60.6, 71.3]	4734.1 [4308.9, 5201.2]	1559.4 [1459.2, 1666.6]
	N1	306		314	
	GMFR from pre-booster dose [two-sided 95% CI][b)]	21.9 [19.8, 24.3]		13.2 [12.1, 14.5]	
	GLSM [two-sided 95% CI][c)]	792.1 [716.5, 875.6]	65.7 [60.0, 72.0]	4734.1 [4328.0, 5178.4]	1559.4 [1457.7, 1668.3]
	GMR (P306/P204) [two-sided 95% CI][c)]	12.052 [10.526, 13.799]		3.036 [2.714, 3.396]	
Seroresponse rate					
n1/N1		306/309	210/244	311/311	545/548
Seroresponse rate [two-sided 95%CI][d)] (%)		99.0 [97.2, 99.8]	86.1 [81.1, 90.2]	100 [98.8, 100.0]	99.5 [98.4,99.9]
Seroresponse rate difference (P306−P204) [two-sided 95%CI][e)] (%)		13.0 [8.9, 18.0]		0.5 [−0.7, 1.6]	

Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the ULOQ were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 8-41984 (Omicron BA.1), 10-4505600 (original strain)

N = number of participants evaluated; N1 = number of participants with non-missing data before the primary series and at the time of evaluation; n = number of participants with non-missing data at the time point of evaluation;

n1 = number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ)

a) Study P306: 28 days post-booster dose; Study P204: Day 57 (28 days post-second dose of the primary series)
b) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or log-transformed values for the fold rise in antibody titer
c) An analysis of covariance model with the antibody titer at 28 days post-booster dose in Study P306 or at Day 57 in Study P204 as a dependent variable, and the group variable (bivalent vs. monovalent) as an explanatory variable, with adjustment for age group (6 months through 1 year of age vs. 2 years through 5 years of age)
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 with adjustment for age group

The safety follow-up periods were as follows:

- Solicited adverse events[7] (local events [pain, erythema/redness, swelling/induration, lymphadenopathy[8] and systemic events [fever ≥38°C, irritability/crying, sleepiness, and poor appetite for children 6 through 36 months of age; fever ≥38°C, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills for children 37 months through 5 years of age]): through 7 days after study vaccination (reported in the participant diary by parents/guardians)
- Unsolicited adverse events (excluding solicited adverse events that occurred during the 7 days after study vaccination): through 28 days after study vaccination
- Serious adverse events, acute myocarditis, or pericarditis,[9] AESI,[10] MAAE: after study vaccination throughout the entire study period

Table 11 shows solicited adverse events through 7 days after study vaccination.

Table 11. Incidence of solicited adverse events through 7 days after study vaccination (Study P306 Part 2, solicited adverse event analysis set)

Event		N = 539		
		N1	All Grades n (%)	Grade ≥3 n (%)
Local	Any local adverse event	539	269 (49.9)	6 (1.1)
	Pain	539	243 (45.1)	3 (0.6)
	Erythema/redness	539	35 (6.5)	2 (0.4)
	Swelling/induration	539	31 (5.8)	3 (0.6)
	Lymphadenopathy[a]	539	34 (6.3)	0
Systemic	Any systemic adverse event	539	265 (49.2)	13 (2.4)
	Fever[b]	539	39 (7.2)	3 (0.6)
	Headache	274	39 (14.2)	3 (1.1)
	Fatigue	274	88 (32.1)	5 (1.8)
	Myalgia	274	34 (12.4)	1 (0.4)
	Arthralgia	274	25 (9.1)	1 (0.4)
	Nausea/vomiting	275	22 (8.0)	1 (0.4)
	Chills	274	16 (5.8)	0
	Irritability/crying	228	121 (53.1)	3 (1.3)
	Sleepiness	228	47 (20.6)	0
	Poor appetite	228	52 (22.8)	1 (0.4)

N = number of participants evaluated; N1 = number of participants who provided the event data; n= number of participants who experienced the event

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

b) For children 6 through 36 months of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-39.5°C; Grade 3, 39.6°C-40.0°C; Grade 4, >40.0°C (tympanic temperature);
For children 37 months through 5 years of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-38.9°C; Grade 3, 39.0°C-40.0°C; Grade 4, >40.0°C

The incidences of unsolicited adverse events through 28 days after study vaccination and those classified as adverse reactions were 22.4% (121 of 539 participants) and 2.4% (13 of 539 participants), respectively. There were no Grade ≥3 events. Adverse events occurring in ≥1% were upper respiratory tract infection (5.8%, 31 participants), otitis media (1.9%, 10 participants), fever (1.7%, 9 participants), rhinorrhoea (1.5%, 8 participants), and COVID-19 (1.1%, 6 participants). There were no adverse reactions occurring in ≥1% of participants.

No deaths or adverse events leading to study discontinuation were reported up to the data cut-off date (March 21, 2023).

No serious adverse events were reported within 28 days of study vaccination. The following serious adverse events occurred in 9 of 539 participants (1.7%) beyond 28 days post-booster dose up to the data cut-off date (March 21, 2023) (respiratory syncytial virus bronchiolitis [2 participants]; otitis media/pneumonia,

parainfluenzae virus infection, respiratory syncytial virus infection, dehydration, cerebellar ataxia, febrile convulsion, adenoidal hypertrophy [1 participant each]). These events were considered unrelated to the study vaccine, and their outcomes were reported "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 Spikevax as a booster dose (0.25 mL/dose [mRNA of 25 μg]) in children 6 months through 4 years of age:

In Japan, Spikevax was approved for the prevention of disease caused by SARS-CoV-2 infection (COVID-19): for vaccine products other than the monovalent (Original) vaccine, 0.5 mL/dose in individuals 12 years of age and older, 0.25 mL/dose in children 5 years of age and older but younger than 12 years of age, and 2 doses of 0.25 mL/dose for the primary series in children 6 months of age and older but younger than 5 years of age. Previously, Spikevax had been approved for the primary series and as a booster dose in individuals ≥6 years of age. In April 2024, however, the dosage regimens for individuals ≥5 years of age were simplified in accordance with the "Modification in the Description of Dosage and Administration for SARS-CoV-2 Vaccines (in Japanese)" (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1, dated March 6, 2024). The "Dosage and Administration" section was revised so that there are two age groups "5 years of age and older but younger than 12 years of age" and "6 months of age and older but younger than 5 years of age." Under the circumstances described above, although the applicant filed a partial change application to add the use as a booster dose (0.25 mL/dose [mRNA of 25 μg]) for children 6 months of age and older but younger than 5 years of age (i.e., 6 months through 4 years of age), the age group of participants in the clinical studies included in the clinical data package is "6 months of age and older but younger than 6 years of age" (i.e., 6 months through 5 years of age).

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, after obtaining safety and efficacy data for adults, the intended populations were shifted sequentially to younger age groups. The FDA guidance documents on COVID-19 vaccine development[18)19)] were used as references, and an immunobridging approach was adopted to evaluate the efficacy of Spikevax. This approach was used to assess whether the immune response to the vaccine product in a target population was comparable to that observed in another population in which the efficacy of the vaccine product (vaccine efficacy in preventing COVID-19) had already been demonstrated in clinical studies.

The pivotal clinical data for the present application consist of data from studies that evaluated the monovalent (Original) or bivalent (Original/BA.1) as a booster dose: data on booster dose from Study P204 Part 1 and data from Study P306 Part 2. These data demonstrate that a booster dose enhances vaccine efficacy in adults. Accordingly, to facilitate an evaluation, the protocol of Study P204 was amended (Protocol Amendment 7, February 18, 2022) to allow all participants in Part 1 and children 6 years through 11 years of age in Part 2 to

18) Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2023)
19) Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19 (March 31, 2022)

be offered a booster dose with the monovalent (Original) vaccine at least 6 months after the second dose of the primary series. The dosage regimens for the booster dose were a single dose of the monovalent (Original) vaccine 25 µg for children 6 years through 11 years of age and a single dose of the monovalent (Original) vaccine 10 µg for children 6 months through 5 years of age. The dosage of the booster dose was determined based on the child's age at the time the booster dose was administered. The monovalent (Original) vaccine 25 µg was administered to children who had been enrolled in the study in the age group of 2 years through 5 years of age but turned 6 years old at the time of receiving a booster dose. The efficacy of the monovalent (Original) vaccine as a booster dose was evaluated using the non-inferiority criteria by comparing the immune response at 28 days after administration of a 10 µg booster dose in children 6 months through 5 years of age in Study P204 Part 1 with the immune response at Day 57 (28 days post-second dose of the primary series) in participants 18 through 25 years of age in Study P301, which evaluated vaccine efficacy in the prevention of COVID-19 in individuals aged ≥18 years. In accordance with the amendment of the protocol (Protocol Amendment 9, [redacted], 20[redacted]), all participants in all age groups in Part 1 and Part 2 who had not yet received a booster dose were to be offered a booster dose with the bivalent (Original/BA.1) vaccine, instead of the monovalent (Original) vaccine. To date, no immunogenicity evaluation has been conducted in participants who received the bivalent (Original/BA.1) vaccine as a booster dose.

To evaluate the bivalent (Original/BA.1) vaccine as a booster dose, participants 6 months through 5 years of age who had received the monovalent (Original) vaccine for the primary series in Study P204 were enrolled in Study P306 Part 2, in which a single dose of the bivalent (Original/BA.1) vaccine 10 µg was administered at ≥4 months after the second dose of the primary series. The efficacy as a booster dose was evaluated using non-inferiority criteria by comparing the immune response at 28 days post-booster dose with the bivalent (Original/BA.1) vaccine with the immune response at Day 57 (28 days post-second dose of the primary series) with the monovalent (Original) vaccine in the same age group in Study P204.

Since the results met the success criteria in both Study P204 Part 1 and Study P306 Part 2, a booster dose with the monovalent (Original) vaccine 10 µg or the bivalent (Original/BA.1) vaccine 10 µg can also be effective in children 6 months through 5 years of age [see Sections 7.2, 7.3, and 7.R.2]. In addition, no serious safety concerns were raised in either of the studies, demonstrating acceptable tolerability [see Section 7.R.3].

