Report on Special Approval for Emergency

February 7, 2023
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Comirnaty Intramuscular Injection for 5 to 11 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredients: (a) Tozinameran [JAN*], (b) Tozinameran [JAN*] and Famtozinameran [JAN*])
Applicant	Pfizer Japan Inc.
Date of Application	October 13, 2022
Dosage Form/Strength	(a) Injection: Each vial contains 0.130 mg of Tozinameran. (b) Injection: Each vial contains a total of 0.130 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1).
Application Classification	Prescription drug, (4) Drug with new indications, (6) Drug with a new dosage, (10-2) Other drugs (among other drugs classified in [10], those pertaining to change in manufacturing method of biological products, etc.)
Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3 of the Act ("Handling of Drugs Submitted for Special Approval for Emergency (Request)" [PSEHB/PED Notification 0113-5, dated January 13, 2023]).
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that a booster dose with the vaccine product which contains messenger ribonucleic acid (mRNA) encoding spike proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Strain Wuhan-Hu-1 [original strain] and Omicron BA.4/BA.5 lineages) can be expected to show a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (Coronavirus disease 2019 [COVID-19]) in children 5 to 11 years of age, and that the product has acceptable safety in the same way as the previous products (see Attachment).

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

Indication

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

The indication applies to the following vaccine products:

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

(Underline denotes additions.)

Dosage and Administration

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

The product is diluted with 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).

For the primary series, 2 doses (0.2 mL each) are injected intramuscularly, usually 3 weeks apart.

For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

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

The product is diluted with 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).

For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

(Underline denotes additions.)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (2) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (3) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at present, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of

the product. Information obtained from the national health survey, etc., should be reflected appropriately.

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

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

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

**Japanese Accepted Name (modified INN)*

Attachment

Report on Special Approval for Emergency

February 6, 2023

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

Product Submitted for Approval

Brand Name	Comirnaty Intramuscular Injection for 5 to 11 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredients: (a) Tozinameran, (b) Tozinameran and Famtozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	October 13, 2022
Dosage Form/Strength	(a) Injection: Each vial contains 0.130 mg of Tozinameran. (b) Injection: Each vial contains a total of 0.130 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1).

Proposed Indication

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

The indication applies to the following vaccine products:

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

(Underline denotes additions.)

Proposed Dosage and Administration

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

The product is diluted with 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).
For the primary series, 2 doses (0.2 mL each) are injected intramuscularly, usually 3 weeks apart.
For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

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

The product is diluted with 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).
For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Multiple therapeutic agents and preventive vaccines have been developed against the global pandemic of disease caused by SARS-CoV-2 infection (COVID-19) since January 2020, and various anti-infection measures including vaccination have been taken. However, because of mutations of SARS-CoV-2 genes that result in emergence in succession of variants with altered infectivity, transmissibility, antigenicity, and pathogenicity, SARS-CoV-2 infection is repeating in ever increasing waves, showing no sign of the end of the pandemic. Omicron variant, which was dominant worldwide in 2022, evades vaccine-induced immunity due to changes in the antigenicity from Strain Wuhan-Hu-1 (original strain), resulting in a decrease in the efficacy of vaccines (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63, etc.). In the face of these circumstances, efforts to develop vaccines effective against Omicron variant were undertaken. In Japan as of February 2023, the following vaccines have been approved for marketing: Comirnaty RTU Intramuscular Injection (bivalent [original strain/Omicron BA.1 lineage] and bivalent [original strain/Omicron BA.4/BA.5 lineages]) and Spikevax Intramuscular Injection (bivalent [original strain/Omicron BA.1 lineage] and bivalent [original strain/Omicron BA.4/BA.5 lineages]). Their age indication is ≥12 years and ≥18 years, respectively, with no vaccines against Omicron variant available for use in children <12 years of age.

Outside Japan, a booster dose of a bivalent vaccine containing tozinameran and famtozinameran (at an RNA mass ratio of 1:1) (bivalent vaccine [original strain/Omicron BA.4/BA.5 lineages]) of Comirnaty intramuscular injection for 5 to 11 years old was granted emergency use authorization in the U.S. on October 12, 2022, and partial change of conditional marketing approval was granted in Europe on November 10, 2022.

In Japan, the applicant has recently submitted an application for partial change of the marketing approval of Comirnaty relating to addition of a bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) for children 5 to 11 years of age. During this review process, the applicant submitted results of the interim analysis of the foreign phase II/III study (Study C4591044, Cohort 2) on the immunogenicity and safety of a booster dose of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) in subjects ≥12 years of age. A foreign phase II study (Study C4591048, Substudy D) on booster dose of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) in subjects 5 to 11 years of age was initiated in September 2022 and is ongoing as of February 2023.

This report contains the result of the review conducted based on the data submitted by the applicant, in accordance with the "Handling of Drugs Submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification 0113-5, dated January 13, 2023).

2. Quality and Outline of the Review Conducted by PMDA

The bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) added in this application is a vaccine containing, encapsulated in lipid nanoparticles (LNP), tozinameran and famtozinameran which are mRNAs encoding spike protein (S-protein) of the original strain of SARS-CoV-2 and the Omicron BA.4/BA.5 lineages, respectively. It is a vaccine product for children 5 to 11 years of age.

The active substances, tozinameran and famtozinameran, are the same as those used in "Comirnaty RTU Intramuscular Injection (bivalent [original strain/Omicron BA.4/BA.5 lineages])," and their data on the quality have already been reviewed.

The manufacturing process of the vaccine products are identical to that of the monovalent vaccine containing tozinameran (parent vaccine) (Comirnaty intramuscular injection for 5 to 11 years old [monovalent: original strain]) of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages), except the process of diluting the active substances. Although the dilution process of the active substances is different from that of the parent vaccine in that the process of mixing 2 types of active substances was added, the parameters of the mixing process are the same as those of mixing the active substance of the parent vaccine with water for injection for adjusting the concentration in the dilution process, and the process has been validated for the parent vaccine. This manufacturing process confirmed that mRNAs of the 2 types of the active substances are mixed in a 1:1 ratio and that the mixture of the 2 types of the active substance thus prepared has the same quality attributes as that of mRNA of the parent vaccine product.

The specifications for the vaccine product include, in addition to those of the parent vaccine, the RNA ratio to confirm the ratio of tozinameran and famtozinameran.

2.R Outline of the review conducted by PMDA

As a result of the review based on the submitted data, no particular problem was identified in the quality of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages).

2.R.1 Shelf-life of the vaccine product

At the time of the marketing application, the shelf-life of 12 months had been proposed for the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) as was the case with the parent vaccine. However, the proposed shelf-life for the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) was extended to 18 months pursuant to the extension of the shelf-life of the parent vaccine to 18 months. However, results of the long-term testing on the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) at 18-month time point are unavailable at present.

The applicant's explanation about the shelf-life of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages):
The quality attributes of the parent vaccine and the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) are similar with each other, suggesting the similarity of their safety profiles. It is therefore considered appropriate to propose the shelf-life of 18 months for the bivalent vaccine as is the case with the parent vaccine. In the ongoing long-term testing on the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages), the 18-month stability will be confirmed.

PMDA's view:
Taking account of the applicant's explanation, it is acceptable to determine the shelf-life of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) to be 18 months when stored at −75℃ ± 15℃ as

is the case with the parent vaccine. The stability should be confirmed in the ongoing long-term testing on the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages).

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

Although the present application relates to a new indication and a new dosage, no new data were submitted under this section, because the non-clinical pharmacology data had been evaluated during the review process for the initial approval for Comirnaty Intramuscular Injection.[1)]

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

Although the present application relates to a new indication and a new dosage, no new data were submitted under this section, because the non-clinical pharmacokinetic data had been evaluated during the review process for the initial approval for Comirnaty Intramuscular Injection.[1)]

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application relates to a new indication and a new dosage, no data relating to toxicity were submitted.