The booster dosage regimens for children 6 months through 5 years of age in Study P204 Part 1 and that in Study P306 Part 2 differ from the dosage regimen in the present application (0.25 mL/dose [mRNA of 25 µg]). This adjustment reflects efforts to simplify the vaccination schedule in the US and Europe by aligning the primary series and booster doses. Accordingly, the dosage of Spikevax as a booster dose for children 6 months through 4 years of age is defined as 25 µg, rather than 10 µg, which was the dosage used in the clinical studies. No clinical data have been obtained to date from studies in which 25 µg was administered as a booster dose to children 6 months through 4 years of age. However, The efficacy of Spikevax as a 25 µg booster dose in children 6 months through 4 years of age should be comparable or higher than the efficacy of a 10 µg booster dose [see Section 7.R.5]. The currently available clinical study data also show that the dosage regimen is safe [see Section 7.R.3]; therefore, a dose of 0.25 mL (mRNA of 25 µg) was selected as the booster dose.

The phase I/II Japanese study in Japanese participants ≥20 years of age (Study TAK-919-1501) has demonstrated the immunogenicity and safety of Spikevax in Japanese recipients. In addition, 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 April 5, 2021) states that if foreign clinical studies has demonstrated that the immunogenicity of variant-adapted vaccines is comparable to that of the parent vaccine, and if immunogenicity and safety have been confirmed in Japanese clinical studies at the time of marketing approval for the parent vaccine, no additional Japanese clinical studies are required. Therefore, no Japanese clinical studies in children were planned in the development of the booster dosage regimen for children 6 months through 5 years of age in Japan.

Accordingly, the applicant filed the present application based on the immunogenicity and safety result data from Study P204 Part 2 (primary series), Study P204 Part 1 (booster dose), and Study P306 Part 2.

PMDA's view:
According to the FDA's "Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19 for Use in Pediatric Populations," 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. In addition, 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). Therefore, 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. In Japan, the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1): Evaluation of Vaccines Against Variants" outlines the method that can be used to evaluate the efficacy of variant-adapted vaccination as a booster dose. This involves comparing the immune response to a variant-adapted vaccine as a booster dose with the immune response to the parent vaccine (approved SARS-CoV-2 vaccine) for the primary series. The "Consideration for Evaluation of SARS-CoV-2 Vaccine (Appendix 3): Consideration for Evaluation of SARS-CoV-2 Vaccine Based on Immunogenicity" (Office of Vaccines and Blood Products, PMDA, dated on October 22, 2021) states that it has gradually become clear that there is a correlation between the neutralizing antibody titer after SARS-CoV-2 vaccination and the vaccine's efficacy in preventing COVID-19 (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11). In this context, it also shows that an immunobridging approach can be employed to evaluate the efficacy of a vaccine based on a measure of immunogenicity, and suggests the possibility of conducting an efficacy evaluation using an immunobridging approach based on data from a study which evaluated efficacy in different age groups. The document, "Principles for the Evaluation of Vaccine Against the Novel Coronavirus SARS-CoV-2 (Appendix 4): Immunogenicity-based evaluation of variant vaccines modified from parent vaccines and booster vaccines with new active ingredients" (Office of Vaccines and Blood Products, PMDA, dated July 15, 2022) outlines key considerations when applying an immunogenicity-based efficacy evaluation, which is described in the "Consideration for Evaluation of SARS-CoV-2 Vaccine (Appendix 3):

Consideration for Evaluation of SARS-CoV-2 Vaccine Based on Immunogenicity," to a vaccine product containing a new active ingredient to be developed for use as a booster dose.

In view of the above guidance documents and reports, PMDA concluded, as stated by the applicant, that the efficacy of Spikevax as a booster dose in children 6 months through 4 years of age can be evaluated based on the results of the following studies: (1) Study P204 Part 1, which evaluated the efficacy of the monovalent (Original) vaccine as a booster dose in children 6 months through 5 years of age by comparison with the immune response in the age group for which vaccine efficacy in preventing COVID-19 has been confirmed; and (2) Study P306 Part 2, which evaluated the bivalent (Original/BA.1) vaccine as a booster dose in children 6 months through 5 years of age by comparison with the immune response elicited after the primary series with the monovalent (Original) vaccine. However, because no clinical study result data for the proposed booster dose of 25 μg have yet been obtained, selection of the dosage regimen will be discussed in Section 7.R.5. For the evaluation of safety, the results for a 10 μg booster dose in Study P204 Part 1 and Study P306 Part 2, the pivotal studies on booster doses, as well as the results for the primary series in Study P204 Part 2 (pre-primary series SARS-CoV-2 positive result [prior SARS-CoV-2 infection] group) submitted as safety data after repeated 25 μg vaccination were assessed.

7.R.2 Efficacy

The applicant's explanation about the efficacy of Spikevax as a booster dose in children 6 months through 4 years of age:

To evaluate the efficacy (immunogenicity) of Spikevax as a booster dose in children 6 months through 5 years of age, data from Study P204 Part 1, which used the monovalent (Original) vaccine, and Study P306 Part 2, which used the bivalent (Original/BA.1) vaccine.

The immune response at 28 days post-booster dose, the primary endpoint for the evaluation of a booster dose in Study P204 Part 1 was compared with the data at Day 57 (28 days post-second dose of the primary series) in the age group of 18 through 25 years in Study P301. Both the lower bound of the two-sided 95% CI of the neutralizing antibody GMR against the original strain and the lower bound of the two-sided 95% CI of difference in seroresponse rate were greater than the non-inferiority margins, indicating that the study results met the prespecified success criteria for non-inferiority [see Section 7.2]. The demographics and baseline characteristics of the group in Study P204 Part 1 were similar to those of the group in Study P301 (control) except for body weight, race, and ethnicity (Table 12). In Study P301, the percentage of participants identified as "Hispanic or Latino" and the percentage of non-White individuals were higher in Study P301 than in the group in Study P204 Part 1. However, the subgroup analysis of Study P204 Part 1 revealed no substantial difference in immune response by race or ethnicity; therefore, it is possible to compare data between these studies.

Table 12. Comparison of demographics and baseline characteristics (Study P204 Part 1, PPIS-Neg)

		P204 Part 1 Booster (6 months-5 years of age)	P301 primary series (18-25 years of age)
		Monovalent (Original) 10 µg N = 76	Monovalent (Original) 100 µg N = 296
		n (%)	n (%)
Sex	Male	40 (52.6)	143 (48.3)
	Female	36 (47.4)	153 (51.7)
Race	White	62 (81.6)	207 (69.9)
	Black or African American	1 (1.3)	29 (9.8)
	Asian	4 (5.3)	30 (10.1)
	Multiracial	6 (7.9)	14 (4.7)
	Other[a)]/unknown	3 (3.9)	16 (5.4)
Ethnicity	Hispanic or Latino	7 (9.2)	78 (26.4)
	Not Hispanic or Latino	69 (90.8)	216 (73.0)
	Unknown	0	2 (0.7)
Body weight (kg)	Median (Min, Max)	11.36 (6.6, 19.5)	73.60 (44.0, 158.2)

N = number of participants evaluated; n = number of participants in the category
a) American Indian, Alaskan Native, Native Hawaiian, and other

Table 13 shows the evaluation results for the primary endpoints in Study P204 Part 1 by pre-booster dose SARS-CoV-2 status. The pre-booster dose serum neutralizing antibody GMC was higher in the SARS-CoV-2 positive group than in the SARS-CoV-2 negative group; however, serum neutralizing antibody titers increased in participants with positive pre-booster dose SARS-CoV-2 status after receiving a booster dose. Therefore, the results show that a booster dose increases serum neutralizing antibody titers regardless of pre-booster dose SARS-CoV-2 status (history of prior SARS-CoV-2 infection).

Table 13. Serum neutralizing antibody titers against the original strain by pre-booster dose SARS-CoV-2 status (Study P204 Part 1, PPIS)

Pre-booster SARS-CoV-2 status		Negative N = 76	Positive N = 20
GMC			
Pre-first dose of the primary series	n	72	18
	GMC [two-sided 95% CI]	9.8 [8.8, 10.9]	8.7 [6.9, 11.0]
Pre-booster dose	n	72	18
	GMC [two-sided 95% CI]	340.6 [283.7, 408.8]	3474.3 [1857.8, 6497.2]
28 days post-booster dose	n	76	20
	GMC [two-sided 95% CI]	5457.2 [4525.7, 6580.3]	11327.7 [8578.2, 14958.4]
GMFR (28 days post-booster / pre-booster dose)	N1	72	18
	GMFR [two-sided 95% CI]	15.8 [12.8, 19.4]	3.1 [1.9, 5.0]
Seroresponse rate			
n1/N1		72/72	18/18
Seroresponse rate [two-sided 95% CI] (%)		100 [95.0, 100.0]	100 [81.5, 100.0]

Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the ULOQ were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 10-111433
N = number of participants evaluated; N1 = number of participants with non-missing data before the booster dose and at the time of evaluation; n = number of participants with non-missing data at the time point of evaluation; n1 = number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ)

The results for the immune response at 28 days post-booster dose in Study P306 Part 2, the primary endpoint, were compared with the results at Day 57 (28 days post-second dose of the primary series) in the same age group (6 months through 5 years of age) in Study P204. Both the lower bound of the two-sided 95% CI of the neutralizing antibody GMR against Omicron BA.1 and that against the original strain were greater than the superiority and non-inferiority margins, and the differences in the neutralizing antibody seroresponse rate against the original strain and that against Omicron BA.1 were both greater than the non-inferiority margins, indicating that the results met the prespecified success criteria [see Section 7.3]. The demographics and baseline characteristics of the group in Study P306 Part 2 were similar to those of the group in Study P204 (control) except for age (Table 14).

Table 14. Comparison of demographics and baseline characteristics (Study P306 Part 2, PPIS-Neg)

		P306 Part 2 Bivalent (Original/BA.1) 10 µg N = 319	P204 Monovalent (Original) 25 µg N = 590
		n (%)	n (%)
Sex	Male	166 (52.0)	301 (51.0)
	Female	153 (48.0)	289 (49.0)
Race	White	259 (81.2)	434 (73.6)
	Black or African American	8 (2.5)	37 (6.3)
	Asian	13 (4.1)	33 (5.6)
	Multiracial	35 (11.0)	65 (11.0)
	Other[a)]/unknown	4 (1.3)	21 (3.6)
Ethnicity	Hispanic or Latino	33 (10.3)	104 (17.6)
	Not Hispanic or Latino	286 (89.7)	483 (81.9)
	Unknown	0	3 (0.5)
Body weight (kg)	Median (Min, Max)	15.09 (8.4, 31.1)	13.23 (7.0, 34.8)
Age (years)	Median (Min, Max)	3 (0.9, 5.0)	2 (0.5, 5.0)

N = number of participants evaluated; n = number of participants in the category

a) American Indian, Alaskan Native, Native Hawaiian, and other

Table 15 shows the evaluation results for the primary endpoints in Study P306 Part 2 by pre-booster SARS-CoV-2 status. The results show that a booster dose with the bivalent (Original/BA.1) vaccine increases neutralizing antibody titers regardless of pre-booster SARS-CoV-2 status.

Table 15. Serum neutralizing antibody titers against Omicron BA.1 or the original strain by pre-booster SARS-CoV-2 status (Study P306 Part 2, PPIS)

		Omicron BA.1		Original strain	
Pre-booster SARS-CoV-2 status		Negative N = 319	Positive N = 148	Negative N = 319	Positive N = 148
GMC					
Pre-first dose of the primary series	n	309	103	311	110
	GMC [two-sided 95% CI][a)]	4.1 [4.1, 4.2]	4.2 [4.0, 4.3]	5.3 [5.2, 5.4]	5.6 [5.3, 6.0]
Pre-booster dose	n	311	138	318	142
	GMC [two-sided 95% CI][a)]	36.3 [33.1, 39.8]	423.5 [351.4, 510.3]	354.6 [328.4, 382.8]	1731.7 [1458.0, 2056.9]
28 days post-booster dose	n	313	137	315	145
	GMC [two-sided 95% CI][a)]	792.1 [708.1, 886.1]	2179.7 [1903.0, 2496.6]	4734.1 [4308.9, 5201.2]	6930.0 [6205.9, 7738.6]
GMFR (28 days post-booster / pre-booster dose)	N1	306	128	314	139
	GMFR [two-sided 95% CI][a)]	21.9 [19.8, 24.3]	5.5 [4.6, 6.6]	13.2 [12.1, 14.5]	4.2 [3.6, 4.8]
Seroresponse rate					
n1/N1		306/309	103/103	311/311	108/108
Seroresponse rate [two-sided 95% CI][b)] (%)		99.0 [97.2, 99.8]	100 [96.5, 100.0]	100 [98.8, 100.0]	100 [96.6, 100.0]

Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the ULOQ were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 8-41984 (Omicron BA.1), 10-4505600 (original strain)

N = number of participants evaluated; N1 = number of participants with non-missing data before the booster dose and at the time of evaluation; n = number of participants with non-missing data at the time point of evaluation;

n1 = number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ)

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values for antibody titers or log-transformed values for the fold rise in antibody titer

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

In view of successful immunobridging between the immune response after a booster dose in children 6 months through 5 years of age in Study P204 Part 1 and the immune response after the primary series in participants 18 years through 25 years of age in Study P301, it is inferred that vaccine efficacy in preventing COVID-19 acquired by the primary series in adults can also be acquired by means of a booster dose in children 6 months through 5 years of age. In addition, the results of the immune response post-booster dose with the bivalent (Original/BA.1) vaccine in Study P306 Part 2 in comparison with the immune response post-primary series with the monovalent (Original) vaccine in the same age group in Study P204, as well as results from clinical studies of various variant-adapted vaccines conducted in the past, suggest that efficacy comparable to that of

the monovalent (Original) vaccine can also be achieved by a booster dose with a variant-adapted vaccine. Based on the results by pre-booster SARS-CoV-2 status, similar efficacy can also be expected in children with a history of SARS-CoV-2 infection prior to booster dose, a population that is expected to grow further going forward.

PMDA's view:
In the evaluation of efficacy of a booster dose in children 6 months through 5 years of age, the success criteria were met for immunobridging between the immune response post-booster dose with the monovalent (Original) vaccine in children 6 months through 5 years of age in Study P204 Part 1 and the immune response post-primary series with the monovalent (Original) vaccine in participants 18 years through 25 years of age in Study P301 as a control; and the neutralizing antibody titers increased after administration of the monovalent (Original) vaccine as a booster dose regardless of pre-booster SARS-CoV-2 status. Therefore, the efficacy of the monovalent (Original) vaccine as a booster dose in children 6 months through 5 years of age can also be expected. In the evaluation of the immune response post-booster dose with the bivalent (Original/BA.1) vaccine in children 6 months through 5 years of age in Study P306 Part 2 compared with the immune response post-primary series with the monovalent (Original) vaccine in the same age group in Study P204 as a control, the success criteria were met, and the neutralizing antibody titers increased after administration of the bivalent (Original/BA.1) vaccine as a booster dose regardless of pre-booster SARS-CoV-2 status. Therefore, the efficacy of the bivalent (Original/BA.1) vaccine 10 μg as a booster dose in children 6 months through 5 years of age who have already received 2 doses of 25 μg for the primary series can be expected. Based on these results, The dosage of 25 μg selected for a booster dose will be discussed in Section 7.R.5.

Although no clinical study data have yet been obtained for Spikevax as a booster dose in Japanese children 6 months through 4 years of age, the efficacy of the monovalent (Original) vaccine 10 μg or the bivalent (Original/BA.1) vaccine 10 μg as a booster dose can also be expected in Japanese children 6 months through 4 years of age given the fact that the immune responses observed in a Japanese clinical study conducted during the development stage of Spikevax for the primary series in adults, were similar to those in foreign clinical studies (Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated May 17, 2021), as well as the results from Study P204 Part 1 and Study P306 Part 2.

The clinical study data submitted for the present application are the result data after administration of the monovalent (Original) vaccine or the bivalent (Original/BA.1) vaccine. Given the circumstances where SARS-CoV-2 variants continue to emerge, resulting in recurrence of sporadic outbreaks, there is an ongoing need for SARS-CoV-2 vaccines adapted to the variants circulating at any given time. For Spikevax, updates of the antigenic composition based on quality attribute analysis/evaluation, clinical study results and other data have been approved. In addition, the monovalent (XBB.1.5) vaccine 2023-2024 formula and SARS-CoV-2 Omicron JN.1 vaccine 2024-2025 formula have been approved as vaccine products that are highly unlikely to be adversely affected in terms of the quality and safety by updating of the antigenic composition, and their immunogenicity can be predicted based on non-clinical studies. It is expected that updating of the antigenic composition for a vaccine will continue by obtaining the quality study data and non-clinical study data in

accordance with the "Regarding the Handling of Changes to COVID-19 Vaccine Strains" (PSB/PMDA Notification No. 0523-1 and PSB/CND Notification No. 0523-3, dated May 23, 2024). As mentioned above, the results from Study P306 Part 2 showed that the neutralizing antibody titers increased after a booster dose with the variant-adapted bivalent (Original/BA.1) vaccine, indicating that the vaccine is effective. In addition, the clinical study data currently available suggest the efficacy of the vaccine product, regardless of the age group. Given these results, the efficacy of variant-adapted vaccines can also be expected as a booster dose in children 6 months through 4 years of age as with the case of the approved intended population.

7.R.3 Safety

The applicant's explanation about the safety of Spikevax administered to children 6 months through 4 years of age as a booster dose:

The dosage regimen currently approved for the primary series in children 6 months through 4 years of age is a 2-dose series of 0.25 mL (25 µg each). While the proposed dosage as a booster dose in the present application is 25 µg per dose, no results from a clinical study in which 25 µg was administered as a booster dose to children 6 months through 4 years of age have yet been obtained to date. However, the applicant considers that the discussions in the following sections will support the safety of the dosage of 25 µg in children 6 months through 4 years of age.

(1) Incidence of adverse events in clinical studies

1) Study P204 Part 2 (primary series)

The incidence of solicited local adverse events following the primary series (first or second dose) with the monovalent (Original) vaccine 25 µg in children 6 months through 1 year of age was similar regardless of pre-primary series SARS-CoV-2 status (Table 2). The incidence of solicited local adverse events after the second dose was higher than that after the first dose in both pre-primary series SARS-CoV-2 positive and negative participants. Only a small number of events were classified as Grade 3, and there were no Grade 4 events. The incidence of solicited systemic adverse events was similar in children 6 months through 1 year of age regardless of pre-primary series SARS-CoV-2 status, while the incidence of such adverse events after the first dose was comparable to that after the second dose, except for fever (Table 2). The incidence of fever increased after the second dose compared to that after the first dose in both pre-primary series SARS-CoV-2 positive and negative participants, with the majority being Grade <3.

The incidence of solicited local adverse events following the primary series (first or second dose) with the monovalent (Original) vaccine 25 µg in children 2 years through 5 years of age did not clinically significantly differ between the pre-primary series SARS-CoV-2 positive and negative participants. The incidence of solicited systemic adverse events (after the first or second dose) was similar in children 2 years through 5 years of age regardless of pre-primary series SARS-CoV-2 status (Table 3). The incidence of fever was higher in SARS-CoV-2 positive participants than in SARS-CoV-2 negative participants both after the first dose and after the second dose (13.1% and 8.5% after the first dose in SARS-CoV-2 positive and negative participants, respectively; 20.2% and 16.6% after the second dose in SARS-CoV-2 positive and negative participants, respectively), with the majority being Grade <3.

In both age groups, the incidence of unsolicited adverse events through 28 days after study vaccination shows no clinically significant differences by pre-primary series SARS-CoV-2 status (Table 16).