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

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

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

The applicant submitted interim analysis results of the foreign phase II/III study (Study C4591044, Cohort 2) shown in Table 1 as the efficacy and safety evaluation data.

Table 1. Summary of clinical study

Data category	Country	Study ID	Phase	Population	No. of subjects enrolled	Dosage regimen	Study objective
Evaluation	U.S.	Study C4591044 Cohort 2	II/III	Healthy subjects aged ≥12 years who completed 3 doses of parent vaccine 30 µg with the third dose administered 5-12 months earlier	530	Intramuscular injection of bivalent vaccine (original strain/BA.4/BA.5 lineages) as the fourth dose 12-17 years of age: 30 µg 18-55 years and >55 years of age: 30 or 60 µg	Safety Immunogenicity

7.1 Foreign phase II/III study (CTD 5.3.5.1.1 to 5.3.5.1.4; Study C4591044, Cohort 2; study period, ongoing since August 2022 [data cutoff date, October 12, 2022])

This clinical study was conducted to evaluate the safety and immunogenicity of the bivalent vaccine at a dose of 30 or 60 µg to healthy subjects aged ≥12 years who completed 3 doses of the parent vaccine 30 µg (2 doses as the primary series, 1 dose as a booster) with the third dose administered 5 to 12 months

1) Comirnaty Intramuscular Injection: Report on Special Approval for Emergency (dated February 8, 2021)

earlier (target sample size, 500 subjects [100 subjects 12-17 years of age, 200 subjects 18-55 years of age (100 in each dose group), 200 subjects >55 years of age (100 in each dose group)]). The study was conducted as an open-label, uncontrolled study in subjects 12 to 17 years of age and as a randomized, observer-blind, parallel-group study in subjects 18 to 55 years of age and in subjects >55 years of age. The study was conducted in 25 study sites in the U.S.

Subjects 12 to 17 years of age received the bivalent vaccine (original strain/BA.4/BA.5 lineages) 30 μg, and subjects 18 to 55 years of age and subjects >55 years of age received the bivalent vaccine (original strain/BA.4/BA.5 lineages) 30 or 60 μg. The vaccine was administered intramuscularly as a single dose.

During this review process, the applicant submitted safety data in subjects 12 to 17 years of age, and immunogenicity data (30 μg group only) and safety data in subjects 18 to 55 years of age and subjects >55 years of age.

Of 108 subjects 12 to 17 years of age who were enrolled in the study and received the study vaccine, 107 subjects were included in the safety analysis set. The remaining 1 subject was excluded because the subject did not provide informed consent.

Of 214 randomized subjects 18 to 55 years of age (104 in the 30 μg group, 110 in the 60 μg group), 213 subjects (103 in the 30 μg group, 110 in the 60 μg group) received the study vaccine, and all were included in the safety analysis set. Of 104 subjects assigned to the 30 μg group, 97 subjects were included in the all-available immunogenicity population, and the remaining 7 subjects were excluded for the following reasons: 1 subject did not receive the study vaccine, and 7 subjects did not have valid and definitive immunogenicity data after the study vaccine administration [including duplicate counting]). Of 104 subjects assigned to the 30 μg group, 95 subjects were included in the evaluable immunogenicity population, and the remaining 9 subjects were excluded for the following reasons: 1 subject did not receive the study vaccine, 5 subjects did not meet the inclusion criteria, 9 subjects did not have any valid and definitive immunogenicity data during the defined period [Days 28-42] after the study vaccine administration, and 5 subjects had other important protocol deviations [including duplicate counting]).

All of 208 randomized subjects >55 years of age (106 in the 30 μg group, 102 in the 60 μg group) received the study vaccine and were included in the safety analysis set. Of 106 subjects assigned to the 30 μg group, 105 subjects were included in the all-available immunogenicity population, and the remaining 1 subject was excluded because the subject did not have any valid and definitive immunogenicity data after the study vaccine administration. Of 106 subjects assigned to the 30 μg group, 102 subjects were included in the evaluable immunogenicity population, and the remaining 4 subjects were excluded because the subjects did not have any valid and definitive immunogenicity data during the defined period (Days 28-42) after the study vaccine administration.

In evaluation of immunogenicity, data of 100 subjects were extracted as the reference group from among subjects 18 to 55 years of age and subjects >55 years of age who received bivalent vaccine containing tozinameran and riltozinameran [at an RNA mass ratio of 1:1]) (bivalent vaccine [original strain/BA.1

lineage]) 30 μg in Study C4591031 Substudy E, and compared with the data obtained in Study C4591044 Cohort 2 in a descriptive manner. In order to adjust, as closely as possible, the ratio of subjects in the reference group with and without a history of SARS-CoV-2 infection to the ratio in Study C4591044 Cohort 2, data were extracted from the evaluable immunogenicity population in Study C4591031 Substudy E according to the following method: Data of all subjects with a history of SARS-CoV-2 infection before the study vaccine administration were used, and the rest of the data were extracted randomly from subjects without a history of SARS-CoV-2 infection.

The primary immunogenicity endpoints were as shown below and evaluated in the population without a history of SARS-CoV-2 infection within 1 month after the study vaccine administration and in the population regardless of the history of SARS-CoV-2 infection.

(a) "Geometric mean titer (GMT) of neutralizing antibody titer (50% neutralizing antibody titer)" and "geometric mean-fold rise (GMFR) of neutralizing antibody titer after study vaccine administration versus the level before the administration" against Omicron BA.4/BA.5 lineages, Omicron BA.1 lineage, and Strain USA-WA1/2020 (reference strain) of SARS-CoV-2, and

(b) "Antibody response rate after study vaccine administration (percentage of subjects showing a ≥4-fold increase in neutralizing antibody titer [titer below the lower limit of quantitation (LLOQ) was imputed by LLOQ] from before the study vaccine administration)"

Tables 2 and 3 show the results of the primary endpoints in the evaluable immunogenicity population.

Table 2. Serum SARS-CoV-2 neutralizing antibody titer (evaluable immunogenicity population)