Table 16. Summary of unsolicited adverse events occurring through 28 days after each dose by pre-primary series SARS-CoV-2 status (Study P204 Part 2, safety analysis set)

	Monovalent (Original) 25 µg		Placebo	
6 months through 1 year of age				
Pre-primary series SARS-CoV-2 status	Negative N = 1767	Positive N = 133	Negative N = 594	Positive N = 47
Unsolicited adverse events	941 (53.3)	69 (51.9)	306 (51.5)	22 (46.8)
Serious	12 (0.7)	0	0	0
MAAE	559 (31.6)	43 (32.3)	180 (30.3)	18 (38.3)
Grade ≥3	25 (1.4)	1 (0.8)	4 (0.7)	0
AESI	5 (0.3)	0	0	0
Unsolicited adverse reactions	310 (17.5)	20 (15.0)	89 (15.0)	5 (10.6)
Serious	1 (<0.1)	0	0	0
MAAE	28 (1.6)	1 (0.8)	7 (1.2)	0
Grade ≥3	13 (0.7)	1 (0.8)	3 (0.5)	0
AESI	2 (0.1)	0	0	0
2 years through 5 years of age				
Pre-primary series SARS-CoV-2 status	Negative N = 2697	Positive N = 267	Negative N = 897	Positive N = 82
Unsolicited adverse events	1121 (41.6)	102 (38.2)	358 (39.9)	31 (37.8)
Serious	2 (<0.1)	1 (0.4)	1 (0.1)	0
MAAE	636 (23.6)	58 (21.7)	223 (24.9)	18 (22.0)
Grade ≥3	20 (0.7)	2 (0.7)	9 (1.0)	0
AESI	4 (0.1)	0	1 (0.1)	0
Unsolicited adverse reactions	264 (9.8)	18 (6.7)	77 (8.6)	7 (8.5)
Serious	0	0	0	0
MAAE	34 (1.3)	1 (0.4)	7 (0.8)	2 (2.4)
Grade ≥3	17 (0.6)	1 (0.4)	8 (0.9)	0
AESI	2 (<0.1)	0	1 (0.1)	0

N = number of participants evaluated;
n = number of participants who experienced the event

2) Study P204 Part 1 (booster dose)

Solicited local or systemic adverse events following the administration of the monovalent (Original) vaccine 10 µg as a booster dose to participants 6 months through 5 years of age who had received 2 doses of the monovalent (Original) vaccine 25 µg for the primary series were generally consistent with the known safety profile of Spikevax administered as a booster dose to older populations. The majority of the events were Grade <3, with a small number of Grade 3 events (3.9%) and Grade 4 events (0.7%, fever in 1 participant). The time to onset of solicited adverse events was generally within 1 to 2 days (median, 1.0 days) of vaccination, while the median duration was 2.0 days.

The incidences of solicited local and systemic adverse events by pre-booster SARS-CoV-2 status are shown in Table 17 and Table 18. The results demonstrated that Spikevax as a booster dose (third dose) was well tolerated regardless of the SARS-CoV-2 status.

Table 17. Incidence of solicited adverse events that occurred during the 7 days after study vaccination by pre-booster SARS-CoV-2 status (6 months through 1 year of age) (Study P204 Part 1, solicited adverse event analysis set)

Pre-booster SARS-CoV-2 status		Negative N = 75		Positive N = 29	
Event		All Grades	Grade ≥3	All Grades	Grade ≥3
		n (%)	n (%)	n (%)	n (%)
Local	Any local adverse event	38 (50.7)	1 (1.3)	13 (44.8)	1 (3.4)
	Pain	34 (45.3)	0	10 (34.5)	0
	Erythema/redness	7 (9.3)	1 (1.3)	5 (17.2)	1 (3.4)
	Swelling/induration	9 (12.0)	1 (1.3)	3 (10.3)	0
	Lymphadenopathy[a)]	4 (5.3)	0	1 (3.4)	0
Systemic	Any systemic adverse event	51 (68.0)	2 (2.6)	18 (62.1)	2 (6.9)
	Fever[b)]	8 (10.8)*	1 (1.4)	3 (10.3)	2 (6.9)
	Irritability/crying	42 (56.0)	0	14 (48.3)	0
	Sleepiness	23 (30.7)	1 (1.3)	7 (24.1)	0
	Poor appetite	21 (28.0)	0	7 (24.1)	0

N = number of participants evaluated; n = number of participants who experienced the event; *, 74 participants were analyzed
a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site
b) Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-39.5°C; Grade 3, 39.6°C-40.0°C; Grade 4, >40.0°C (tympanic temperature)

Table 18. Incidence of solicited adverse events that occurred during the 7 days after study vaccination by pre-booster SARS-CoV-2 status (2 years through 5 years of age) (Study P204 Part 1, solicited adverse event analysis set)

Pre-booster SARS-CoV-2 status		Negative		Positive	
Event		All Grades	Grade ≥3	All Grades	Grade ≥3
		n (%)	n (%)	n (%)	n (%)
Local	2 years through 5 years of age	N=23		N=6	
	Any local adverse event	15 (65.2)	0	3 (50.0)	0
	Pain	14 (60.9)	0	3 (50.0)	0
	Erythema/redness	1 (4.3)	0	0	0
	Swelling/induration	3 (13.0)	0	0	0
	Lymphadenopathy[a]	1 (4.3)	0	0	0
Systemic	2 years through 36 months of age	N=5		N=1	
	Any systemic adverse event	3 (60.0)	0	1 (100.0)	0
	Fever[b)]	0	0	0	0
	Irritability/crying	3 (60.0)	0	1 (100.0)	0
	Sleepiness	2 (40.0)	0	0	0
	Poor appetite	1 (20.0)	0	0	0
	37 months through 5 years of age	N=18		N=5	
	Any systemic adverse event	11 (61.1)	1 (5.6)	0	0
	Fever[b)]	1 (5.6)	1 (5.6)	0	0
	Headache	4 (22.2)	0	0	0
	Fatigue	7 (38.9)	0	0	0
	Myalgia	3 (16.7)	0	0	0
	Arthralgia	2 (11.1)	0	0	0
	Nausea/vomiting	0	0	0	0
	Chills	2 (11.1)	0	0	0

N = number of participants evaluated; n = number of participants who experienced the event;
a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site
b) For children 37 months through 5 years of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-38.9°C; Grade 3, 39.0°C-40.0°C; Grade 4, >40.0°C; For children 2 years through 36 months of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-39.5°C; Grade 3, 39.6°C-40.0°C; Grade 4, >40.0°C (oral temperature for children >4 years of age; tympanic temperature for children ≤4 years of age)

Overall, the incidence of unsolicited adverse events through 28 days after the booster dose was low (Table 9), with no Grade ≥3 events. Many of the reported events reflected respiratory infections and related symptoms typically observed in this age group. Up to the data cut-off date, there were no reports of adverse events leading to study discontinuation, MIS-C, study vaccine-associated serious adverse events, or study vaccine-associated AESI. No myocarditis or pericarditis occurred. Beyond 28 days post-booster dose, epilepsy and erythema multiforme (1 event each), both classified as AESI, were reported, and these events were considered unrelated to the study vaccine. Serious adverse events (2 events in 1 participant; pharyngeal abscess and streptococcal infection) occurred beyond 28 days post-booster dose, and these events were considered unrelated to the study vaccine, with the outcomes reported as “resolved.” Overall, reported events were consistent with the known safety profile of Spikevax. The incidence of unsolicited adverse events through 28 days after the booster dose shows no clinically significant difference by pre-booster SARS-CoV-2 status (Table 19).

Table 19. Summary of unsolicited adverse events occurring through 28 days after the booster dose by pre-booster SARS-CoV-2 status (Study P204 Part 1, safety analysis set)

	6 months through 1 year of age		2 years through 5 years of age	
Pre-booster dose SARS-CoV-2 status	Negative N = 75	Positive N = 29	Negative N = 23	Positive N = 6
	n (%)	n (%)	n (%)	n (%)
Unsolicited adverse events	24 (32.0)	2 (6.9)	5 (21.7)	3 (50.0)
Serious	0	0	0	0
MAAE	11 (14.7)	0	4 (17.4)	1 (16.7)
Unsolicited adverse reactions	3 (4.0)	0	1 (4.3)	1 (16.7)
Serious	0	0	0	0
MAAE	0	0	0	0

N = number of participants evaluated; n = number of participants who experienced the event

3) Study P306 Part 2 (booster dose)

A booster dose with the bivalent (Original/BA.1) vaccine was administered to participants who had received 2 doses of the monovalent (Original) vaccine 25 μg for the primary series. The majority of the solicited local and systemic adverse events were Grade 1 or 2, with a small number of events classified as Grade 3 (3.5% in total) and no Grade 4 events (Table 11). The time to onset of solicited adverse events was generally within 1 to 2 days and the duration was 1 day for the majority of events.

Table 20 shows the incidence of solicited local and systemic adverse events by pre-booster SARS-CoV-2 status. The results demonstrated that Spikevax as a booster dose (third dose) was well tolerated regardless of pre-booster SARS-CoV-2 status.

Table 20. Incidence of solicited adverse events by pre-booster SARS-CoV-2 status (Study P306 Part 2, solicited adverse event analysis set)

Pre-booster SARS-CoV-2 status		Negative N = 353		Positive N = 170	
Event		All Grades	Grade ≥3	All Grades	Grade ≥3
		n (%)	n (%)	n (%)	n (%)
Local	6 months through 5 years	N1 = 353		N1 = 170	
	Any local adverse event	176 (49.9)	4 (1.1)	86 (50.6)	2 (1.2)
	Pain	159 (45.0)	2 (0.6)	80 (47.1)	1 (0.6)
	Erythema/redness	24 (6.8)	2 (0.6)	9 (5.3)	0
	Swelling/induration	21 (5.9)	2 (0.6)	7 (4.1)	1 (0.6)
	Lymphadenopathy[a)]	25 (7.1)	0	8 (4.7)	0
Systemic		N1 = 353		N1 = 170	
	Any systemic adverse event	175 (49.6)	6 (1.7)	83 (48.8)	7 (4.1)
	Fever[b)]	23 (6.5)	1 (0.3)	15 (8.8)	2 (1.2)
		N1 = 148		N1 = 72	
	Irritability/crying	83 (56.1)	2 (1.4)	33 (45.8)	1 (1.4)
	Sleepiness	38 (25.7)	0	7 (9.7)	0
	Poor appetite	38 (25.7)	1 (0.7)	14 (19.4)	0
		N1 = 177		N1 = 91	
	Headache	23 (13.0)	1 (0.6)	15 (16.5)	2 (2.2)
	Fatigue	55 (31.1)	1 (0.6)	31 (34.1)	4 (4.4)
	Myalgia	20 (11.3)	1 (0.6)	13 (14.3)	0
	Arthralgia	13 (7.3)	1 (0.6)	11 (12.1)	0
	Nausea/vomiting	13 (7.3)	0	9 (9.8)*	1 (1.1)
	Chills	11 (6.2)	0	5 (5.5)	0

N = number of participants evaluated; N1 = number of participants who provided the event data; n = number of participants who experienced the event;
* 92 participants provided data
a) Axillary (or inguinal) swelling or tenderness ipsilateral to the injection site
b) For children 37 months through 5 years of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-38.9°C; Grade 3, 39.0°C-40.0°C; Grade 4, >40.0°C; For children 2 years through 36 months of age, Grade 1, 38.0°C-38.4°C; Grade 2, 38.5°C-39.5°C; Grade 3, 39.6°C-40.0°C; Grade 4, >40.0°C (oral temperature for children >4 years of age; tympanic temperature for children ≤4 years of age)

Overall, the incidence of unsolicited adverse events through 28 days after the booster dose was low, with no Grade ≥3 events. Many of the reported events reflected respiratory infections and related conditions typically

observed in children 6 months through 5 years of age. Up to the data cut-off date, there were no reports of deaths or adverse events leading to study discontinuation. Serious adverse events were not reported within 28 days of the booster dose but occurred in 9 of 539 participants (1.7%) beyond 28 days post-booster dose (respiratory syncytial virus bronchiolitis [2 participants]; otitis media/pneumonia, parainfluenzae virus infection, respiratory syncytial virus infection, dehydration, cerebellar ataxia, febrile convulsion, adenoidal hypertrophy [1 participant each]). All of these events were considered unrelated to the study vaccine, with the outcomes reported as "resolved." Up to 28 days post-booster dose, AESI occurred in 1 participant (erythema multiforme),[20)] while beyond 28 days post-booster dose up to the data cut-off date, AESI occurred in 3 participants (febrile convulsion [2 participants] and seizure [1 participant]). Among these events, erythema multiforme was considered related to the study vaccine. No myocarditis, pericarditis, MIS-C, anaphylaxis, or severe hypersensitivity occurred. Table 21 shows the incidence of unsolicited adverse events through 28 days after the booster dose by pre-booster SARS-CoV-2 status, suggesting no clinically significant differences by pre-booster SARS-CoV-2 status.

Table 21. Summary of unsolicited adverse events occurring through 28 days after the booster dose by pre-booster SARS-CoV-2 status (Study P306 Part 2, safety analysis set)

Pre-booster SARS-CoV-2 status	Negative N = 353	Positive N = 170
	n (%)	n (%)
Unsolicited adverse events	77 (21.8)	43 (25.3)
Serious	0	0
MAAE	53 (15.0)	28 (16.5)
AESI	0	1 (0.6)
Unsolicited adverse reactions	6 (1.7)	6 (3.5)
Serious	0	0
MAAE	1 (0.3)	2 (1.2)
AESI	0	1 (0.6)

N = number of participants evaluated;
N = number of participants who experienced the event

4) Results of the clinical study in which Spikevax 25 μg was administered as a booster dose

In Study P204 Part 1, the booster dosage was determined based on the age at the time of booster vaccination. Participants who were in the age group of 2 years through 5 years at enrollment (primary series) but turned 6 years of age prior to booster dose vaccination were to receive 25 μg, the dosage for individuals ≥6 years of age. Nine participants received a single booster dose of the monovalent (Original) vaccine 25 μg after receiving 2 doses of the monovalent (Original) vaccine 25 μg for the primary series.

No Grade ≥3 local or systemic adverse events occurred in these participants. The median time to onset of solicited adverse events was 1.0 days with a median duration of 3.0 days. Unsolicited adverse events occurred in 1 of 9 participants (11.1%) within 28 days of the booster dose and 5 of 9 participants (55.6%) up to the data cut-off date. All these events were non-serious and were considered unrelated to the study vaccine. There were no reports of serious adverse events, AESI, or adverse events leading to study discontinuation. Although the number of participants who received a booster dose (25 μg) after 2 doses (25 μg each) of the primary series with Spikevax was small, overall, there were no safety concerns.

[20)] A girl aged [redacted] years developed the event at 1 day post-study vaccination and recovered 7 days after onset of the event, which was mild in severity. Immediately before the event, to treat bacterial folliculitis, this girl had received sulfadiazine silver, which is known to be associated with erythema multiforme.

Of the 9 participants who received the monovalent (Original) vaccine 25 µg as a booster dose after 2 doses (25 µg each) of the monovalent (Original) vaccine for the primary series, 6 participants were included in the pre-booster SARS-CoV-2 negative population for immunogenicity evaluation. The serum neutralizing antibody GMC [two-sided 95% CI] against the original strain at 28 days post-booster dose in these 6 participants was 6,223.7 [2,801.3, 13,827.2]. This was comparable to the result (5,457.2 [4,525.7, 6,580.3]) in participants who received the monovalent (Original) vaccine 10 µg as a booster dose after 2 doses (25 µg each) of the monovalent (Original) vaccine for the primary series.

(2) Post-marketing safety information

The post-marketing safety information in children 6 months through 5 years of age accrued until September 17, 2024 (database lock) is summarized below. Overall, most events were vaccination-related events associated with no adverse events, and reported reactogenicity events were those already known to occur after vaccination with Spikevax. No new or specific trends were identified among other reported events.

1) Reports on the monovalent (Original) vaccine

A total of 3,945 events in 1,830 recipients (including 214 serious events in 94 recipients) were reported, among which, 1,629 recipients had medically confirmed events and 2 recipients died. Of the reported pediatric cases, 834 recipients (45.6%) were females, 871 recipients (47.6%) were males, and 125 (6.8%) were of unknown sex or not reported, with a mean age of 2.4 years (standard deviation, 1.3). Reports were from Latin America (47.7%), the US (36.9%), the European Economic Area (8.7%), and other regions. Reported preferred terms (PTs) included (descending order) “no adverse event” (563 events), “fever” (533 events), and “vaccination site pain” (499 events). Dose number information was missing in approximately 60% of the reported events. Among reports for which the dose number was known, 824 events occurred after the first dose, 603 events after the second dose, 73 events after the third dose, and 2 events after the fourth dose.

2) Reports on the bivalent (Original/BA.1) vaccine

A total of 21 events in 8 recipients (including 9 serious events in 4 recipients) were reported, among which 3 recipients had medically confirmed events and 1 recipient died. Of the reported pediatric cases, 5 recipients (62.5%) were females, 2 recipients (25.0%) were males, and 1 recipient (12.5%) was of unknown sex or not reported, with a mean age of 1.9 years (standard deviation, 1.4). The majority of reports were from the UK (62.5%) and Canada (37.5%). Reported PTs included “foetal exposure during pregnancy” (2 events) and “product administered to patient of inappropriate age” (2 events). Among the events reported, 2 events occurred after the second dose, 3 events after the fourth dose, and there were 16 events for which the dose number was unknown.

3) Reports on the bivalent (Original.BA.4-5) vaccine

In children 6 months through 1 year of age, a total of 461 events (no serious events) were reported in 188 recipients, among which, 187 recipients had medically confirmed events. Of the reported pediatric cases, 86 recipients (45.7%) were females, 81 recipients (43.1%) were males, and 21 recipients (11.2%) were of unknown sex or not reported, with a mean age of 0.8 years (standard deviation, 0.4). The majority of reports

were from the US (96.8%). Reported PTs included (descending order) “no adverse events” (306 events), “wrong product administered” (161 events), and “expired product administered” (97 events). Most events were vaccination-related issues. Dose number information was missing in approximately half of the reported events. Among reports for which the dose number was known, 120 events occurred after the first dose, 72 events after the second dose, and 16 events after the third dose.

For children 2 years through 5 years of age, a total of 378 events in 155 recipients (including 2 serious events in 2 recipients) were reported, among which 152 recipients had medically confirmed events and 2 recipients died. Of the reported pediatric cases, 61 recipients (39.4%) were females, 66 recipients (42.6%) were males, and 28 recipients (18.1%) were unknown sex or not reported, with a mean age of 3.4 years (standard deviation, 1.1). The majority of reports were from the US (91.0%). Reported PTs included “no adverse events” (136 events), “wrong product administered” (51 events), and “expired product administered” (51 events). Most events were vaccination-related events. Dose number information was missing in approximately 70% of the reported events. Among reports for which the dose number was known, 42 events occurred after the first dose, 43 events after the second dose, 23 events after the third dose, and 2 events after the fourth dose.

4) Reports on the monovalent (XBB.1.5) vaccine

For children 6 months through 1 year of age, a total of 246 events (no serious events) were reported in 101 recipients, among which, 100 recipients had medically confirmed events, and there were no reports of death. Of the reported pediatric cases, 40 recipients (39.6%) were females, 49 recipients (48.5%) were males, 12 recipients (11.9%) were of unknown sex or not reported, with a mean age of 1.0 years (standard deviation, 0.4). Reports were from the US (91.1%), Canada (7.9%), and Japan (1.0%). Reported PTs included (descending order) “no adverse events” (91 events), “expired product administered” (39 events), and “overdose” (21 events). Most events were vaccination-related events. Dose number information was missing in approximately 60% of the reported events. Among reports for which the dose number was known, 52 events occurred after the first dose, 34 events after the second dose, 2 events after the third dose, and 2 events after the fourth dose.