		Bivalent vaccine (original strain/BA.4/BA.5 lineages) 30 μg				Reference: Study C4591031 Substudy E Bivalent vaccine (original strain/BA.1 lineage) 30 μg			
		n	GMT or GMFR [2-sided 95% CI]	n	GMT or GMFR [2-sided 95% CI]	n	GMT or GMFR [2-sided 95% CI]	n	GMT or GMFR [2-sided 95% CI]
Without history of SARS-CoV-2 infection within 1 month after study vaccine administration									
		18-55 years of age (N = 32)		>55 years of age (N = 40)		18-55 years of age (N = 67)		>55 years of age (N = 64)	
BA.4/ BA.5	GMT before dose	32	54.5 [41.3, 71.9]	40	76.0 [54.7, 105.7]	67	79.7 [62.7, 101.1]	63	99.1 [78.1, 125.8]
	GMT at 1 month after dose	32	1029.6 [702.6, 1508.9]	40	1668.1 [1089.6, 2553.7]	67	740.6 [557.2, 984.2]	64	566.7 [466.2, 719.9]
	GMFR	32	18.9 [12.8, 27.8]	40	21.9 [14.2, 33.8]	67	9.3 [7.2, 12.1]	63	5.8 [4.5, 7.5]
BA.1	GMT before dose	32	52.6 [34.0, 81.3]	40	84.7 [55.7, 128.6]	67	99.3 [75.4, 130.8]	64	114.5 [82.4, 159.3]
	GMT at 1 month after dose	32	910.9 [634.8, 1307.1]	40	1481.5 [1020.3, 2151.2]	67	1338.6 [998.9, 1793.9]	64	944.7 [746.2, 1196.1]
	GMFR	32	17.3 [11.1, 26.9]	40	17.5 [12.2, 25.1]	67	13.5 [10.3, 17.7]	64	8.2 [6.1, 11.2]
Reference strain	GMT before dose	32	455.3 [286.2, 724.2]	40	881.9 [601.6, 1292.7]	67	873.5 [682.8, 1117.3]	64	1028.9 [795.8, 1330.3]
	GMT at 1 month after dose	32	6431.7 [4542.9, 9106.0]	40	8386.3 [6235.4, 11279.2]	67	5763.8 [4550.1, 7301.1]	64	5230.2 [4357.9, 6277.2]
	GMFR	32	14.1 [9.1, 22.0]	40	9.5 [6.4, 14.0]	67	6.6 [5.2, 8.3]	64	5.1 [3.9, 6.5]
Regardless of history of SARS-CoV-2 infection within 1 month after study vaccine administration									
		18-55 years of age (N = 95)		>55 years of age (N = 102)		18-55 years of age (N = 100)		>55 years of age (N = 100)	
BA.4/ BA.5	GMT before dose	95	338.3 [238.1, 480.7]	101	301.9 [215.6, 422.8]	100	151.5 [113.4, 202.3]	99	225.4 [164.1, 309.6]
	GMT at 1 month after dose	95	2839.0 [2150.0, 3748.8]	102	3001.1 [2318.2, 3885.1]	100	1072.0 [816.1, 1408.1]	100	944.5 [733.8, 1215.6]
	GMFR	95	8.4 [6.3, 11.1]	101	9.9 [7.4, 13.2]	100	7.1 [5.7, 8.9]	99	4.2 [3.4, 5.2]
BA.1	GMT before dose	95	346.0 [240.0, 498.9]	102	365.1 [260.8, 511.1]	100	194.6 [142.4, 266.0]	100	316.3 [215.9, 463.4]
	GMT at 1 month after dose	95	2407.2 [1884.9, 3074.2]	102	2656.1 [2089.6, 3376.3]	100	1819.0 [1401.6, 2360.6]	100	1617.7 [1274.7, 2053.0]
	GMFR	95	7.0 [5.3, 9.1]	102	7.3 [5.6, 9.5]	100	9.3 [7.3, 12.0]	100	5.1 [3.9, 6.6]
Reference strain	GMT before dose	95	2349.0 [1693.4, 3258.4]	101	2643.1 [1990.8, 3509.1]	100	1338.4 [1056.9, 1695.1]	100	1985.7 [1510.1, 2611.0]
	GMT at 1 month after dose	95	11919.3 [9839.1, 14439.3]	102	12103.8 [9992.0, 14662.0]	99	6913.9 [5690.4, 8400.5]	100	7128.6 [5954.4, 8534.3]
	GMFR	95	5.1 [3.9, 6.6]	101	4.6 [3.7, 5.8]	99	5.2 [4.3, 6.3]	100	3.6 [2.9, 4.4]

N = Number of subjects analyzed, n = Number of subjects available with the data of antibody titer at the evaluation time point

Table 3. Serum SARS-CoV-2 neutralizing antibody response rate (evaluable immunogenicity population)

	Bivalent vaccine (original strain/BA.4/BA.5 lineages) 30 μg				Reference: Study C4591031 Substudy E Bivalent vaccine (original strain/BA.1 lineage) 30 μg			
	n2/n1	Antibody response rate (%) [2-sided 95% CI]	n2/n1	Antibody response rate (%) [2-sided 95% CI]	n2/n1	Antibody response rate (%) [2-sided 95% CI]	n2/n1	Antibody response rate (%) [2-sided 95% CI]
Without history of SARS-CoV-2 infection within 1 month after study vaccine administration								
	18-55 years of age (N = 32)		>55 years of age (N = 40)		18-55 years of age (N = 67)		>55 years of age (N = 64)	
BA.4/BA.5	26/32	81.3 [63.6, 92.8]	36/40	90.0 [76.3, 97.2]	47/67	70.1 [57.7, 80.7]	31/63	49.2 [36.4, 62.1]
BA.1	23/32	71.9 [53.3, 86.3]	37/40	92.5 [79.6, 98.4]	59/67	88.1 [77.8, 94.7]	44/64	68.8 [55.9, 79.8]
Reference strain	26/32	81.3 [63.6, 92.8]	30/40	75.0 [58.8, 87.3]	48/67	71.6 [59.3, 82.0]	35/64	54.7 [41.7, 67.2]
Regardless of history of SARS-CoV-2 infection within 1 month after study vaccine administration								
	18-55 years of age (N = 95)		>55 years of age (N = 102)		18- 55 years of age (N = 100)		>55 years of age (N = 100)	
BA.4/BA.5	61/95	64.2 [53.7, 73.8]	72/101	71.3 [61.4, 79.9]	62/100	62.0 [51.7, 71.5]	38/99	38.4 [28.8, 48.7]
BA.1	52/95	54.7 [44.2, 65.0]	65/102	63.7 [53.6, 73.0]	75/100	75.0 [65.3, 83.1]	52/100	52.0 [41.8, 62.1]
Reference strain	47/95	49.5 [39.1, 59.9]	51/101	50.5 [40.4, 60.6]	59/99	59.6 [49.3, 69.3]	41/100	41.0 [31.3, 51.3]

N = Number of subjects analyzed, n1 = Number of subjects available with the data of antibody titer at the evaluation time point,
n2 = Number of subjects showing a ≥4-fold increase in the antibody titer from baseline (LLOQ, if baseline titer is below the LLOQ)

As for safety, the severity of adverse events was evaluated according to Food and Drug Administration (FDA) Guidance "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).[2)]

- Reactogenicity events (local reactions of injection site pain, redness, and swelling; systemic events of pyrexia [≥38℃], fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia) were collected by the subject diary for 7 days after the study vaccine administration.
- Adverse events (excluding reactogenicity events for 7 days after the study vaccine administration) were collected through 1 month after the study vaccine administration.
- Serious adverse events were collected through 6 months after the study vaccine administration.
- Deaths were collected up to the end of the study.

Table 4 shows reactogenicity events observed within 7 days after the study vaccine administration.

Table 4. Reactogenicity events within 7 days after study vaccine administration (safety analysis set)

	Event terms	30 μg			60 μg	
		12-17 years of age N = 107	18-55 years of age N = 102	>55 years of age N = 105	18-55 years of age N = 110	>55 years of age N = 101
		n (%)	n (%)	n (%)	n (%)	n (%)
Local reactions	Total	75 (70.1)	85 (83.3)	60 (57.1)	103 (93.6)	73 (71.6)
	Injection site pain	75 (70.1)	81 (79.4)	59 (56.2)	103 (93.6)	72 (70.6)
	Redness	6 (5.6)	6 (5.9)	3 (2.9)	12 (10.9)	7 (6.9)
	Swelling	8 (7.5)	7 (6.9)	2 (1.9)	17 (15.5)	9 (8.9)
Systemic events	Total	86 (80.4)	77 (75.5)	59 (56.2)	90 (81.8)	64 (63.4)
	Fatigue	72 (67.3)	64 (62.7)	41 (39.0)	76 (69.1)	54 (53.5)
	Headache	54 (50.5)	45 (44.1)	31 (29.5)	50 (45.5)	36 (35.6)
	Chills	25 (23.4)	15 (14.7)	13 (12.4)	30 (27.3)	23 (22.8)
	Vomiting	3 (2.8)	2 (2.0)	1 (1.0)	2 (1.8)	3 (3.0)
	Diarrhoea	7 (6.5)	14 (13.7)	9 (8.6)	14 (12.7)	7 (6.9)
	Myalgia	28 (26.2)	32 (31.4)	21 (20.0)	46 (41.8)	23 (22.8)
	Arthralgia	13 (12.1)	17 (16.7)	12 (11.4)	27 (24.5)	15 (14.9)
	Pyrexia[a)]	10 (9.3)	5 (4.9)	8 (7.6)	13 (11.8)	14 (13.9)

N = Number of subjects analyzed, n = Number of subjects with events
a) ≥38°C

Table 5 shows the incidences of adverse events and adverse reactions within 1 month after the study vaccine administration and adverse events observed in ≥2 subjects.

2) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (last accessed on February 6, 2023)

Table 5. Incidences of adverse events and adverse reactions within 1 month after the study vaccine administration and adverse events observed in ≥2 subjects (safety analysis set in Cohort 2)

	Adverse events					Adverse reactions				
	30 µg			60 µg		30 µg			60 µg	
Event terms	12-17 years of age N = 107	18-55 years of age N = 103	>55 years of age N = 106	18-55 years of age N = 110	>55 years of age N = 102	12-17 years of age N = 107	18-55 years of age N = 103	>55 years of age N = 106	18-55 years of age N = 110	>55 years of age N = 102
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	8 (7.5)	3 (2.9)	4 (3.8)	9 (8.2)	7 (6.9)	6 (5.6)	1 (1.0)	1 (0.9)	3 (2.7)	1 (1.0)
Fatigue	3 (2.8)	0 (-)	0 (-)	1 (0.9)	0 (-)	3 (2.8)	0 (-)	0 (-)	1 (0.9)	0 (-)
Injection site pain	2 (1.9)	0 (-)	0 (-)	0 (-)	1 (1.0)	2 (1.9)	0 (-)	0 (-)	0 (-)	1 (1.0)
Sinusitis	2 (1.9)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Myalgia	2 (1.9)	0 (-)	0 (-)	0 (-)	0 (-)	2 (1.9)	0 (-)	0 (-)	0 (-)	0 (-)
Headache	2 (1.9)	0 (-)	0 (-)	0 (-)	0 (-)	2 (1.9)	0 (-)	0 (-)	0 (-)	0 (-)
Lymphadenopathy	0 (-)	1 (1.0)	0 (-)	1 (0.9)	0 (-)	0 (-)	1 (0.9)	0 (-)	1 (0.9)	0 (-)
Dyspnoea	0 (-)	0 (-)	1 (0.9)	0 (-)	1 (1.0)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)

Medical Dictionary for Regulatory Activities (MedDRA) v 25.0, N = Number of subjects analyzed, n = Number of subjects with events

A serious adverse event was observed in 1 subject (dyspnoea in a subject >55 years of age in the 30 µg group) on or before the data cutoff date (October 12, 2022). The outcome of the event at the data cutoff date was "resolving." Its causal relationship to the study vaccine was denied. There were no deaths nor adverse events leading to study discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical significance and data for review

PMDA's view:

Although a booster dose with the parent vaccine has a certain efficacy against symptomatic diseases caused by the Omicron variant pandemic in 2022, the efficacy was lower and of shorter duration than that against the Delta variant which was the pandemic in the past (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). BA.4/BA.5 lineages, in particular, have higher infectivity and immune evasion than other Omicron lineages (*Nature.* 2022;608:603-8). In the face of these circumstances, anti-Omicron vaccines were developed based on the modification from the parent vaccine. As of January 2023 in Japan, Comirnaty RTU Intramuscular Injection (bivalent [original strain/Omicron BA.1 lineage] and bivalent [original strain/Omicron BA.4/BA.5 lineages]) and Spikevax Intramuscular Injection (bivalent [original strain/Omicron BA.1 lineage] and bivalent [original strain/Omicron BA.4/BA.5 lineages]) are available for use in individuals ≥12 years of age. As for the efficacy of the bivalent vaccine (original strain/BA.4/BA.5 lineages), there are reports in the U.S. on the preventive effect against symptomatic SARS-CoV-2 infection during the prevalence of the Omicron variant and on the preventive effect against an emergency visit or hospitalization due to COVID-19-like disease. The booster dose with the bivalent vaccine (original strain/BA.4/BA.5 lineages) in adults who had already received the parent vaccine exhibited a greater preventive effect than in those who did not receive the bivalent vaccine (*MMWR Morb Mortal Wkly Rep.* 2022;71:1526-30, *MMWR Morb Mortal Wkly Rep.* 2022;71:1616-24, *MMWR Morb Mortal Wkly Rep.* 2022;71:1625-30).

Pediatric COVID-19 is considered to be comparatively mild, but the number of children with severe COVID-19 and fatal cases increased with the increase in the total number of infected people during the epidemic of the Omicron variant (MHLW website, Visualizing the data: Information on COVID-19 infections; Number of newly confirmed cases by age [weekly], Number of severe cases by sex and age [https://covid19.mhlw.go.jp/ (last accessed on February 6, 2023)]). Complication with multisystem

inflammatory syndrome in children/pediatric inflammatory multisystem syndrome (MIS-C/PIMS) accompanied by pyrexia and multi-organ disorder (CDC website; Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children [MIS-C] in the United States[3)]) may occur albeit seldom, and symptoms such as fatigue, headache, and shortness of breath may persist for a long time after SARS-CoV-2 infection (*Lancet Child Adolesc Health.* 2022;6:240-8). COVID-19 prevention by vaccines continues to have an important role in children as well as in adults. Although a booster dose of the parent vaccine is effective in recovering the attenuated preventive effect of the vaccine against symptomatic SARS-CoV-2 caused by the Omicron variant (*JAMA Netw Open.* 2022;5:e2246915), given the continuing epidemic caused by the Omicron variant and increasing numbers of patients with severe disease and fatal cases as of January 2023 (MHLW website, Visualizing the data: Information on COVID-19 infections; Trends in the number of severe cases, Trends in the number of deaths [https://covid19.mhlw.go.jp/ (last accessed on February 6, 2023)]), it is of public health significance to make vaccines against the Omicron variant available promptly to children.

This application relates to the addition of the bivalent vaccine (original strain/BA.4/BA.5 lineages) for children 5 to 11 years of age, but clinical study data of the bivalent vaccine (original strain/BA.4/BA.5 lineages) in this age group (Study C4591048 Substudy D) are unavailable as of this application. In the U.S. and Europe, the bivalent vaccine (original strain/BA.4/BA.5 lineages) can be used in children 5 to 11 years of age. It is of clinical significance to make vaccines tailored to the Omicron variant available for use promptly to children 5 to 11 years of age, as discussed above. PMDA reviewed the efficacy and safety of the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age based on the immunogenicity and safety data in the clinical study on the bivalent vaccine (original strain/BA.4/BA.5 lineages) in subjects ≥12 years of age (Study C4591044 Cohort 2) submitted during the review process, as well as on the data so far obtained. During the process of this review, the applicant submitted, in the form of response to inquiries, safety data at 1-month time point after study vaccine administration in a part of subjects in Study C4591048 Substudy D. The data were included in the review [see Section 7.R.3].

Given the clinical study data submitted in the present application and the findings so far available on the parent vaccine, the bivalent vaccine (original strain/BA.4/BA.5 lineages) is expected to demonstrate efficacy in children 5 to 11 years of age as well [see Section 7.R.2], with roughly similar safety profiles as those of the parent vaccine [see Section 7.R.3]. On the basis of the above, PMDA concluded that it is of clinical significance to make the bivalent vaccine (original strain/BA.4/BA.5 lineages) available for use in children 5 to 11 years of age.

Novel variants may emerge in the future, possibly resulting in change in the usefulness of the vaccine depending on the property of the variants. Appropriate measures should be taken depending on the situation.

7.R.2 Efficacy

The applicant's explanation about the efficacy of the bivalent vaccine (original strain/BA.4/BA.5 lineages):

3) https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (last accessed on February 6, 2023)

Tables 2 and 3 show the neutralizing antibody titer after administration of the bivalent vaccine (original strain/BA.4/BA.5 lineages) 30 µg in subjects 18 to 55 years of age and subjects >55 years of age in Study C4591044 Cohort 2. It was confirmed that the bivalent booster dose (original strain/BA.4/BA.5 lineages) improved the immune response against BA.4/BA.5 lineages without compromising the immune response against the reference strain, as compared with the response in the group receiving the bivalent vaccine (original strain/BA.1 lineage) in Study C4591031 Substudy E. Tables 6 and 7 show the immunogenicity by presence or absence of the history of SARS-CoV-2 infection at baseline (based on the results of test for N-binding antibody or nucleic acid amplification test [NAAT] at baseline or on the past history of COVID-19). Immune enhancement was observed in all populations, although the antibody response rate in subjects with a history of infection was lower than in subjects without a history of infection due to the higher GMT before study vaccine administration.