For children 2 years through 5 years of age, a total of 322 events in 139 recipients (including 5 serious events in 4 recipients) were reported, and all were medically confirmed cases. There were no reports of death. Of the reported pediatric cases, 63 recipients (45.3%) were females, 51 recipients (36.7%) were males, and 25 recipients (18.0%) were of unknown sex or not reported, with a mean age of 3.5 years (standard deviation, 1.2). The majority of reports were from the US (83.5%), Canada (5.0%), and Taiwan (5.0%). Reported PTs included (descending order) “no adverse events” (107 events), “expired product administered” (44 events), and “accidental overdose” (22 events). Most events were vaccination-related events. Dose number information was missing in approximately 60% of the reported events. Among reports for which the dose number was known, 60 events occurred after the first dose, 18 events after the second dose, 26 events after the third dose, 11 events after the fourth dose, and 2 events after the fifth dose.

5) Case reports in Japan

For children 6 months through 4 years of age, there were reports on events in 4 recipients in Japan: “feeling abnormal/injection site hypoaesthesia/vaccination site pain,” “decreased appetite/sluggishness,” “no adverse events/overdose/wrong product administered,” and “fever” (1 recipient each). All events were non-serious. Three of the recipients were females and the remaining 1 recipient was of unknown sex. Of the 4 recipients, 2 reported events following administration of the monovalent (Original) vaccine and the other 2 reported events following administration of the monovalent (XBB.1.5) vaccine.

While events reported during the period between September 18, 2024 and December 17, 2024 included events that occurred after administration of the SARS-CoV-2 Omicron JN.1-adapted vaccine and KP.2-adapted vaccine, no new or specific trends were noted, and no new clinically important safety information was identified for vaccination with Spikevax in children 6 months through 5 years of age.

Taken together, the safety of Spikevax 25 µg administered as a booster dose to children 6 months through 4 years of age can be supported by the following reasons.

- In Study P204 Part 1 and Study P306 Part 2, the safety profile of a single dose of the monovalent (Original) vaccine 10 µg or the bivalent (Original/BA.1) vaccine 10 µg administered as a booster dose following 2 doses of the monovalent (Original) vaccine 25 µg for the primary series in children 6 months through 5 years of age was similar to that after the primary series. No new safety concerns were noted.
- The safety profile after Spikevax vaccination did not show clinically significant differences regardless of the pre-primary series or pre-booster SARS-CoV-2 status (prior SARS-CoV-2 infection status), and Spikevax was well tolerated.
- It can be inferred that safety profile after repeated vaccinations with 25 µg would be aligned with the safety results from the following studies: (1) safety results from Study P204 Part 2, in which 2 doses (25 µg each) of the monovalent (Original) vaccine was administered to children 6 months through 5 years of age who had tested positive for pre-primary series SARS-CoV-2; and (2) safety results from Study P306 Part 2, in which the bivalent (Original/BA.1) vaccine 10 µg was administered as a booster dose to children 6 months through 5 years of age who had tested positive for pre-booster SARS-CoV-2 following the primary series (25 µg). No new safety concerns were identified in these safety results.
- In the entire pediatric development program (Studies P203,[21)] P204, and P306), ≥10,000 children <17 years of age received the primary series 100 µg, 50 µg, or 25 µg, and approximately 3,000 of the recipients received 50 µg, 25 µg, or 10 µg as a booster dose. A comprehensive evaluation of these data support vaccination of children 6 months through 4 years of age with 25 µg.
- Spikevax 25 µg as a booster dose for children 6 months through 4 years of age has already been approved in the US, Canada, Europe, and other countries, and no new safety concerns have been identified.

[21)] A foreign phase II/III study (randomized, observer-blind, placebo-controlled study) conducted in the US in adolescents 12 years through 17 years of age. This study was initiated to evaluate the safety, immunogenicity, and efficacy of the monovalent (Original) vaccine 100 µg for the primary series. Subsequently, per protocol amendment, an additional part was established to evaluate the safety and immunogenicity of the monovalent (Original) vaccine 50 µg as a booster dose.

PMDA's view:
In Study P204 Part 1, which evaluated the monovalent (Original) vaccine 10 µg as a booster dose in children 6 months through 5 years of age and Study P306 Part 2, which evaluated the bivalent (Original/BA.1) vaccine 10 µg as a booster dose in the same age group, there were no reports of death or serious adverse events causally related to the study vaccine. The majority of solicited local and systemic adverse events reported after the booster dose were Grade 1 or 2, while all the unsolicited adverse events were Grade 1 or 2, and many of these events were considered unrelated to the study vaccine. There were no clinically significant differences in safety data regardless of the pre-booster SARS-CoV-2 status. These study results are generally consistent with the known safety information on the primary series and on a booster dose in adolescents and adults, and the known safety information on the primary series in children 6 months through 5 years of age. Thus, there are no new safety concerns.

Under the circumstances where SARS-CoV-2 variants continue to emerge, resulting in recurrence of sporadic outbreaks, a need remains for the provision of SARS-CoV-2 vaccines adapted to variants circulating at any given time. Based on the safety data of the monovalent (Original) vaccine or the bivalent (Original/BA.1) vaccine administered as a booster dose to children 6 months through 5 years of age, overseas post-marketing safety information, and the absence of safety concerns attributable to differences in the antigenic composition of variant-adapted vaccines distributed in Japan, it can be inferred that the booster dose in children 6 months through 4 years of age will be well tolerated regardless of any differences in the antigenic composition. Therefore, Spikevax 10 µg as a booster dose in children 6 months through 4 years of age has acceptable safety.

Although no clinical study data are available for Spikevax 25 µg as a booster dose in children 6 months through 4 years of age, 9 participants in Study P204 Part 1 received the monovalent (Original) vaccine 25 µg as a booster dose after completion of the primary series with the monovalent (Original) vaccine 25 µg. No adverse events of significant concern were observed in these participants compared to the safety data in participants receiving the 10 µg booster dose. In addition, the results from Study P204 Part 2 demonstrated there were no clinically significant differences in the safety profiles for the 2 doses of the Spikevax 25 µg depending on the pre-primary series SARS-CoV-2 status (positive/negative). Furthermore, according to the overseas post-marketing safety information, there have been no reports suggestive of safety concerns in children 6 months through 4 years of age receiving a single dose of 25 µg as a booster dose. Taken together, the safety of Spikevax 25 µg as a booster dose in children aged 6 months to 4 years is acceptable.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning:
Since its identification in December 2019, COVID-19 has spread rapidly worldwide. Although the public urgency to tackle COVID-19 has declined compared to the period when SARS-CoV-2 first emerged, COVID-19 remains a significant public health issue. Early in the pandemic, cases of severe COVID-19, hospitalization, and death were less common in children than in adults (*MMWR Morb Mortal Wkly Rep.* 2020;60:1081-8); however, during the period when Omicron variants circulated (January 2022 to January 2023), the rates of severe COVID-19 in infants and young children (rates of cumulative COVID-19-associated hospitalizations

by age group) were high (COVID-NET Interactive Dashboard[22)]). Furthermore, COVID-19 continues to be a leading cause of death caused by infectious and respiratory diseases in young people aged 0 to 19 years, surpassing deaths caused by influenza and pneumonia (*JAMA Netw Open.* 2023; 6:e2253590).

The efficacy of the monovalent (Original) vaccine against the SARS-CoV-2 Omicron variant is lower than that against the original strain of SARS-CoV-2 or the Delta variant. It has been shown that booster vaccinations with a vaccine adapted to currently circulating variants is needed in adults and children to maintain vaccine efficacy against COVID-19 (*Nat Med.* 2022;28:1042-9, *Nat Med.* 2022;28:1063-71). Even today, there are the following unmet medical needs for children <5 years of age: prevention of COVID-19, hospitalization due to COVID-19, long COVID (e.g., MIS-C and post-acute sequelae of SARS-CoV-2 [PASC]), and death. Therefore, as with individuals 5 years of age and older, making a booster dose with Spikevax available to children 6 months through 4 years of age is considered meaningful.

PMDA's view regarding the clinical positioning of Spikevax:
Since October 1, 2024, local governments have been conducting routine SARS-CoV-2 vaccinations once a year in populations including individuals ≥65 years. The Japanese Association for Infectious Diseases recommends the SARS-CoV-2 vaccine for any individuals in addition to those included in the population eligible for routine vaccination for the following reasons: (i) SARS-CoV-2 variants keep emerging and COVID-19 outbreaks will continue; and (ii) as the efficacy of SARS-CoV-2 vaccines to prevent COVID-19 wanes within a few months, repeated booster doses of the vaccines are desirable to maintain immunity ("Recommendation on COVID-19 Vaccination ver.10: Optional Vaccination with JN.1-Adapted Vaccine" [in Japanese] by COVID-19 Vaccine Taskforce, Vaccine Committee, the Japanese Association for Infectious Diseases, dated December 16, 2024). The Japan Pediatric Society states that it is desirable that all children 6 months through 17 years of age receive the SARS-CoV-2 vaccine (primary series as well as a booster dose in a timely manner), and in particular, vaccination is recommended for children with underlying medical conditions who are at higher risk of severe COVID-19, because COVID-19 still represents a burden on children in Japan, and vaccination is an effective measure to prevent severe COVID-19, such as symptoms requiring hospitalization ("2024 to 2025 Season: Novel Coronavirus Vaccination in Children" [in Japanese] dated October 27, 2024, issued by the Committee on Immunization and Prevention of Infectious Diseases of the Japan Pediatric Society).

Data from Study P204 Part 1 and Study P306 Part 2 were submitted as pivotal data for the present application; however, there are no data from clinical studies in which the proposed dose of 25 µg was used as a booster dose. Nevertheless, the evaluation of submitted data on efficacy [see Section 7.R.2], safety [see section 7.R.3], and dosage and administration [see Section 7.R.5] resulted in the conclusion that the efficacy of Spikevax 25 µg as a booster dose can be expected in children 6 months through 4 years of age and that its safety is acceptable.

22) https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html (last accessed on March 5, 2025)

The "2024 to 2025 Season: Novel Coronavirus Vaccination in Children" (issued by the Japan Pediatric Society) lists the following reasons why SARS-CoV-2 vaccines are desirable for children: (1) although the higher percentage of children ≥5 years of age who possess anti-SARS-CoV-2 antibodies, either through prior infection or vaccination, is high, a higher percentage of children ≤4 years of age, particularly infants, have no anti-SARS-CoV-2 antibodies; (2) of the 62 children and adolescents <20 years of age who died of SARS-CoV-2-related causes during the period from January 1 to September 30, 2022, forty-six were evaluable for the on-site survey (those who had died of extrinsic factors were excluded): 7 patients were <1 year of age; 27 patients had no underlying medical conditions; at the time of survey, 24 patients were eligible for vaccination (≥5 years of age), 21 of whom (88%) were reported to be unvaccinated (*Emerg Infedt Dis.* 2024;30:1589-98); (3) during and after the SARS-CoV-2 Omicron phase, the percentage of children developing febrile convulsions increased (*J Pediatric Infect Dis Soc.* 2022;11:514-517). Based on these findings, the burden of COVID-19 on children remains present, and vaccination continues to be an important preventative measure. In addition, circulating variants continue to evolve and new variants will emerge in the future; therefore, implementing booster vaccination remains important. Given that, in Japan, Comirnaty Intramuscular Injection[23)] is the only vaccine currently available for booster vaccination in children 6 months through 4 years of age, enabling Spikevax to be used as a booster in this age group would provide an additional vaccine option. This is considered to have clinical significance by expanding the choices for booster immunization in children 6 months through 4 years of age.

7.R.5 Dosage and administration

The proposed dosage and administration for the "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)" as a booster dose in children 6 months of age and older but younger than 5 years of age in the present partial change application were as follows:

Individuals 12 years of age and older

A single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children 5 years of age and older but younger than 12 years of age

A single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 months of age and older but younger than 5 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.

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

(Underline denotes additions)

The applicant's explanation about the dosage and administration:

The present application was filed based on pivotal efficacy and safety data from Study P204 Part 1 and Study P306 Part 2, in which a booster dose of 10 µg was administered. However, to simplify the regimen, in the US and Europe, 25 µg was established as the booster dose for children 6 months through 4 years of age.

23) The brand name: "Comirnaty Intramuscular Injection for 6 months to 4 years old for three people"

Accordingly, 25 µg, the same dosage as that approved in the US and Europe, was selected as the proposed dosage for Japan. The circumstances that led to the selection of 25 µg as the booster dose for children 6 months through 4 years of age in the US and Europe are summarized below.

US

- At the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC)[24] meeting held on January 26, 2023, simplification of the dosage regimen of SARS-CoV-2 vaccines was recommended. The FDA requested that the dosage regimens for all pediatric populations should be standardized to 25 µg, including children 6 months through 5 years of age for whom 10 µg had previously been established as the booster dose. Accordingly, Moderna TX, Inc. filed a supplemental application for a change in dosage regimen to the FDA on April 7, 2023, and the change for the booster dose for children 6 months through 5 years of age from 10 µg to 25 µg was authorized under EUA on April 18, 2023.
- At the ACIP meeting held on April 19, 2023, it was pointed out that differences in the dosage regimens and age groups for SARS-CoV-2 vaccines among vaccine manufacturers were causing confusion in clinical practice. Accordingly, to change the age group of Spikevax to match that of another SARS-CoV-2 vaccine manufacturer, Moderna TX, Inc. proposed to the FDA the following revised regimen for children 6 months through 4 years of age: 2 doses of 25 µg to those who have not previously received SARS-CoV-2 vaccine, and 1 dose of 25 µg to those who have previously received SARS-CoV-2 vaccine. The FDA agreed with these changes in [redacted] 2023.
- On September 11, 2023, the FDA approved the simplified dosage regimen for the Spikevax 2023-2024 formula (monovalent [XBB.1.5] vaccine): a single dose (50 µg) of the vaccine for children ≥5 years of age, and 2 doses (25 µg each) of the vaccine for children 6 months through 4 years of age who have not previously received SARS-CoV-2 vaccine, and a single dose (25 µg) for those who have.

Europe

- The Emergency Task Force (ETF) of the European Medicines Agency (EMA) stated on December 6, 2022 that the SARS-CoV-2 vaccine, which had only been authorized for booster use (bivalent [Original/BA.4-5] vaccine), may also be used for the primary series.[25] Moderna TX, Inc. submitted a type II variation to update the Spikevax's summary of product characteristics (SmPC) in accordance with the ETF's perspective.
- On July 20, 2023, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion regarding the simplified dosage regimen for individuals ≥6 years of age and 2 doses (25 µg each) for the primary series in children 6 months through 5 years of age. Subsequently, a booster dose (25 µg) in children 6 months through 4 years of age was also added at the time of authorization by the European Commission.

[24] VRBPAC January 26, 2023 FDA Briefing Document, https://www.fda.gov/media/164699/download (last accessed on March 5, 2025)
[25] ETF statement on the use of the EMA approved bivalent original/ Omicron BA.4-5 mRNA vaccines for primary series (EMA/922920/2022) (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 March 5, 2025])

- The pediatric age category for Spikevax was initially defined as 6 years through 11 years of age. However, in accordance with the joint statement released on June 7, 2023[26] by the European Centre for Disease Prevention and Control (ECDC) and the EMA regarding the composition of SARS-CoV-2 vaccines adapted to newly emerging variants, the age group was changed to 5 years through 11 years of age.

In Japan, previously, the dosage regimen of Spikevax was established for each of the age groups: "6 months of age and older but younger than 6 years of age," "6 years of age and older but younger than 12 years of age," and "12 years of age and older." In April 2024, in accordance with the "Modification in the Description of Dosage and Administration for SARS-CoV-2 Vaccines (in Japanese)" (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1, dated March 6, 2024), the Dosage and Administration section of Spikevax for individuals 5 years of age and older was changed and primarily addresses use as a booster dose. Accordingly, the age classification was changed: "6 months of age and older but younger than 5 years," "children 5 years of age and older but younger than 12 years," and "individuals 12 years of age and older."

Based on the above circumstances, an age group "6 months through 4 years of age" was selected as the intended age group for booster vaccination for the present application, instead of "6 months through 5 years of age," the clinical study population. The dosage for a booster dose was changed to 25 µg from 10 µg, the dose level used in the clinical studies.

Although there are no data from clinical studies in which the proposed dose of 25 µg was administered as a booster dose to children 6 months through 4 years of age, the immune response value increased consistently with an increase in dose in dose-finding studies conducted before as shown below. Therefore, the applicant considers that the same or higher efficacy can be expected with a booster dose with Spikevax 25 µg compared to that with Spikevax 10 µg.

- In a foreign phase I open-label dose-finding study (DMID Study 20-0003 [NCT04283461]) in healthy men and non-pregnant women aged ≥18 years, Spikevax at 25 µg, 50 µg, 100 µg, and 250 µg was evaluated. Neutralizing antibody titers increased in a dose-dependent manner after the second dose in each of the 3 age groups: 18 through 55 years of age, 56 through 70 years of age, and 71 years of age and older. At all of the evaluation timepoints, i.e., 7 days, 14 days, 28 days, and 90 days post-second dose, the GMT was generally higher in the 100 µg group than in 25 µg or 50 µg group.
- In Part A of a foreign phase II study (Study mRNA-1273-P201) in individuals ≥18 years of age, at 28 days after the first vaccination, anti-SARS-CoV-2 spike-binding antibodies and neutralizing antibodies were elicited by both Spikevax 50 µg and 100 µg. The geometric mean fold rise (GMFR) was higher at 100 µg than at 50 µg (Report on Special Approval for Emergency of COVID-19 Vaccine Moderna Intramuscular Injection, dated May 17, 2021).
- For the primary series in Study P204 Part 1, children 6 years through 11 years of age received 50 µg or 100 µg, children 2 years through 5 years of age received 25 µg or 50 µg, and children 6 months through 1 year of age received 25 µg. Neutralizing antibody titers (PsVNA [inhibitory dilution 50%]) GMT [95%

[26] ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants (https://www.ecdc.europa.eu/en/news-events/ecdc-ema-statement-updating-covid-19-vaccines-composition-new-sars-cov-2-virus-variants [last accessed on March 5, 2025])

CI] against SARS-CoV-2 (original strain) at 28 days post-second dose of the primary series (analysis set, PPIS) was as follows: in children 6 years through 11 years of age, 1,669.1 [1,504.5, 1,851.6] in the 50 µg group and 1,890.2 [1,603.8, 2,227.7] in the 100 µg group; in children 2 years through 5 years of age, 1,012.5 [848.2, 1,208.6] in the 25 µg group and 1,844.1 [1,602.3, 2,122.4] in the 50 µg group. In the age groups in which more than 1 dose level was evaluated, the immune response at the higher dose level was comparable to or higher than that at the lower dose level.

Although there are no safety data from clinical studies in which a 25 µg booster dose was administered to children 6 months through 4 years of age, currently available clinical study data support the safety of a 25 µg booster dose, and the dosage is well tolerated [see Section 7.R.3].

According to the protocols of Study P204 Part 1 and Study P306 Part 2, the minimum intervals between the second dose of the primary series and the booster dose were 4 months and 6 months, respectively. The median interval between the doses [range] was 10.2 months [7.8, 13.8] and 7.85 months [4.0, 12.1] in Study P204 Part 1 and Study P306 Part 2, respectively. Although the interval of the previous doses varied, antibody response is considered consistent regardless of vaccination interval as shown below.

- In Study P204 Part 1, among participants with negative pre-booster SARS-CoV-2 status, the neutralizing antibody GMT [95% CI] against SARS-CoV-2 (original strain) at 28 days post-booster in participants receiving a booster <303 days after the previous dose (5,124.1 [4,022.4, 6,527.5]) was similar to that in participants receiving a booster ≥303 days after the previous dose (5,874.9 [4,339.9, 7,952.9]).
- In Study P306 Part 2, among participants with negative pre-booster SARS-CoV-2 status, the neutralizing antibody GMT [95% CI] against SARS-CoV-2 (original strain) and the neutralizing antibody GMT [95% CI] against SARS-CoV-2 (Omicron BA.1) at 28 days post-booster with the bivalent (Original/BA.1) vaccine increased sufficiently in participants receiving a booster <7.85 months after the previous dose (4,200.2 [3,653.3, 4,828.9] against the original strain and 663.3 [558.2, 788.1] against Omicron BA.1) and in participants receiving a booster ≥7.85 months after the previous dose (5,357.6 [4,724.6, 6,075.5] against the original strain and 970.5 [837.8, 1,124.3] against Omicron BA.1).
- In Study P203,[21)] which evaluated a booster dose in participants 12 years through 17 years of age, the neutralizing antibody GMT [95% CI] against SARS-CoV-2 (original strain) at 28 days post-booster in participants receiving a booster <295 days after the previous dose (7,353.6 [6,600.2, 8,192.9]) was similar to that in participants receiving a booster ≥295 days after the previous dose (6,866.2 [6,090.4, 7,740.9]).