Table 6. Serum SARS-CoV-2 neutralizing antibody titer (by presence/absence of SARS-CoV-2 infection at baseline, evaluable immunogenicity population)

	Age group	18-55 years (N = 95)		>55 years (N = 102)	
		n	GMT or GMFR [2-sided 95% CI]	n	GMT or GMFR [2-sided 95% CI]
With SARS-CoV-2 infection at baseline[a)]					
BA.4/ BA.5	GMT before dose	62	900.3 [661.5, 1225.2]	61	745.8 [516.5, 1076.9]
	GMT at 1 month after dose	62	4678.4 [3438.9, 6364.6]	62	4383.6 [3261.9, 5891.1]
	GMFR	62	5.2 [3.8, 7.1]	61	5.9 [4.2, 8.1]
BA.1	GMT before dose	62	934.3 [697.0, 1252.5]	62	937.3 [689.5, 1274.0]
	GMT at 1 month after dose	62	3938.2 [3069.0, 5053.5]	62	3871.0 [2919.8, 5132.2]
	GMFR	62	4.2 [3.2, 5.6]	62	4.1 [3.1, 5.6]
Reference strain	GMT before dose	62	5615.4 [4406.4, 7156.1]	61	5428.8 [4112.6, 7166.3]
	GMT at 1 month after dose	62	16214.4 [13340.3, 19707.6]	62	15336.7 [12079.9, 19471.6]
	GMFR	62	2.9 [2.3, 3.6]	61	2.9 [2.3, 3.6]
Without SARS-CoV-2 infection at baseline[b)]					
BA.4/ BA.5	GMT before dose	33	53.8 [41.1, 70.5]	40	76.0 [54.7, 105.7]
	GMT at 1 month after dose	33	1110.7 [743.9, 1658.4]	40	1668.1 [1089.6, 2553.7]
	GMFR	33	20.6 [13.6, 31.3]	40	21.9 [14.2, 33.8]
BA.1	GMT before dose	33	53.5 [35.0, 81.8]	40	84.7 [55.7, 128.6]
	GMT at 1 month after dose	33	954.7 [664.4, 1371.8]	40	1481.5 [1020.3, 2151.2]
	GMFR	33	17.8 [11.6, 27.5]	40	17.5 [12.2, 25.1]
Reference strain	GMT before dose	33	456.8 [291.5, 716.0]	40	881.9 [601.6, 1292.7]
	GMT at 1 month after dose	33	6685.8 [4731.8, 9446.9]	40	8386.3 [6235.4, 11279.2]
	GMFR	33	14.6 [9.5, 22.6]	40	9.5 [6.4, 14.0]

N = Number of subjects analyzed, n = Number of subjects available with the data of antibody titer at the evaluation time point
a) Positive for N-binding antibody or for NAAT test at baseline, or history of COVID-19 infection
b) Negative for N-binding antibody or for NAAT test at baseline, or without history of COVID-19 infection

Table 7. Serum SARS-CoV-2 neutralizing antibody response rate (by presence/absence of SARS-CoV-2 infection at baseline, evaluable immunogenicity population)

Age group	18-55 years (N = 95)		>55 years (N = 102)	
	n2/n1	Antibody response rate (%) [2-sided 95% CI]	n2/n1	Antibody response rate (%) [2-sided 95% CI]
With SARS-CoV-2 infection at baseline[a)]				
BA.4/ BA.5	34/62	54.8 [41.7, 67.5]	36/61	59.0 [45.7, 71.4]
BA.1	28/62	45.2 [32.5, 58.3]	28/62	45.2 [32.5, 58.3]
Reference strain	20/62	32.3 [20.9, 45.3]	21/61	34.4 [22.7, 47.7]
Without SARS-CoV-2 infection at baseline[b)]				
BA.4/ BA.5	27/33	81.8 [64.5, 93.0]	36/40	90.0 [76.3, 97.2]
BA.1	24/33	72.7 [54.5, 86.7]	37/40	92.5 [79.6, 98.4]
Reference strain	27/33	81.8 [64.5, 93.0]	30/40	75.0 [58.8, 87.3]

N = Number of subjects analyzed, n1 = Number of subjects available with the data of antibody titer at the evaluation time point,
n2 = Number of subjects showing a ≥4-fold increase in the antibody titer from baseline (LLOQ if baseline titer is below the LLOQ)
a) Positive for N-binding antibody or for NAAT test at baseline, or history of COVID-19 infection
b) Negative for N-binding antibody or for NAAT test at baseline, or without history of COVID-19 infection

The evaluable immunogenicity population included the following 4 subjects with important protocol deviations: 1 subject 18 to 55 years of age in the bivalent vaccine (original strain/BA.4/BA.5 lineages)

group (did not receive the study vaccine within 150-365 days after the third dose); 1 subject 18 to 55 years of age in the reference group (had received the fourth dose of vaccine before the administration of the study vaccine); and 2 subjects >55 years of age in the reference group (did not receive the study vaccine within 150-365 days after the third dose). These subjects should have been excluded from the evaluable immunogenicity population but were included because the protocol deviations were reported after the data fixation or release. However, the applicant confirmed that the results obtained from the evaluable immunogenicity population were similar to those based on the analysis using all evaluable subject data, indicating that the above deviations had little effect on the evaluation of immunogenicity, requiring no change in the interpretation of the study results.

Subjects in Study C4591044 Cohort 2 were the population of an age group different from that of the present application. The efficacy of 2 or 3 doses of the parent vaccine against COVID-19 during the epidemic of the Omicron variant was similar among age groups 5 to 11 years of age, those 12 to 15 years of age, and those ≥18 years of age (ACIP (Sep/1/2022) Updates on COVID-19 Vaccine Effectiveness During Omicron,[4)] *JAMA.* 2022;327:2210-9). From the above, an immune response similar to that in Study C4591044 Cohort 2 is expected to be obtained in children 5 to 11 years of age, suggesting efficacy in this age group as well.

PMDA's view:
Since Study C4591044 Cohort 2 did not include the concurrent control group, immunogenicity was evaluated by descriptive comparison using the bivalent vaccine (original strain/BA.1 lineage) evaluated in another study (Study C4591031 Substudy E) as the reference group, instead of comparison based on the statistical hypothesis. It is difficult to discuss the immunogenicity and efficacy of the bivalent vaccine (original strain/BA.4/BA.5 lineages) observed in Study C4591044 Cohort 2 based on the strict comparison with the results obtained from the parent vaccine or the bivalent vaccine (original strain/BA.1 lineage). Nevertheless, PMDA confirmed that administration of the bivalent vaccine (original strain/BA.4/BA.5 lineages) in subjects ≥18 years of age increased the neutralizing antibody titer against Omicron BA.4/BA.5 lineages, BA.1 lineage, and the reference strain after the dose in subjects both with and without a history of SARS-CoV-2 infection.

The clinical study (Study C4591048 Substudy D) to evaluate the immunogenicity of the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age, the target age group in this application, is currently ongoing, and relevant data are unavailable during the process of this review. Nevertheless, given the following, the applicant's view that the bivalent vaccine (original strain/BA.4/BA.5 lineages) is expected to show the efficacy in children 5 to 11 years of age as well is acceptable:
(a) The booster dose of the parent vaccine recovered the immunogenicity in children 5 to 11 years of age (Comirnaty Intramuscular Injection for 5 to 11 years old: Report on Special Approval for Emergency [dated August 17, 2022]).

4) https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/04-covid-link-gelles-508.pdf (last accessed on February 6, 2023)

(b) The efficacy of bivalent vaccine (original strain/BA.4/BA.5 lineages) is shown in adults (preventive effect against symptomatic SARS-CoV-2 infection and preventive effect against an emergency visit or hospitalization due to COVID-19-like disease) [see Section 7.R.1].
(c) The efficacy of the parent vaccine during the pandemic of the Omicron variant was similar among the age groups of 5 to 11 years of age, 12 to 15 years of age, and ≥18 years of age (ACIP (Sep/1/2022) Updates on COVID-19 Vaccine Effectiveness During Omicron,[4] *JAMA.* 2022;327:2210-9).

Results of immunogenicity and efficacy of bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age should be evaluated as soon as they become available, and necessary measures including the information provision to healthcare professionals should be taken. The prevalent strain of SARS-CoV-2 evolves rapidly, and novel Omicron sublineages have been reported. As of January 2023, BQ.1 lineage is detected at an increasing rate also in Japan. The immunogenicity of the bivalent vaccine (original strain/BA.4/BA.5 lineages) against these sublineages (BQ.1.1, XBB, etc.) is lower than the immunogenicity against BA.5 lineage (*Nat Med.* 2022;doi:10.1038/s41591-022-02162-x, *N Engl J Med.* 2023;388:183-5). On the other hand, vaccine effectiveness of the bivalent booster dose (original strain/BA.4/BA.5 lineages) during the period from December 1, 2022 through January 13, 2023 was reported in the U.S, suggesting that the bivalent booster dose (original strain/BA.4/BA.5 lineages) provided additional protection for ≥3 months against symptomatic infection by XBB/XBB.1.5 lineages (*MMWR Morb Mortal Wkly Rep.* 2023;72:119-24). Since different Omicron lineages and novel variants are likely to emerge in the future, information on the efficacy (including immunogenicity) of the bivalent vaccine (original strain/BA.4/BA.5 lineages) should be collected from data accumulated in each country and from study reports, and appropriate measures should be taken based on the information thus obtained.

7.R.3 Safety

The applicant's explanation about the safety of the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age, based on the data of Study C4591044 Cohort 2, submitted as the evaluation data as well as on a part of the data of Study C4591048 Substudy D obtained during the review process and on the post-marketing information in foreign countries:
(a) Study C4591044 Cohort 2 (subjects ≥12 years of age)
The incidence of reactogenicity events within 7 days after the study vaccine administration tended to be lower in the age group of >55 years than in other age groups, and the incidence of most events was higher in the 60 μg group than in the 30 μg group (Table 4). Most of the reactogenicity events were Grade 1 or 2. Grade ≥3 events (>38.9℃ for pyrexia) were injection site pain (1 subject in age group of 12-17 years), redness (1 subject in the 60 μg group of 18-55 years), fatigue (2 subjects in the 30 μg group and 1 subject in the 60 μg group of 18-55 years; 1 subject in the 30 μg group and 4 subjects in the 60 μg group of >55 years), headache (1 subject in the 60 μg group of 18-55 years; 1 subject in the 60 μg group of >55 years), chills (1 subject in the 60 μg group of 18-55 years), diarrhoea (1 subject in the 30 μg group of 18-55 years), myalgia (1 subject in the 60 μg group of >55 years), arthralgia (1 subject in the 60 μg group of 18-55 years, 1 subject in the 60 μg group of >55 years), and pyrexia (1 subject in age group of 12-17 years, 2 subjects in the 60 μg group of 18-55 years, 2 subjects in the 60 μg group of >55 years). The median time to onset was 1 to 3 days for local reactions and 2 to 4 days for systemic events, and the median duration was 1 to 3 days for local reactions and 1 to 2 days for systemic events.

The trend of the occurrence of reactogenicity events after the administration of the bivalent vaccine (original strain/BA.4/BA.5 lineages) 30 μg was similar to that observed after the booster dose with the parent vaccine or vaccines tailored to Omicron BA.1 lineage (Table 8).

Table 8. Reactogenicity events within 7 days after the study vaccine administration (safety analysis set)

	Event terms	Bivalent vaccine (original strain/BA.4/BA.5 lineages) 30 μg			Study C4591031 Substudy D[b, c)]		Study C4591031 Substudy E[b, d)]		
					Parent vaccine 30 μg	BA.1 monovalent vaccine 30 μg	Parent vaccine 30 μg	BA.1 monovalent vaccine 30 μg	Bivalent vaccine (original strain/ BA.1 lineage) 30 μg
		12-17 years of age	18-55 years of age	>55 years of age	18-55 years of age		>55 years of age		
		N = 107	N = 102	N = 105	N = 306	N = 294	N = 298	N = 301	N = 301
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reactions	Total	75 (70.1)	85 (83.3)	60 (57.1)	243 (79.4)	231 (78.6)	182 (61.1)	205 (68.1)	179 (59.5)
	Injection site pain	75 (70.1)	81 (79.4)	59 (56.2)	240 (78.4)	229 (77.9)	179 (60.1)	199 (66.1)	175 (58.1)
	Redness	6 (5.6)	6 (5.9)	3 (2.9)	13 (4.2)	21 (7.1)	19 (6.4)	19 (6.3)	21 (7.0)
	Swelling	8 (7.5)	7 (6.9)	2 (1.9)	27 (8.8)	25 (8.5)	18 (6.0)	25 (8.3)	20 (6.6)
Systemic events	Total	86 (80.4)	77 (75.5)	59 (56.2)	223 (72.9)	228 (77.6)	167 (56.0)	192 (63.8)	182 (60.5)
	Fatigue	72 (67.3)	64 (62.7)	41 (39.0)	185 (60.5)	189 (64.3)	135 (45.3)	158 (52.5)	148 (49.2)
	Headache	54 (50.5)	45 (44.1)	31 (29.5)	138 (45.1)	140 (47.6)	79 (26.5)	110 (36.5)	101 (33.6)
	Chills	25 (23.4)	15 (14.7)	13 (12.4)	80 (26.1)	93 (31.6)	49 (16.4)	77 (25.6)	39 (13.0)
	Vomiting	3 (2.8)	2 (2.0)	1 (1.0)	5 (1.6)	8 (2.7)	4 (1.3)	9 (3.0)	5 (1.7)
	Diarrhoea	7 (6.5)	14 (13.7)	9 (8.6)	36 (11.8)	25 (8.5)	13 (4.4)	24 (8.0)	27 (9.0)
	Myalgia	28 (26.2)	32 (31.4)	21 (20.0)	87 (28.4)	99 (33.7)	59 (19.8)	72 (23.9)	67 (22.3)
	Arthralgia	13 (12.1)	17 (16.7)	12 (11.4)	46 (15.0)	69 (23.5)	27 (9.1)	50 (16.6)	34 (11.3)
	Pyrexia[a)]	10 (9.3)	5 (4.9)	8 (7.6)	22 (7.2)	25 (8.5)	11 (3.7)	25 (8.3)	15 (5.0)

N = Number of subjects analyzed, n = Number of subjects with events
a) ≥38℃
b) Comirnaty RTU Intramuscular Injection: Report on Special Approval for Emergency (dated September 7, 2022)
c) Study vaccine administered 3 to 6 months after the third dose of vaccine
d) Study vaccine administered 5 to 12 months after the third dose of vaccine

There were few adverse events within 1 month after the study vaccine administration. Other than events specified as reactogenicity events (fatigue, injection site pain, headache, and myalgia), adverse events observed in ≥2 subjects in total were lymphadenopathy, sinusitis, and dyspnoea in 2 subjects each (Table 5). A causal relationship to the study vaccine could not be ruled out for the events specified as reactogenicity events and for lymphadenopathy in both subjects, but the outcome was “recovered” for all of them.

A Grade ≥3 adverse event (dyspnoea) was observed in 1 subject (>55 years of age, 30 μg group). Its causal relationship to the study vaccine was denied, and the outcome was “resolving” at the data cutoff time point. A serious adverse event was observed in 1 subject (the same subject who had Grade ≥3 adverse event). There were no deaths or adverse events leading to study discontinuation.

(b) Study C4591048 Substudy D (subjects 5-11 years of age)

Study C4591048 Substudy D is a foreign phase II study to evaluate the immunogenicity and safety of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) in children 5 to 11 years of age who completed 2 or 3 prior doses of the parent vaccine with the last dose being administered 90 to 240 days earlier (target sample size, approximately 250 subjects). After the submission of this application, data of reactogenicity events within 7 days after the vaccine administration and data of adverse events within 1 month after the vaccine administration became available in a part of subjects (113 subjects who had

received 3 prior doses of the parent vaccine 10 μg and received, as the fourth dose, the bivalent vaccine [original strain/Omicron BA.4/BA.5 lineages]).

Reactogenicity events observed within 7 days after the study vaccine administration (111 subjects evaluated; the number of subjects who entered response [yes/no] on at least 1 reactogenicity events in the electronic diary for 7 days after the study vaccine administration) were as follows: Local reactions, total 66.7% (74 of 111 subjects), injection site pain 64.0% (71 of 111 subjects), redness 7.2% (8 of 111 subjects), and swelling 4.5% (5 of 111 subjects); systemic events, total 52.3% (58 of 111 subjects), fatigue 40.5% (45 of 111 subjects), headache 25.2% (28 of 111 subjects), myalgia 13.5% (15 of 111 subjects), chills 9.0% (10 of 111 subjects), arthralgia 9.0% (10 of 111 subjects), pyrexia 4.5% (5 of 111 subjects), vomiting 3.6% (4 of 111 subjects), and diarrhoea 3.6% (4 of 111 subjects). Grade ≥3 events (>38.9℃ for pyrexia) were pyrexia in 2 subjects and fatigue and headache in 1 subject each. The incidence of adverse events within 1 month after the vaccine administration was 3.5% (4 of 113 subjects; influenza, otitis media, lymph node palpable, and oropharyngeal pain in 1 subject each). A causal relationship to the study vaccine could not be ruled out for lymph node palpable in 1 subject. A Grade ≥3 adverse event (influenza) was observed in 1 subject. There were no reports of serious adverse events, deaths, or adverse events leading to study discontinuation until the data cutoff date (November 25, 2022).

(c) Post-marketing safety information in foreign countries

The applicant's safety database on Comirnaty (parent vaccine, bivalent vaccine [original strain/BA.4/BA.5 lineages], and bivalent vaccine [original strain/BA.1 lineage]) included 2,808 reports of adverse events related to the bivalent vaccine (original strain/BA.4/BA.5 lineages) up to November 15, 2022, and 415 of them were reported in 163 children 5 to 11 years of age. Of the adverse events reported in 163 subjects, events in 157 subjects were reports related to vaccination error (overdose, wrong product administered, etc.), and clinical events were not reported in 146 of them. Vomiting, diarrhoea, and pyrexia observed in 1 subject were reported as serious events, but the outcome was "resolving" for all of them. Among nonserious events, clinical events reported in ≥3 subjects were pyrexia and pain in extremity in 8 subjects each, fatigue and pain in 6 subjects each, vaccination site pain in 5 subjects, headache in 4 subjects, nausea, dyspnoea, pruritus, and flushing in 3 subjects each. During the period from November 16 to December 15 in 2022 as well, most (94 of 109 subjects) of reports related to the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age were related to vaccination error.

Most of reactogenicity events reported in the safety data obtained from subjects ≥12 years of age in Study C4591044 Cohort 2 and subjects 5 to 11 years of age in Study C4591048 Substudy D were mild or moderate, and there were few other adverse events reported, showing well tolerability.

The reports related to the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age included in the applicant's safety database contained many reports related to vaccination errors, but few of them were accompanied by clinical events, with none of them resulting in serious health damage. The reports related to clinical events were consistent with the safety profile so far confirmed on the parent vaccine.

The above results suggest that the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age has an acceptable safety profile as that of the parent vaccine, although it is necessary to lower the risk by promoting the proper use (through education and support of personnel engaged in immunization).

PMDA's view:
The safety profile of the bivalent vaccine (original strain/BA.4/BA.5 lineages) is considered to be comparable to that of the parent vaccine, based on the data of Study C4591044 Cohort 2 and on a part of the data of Study C4591048 Substudy D, and there have been no new safety concerns at present in the safety information in post-marketing reports in foreign countries, suggesting that the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age can be assumed to have an acceptable safety profile. After the marketing, the safety of the bivalent vaccine (original strain/BA.4/BA.5 lineages) should be evaluated promptly based on the safety data of Study C4591048 Substudy D and on the post-marketing safety information, and appropriate measures should be taken including provision of necessary information to healthcare professionals.

7.R.4 Indication

On the basis of the reviews on the efficacy and safety [see Sections 7.R.2 and 7.R.3], PMDA considers that "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" is acceptable for the indication of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) as is the case with the parent vaccine.

7.R.5 Dosage and administration

7.R.5.1 Dose setting

The applicant's explanation about dose-setting:
In the clinical study (Study C4591031 Substudy E) conducted in the development of the bivalent vaccine (original strain/BA.1 lineage), the dose of 30 μg was selected, as was the case with the parent vaccine, from the results of the immunogenicity and safety obtained from administration of the bivalent vaccine (original strain/BA.1 lineage) 30 μg or 60 μg (tozinameran and riltozinameran [at an RNA mass ratio of 1:1]) to subjects ≥12 years of age (Comirnaty RTU Intramuscular Injection: Report on Special Approval for Emergency [dated September 7, 2022]). The parent vaccine, the bivalent vaccine (original strain/BA.1 lineage), and the bivalent vaccine (original strain/BA.4/BA.5 lineages) were manufactured on the same platform, and the active ingredients of tozinameran, riltozinameran, and famtozinameran have highly similar mRNA sequences with one another. Accordingly, the dose of the bivalent vaccine (original strain/BA.4/BA.5 lineages) for subjects ≥12 years of age was selected to be 30 μg (tozinameran and famtozinameran [at an RNA mass ratio of 1:1]), and the dose was approved in Japan as well. As described in Sections 7.R.2 and 7.R.3, the immunogenicity and safety at this dose were confirmed from the results obtained from Study C4591044 Cohort 2.

The above investigations suggested that the bivalent vaccine (original strain/BA.4/BA.5 lineages) 10 μg is expected to demonstrate the efficacy and safety in children 5 to 11 years of age, the dose for this age group was determined to be 10 μg (tozinameran and famtozinameran [at an RNA mass ratio of 1:1]) as is the case with the parent vaccine.

PMDA accepted the proposed dosage and administration of bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age. The appropriateness of the dose should be assessed based on the results to be obtained in the future, such as the data of Study C4591048 Substudy D, and measures should be taken as appropriate.

7.R.5.2 Interval between doses

The interval of booster doses in ≥12 years of age was discussed at the Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council on October 19, 2022. The proposed interval of ≥5 months from the last vaccine administration was changed to ≥3 months, taking account of the situations in foreign countries. It was also decided to investigate the interval of booster doses in children 5 to 11 years of age in the future (meeting minutes of the Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, October 19, 2022, https://www.mhlw.go.jp/stf/newpage_29042.html [last accessed on February 6, 2023]).

Currently, the interval of booster doses from the last dose in children 5 to 11 years of age is ≥5 months in Japan, ≥2 months in the U.S, and ≥3 months in Europe.

PMDA asked the applicant to explain the influences on the efficacy and safety of shortening the interval of booster doses to 3 months.

The applicant's explanation:
In some countries, the booster dose is administered at a shorter interval than that used in clinical studies according to the request of regulatory agencies from the point of view of public hygiene. There have been no reports of particular concern as explained in Section 7.R.3 even under the situation where the booster dose is administered at various intervals specified in each country. Study C4591048 Substudy D in children 5 to 11 years of age plans to use the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) 90 to 240 days after the second or third dose of the parent vaccine. Of 113 subjects with available safety data at present, 61 subjects received the bivalent vaccine within 6 months after the last dose (<3 months in 1 subject, ≥3 and <4 months in 7 subjects, ≥4 and <5 months in 29 subjects, ≥5 and <6 months in 24 subjects), but there were no safety concerns, as explained in Section 7.R.3.

Taking account of the applicant's explanation, PMDA concluded that it is acceptable to determine, in the package insert, the interval of booster doses at ≥3 months after the last dose in children 5 to 11 years of age as is the case with vaccinees ≥12 years of age.

7.R.6 Post-marketing investigations and risk management plan (draft)

The applicant's explanation about the post-marketing investigations:
Results of Study C4591044 Cohort 2 showed a favorable safety profile of the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) in subjects ≥12 years of age similar to that of the parent vaccine. The currently available data including Study C4591048 Substudy D, the post-marketing information in foreign countries, and the safety information of the parent vaccine in Japan indicated no safety concerns unique to children 5 to 11 years of age, suggesting that the bivalent vaccine (original strain/BA.4/BA.5

lineages) in children 5 to 11 years of age is unlikely to pose any safety concerns [see Section 7.R.3]. The data presented in this application do not reveal any new safety concerns, suggesting little need to immediately conduct a new post-marketing investigation on the bivalent vaccine. It will suffice to collect safety information in the usual pharmacovigilance activities. A system will be developed that allows prompt planning and conduct of a post-marketing surveillance, etc., in case issues of particular concern with the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age are raised from the information collected from the early post-marketing phase vigilance and routine pharmacovigilance activities in Japan and foreign countries.

PMDA's view:
The applicant's explanation is acceptable. PMDA has concluded that the risk management plan (draft) should include the safety specifications presented in Table 9, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 10.

Table 9. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Myocarditis, pericarditis	• Vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD) • Guillain-Barre syndrome	• Safety in pregnant and lactating women (Comirnaty Intramuscular Injection, Comirnaty Intramuscular Injection for 5 to 11 years old, and Comirnaty RTU Intramuscular Injection)
Efficacy specification		
None		

No change pertaining to the present application

Table 10. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (child vaccine recipients 6 months-4 years of age: Comirnaty Intramuscular Injection for 6 months-4 years old [monovalent: original strain]) • Early post-marketing phase vigilance (vaccine recipients ≥12 years of age: Comirnaty RTU Intramuscular Injection [bivalent: original strain/Omicron BA.1 lineage]), [bivalent: original strain/Omicron BA.4/BA.5 lineages]) • Early post-marketing phase vigilance (vaccine recipients 5-11 years of age: Comirnaty Intramuscular Injection for 5-11 years old [bivalent: original strain/Omicron BA.4/BA.5 lineages]) • Post-marketing clinical study (C4591005) (Comirnaty Intramuscular Injection [monovalent: original strain]) • Use-results survey on post-approval early vaccine recipients (healthcare professionals) (follow-up study) (C4591006) (Comirnaty Intramuscular Injection [monovalent: original strain]) • Specified use-results survey in individuals with underlying diseases who are at high risk of severe COVID-19 (C4591019) (Comirnaty Intramuscular Injection [monovalent: original strain]) • Foreign phase II/III study (C4591001) (Comirnaty Intramuscular Injection [monovalent: original strain]) • Foreign phase II/III study in pregnant women (C4591015) (Comirnaty Intramuscular Injection [monovalent: original strain])	• Disseminate data gathered during early post-marketing phase vigilance (vaccine recipients 6 months-4 years of age: Comirnaty Intramuscular Injection for 6 months-4 years old [monovalent: original strain]) • Disseminate data gathered during early post-marketing phase vigilance (vaccine recipients ≥12 years of age: Comirnaty RTU Intramuscular Injection [bivalent: original strain/Omicron BA.1 lineage], bivalent vaccine [original strain/Omicron BA.4/BA.5 lineages]) • Disseminate data gathered during early post-marketing phase vigilance (vaccine recipients 5-11 years of age: Comirnaty Intramuscular Injection for 5-11 years old [bivalent: original strain/Omicron BA.4/BA.5 lineages]) • Organize and disseminate information for healthcare professionals • Organize and disseminate information (a brochure) for vaccine recipients • Organize and disseminate information (a brochure) for child vaccine recipients • Periodical publication of the occurrence of adverse reactions (child vaccine recipients 6 months-4 years of age: Comirnaty Intramuscular Injection for 6 months-4 years old [monovalent: original strain]) • Periodical publication of the occurrence of adverse reactions (vaccine recipients ≥12 years of age: Comirnaty RTU Intramuscular Injection [bivalent: original strain/Omicron BA.1 lineage], bivalent vaccine [original strain/Omicron BA.4/BA.5 lineages]) • Periodical publication of the occurrence of adverse reactions (vaccine recipients 5-11 years of age: Comirnaty Intramuscular Injection for 5-11 years old [bivalent: original strain/Omicron BA.4/BA.5 lineages])

Underline denotes additions pertaining to the present application.

There are many reports of vaccination errors after the market launch in foreign countries [see Section 7.R.3]. Under the circumstances where multiple vaccine products with varying active ingredients are used for different vaccine recipients, there is a risk of vaccination using a wrong vaccine product or by a wrong dosage regimen in the use of the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age. In addition to the protection measures against administration errors already in practice, it is essential to raise further caution and collect information for the proper use.

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 5.3.5.1.3 and 5.3.5.1.4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation

On the basis of the submitted data showing the results obtained from studies on subjects of other age groups and the findings available so far, PMDA has concluded that the booster dose with the bivalent vaccine (original strain/Omicron BA.4/BA.5 lineages) in children 5 to 11 years of age is expected to show a certain level of efficacy in preventing disease caused by SARS-CoV-2 infection (COVID-19) and that the vaccine is considered to have the acceptable safety profile as that of the parent vaccine. It is necessary to take prompt and appropriate measures such as providing information to healthcare professionals and taking additional measures as soon as results of the clinical study on the bivalent vaccine (original strain/BA.4/BA.5 lineages) in children 5 to 11 years of age become available. In view of its benefit/risk balance by considering the status of COVID-19 outbreaks and the risk factors in individuals, PMDA considers that it is clinically significant to make the booster dose with the bivalent vaccine (original strain/BA.4/BA.5 lineages) available for children 5 to 11 years of age.

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until February 13, 2029).

Indication

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

The indication applies to the following vaccine products:

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

(Underline denotes additions.)

Dosage and Administration

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

The product is diluted with 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).
For the primary series, 2 doses (0.2 mL each) are injected intramuscularly, usually 3 weeks apart.
For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

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

The product is diluted with 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).
For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

(Underline denotes additions.)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (2) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (3) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at present, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.
   (4) The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form and have provided written informed consent through the vaccine screening questionnaire in advance.

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

Appendix

List of Abbreviations

Adverse reaction	Adverse event for which a causal relation to the study vaccine cannot be ruled out
BA.1 monovalent vaccine	Monovalent vaccine containing riltozinameran
Bivalent vaccine (original strain/BA.1 lineage)	Bivalent vaccine containing tozinameran and riltozinameran [at an RNA mass ratio of 1:1])
Bivalent vaccine (original strain/ BA.4/BA.5 lineages)	Bivalent vaccine containing tozinameran and famtozinameran [at an RNA mass ratio of 1:1])
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CTD	Common technical document
FDA	Food and Drug Administration
GCP	Good clinical practice
GMFR	Geometric mean-fold rise
GMT	Geometric mean titer
LLOQ	Lower limit of quantitation
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
NAAT	Nucleic acid amplification test
Original strain	Strain Wuhan-Hu-1
Parent vaccine	Monovalent vaccine containing tozinameran
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
Reference strain	Strain USA-WA1/2020
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S-protein	Spike protein