In Study DMID21-0012, a study sponsored by the US National Institutes of Health (NIH), vaccinations at an interval of at least 3 months (12 weeks) was evaluated. When a booster dose was administered at least 12 weeks after the primary series, the dose was well tolerated, and the booster dose was shown to increase the neutralizing antibody titers compared to the pre-booster level. In many countries, including the US, Canada, the UK, France, and Germany, the governments commonly recommend administration of a booster dose at least 3 months after the previous dose.

Based on the above, the applicant considers it possible to specify that the booster dose for children 6 months through 4 years of age can be administered at least 3 months after the previous dose of the SARS-CoV-2 vaccine.

PMDA's view:
No data from clinical studies in which a 25 µg booster dose was administered to children 6 months through 4 years of age are available for the present application. However, the applicant explained that given that a booster dose of 25 µg has been established for infants and young children in the US and Europe to simplify dosing, a booster dose of 25 µg, the same as that used as a booster dose in the US and Europe, was selected. The applicant's rationale for selecting the 25 µg booster dose in Japan for children 6 months through 4 years of age is understandable. As a result of the change in the dosage of Spikevax for individuals ≥5 years of age in accordance with the "Modification in the Description of Dosage and Administration for SARS-CoV-2 Vaccines" (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1, dated March 6, 2024), the dosage as a booster dose is the same as the dosage for the primary series (2 doses administered to individuals who have not yet received the SARS-CoV-2 vaccine). Using the same dosage for the primary series and booster dose also for children 6 months through 4 years of age is meaningful as a safety management measure to avoid confusion in clinical practice and to prevent vaccine administration errors, such as wrong dosage.

The data from Study P204 Part 1 and Study P306 Part 2 support the efficacy of a 10 µg booster dose in children 6 months through 4 years of age [see Section 7.R.2]. The safety of a 25 µg booster dose is acceptable as discussed in Section 7.R.3. Based on the applicant's explanation that the immune response value increases with an increase in dose, the same or higher efficacy can be expected with a 25 µg booster dose compared to that with a 10 µg booster dose. Therefore, a dose of 25 µg can be selected as a booster dose for children 6 months through 4 years of age.

Based on the applicant's explanation about the timing of a booster dose as well as the interval between Spikevax doses in individuals ≥5 years of age, which is defined as "the Spikevax vaccine can be administered at least 3 months after the previous dose of a SARS-CoV-2 vaccine," the timing of a booster dose for children 6 months through 4 years of age can also be defined as "at least 3 months after the previous dose of a SARS-CoV-2 vaccine."

To avoid confusion in clinical practice, the descriptions for the age classification were modified in alignment with those used for other SARS-CoV-2 vaccines: changing to "through" from "younger than" in the current description. PMDA concluded that the Dosage and Administration statement for the "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)" should be as follows:

Individuals 12 years of age and older
A single dose (0.5 mL) of Spikevax is administered intramuscularly.
Children 5 years <u>through 11 years of age</u>

A single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 months <u>through 4 years of age</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>For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.</u>

(Underline denotes additions or changes)

7.R.6 Post-marketing investigations

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

In Studies P204 and P306, no significant safety concerns were noted in children 6 months through 4 years of age after administration of the monovalent (Original) vaccine or the bivalent (Original/BA.1) vaccine as a booster dose; however, no safety information on Spikevax as a booster dose in this age group of Japanese children is available. Conversely, Spikevax has already been approved for the primary series in children 6 months through 4 years of age in Japan, and a specified use-results survey is currently underway to collect safety data, including the incidence of adverse events after vaccination with Spikevax for the primary series in children 6 months through 4 years of age and data on proper use, such as vaccine administration errors. Based on the post-marketing data on Spikevax, no significant safety concerns have been identified in children 6 months through 4 years of age. Given that similarity of the safety profile for a booster dose and that for the primary series has been shown in the clinical study data and post-marketing experience from Spikevax vaccination in and outside Japan, there are no new issues that should be included in the safety specification for Spikevax in the present application. The safety data on Spikevax in Japanese children 6 months through 4 years of age will be gathered proactively through the ongoing specified use-results survey. In addition, as routine pharmacovigilance activities, the applicant plans to collect safety data through spontaneous adverse event reports and other means without specifying recipients. If consideration of a new safety specification becomes necessary, the need for additional post-marketing surveillance will be assessed.

PMDA's view:

On the basis of the safety evaluation for currently available clinical study data as well as post-marketing data on Spikevax, Spikevax has acceptable safety as a booster dose in children 6 months through 4 years of age [see Section 7.R.3]. Although safety information on Spikevax administered as a booster dose in Japanese children 6 months through 4 years of age is not yet available, the clinical study data and post-marketing experience of Spikevax vaccination available in and outside of Japan to date suggest that the safety profile of Spikevax used as a booster dose in children 6 months through 4 years of age is similar to that for the primary series already approved in Japan. Since the launch of Spikevax on the market, a certain amount of safety data have been accrued from the post-marketing experience in and outside of Japan. Given that no new safety concerns have been identified for children 6 months through 4 years of age, the risk management for Spikevax can be implemented by the ongoing specified use-results survey and routine pharmacovigilance activities without early post-marketing phase vigilance or additional post-marketing surveillance.

The appropriateness of the post-marketing investigations 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 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Spikevax, defined as "the vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant) or mRNA encoding the spike proteins of SARS-CoV-2 (Omicron variant)," as a booster dose has a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in children 6 months through 4 years of age, and that Spikevax has acceptable safety with no significant safety concerns. Making Spikevax available for use as a booster dose in children 6 months through 4 years of age has clinical significance when its benefit-risk balance is assessed 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.

Review Report (2)

April 10, 2025

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	June 28, 2024

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," and "7.R.4 Clinical positioning" in Review Report (1).

1.1 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Section "7.R.5 Dosage and administration" in Review Report (1).

In the proposed dosage and administration, the regimen was specified for each of the vaccine products with different antigenic compositions. During the review process, however, the applicant explained that there is no plan to manufacture any vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain) or any vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant). Accordingly, PMDA concluded that the Dosage and Administration section should be revised by deleting the description of applicable vaccine products and specifying the regimen for any vaccine products to be distributed.

- ~~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

A single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children 5 years ~~of age and older but younger than 12 years of age~~ <u>through 11 years of age</u>

A single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 months ~~of age and older but younger than 5 years of age~~ <u>through 4 years of age</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>For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.</u>

(Strikethrough denotes deletions and underline denotes additions or changes)

1.2 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 Review Report (1): the risk management for Spikevax can be implemented by the ongoing specified use-results survey and routine pharmacovigilance activities without additional post-marketing surveillance, etc. concerning Spikevax administered as a booster dose in Japanese children 6 months through 4 years of age.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for Spikevax should include the safety specification presented in Table 22, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 23.

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

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

(No changes in the present application)

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

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified use-results survey (in pediatric recipients 6 months and older but younger than 12 years of age) [Spikevax Intramuscular Injection]	• Develop and disseminate information for healthcare professionals (guide to 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)

(No changes in the present application)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval condition. 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**~~

~~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

A single dose (0.5 mL) of Spikevax is administered intramuscularly.

Children 5 years ~~of age and older but younger than 12 years of age~~ <u>through 11 years of age</u>

A single dose (0.25 mL) of Spikevax is administered intramuscularly.

Children 6 months ~~of age and older but younger than 5 years of age~~ <u>through 4 years of age</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>For a booster dose, a single dose (0.25 mL) of Spikevax is administered intramuscularly.</u>

(Strikethrough denotes deletions and underline denotes additions or changes)

Approval Condition

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

Appendix

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AESI	Adverse events of special interest
Bivalent (Original/BA.1) vaccine	Bivalent vaccine containing mRNA (elasomeran) encoding the spike protein of SARS-CoV-2 (original strain) and mRNA (imelasomeran) encoding the spike protein of SARS-CoV-2 (Omicron BA.1) at a mass ratio of 1:1
Bivalent (Original/BA.4-5) vaccine	Bivalent vaccine containing mRNA (elasomeran) encoding the spike protein of SARS-CoV-2 (original strain) and mRNA (davesomeran) encoding the spike protein of SARS-CoV-2 (Omicron BA.4-5) at a mass ratio of 1:1
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence interval
COVID-19	Coronavirus disease 2019
EB virus	Epstein-Barr virus
EMA	European Medicines Agency
ETF	Emergency Task Force
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
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
LLOQ	Lower limit of quantification
MAAE	Medically-attended adverse event
MIS-C	Multisystem inflammatory syndrome in children
Monovalent (Original) vaccine	Monovalent vaccine containing mRNA (elasomeran) encoding the spike protein of SARS-CoV-2 (original strain)
Monovalent (XBB.1.5) vaccine	Monovalent vaccine containing mRNA (andusomeran) encoding the spike protein of SARS-CoV-2 (Omicron XBB.1.5)
mRNA	Messenger RNA
Original strain	SARS-CoV-2 Wuhan-Hu-1 strain (D614G)
PASC	Post-acute sequelae of SARS-CoV-2
PMDA	Pharmaceuticals and Medical Devices Agency
PPIS	Per protocol immunogenicity subset
PsVNA	Pseudovirus neutralization assay
PT	Preferred term
RS virus	Respiratory syncytial virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Spikevax	Spikevax Intramuscular Injection
Study P204	Study mRNA-1273-P204
Study P301	Study mRNA-1273-P301

Study P306	Study mRNA-1273-P306
ULOQ	Upper limit of quantification
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization