Report on Special Approval for Emergency

July 25, 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	(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old, (d) Comirnaty Intramuscular Injection for 6 months to 4 years old
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine (Active ingredients: (a) 1) Tozinameran [JAN*], 2) Tozinameran [JAN*] and Famtozinameran [JAN*], 3) Tozinameran [JAN*] and Riltozinameran [JAN*] (b) 1) Tozinameran, 2) Tozinameran and Famtozinameran (c) 1) Tozinameran, 2) Tozinameran and Famtozinameran (d) 1) Tozinameran, 2) Tozinameran and Famtozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	April 11, 2023
Dosage Form/Strength	(a) 1) Injection: Each vial (2.25 mL) contains 0.225 mg of Tozinameran. 2) Injection: Each vial (2.25 mL) contains a total of 0.225 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1). 3) Injection: Each vial (2.25 mL) contains a total of 0.225 mg of Tozinameran and Riltozinameran (at an RNA mass ratio of 1:1). (b) 1) Injection: Each vial (0.3 mL) contains 0.030 mg of Tozinameran. 2) Injection: Each vial (0.3 mL) contains a total of 0.030 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1). (c) 1) Injection: Each vial (1.3 mL) contains 0.130 mg of Tozinameran. 2) Injection: Each vial (1.3 mL) contains a total of 0.130 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1). (d) 1) Injection: Each vial (0.4 mL) contains 0.040 mg of Tozinameran. 2) Injection: Each vial (0.4 mL) contains a total of 0.040 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1).
Application Classification	(a)-(c): 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.)

(d): Prescription drug, (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, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act ("Handling of Drugs Submitted for Special Approval for Emergency (Request)" [PSEHB/PED Notification 0502-4, dated May 2, 2023]).

Reviewing Office Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the booster dose in children 6 months to 4 years of age and the primary series in all age groups ≥6 months with the vaccine product which contains messenger ribonucleic acid (mRNA) encoding the spike proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Wuhan-Hu-1 strain [the original strain] and Omicron BA.4-5 lineages [Omicron variant]) have a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (Coronavirus disease 2019 [COVID-19]), and that the product has acceptable safety without serious 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 approval conditions.

Indication

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old

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 (the original strain)~~

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

(Strikethrough denotes deletions.)

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old

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

(No change)

Dosage and Administration

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person

~~• Vaccine product containing mRNA encoding spike protein of SARS-CoV-2 (the original strain):~~
~~For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.~~
~~For a booster dose, a single dose of 0.3 mL is injected intramuscularly.~~
~~• Vaccine product containing mRNA encoding spike protein of SARS-CoV-2 (the original strain and Omicron variant)~~
For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.
For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

(c) Comirnaty Intramuscular Injection for 5 to 11 years old
~~• Vaccine product containing mRNA encoding spike protein of SARS-CoV-2 (the 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 (the original strain and Omicron variant)~~
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.

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old
The product is diluted with 2.2 mL of physiological saline (Japanese Pharmacopoeia grade).
For the primary series, 3 doses (0.2 mL each) are injected intramuscularly. The second dose is administered 3 weeks apart usually. The third dose is administered at least 8 weeks after the second dose.
For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

(Strikethrough denotes deletions. Underline denotes additions.)

Approval Conditions

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old, (d) Comirnaty Intramuscular Injection for 6 months to 4 years old

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 the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.
   (4) The efficacy and safety data of the product will be accrued with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form and 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

July 24, 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	(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old, (d) Comirnaty Intramuscular Injection for 6 months to 4 years old
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine (Active ingredients: (a) 1) Tozinameran, 2) Tozinameran and Famtozinameran, 3) Tozinameran and Riltozinameran (b) 1) Tozinameran, 2) Tozinameran and Famtozinameran (c) 1) Tozinameran, 2) Tozinameran and Famtozinameran (d) 1) Tozinameran, 2) Tozinameran and Famtozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	April 11, 2023
Dosage Form/Strength	(a) 1) Injection: Each vial (2.25 mL) contains 0.225 mg of Tozinameran. 2) Injection: Each vial (2.25 mL) contains a total of 0.225 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1). 3) Injection: Each vial (2.25 mL) contains a total of 0.225 mg of Tozinameran and Riltozinameran (at an RNA mass ratio of 1:1). (b) 1) Injection: Each vial (0.3 mL) contains 0.030 mg of Tozinameran. 2) Injection: Each vial (0.3 mL) contains a total of 0.030 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1). (c) 1) Injection: Each vial (1.3 mL) contains 0.130 mg of Tozinameran. 2) Injection: Each vial (1.3 mL) contains a total of 0.130 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1). (d) 1) Injection: Each vial (0.4 mL) contains 0.040 mg of Tozinameran. 2) Injection: Each vial (0.4 mL) contains a total of 0.040 mg of Tozinameran and Famtozinameran (at an RNA mass ratio of 1:1).

Proposed Indication

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old

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 (the original strain)

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

(No change)

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old

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 (the original strain)

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

(Underline denotes additions.)

Proposed Dosage and Administration

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person

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

~~For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.~~

~~For a booster dose, a single dose of 0.3 mL is injected intramuscularly.~~

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

For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.

For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

(c) Comirnaty Intramuscular Injection for 5 to 11 years old

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

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.

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old

The product is diluted with 2.2 mL of physiological saline (Japanese Pharmacopoeia grade).

For the primary series, 3 doses (0.2 mL each) are injected intramuscularly. The second dose is administered 3 weeks apart usually. The third dose is administered at least 8 weeks after the second dose.

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

(Strikethrough denotes deletions. Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

The COVID-19 global pandemic emerged in January 2020, and various preventive measures including vaccinations have been taken since then. However, genetic mutations of SARS-CoV-2 have resulted in successive emergence of variants with altered infectivity, transmissibility, antigenicity, and pathogenicity and have caused multiple waves of SARS-CoV-2 infection. On May 5, 2023, the World Health Organization (WHO) declared an end to COVID-19 as a public health emergency of international concern,[1)] but a possibility remains that the number of infected patients may increase significantly in the future as a result of virus genetic mutations.

The applicant has been granted the marketing approval of monovalent vaccine (against the original strain [Original]) and bivalent vaccines against both the Original and Omicron variant, containing tozinameran and riltozinameran (at an RNA mass ratio of 1:1) (Omicron BA.1) or containing tozinameran and famtozinameran (at an RNA mass ratio of 1:1) (Omicron BA.4-5) (Table 1).

Table 1. SARS-CoV-2 vaccines for which the applicant is granted marketing approval in Japan

Age group	Monovalent vaccine/bivalent vaccine	Approved dosage regimens	
		Primary series	Booster dose
≥12 years	Monovalent vaccine (Original)	○	○
	Bivalent vaccine (Original and Omicron BA.1) Bivalent vaccine (Original and Omicron BA.4-5)	×	○
5-11 years	Monovalent vaccine (Original)	○	○
	Bivalent vaccine (Original and Omicron BA.4-5)	×	○
6 months to 4 years	Monovalent vaccine (Original)	○	×
	Bivalent vaccine (Original and Omicron BA.4-5)	×	×

○, Approved; ×, Not approved

In March 2023, emergency use authorization of the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age was granted in the US, allowing the booster dose in children of this age group. In April 2023, emergency use authorization was granted regarding the dosage regimen of the bivalent vaccine for the primary series in all age groups ≥6 months. In view of these approvals, the same partial change application was submitted in Japan.

For the present application, the applicant submitted data of the foreign clinical studies administering a booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children of each age group and in adults (Study C4591048 Substudy B in subjects ≥6 months to <5 years of age [Group 2], Study C4591048 Substudy D in subjects ≥5 and <12 years of age [Group 2], and Cohorts 2 and 3 of Study C4591044 in subjects ≥12 years of age).

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 No. 0502-4, dated May 2, 2023).

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 July 14, 2023)

2. Quality and Outline of the Review Conducted by PMDA

The bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old, added in this application, is a vaccine containing, encapsulated in lipid nanoparticles (LNP), tozinameran and famtozinameran which are messenger ribonucleic acid (mRNAs) encoding spike proteins of the original strain of SARS-CoV-2 and the Omicron BA.4-5 lineages, respectively. Two active substances, tozinameran and famtozinameran, are the same as those used in the manufacture of Comirnaty RTU Intramuscular Injection (bivalent, Original and Omicron BA.4-5), etc., and their data on the quality have already been reviewed.

The manufacturing process of vaccine product for the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old is identical to that for the existing monovalent vaccine (Original) of Comirnaty Intramuscular Injection for 6 months to 4 years old, except for the dilution process of the active substance. Although the dilution process of the active substances is different from that of the monovalent vaccine (Original) in that a 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 monovalent vaccine (Original) with water for injection for adjusting the concentration in the dilution process, and the manufacturing process has been validated for the monovalent vaccine (Original). 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 thus prepared has the same quality attributes as that of the monovalent vaccine (Original).

Changes were made to some parameters of the manufacturing process of the following active substances: (1) Riltozinameran, one of the active substances of Comirnaty RTU Intramuscular Injection; and (2) famtozinameran, one of the active substances of Comirnaty RTU Intramuscular Injection, Comirnaty RTU Intramuscular Injection for 1 person, and Comirnaty Intramuscular Injection for 5 to 11 years old.

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 associated with the changes proposed in the present applications.

2.R.1 Shelf-life of Comirnaty Intramuscular Injection for 6 months to 4 years old

The proposed shelf life for the bivalent vaccine product (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old was 18 months, the same period as that of the monovalent vaccine (Original), but it was extended to 24 months during the review process, pursuant to the extension of the shelf life of the monovalent vaccine (Original) to 24 months. However, results from the 24-month long-term testing on the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old have not been submitted during the review process.

The applicant's explanation about the shelf life of the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old:
The shelf-life of the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old can be determined as 24 months, the same shelf-life as approved for the monovalent vaccine (Original) of Comirnaty Intramuscular Injection for 6 months to 4 years old,

given the following: (1) The quality attributes of Comirnaty Intramuscular Injection for 6 months to 4 years old are similar between the monovalent vaccine (Original) and the bivalent vaccine (Original and Omicron BA.4-5); and (2) the safety profiles of the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for children 6 months to 4 years of age and the bivalent vaccine (Original and Omicron BA.4-5) which is filled at a different volume are similar to those of the monovalent vaccine (Original). The 24-month stability will be confirmed in the ongoing long-term testing on the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old.

PMDA's view:
Taking account of the applicant's explanation, it is acceptable to determine the shelf-life of the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old to be 24 months when stored at −75℃ ± 15℃ as is the case with the monovalent vaccine (Original). The stability should be confirmed in the ongoing long-term testing on the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old.

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

The applicant submitted results of primary pharmacodynamics studies as data of the nonclinical pharmacological studies.

3.1 Primary pharmacodynamics (CTD 4.2.1.1)

The bivalent vaccine (Original and Omicron BA.4-5) was administered intramuscularly twice (21 days apart) to BALB/c mice (n = 10 females/group), and neutralizing antibody in serum was measured on Day 7 and at Month 1, using pseudovirus.[2)] At both time points, production of neutralizing antibodies against the original strain and Omicron variants (BA.1, BA.2, BA.2.12.1, and BA.4-5) was observed.

As described above, the applicant explained that vaccination with the bivalent vaccine (Original and Omicron BA.4-5) is expected to produce neutralizing antibodies against the original strain and Omicron sublineages.

3.R Outline of the review conducted by PMDA

On the basis of the submitted document, PMDA concluded that the applicant's explanation about the non-clinical pharmacology is acceptable.

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

Although the present application relates to new indications, new dosage, etc., no new data were submitted under this section because conducting non-clinical pharmacokinetics is usually not required for vaccines.[3)]

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2) Vesicular stomatitis virus inserted with a gene encoding spike protein derived from SARS-CoV-2
3) WHO Technical Report Series No. 927 (Annex 1 Guidelines on nonclinical evaluation of vaccines; 2005) and "Guidelines for Nonclinical Studies of Preventive Vaccines for Infectious Diseases (in Japanese)" (PFSB/ELD Notification No. 0527-1, dated May 27, 2010)

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application relates to new indications, new dosage, etc., 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 this application.

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

The applicant submitted efficacy and safety evaluation data shown in Table 2.

Table 2. Outline of clinical studies

Data category	Country	Study ID	Phase	Population	No. of subjects enrolled	Dosage regimen	Study objective
Evaluation	US	Study C4591048 Substudy B (Group 2)	I/II/III	Healthy children aged ≥6 months to <5 years who completed 3 prior doses of the monovalent vaccine (Original) 3 µg with the last dose being administered 60-240 days earlier	60	Intramuscular injection of bivalent vaccine (Original and Omicron BA.4-5) 3 µg as the fourth dose	Safety Immunogenicity
Evaluation	US	Study C4591048 Substudy D (Group 2)	I/II/III	Healthy children aged ≥5 and <12 years who completed 3 prior doses of the monovalent vaccine (Original) 10 µg with the last dose being administered 90-240 days earlier	113	Intramuscular injection of bivalent vaccine (Original and Omicron BA.4-5) 10 µg as the fourth dose	Safety Immunogenicity
Evaluation	US	Study C4591044 Cohorts 2 and 3	II/III	Healthy subjects aged ≥12 years who completed 3 prior doses of the monovalent vaccine (Original) 30 µg with the last dose being administered 5-12 months earlier	619	Intramuscular injection of bivalent vaccine (Original and Omicron BA.4-5) 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 I/II/III study (CTD 5.3.5.1.1 to 5.3.5.1.2; Study C4591048 Substudy B [Group 2]; study period, ongoing since September 2022 [data cutoff date, November 25, 2022])

An open-label, uncontrolled study was conducted at 6 study sites in the US to investigate the safety and immunogenicity of the bivalent vaccine (Original and Omicron BA.4-5) administered as the fourth dose in healthy children ≥6 months to <5 years of age (target sample size, approximately 300 subjects) who completed 3 prior doses of the monovalent vaccine (Original) 3 µg as the primary series with the last dose being administered 60 to 240 days earlier.

The bivalent vaccine (Original and Omicron BA.4-5) 3 µg was administered once intramuscularly.

For this review, the applicant submitted results of the immunogenicity and safety analysis in subjects with available data of 1 month after vaccination on or before the data cutoff date (November 25, 2022).

Of the 60 subjects with available data of 1 month after the study vaccine administration on or before the data cutoff date (24 subjects ≥6 months to <2 years of age, 36 subjects ≥2 to <5 years of age), all subjects were included in the safety analysis set. A total of 58 of 60 subjects (23 subjects ≥6 months to <2 years of age, 35 subjects ≥2 to <5 years of age) were included in the evaluable immunogenicity set. The remaining 2 subjects were excluded because they had no blood collected within the specified time frame and had no immunogenicity data available after the study vaccine administration (1 subject ≥6 months to <2 years of age, 1 subject ≥2 to <5 years of age).

For immunogenicity evaluation, the immunogenicity data of 60 subjects (24 subjects ≥6 months to <2 years of age, 36 subjects ≥2 to <5 years of age) at 1 month after vaccination were extracted[4)] from the immunogenicity data of children 6 months to 4 years of age who received 3 doses of the monovalent vaccine (Original) 3 μg as the primary series in phase II/III part[5)] of Study C4591007. The immunogenicity data of 54 subjects (23 subjects ≥6 months to <2 years of age, 31 subjects ≥2 to <5 years of age) were used as the control and compared with the immunogenicity data of Study C4591048 Substudy B Group 2.[6)] The remaining 6 subjects were excluded because they had no blood collected within the specified time frame and had no immunogenicity data available after the study vaccine administration (1 subject ≥6 months to <2 years of age, 5 subjects ≥2 to <5 years of age).

Table 3 shows the results of the immunogenicity at 1 month after the study vaccine administration.

4) Data of subjects 6 months to 4 years of age in phase II/III part of Study C4591007, matched for age, history of SARS-CoV-2 infection, and interval from the previous vaccination with subjects in Study C4591048 Substudy B Group 2, were extracted.

5) Refer to Report on Special Approval for Emergency for Comirnaty Intramuscular Injection for 6 months to 4 years old, dated September 15, 2022. A foreign multicenter, randomized, observer-blind, placebo-controlled phase I/II/III study to investigate the safety, tolerability, and immunogenicity of the monovalent vaccine (Original) in children 6 months to 12 years of age. Children 6 months to 4 years of age received the monovalent vaccine (Original) 3 μg or placebo intramuscularly twice 21 days apart, followed by an additional vaccination once after ≥8 weeks.

6) The primary immunogenicity endpoints were GMT of the neutralizing antibody titer (50% neutralizing antibody titer) against SARS-CoV-2 Omicron BA.4-5 lineages at 1 month after the fourth dose and antibody response rate (percentage of subjects who achieved a ≥4-fold increase in the neutralizing antibody titer from baseline [LLOQ if baseline value is below LLOQ]). It is planned to evaluate the superiority and non-inferiority of the immunogenicity after the fourth dose with the bivalent vaccine compared with the immunogenicity after the third dose of the monovalent vaccine (Original) in Study C4591007 phase II/III part, with superiority assessment based on the GMT ratio and the non-inferiority assessment based on the difference in the antibody response rate. At the time point of data submission for the present application, no assessment has been made on superiority or non-inferiority.

Table 3. Serum SARS-CoV-2-neutralizing antibody titer in children aged ≥6 months to <5 years (evaluable immunogenicity set, Study C4591048 Substudy B [Group 2])

		After the fourth dose with bivalent vaccine (Original/Omicron BA.4-5)		Study C4591007 phase II/III part After the third dose of the monovalent vaccine (Original)	
Viral strain		n1 or n2/n1	GMT, GMFR, or antibody response rate [two-sided 95% CI]	n1 or n2/n1	GMT, GMFR, or antibody response rate [two-sided 95% CI]
Without history of SARS-CoV-2 infection up to 1 month after study vaccine administration					
BA.4/BA.5	GMT	38	1146.6 [701.9, 1872.9]	34	401.3 [272.7, 590.5]
	GMFR	35	13.6 [8.4, 21.9]	34	10.7 [7.3, 15.8]
	Antibody response rate (%)	27/35	77.1 [59.9, 89.6]	21/34	61.8 [43.6, 77.8]
Original strain	GMT	38	9253.1 [6884.5, 12436.7]	33	8341.2 [6313.1, 11020.9]
	GMFR	38	4.4 [3.1, 6.3]	32	19.8 [13.4, 29.2]
	Antibody response rate (%)	20/38	52.6 [35.8, 69.0]	29/32	90.6 [75.0, 98.0]
With or without history of SARS-CoV-2 infection up to 1 month after study vaccine administration					
BA.4/BA.5	GMT	58	1695.2 [1151.8, 2494.9]	54	607.9 [431.1, 857.2]
	GMFR	54	9.1 [6.3, 13.3]	54	8.6 [6.3, 11.7]
	Antibody response rate (%)	38/54	70.4 [56.4, 82.0]	33/54	61.1 [46.9, 74.1]
Original strain	GMT	58	9733.0 [7708.2, 12289.6]	53	9057.3 [7223.4, 11356.8]
	GMFR	57	3.6 [2.7, 4.8]	52	11.4 [8.1, 16.1]
	Antibody response rate (%)	25/57	43.9 [30.7, 57.6]	39/52	75.0 [61.1, 86.0]

N = Number of subjects analyzed, n1 = Number of subjects with available data of antibody titer at the evaluation time point,
n2 = Number of subjects who achieved a ≥4-fold increase in the neutralizing antibody titer from baseline (Lower limit of quantitation [LLOQ] if baseline value is below LLOQ)
Geometric mean titer (GMT): If antibody titer was below LLOQ, the value 0.5 × LLOQ was used for the analysis.
Geometric mean-fold rise (GMFR): GMT after the fourth dose/GMT before the fourth dose or GMT after the third dose/GMT before the third dose

In the safety assessment, the severity of adverse events was evaluated according to the Food and Drug Administration (FDA) Guidance "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).[7)] The definition of observation periods was as follows:

- Reactogenicity events (local reactions and systemic reactions) were collected by the subject diary for 7 days after the study vaccine administration.
  - Local reactions (injection site pain, redness, and swelling in subjects 2-4 years of age; injection site tenderness, redness, and swelling in subjects 6 months to 1 year of age)
  - Systemic reactions (pyrexia [≥38℃[8)]], fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia in subjects 2-4 years of age; pyrexia [≥38℃[8)]], decreased appetite, drowsiness, and irritability in subjects 6 months to 1 year of age)
- Adverse events (excluding reactogenicity events) were collected during 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 reported within 7 days after the study vaccine administration.

7) https://www.fda.gov/media/73679/download (last accessed on July 14, 2023)
8) Pyrexia was evaluated according to the following 4 classifications: ≥38.0℃ to ≤38.4℃, >38.4℃ to ≤38.9℃, >38.9℃ to ≤40.0℃, and >40.0℃.

Table 4. Incidence of reactogenicity events within 7 days after study vaccine administration (safety analysis set, Study C4591048 Substudy B [Group 2])

6 months to 1 year of age (N = 24)			2-4 years of age (N = 36)		
Event terms		n (%)	Event terms		n (%)
Local reactions	Total	2 (8.3)	Local reactions	Total	12 (33.3)
	Injection site tenderness	0 (—)[a)]		Injection site pain	10 (27.8)
	Redness	2 (8.3)		Redness	3 (8.3)
	Swelling	1 (4.2)		Swelling	1 (2.8)
Systemic reactions	Total	5 (20.8)	Systemic reactions	Total	12 (33.3)
	Pyrexia	1 (4.2)		Pyrexia	0 (—)
	Decreased appetite	1 (4.5)[a)]		Fatigue	11 (30.6)
	Drowsiness	2 (9.1)[a)]		Headache	1 (2.8)
	Irritability	4 (18.2)[a)]		Chills	1 (2.8)
				Vomiting	1 (2.8)
				Diarrhoea	2 (5.6)
				Myalgia	0 (—)
				Arthralgia	1 (2.8)

N = Number of subjects analyzed, n = Number of subjects with events
a) N=22

Within 1 month after the study vaccine administration, adverse events (except reactogenicity events) were reported in 3 of 24 subjects 6 months to 1 year of age (diarrhoea, fatigue, injection site pain, and pyrexia in 1 subject each [1 subject had >1 event]) and in 1 of 36 subjects 2 to 4 years of age (injection site warmth and erythema in 1 subject [1 subject had >1 event]). A causal relationship to the study vaccine could not be ruled out for fatigue and injection site pain reported in subjects 6 months to 1 year of age.

There were no serious adverse events or adverse events leading to death or study discontinuation within 1 month after the study vaccine administration.

7.2 Foreign phase I/II/III study (CTD 5.3.5.1.3; Study C4591048 Substudy D [Group 2]; study period, ongoing since September 2022 [data cutoff date, November 25, 2022])

An open-label, uncontrolled study was conducted at 10 study sites in the US to investigate the safety and immunogenicity of the bivalent vaccine administered as the fourth dose in healthy children ≥5 and <12 years of age (target sample size, approximately 100 subjects) who completed 3 prior doses (2 doses as the primary series, 1 dose as a booster) of the monovalent vaccine (Original) 10 μg with the last dose being administered 90 to 240 days earlier.

The bivalent vaccine (Original and Omicron BA.4-5) 10 μg was administered once intramuscularly.

The safety data 1 month after vaccination were submitted for the review.

Of 115 subjects enrolled in Group 2, 113 subjects received the study vaccine and were included in the safety analysis set. Of the 115 subjects, 103 subjects were included in the evaluable immunogenicity set. The remaining 12 subjects were excluded for the following reasons: No blood sample collected within the specified time frame in 9 subjects; no blood sample collected at 1 month after vaccination in 8 subjects; no study vaccine administered in 2 subjects; no immunogenicity data available after the study vaccine administration in 1 subject; and other serious protocol deviation found in 2 subjects (some subjects had ≥2 reasons).

In the immunogenicity evaluation, data of 113 subjects at 1 month after vaccination were extracted[9] from among subjects 5 to 11 years of age who received a total of 3 doses of the monovalent vaccine (Original) 10 μg as the primary series and the booster dose in phase II/III part of Study C4591007.[10] The data thus obtained were used as the control data and compared with the data obtained in Study C4591048 Substudy D Group 2.

Table 5 shows the results of the immunogenicity at 1 month after the study vaccine administration.

Table 5. Serum SARS-CoV-2 neutralizing antibody titer in children aged ≥5 and <12 years (evaluable immunogenicity set, Study C4591048 Substudy D [Group 2])

		After the fourth dose with bivalent vaccine (Original/Omicron BA.4-5)		Study C4591007 phase II/III part After the third dose of the monovalent vaccine (Original)	
Viral strain		n1 or n2/n1	GMT, GMFR, or antibody response rate [two-sided 95% CI]	n1 or n2/n1	GMT, GMFR, or antibody response rate [two-sided 95% CI]
Without history of SARS-CoV-2 infection up to 1 month after study vaccine administration					
BA.4/BA.5	GMT	43	1227.5 [869.2, 1733.5]	45	899.2 [699.3, 1156.1]
	GMFR	43	6.9 [5.4, 8.8]	45	15.0 [12.2, 18.4]
	Antibody response rate (%)	32/43	74.4 [58.8, 86.5]	41/45	91.1 [78.8, 97.5]
Original strain	GMT	43	7215.6 [5593.5, 9308.1]	45	6534.3 [5203.6, 8205.4]
	GMFR	43	4.0 [3.3, 4.8]	45	13.1 [10.5, 16.4]
	Antibody response rate (%)	21/43	48.8 [33.3, 64.5]	43/45	95.6 [84.9, 99.5]
With or without history of SARS-CoV-2 infection up to 1 month after study vaccine administration					
BA.4/BA.5	GMT	102	2189.9 [1742.8, 2751.7]	113	1393.6 [1175.8, 1651.7]
	GMFR	101	4.5 [3.8, 5.4]	112	5.6 [4.5, 6.9]
	Antibody response rate (%)	54/101	53.5 [43.3, 63.5]	59/112	52.7 [43.0, 62.2]
Original strain	GMT	102	8245.9 [7108.9, 9564.9]	113	7235.1 [6331.5, 8267.8]
	GMFR	101	2.8 [2.5, 3.2]	113	5.5 [4.5, 6.7]
	Antibody response rate (%)	31/101	30.7 [21.9, 40.7]	62/113	54.9 [45.2, 64.2]

N = Number of subjects analyzed, n1 = Number of subjects with available data of antibody titer at the evaluation time point,
n2 = Number of subjects who achieved a ≥4-fold increase in the neutralizing antibody titer from baseline (LLOQ if baseline value is below LLOQ)
GMT: If antibody titer was below LLOQ, the value 0.5 × LLOQ was used for the analysis.
GMFR: GMT after the fourth dose/GMT before the fourth dose, or GMT after the third dose/GMT before the third dose

In the safety assessment, the severity of adverse events was evaluated according to the FDA Guidance "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).[7] The definition of observation periods was as follows:

- Reactogenicity events (local reactions and systemic reactions) were collected by the subject diary for 7 days after administration of the study vaccine.
  - Local reactions (injection site pain, redness, and swelling)
  - Systemic reactions (pyrexia [≥38°C[8]]), fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia)
- Adverse events (excluding reactogenicity events) were collected from the study vaccine administration through 1 month after the last dose.

[9] Data of subjects in phase II/III part of Study C4591007, matched for age and history of SARS-CoV-2 infection with subjects in Study C4591048 Substudy D Group 2, were extracted.

[10] Refer to Report on Special Approval for Emergency for Comirnaty Intramuscular Injection for 5 to 11 years old, dated August 17, 2022. A foreign multicenter, randomized, observer-blind, placebo-controlled phase I/II/III study to investigate the safety, tolerability, and immunogenicity of the monovalent vaccine (Original) in children 6 months to 12 years of age. Children 5 to 11 years of age received a total of 3 doses of the monovalent vaccine (Original) 10 μg or placebo intramuscularly as the primary series and as the booster dose.

- Serious adverse events were collected from the study vaccine administration through 6 months after the last dose.
- Deaths were collected up to the end of the study.

Table 6 shows reactogenicity events reported within 7 days after the study vaccine administration.

Table 6. Incidence of reactogenicity events within 7 days after study vaccine administration (safety analysis set, Study C4591048 Substudy D [Group 2])

5-11 years of age (N = 111)[a)]		
Event terms		n (%)
Local reactions	Total	74 (66.7)
	Injection site pain	71 (64.0)
	Redness	8 (7.2)
	Swelling	5 (4.5)
Systemic reactions	Total	58 (52.3)
	Pyrexia	5 (4.5)
	Fatigue	45 (40.5)
	Headache	28 (25.2)
	Chills	10 (9.0)
	Vomiting	4 (3.6)
	Diarrhoea	4 (3.6)
	Myalgia	15 (13.5)
	Arthralgia	10 (9.0)

N = Number of subjects analyzed, n = Number of subjects with events
a) Number of subjects with presence/absence of ≥1 symptom entered in the diary

Within 1 month after the study vaccine administration, adverse events (except reactogenicity events) were reported in 4 of 113 subjects (influenza, otitis media, lymph node palpable, oropharyngeal pain in 1 subject each). A causal relationship to the study vaccine could not be ruled out for lymph node palpable.

There were no serious adverse events or adverse events leading to death or study discontinuation within 1 month after the study vaccine administration.

7.3 Foreign phase II/III study (CTD 5.3.5.1.4; pooled analysis of Study C4591044 Cohorts 2 and 3; study period, ongoing since July 2022 [data cutoff dates, October 12, 2022 (Cohort 2) and October 31, 2022 (Cohort 3)])

An open-label, uncontrolled study (subjects 12-17 years of age in Cohort 2, all subjects in Cohort 3) and a randomized, observer-blind, parallel-group study (subjects 18-55 years of age and subjects >55 years of age in Cohort 2) were conducted at 30 study sites in the US to investigate the safety and immunogenicity of the bivalent vaccine. Subjects were healthy subjects ≥12 years of age (Cohort 2) and subjects ≥18 years of age (Cohort 3) who completed 3 prior doses (2 doses as the primary series, 1 dose as a booster) of the monovalent vaccine (Original) 30 μg, with the last dose being administered 150 to 365 days earlier (target sample size, approximately 500 subjects in Cohort 2, approximately 400 subjects in Cohort 3).

In Cohort 2, a single dose of the bivalent vaccine (Original and Omicron BA.4-5) was administered intramuscularly at a dose of 30 μg to subjects 12 to 17 years of age and at a dose of either 30 μg or 60 μg to subjects 18 to 55 years and >55 years of age.

In Cohort 3, a single dose of the bivalent vaccine (Original and Omicron BA.4-5) was administered intramuscularly at a dose of 30 μg.

For this review, the applicant submitted pooled analysis results of the immunogenicity and safety up to 1 month after vaccination in subjects ≥18 years of age in Cohorts 2 and 3 who received the bivalent vaccine (Original and Omicron BA.4-5) 30 μg. The applicant also submitted the immunogenicity and safety results in Cohort 2 alone for the current review but the results have already been reviewed in the past approval (Report on Special Approval for Emergency for Comirnaty Intramuscular Injection for 5 to 11 years old, dated February 7, 2023).

Of 314 subjects 18 to 55 years of age and 306 subjects >55 years of age who were enrolled in Cohort 2 or 3 and randomized, 313 and 306 subjects, respectively, received the study vaccine and were included in the safety analysis set. Of the 314 subjects 18 to 55 years of age and 306 subjects >55 years of age who were randomized, 297 and 286 subjects, respectively, were included in the evaluable immunogenicity set. The remaining 17 and 20 subjects, respectively, were excluded for the following reasons: (1) Of 17 subjects in Cohort 2, 16 subjects failed to obtain immunogenicity data in the specified period, 7 subjects had serious protocol deviations, 6 subjects failed to fulfill the eligibility or randomization criteria, and 1 subject received no study vaccine (some had ≥2 reasons); (2) of 20 subjects in Cohort 3, 16 subjects failed to obtain immunogenicity data in the specified period, 6 subjects had serious protocol deviations, and 4 subjects failed to fulfill the eligibility or randomization criteria (some had ≥2 reasons). For the immunogenicity evaluation in subjects >55 years of age, data for 289 subject were extracted from the population[11] of subjects >55 years of age receiving the monovalent vaccine (Original) 30 μg in Study C4591031 Substudy E and were compared with the results of the pooled analysis of Study C4591044 Cohorts 2 and 3.

The primary immunogenicity endpoints were geometric mean titer (GMT) of the neutralizing antibody titer (50% neutralizing antibody titer) against SARS-CoV-2 Omicron BA.4/BA.5 lineages at 1 month after the study vaccine administration and the antibody response rate (percentage of subjects who achieved a ≥4-fold increase in the neutralizing antibody titer from baseline [Lower limit of quantitation (LLOQ) if baseline value is below LLOQ]). The following major hypotheses were specified for the primary endpoints in the subject population >55 years of age and in the subject population 18 to 55 years of age, with or without history of SARS-CoV-2 infection within 1 month after the study vaccine administration:[12]

Primary endpoints in subject population >55 years of age

(a) Superiority of the fourth dose with the bivalent vaccine (pooled analysis of Study C4591044 Cohorts 2 and 3) to the fourth dose with the monovalent vaccine (Original) (Study C4591031

[11] Refer to Report on Special Approval for Emergency for Comirnaty RTU Intramuscular Injection, dated September 7, 2022. A foreign phase III study consisting of multiple substudies to evaluate the safety, tolerability, and immunogenicity of the booster dose of the monovalent vaccine (Original) or the primary series or the booster dose of the variant vaccine. In the expanded cohort of Substudy E, healthy subjects >55 years of age who completed 3 doses of the monovalent vaccine (Original) were enrolled in the study.

[12] The test hypothesis was evaluated according to the following order: (1) The primary endpoint in the subject >55 years of age; (2) the secondary endpoint in subjects >55 years of age (non-inferiority of GMR of neutralizing antibody against the original strain); and (3) the primary endpoint in subject population 18 to 55 years of age. Only if hypotheses on all of the preceding endpoints were supported, the hypothesis on the next endpoint was evaluated.

Substudy E) based on GMR of the neutralizing antibody (success criteria, the lower limit of two-sided 95% confidence interval of GMR >1)

(b) Non-inferiority of the fourth dose with the bivalent vaccine (pooled analysis of Study C4591044 Cohorts 2 and 3) to the fourth dose with the monovalent vaccine (Original) (Study C4591031 Substudy E) based on the difference in the antibody response rate (success criteria, the lower limit of two-sided 95% confidence interval of the difference in the antibody response rate >-5%)

Primary endpoints in subject population 18 to 55 years of age

(a) Non-inferiority of subject population 18 to 55 years of age to subject population >55 years of age based on GMR of the neutralizing antibody (success criteria, the lower limit of two-sided 95% confidence interval of GMR >0.67)

(b) Non-inferiority of subject population 18 to 55 years of age to subject population >55 years of age based on the difference in the antibody response rate (success criteria, the lower limit of two-sided 95% confidence interval of the difference in the antibody response rate >-10%)

Table 7 shows the results of the primary endpoints of immunogenicity, demonstrating that the predefined success criteria for superiority or non-inferiority were achieved in the subject populations of >55 years of age and 18 to 55 years of age with or without history of SARS-CoV-2 infection.

Table 7. Serum SARS-CoV-2 (Omicron variant BA.4/BA.5 lineages)-neutralizing antibody titer (evaluable immunogenicity set, Study C4591044 Cohorts 2 and 3 combined)

	Bivalent vaccine (Original and Omicron BA.4-5) fourth dose				Study C4591031 Substudy E Monovalent vaccine (Original) fourth dose		GMR [two-sided 95% CI]
	n1	GMT [two-sided 95% CI]	n1	GMT [two-sided 95% CI]	n1	GMT [two-sided 95% CI]	
With or without SARS-CoV-2 infection	18-55 years of age (N = 297)		>55 years of age (N = 286)		>55 years of age (N = 289)		
			282	3373.4 [3000.3, 3793.0][a)]	273	1160.7 [1030.3, 1307.7]	2.91 [2.45, 3.44]
	294	4254.2 [3779.6, 4788.4]	282	4344.4 [3850.2, 4902.1][b)]			0.98 [0.83, 1.16]
Without history of SARS-CoV-2 infection	18-55 years of age (N = 77)		>55 years of age (N = 105)		>55 years of age (N = 238)		
			103	2157.1 [1771.7, 2626.3][a)]	224	639.2 [559.8, 729.8]	3.37 [2.66, 4.29]
	77	1826.3 [1408.4, 2368.3]	103	1820.8 [1454.4, 2279.4][b)]			1.00 [0.71, 1.41]
	n2/n1	Antibody response rate [two-sided 95% CI]	n2/n1	Antibody response rate [two-sided 95% CI]	n2/n1	Antibody response rate [two-sided 95% CI]	Difference in antibody response rate [two-sided 95% CI]
With or without SARS-CoV-2 infection	18-55 years of age (N = 297)		>55 years of age (N = 286)		>55 years of age (N = 289)		
			188/282	66.7 [60.8, 72.1]	127/273	46.5 [40.5, 52.6]	26.77 [19.59, 33.95]
	180/294	61.2 [55.4, 66.8]					-3.03 [-9.68, 3.63]
Without history of SARS-CoV-2 infection	18-55 years of age (N = 77)		>55 years of age (N = 105)		>55 years of age (N = 238)		
			89/103	86.4 [78.2, 92.4]	113/224	50.4 [43.7, 57.2]	32.61 [22.99, 42.23]
	65/77	84.4 [74.4, 91.7]					-2.43 [-13.21, 8.35]

N = Number of subjects analyzed, n1 = Number of subjects with available data of antibody titer at the evaluation time point,
n2 = Number of subjects who achieved a ≥4-fold increase in the neutralizing antibody titer from baseline (LLOQ if baseline value is below LLOQ)
GMT: If antibody titer was below LLOQ, the value 0.5 × LLOQ was used for the analysis.

a) Calculated by antilogarithmic conversion of the least squares estimate of the mean and its CI, estimated by the linear regression model including baseline neutralizing antibody titer (log base) and vaccine group as factors

b) Calculated by antilogarithmic conversion of the least squares estimate of the mean and its CI, estimated by the linear regression model including baseline neutralizing antibody titer (log base) and age group as factors

In the safety assessment, the severity of adverse events was evaluated according to the FDA Guidance "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).[7)]

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

Table 8 shows the incidence of reactogenicity events reported within 7 days after the study vaccine administration.

Table 8. Incidence of reactogenicity events within 7 days after study vaccine administration (safety analysis set, Study C4591044 Cohorts 2 and 3 combined)

Event terms		18-55 years of age (N = 310)	>55 years of age (N = 301)
		n (%)	n (%)
Local reactions	Total	240 (77.4)	174 (57.8)
	Injection site pain	236 (76.1)	172 (57.1)
	Redness	20 (6.5)[a)]	14 (4.0)[b)]
	Swelling	22 (7.1)[a)]	8 (2.7)[b)]
Systemic reactions	Total	229 (74.1)[a)]	162 (53.8)
	Pyrexia	15 (4.9)[a)]	13 (4.3)[b)]
	Fatigue	189 (61.2)[a)]	116 (38.5)
	Headache	144 (46.6)[a)]	92 (30.7)[b)]
	Chills	68 (22.0)[a)]	36 (12.0)[b)]
	Vomiting	6 (1.9)[a)]	2 (0.7)[b)]
	Diarrhoea	33 (10.7)[a)]	29 (9.6)
	Myalgia	94 (30.4)[a)]	54 (18.0)[b)]
	Arthralgia	46 (14.9)[a)]	36 (12.0)[b)]

N = Number of subjects analyzed, n = Number of subjects with events
a) N = 309, b) N = 300

Table 9 shows the incidence of adverse events (except reactogenicity events) and adverse reactions reported in ≥2 subjects within 1 month after the study vaccine administration.

Table 9. Incidence of adverse events and adverse reactions reported in ≥2 subjects within 1 month after the study vaccine administration (safety analysis set, Study C4591044 Cohorts 2 and 3 combined)

Event terms	Adverse events		Adverse reactions	
	18-55 years of age (N = 313)	>55 years of age (N = 306)	18-55 years of age (N = 313)	>55 years of age (N = 306)
	n (%)	n (%)	n (%)	n (%)
Total	19 (6.1)	21 (6.9)	12 (3.8)	6 (2.0)
Lymphadenopathy	5 (1.6)	1 (0.3)	5 (1.6)	1 (0.3)
Fatigue	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Injection site pain	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Fall	0 (—)	2 (0.7)	0 (—)	0 (—)
Back pain	1 (0.3)	1 (0.3)	0 (—)	0 (—)
Headache	1 (0.3)	1 (0.3)	1 (0.3)	0 (—)
Anxiety	0 (—)	2 (0.7)	0 (—)	0 (—)

N = Number of subjects analyzed, n = Number of subjects with events, Medical Dictionary for Regulatory Activities (MedDRA) v25.1

Within 1 month after the study vaccine administration, serious adverse events were reported in 1 subject 18 to 55 years of age (hypotension) and in 2 subjects >55 years of age (type 2 diabetes mellitus and dyspnoea in 1 subject each). At the time of data cutoff, the outcome of dyspnoea was "ongoing" and the outcomes of other 2 events were "resolved" or "resolving," and their causal relationship to the study vaccine was denied. There were no adverse events leading to death or study discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical significance and data for review

PMDA's view:

On May 5, 2023, WHO declared an end to COVID-19 as a public health emergency of international concern.[1)] In alignment with this declaration, the category of COVID-19 under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Law) was reclassified from "pandemic influenza (novel influenza or re-emerging influenza)" (that is equivalent to category II) to "category V infectious diseases" starting from May 8, 2023 in Japan, but public health concerns over the spread of infection have not completely disappeared. Several therapeutic agents and preventive vaccines have been developed against COVID-19 since January 2020, and various preventive measures including vaccination have been undertaken. However, mutations of SARS-CoV-2 genes resulted in successive emergence of variants with altered infectivity, transmissibility, antigenicity, and pathogenicity and have caused the multiple waves of SARS-CoV-2 infection. The Omicron variant, which has become the dominant SARS-CoV-2 strain worldwide since 2022, evades vaccine-induced immunity due to changes in the antigenicity, resulting in a decrease in the efficacy and its durability of vaccines (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). The efficacy of the existing SARS-CoV-2 vaccine for original strain against the Omicron variant decreases after the primary series alone, but a booster dose restores neutralization activity against Omicron variant (*Nature Med.* 2022;28:1063-71, *Nature Commun.* 2022;13:3082). In order to cope with the Omicron variant, a vaccine modified from the original strain was developed as a booster dose and, as of June 2023, the vaccine against the Omicron variant is available for a booster dose in individuals ≥5 years of age in Japan.

7.R.1.1 Booster dose with bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age

As of July 4, 2023, the percentage of individuals who completed the primary series in Japan was 80.0% in all-age group, 23.4% in 5 to 11 years of age, and 2.8% in 6 months to 4 years of age; and the percentage of individuals who completed one booster dose was 68.7% in all-age group and 9.8% in 5 to 11 years of age,[13] showing lower percentages of both the primary series and booster dose in children, resulting in the expansion of the epidemics in children in the prevalence of the Omicron variant (*Pediatr Infect Dis J.* 2022;41:e461-7). While COVID-19 is considered to be mild in children, there are reported cases of disease aggravation and death without underlying diseases, and the Japan Pediatric Society recommends SARS-CoV-2 vaccination in all children 6 months to 17 years of age ("On the vaccination of children against COVID-19 [in Japanese] [supplement, June 2023]" [The Committee on Immunization and Prevention of Infectious Disease, the Japanese Pediatric Society, June 9, 2023])[14]. As of July 2023, the policies on SARS-CoV-2 vaccine for children <12 years of age in Japan include the following: (a) To promote administration of vaccine against Omicron in all individuals ≥5 years of age who have completed the primary series; (b) to promote administration of the primary series (against the original strain) and booster dose against Omicron in children 5 to 11 years of age; and (c) to promote administration of primary series (against the original strain) in children 6 months to 4 years of age. In Japan, only the primary series against the original strain are available for children 6 months to 4 years of age, and the dosage regimen for the booster dose has not been approved, and there is no bivalent vaccine (Original and Omicron BA.4-5) available for this age group. Outside Japan, the bivalent vaccine (Original and Omicron BA.4-5) is available for children 6 months to 4 years of age. Given the situation where Omicron variant continues to be dominant as of July 2023 in Japan, it is of significance to make the bivalent vaccine (Original and Omicron BA.4-5) available for children 6 months to 4 years of age in Japan. Accordingly, the application on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) for children 6 months to 4 years of age was reviewed, based on the submitted data of the clinical study (Study C4591048 Substudy B) on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) for children 6 months to 4 years of age.

7.R.1.2 Primary series of bivalent vaccine (Original and Omicron BA.4-5) in all age groups ≥6 months

As of July 2023 in Japan, only the vaccine targeting the original strain is available for use for the primary series in individuals of all-age group, whereas in the US, the bivalent vaccine (Original and Omicron BA.4-5) is available for use for the primary series in all age groups ≥6 months and, in Europe, a statement was issued that allows the use of the bivalent vaccine (Original and Omicron BA.4-5) for the primary series.[15] In Japan, the Omicron variant continues to be dominant as of July 2023, and Omicron sublineages continue to emerge one after another.[16] In March 2023, Strategic Advisory Group of Experts (SAGE) of WHO issued a recommendation to use the bivalent mRNA vaccine against the BA.5 lineage for the primary series (SAGE updates COVID-19 vaccination guidance, March 28, 2023).[17] Given the global consensus on SARS-CoV-2 vaccine above, it is reasonable and clinically significant to make the

[13] https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (last accessed on July 14, 2023)
[14] http://www.jpeds.or.jp/uploads/files/20230609_vaccine_hoi.pdf (last accessed on July 14, 2023)
[15] 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 July 14, 2023)
[16] https://www.niid.go.jp/niid/ja/2019-ncov/2551-cepr/12000-sars-cov-2-27.html (last accessed on July 14, 2023)
[17] https://www.who.int/news/item/28-03-2023-sage-updates-covid-19-vaccination-guidance (last accessed on July 14, 2023)

bivalent vaccine (Original and Omicron BA.4-5) available for use for the primary series in Japan. Although data of clinical studies on primary series with the bivalent vaccine (Original and Omicron BA.4-5) are not submitted in the present application, the review was conducted based on the data of the non-clinical studies, immunogenicity data in the clinical study on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5), etc., submitted in the application. The applicant is conducting Study C4591048 Substudy A in children 6 months to 4 years of age as a clinical study on the primary series of the bivalent vaccine (Original and Omicron BA.4-5) but has not obtained evaluable data as of July 18, 2023.

7.R.2 Efficacy

7.R.2.1 Booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age

The applicant's explanation about the efficacy of the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age:

The efficacy of the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) was investigated in Study C4591048 Substudy B in children 6 months to 4 years of age who had completed 3 doses of the primary series with the monovalent vaccine (Original) 3 μg. This study planned to compare the immunogenicity of the fourth dose with the bivalent vaccine (Original and Omicron BA.4-5) with the immunogenicity obtained after the third dose with the monovalent vaccine (Original) given to children 6 months to 4 years of age in phase II/III part of Study C4591007 conducted in the past, and to estimate the efficacy based on the superiority in the ratio of neutralizing antibody titer (GMT) against Omicron BA.4/BA.5 and the non-inferiority in the difference of the antibody response rate as the primary endpoints. The study data submitted in the present application do not include the evaluation on superiority or non-inferiority of immunogenicity. Instead, they present results of a descriptive analysis of available data in 58 subjects at 1 month after vaccination on or before the data cutoff date (November 25, 2022), in response to the request of the regulatory agencies of the US and Europe. Table 3 [see Section 7.1] shows the results of the neutralizing antibody titer at 1 month after the fourth dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age. Both the population without a history of SARS-CoV-2 infection and the population with or without a history of SARS-CoV-2 infection showed induction of a higher immune response against Omicron BA.4/BA.5 compared with the immunogenicity after 3 doses of the monovalent vaccine (Original) as the primary series, while maintaining the immune response against the original strain. Table 10 shows the results by age group (6 months to 1 year of age, 2-4 years of age). No clear difference was observed between age groups in the immune response after the fourth dose with the bivalent vaccine (Original and Omicron BA.4-5).

Table 10. Serum neutralizing antibody titer against SARS-CoV-2 (evaluable immunogenicity set, Study C4591048 Substudy B [Group 2])

		After fourth dose with the bivalent vaccine (Original and Omicron BA.4-5) 6 months to 1 year of age, N = 24; 2-4 years of age, N = 36					
Viral strain	Age group	n1	GMT [two-sided 95% CI]	n1	GMFR [two-sided 95% CI]	n2/n1	Antibody response rate (%) [two-sided 95% CI]
Without history of SARS-CoV-2 infection up to 1 month after study vaccine administration							
BA.4/BA.5	6 months to 1 year of age	12	1249.6 [521.3, 2995.7]	11	14.6 [6.4, 33.5]	9/11	81.8 [48.2, 97.7]
	2-4 years of age	26	1102.0 [584.8, 2076.4]	24	13.1 [7.0, 24.5]	18/24	75.0 [53.3, 90.2]
Original strain	6 months to 1 year of age	12	9333.0 [5398.7, 16134.5]	12	4.5 [2.0, 9.9]	6/12	50.0 [21.1, 78.9]
	2-4 years of age	26	9216.4 [6321.9, 13436.3]	26	4.4 [2.9, 6.6]	14/26	53.8 [33.4, 73.4]
With or without history of SARS-CoV-2 infection up to 1 month after study vaccine administration							
BA.4/BA.5	6 months to 1 year of age	23	2011.4 [1141.3, 3544.9]	21	8.2 [4.8, 13.9]	14/21	66.7 [43.0, 85.4]
	2-4 years of age	35	1514.9 [882.2, 2601.5]	33	9.7 [5.7, 16.6]	24/33	72.7 [54.5, 86.7]
Original strain	6 months to 1 year of age	23	8737.2 [5959.6, 12809.5]	22	3.5 [2.1, 5.7]	9/22	40.9 [20.7, 63.6]
	2-4 years of age	35	10448.3 [7685.1, 14205.1]	35	3.7 [2.6, 5.4]	16/35	45.7 [28.8, 63.4]

N = Number of subjects analyzed, n1 = Number of subjects with available data of antibody titer at the evaluation time point,
n2 = Number of subjects who achieved a ≥4-fold increase in the neutralizing antibody titer from baseline (LLOQ if baseline value is below LLOQ)
GMT: If antibody titer was below LLOQ, the value 0.5 × LLOQ was used for the analysis.
GMFR: GMT after the fourth dose/GMT before the fourth dose, or GMT after the third dose/GMT before the third dose

An additional analysis was conducted on the immune response to Omicron sublineages (BA.4.6, BA.2.75.2, XBB, and BQ.1.1) other than BA.4 and BA.5 in Study C4591044 Cohort 2, albeit in a different age group (>55 years of age). Table 11 shows the results. Administration of the bivalent vaccine (Original and Omicron BA.4-5) induced an immune response against Omicron sublineages BA.4.6, BA.2.75.2, XBB, and BQ.1.1, but the immune response to XBB was limited compared with the response to other sublineages.

Table 11. Serum SARS-CoV-2 neutralizing antibody titer (evaluable immunogenicity set, Study C4591044 Cohort 2, additional analysis)

		Study C4591044 Cohort 2 After the fourth dose with bivalent vaccine (Original and Omicron BA.4-5)				Study C4591031 Substudy E After the fourth dose with the monovalent vaccine (Original)			
Viral strain	Timing of measurement	n	GMT [two-sided 95% CI]	n	GMFR [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMFR [two-sided 95% CI]
With history of SARS-CoV-2 infection at baseline									
BA.4.6	Before vaccination	19	281.6 [159.5, 497.2]	19	5.6 [3.1, 9.8]	20	283.4 [142.6, 563.2]	20	2.1 [1.5, 2.8]
	1 month after vaccination	19	1564.4 [938.2, 2608.5]			20	586.9 [346.9, 993.0]		
BA.2.75.2	Before vaccination	19	62.0 [32.5, 118.0]	19	5.3 [2.8, 9.8]	20	125.5 [62.1, 253.9]	20	2.1 [1.6, 2.7]
	1 month after vaccination	19	325.9 [183.0, 580.5]			20	264.5 [146.3, 478.0]		
XBB	Before vaccination	19	26.8 [16.2, 44.2]	19	4.9 [2.8, 8.5]	20	54.6 [32.5, 92.0]	20	1.8 [1.5, 2.2]
	1 month after vaccination	19	130.9 [80.0, 214.3]			20	98.5 [58.0, 167.3]		
BQ.1.1	Before vaccination	19	74.4 [34.7, 159.4]	19	6.0 [3.2, 11.2]	20	59.6 [35.0, 101.5]	20	2.2 [1.8, 2.7]
	1 month after vaccination	19	444.4 [259.4, 761.3]			20	132.2 [82.5, 212.0]		
Without history of SARS-CoV-2 infection at baseline									
BA.4.6	Before vaccination	17	26.1 [14.9, 45.6]	17	21.7 [11.6, 40.5]	20	36.1 [20.4, 63.6]	20	2.5 [1.9, 3.5]
	1 month after vaccination	17	566.3 [280.8, 1142.0]			20	91.9 [59.8, 141.1]		
BA.2.75.2	Before vaccination	17	14.4 [10.1, 20.6]	17	8.9 [4.5, 17.5]	20	18.3 [12.1, 27.7]	20	2.0 [1.6, 2.6]
	1 month after vaccination	17	127.9 [61.5, 265.8]			20	37.3 [25.1, 55.4]		
XBB	Before vaccination	17	11.8 [9.0, 15.4]	17	5.0 [2.8, 8.9]	20	13.4 [10.3, 17.5]	20	1.3 [1.1, 1.6]
	1 month after vaccination	17	58.9 [31.6, 109.9]			20	17.4 [12.6, 24.1]		
BQ.1.1	Before vaccination	17	11.5 [9.2, 14.5]	17	13.0 [6.9, 24.8]	20	16.5 [11.0, 24.8]	20	1.5 [1.2, 1.9]
	1 month after vaccination	17	150.5 [77.2, 293.4]			20	25.5 [17.4, 37.4]		

n = Number of subjects with available data of antibody titer at the evaluation time point
GMT: If antibody titer was below LLOQ, the value 0.5 × LLOQ was used for the analysis.
GMFR: GMT after the fourth dose/GMT before the fourth dose

During the prevalence of the Omicron variant, the protective effect against COVID-19 was higher with the bivalent mRNA vaccine (Original and Omicron BA.4-5) than with the monovalent vaccine (Original) (*MMWR Morb Mortal Wkly Rep.* 2022;71:1616-24, *MMWR Morb Mortal Wkly Rep.* 2022;71:1625-30, etc.). In addition, during the prevalence of the Omicron variant, the efficacy of the primary series and the booster dose of the monovalent vaccine (Original) was similar among age groups (5-11 years, 12-15 years, and ≥18 years of age) (*JAMA.* 2022;327:2210-9). Given these findings, the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) is expected to show efficacy in children 6 months to 4 years of age also, as observed in individuals of other age groups.

PMDA's view:

In clinical studies on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age, results of the analysis of the primary endpoint in Study C4591048 Substudy B (Group 2) are unavailable at the time point of this application. However, the available data confirmed, within the range of these data, that the fourth dose with the bivalent vaccine (Original and Omicron BA.4-5) increased the neutralizing antibody titer against Omicron BA.4 and BA.5 and against the original strain in children 6 months to 4 years of age. In addition to the report on efficacy of the

bivalent vaccine (Original and Omicron BA.4-5) and the monovalent vaccine (Original) in individuals of other age groups, as explained by the applicant, the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) has shown efficacy during the epidemic of Omicron variant lineages BA.5 and XBB (*MMWR Morb Mortal Wkly Rep.* 2023;72:119-24). On the basis of the above, the applicant's explanation that the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) is expected to show efficacy in children 6 months to 4 years of age is acceptable. Study C4591048 Substudy B is still ongoing. As soon as results of immunogenicity and efficacy become available, they should be assessed promptly, and necessary measures should be taken including information provision to the healthcare professionals. The prevalent strains of SARS-CoV-2 mutate rapidly, and other Omicron sublineages and new variant strains may emerge in the future. Information on the efficacy (including immunogenicity) of the bivalent vaccine (Original and Omicron BA.4-5) should be collected from accrued data in each country and from research reports, etc. as needed and, based on the information thus obtained, necessary measures should be examined.

7.R.2.2 Primary series with the bivalent vaccine (Original and Omicron BA.4-5) in all age groups ≥6 months

The applicant's explanation about efficacy of the primary series with the bivalent vaccine (Original and Omicron BA.4-5):

No clinical study data have been obtained on the primary series with the bivalent vaccine (Original and Omicron BA.4-5) in any age group. However, clinical studies (Studies C4591044 and C4591048) on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) confirmed that the immune response against Omicron BA.4 and BA.5 was stronger after administration of the bivalent vaccine (Original and Omicron BA.4-5) than after administration of the monovalent vaccine (Original) [see Sections 7.1, 7.2, and 7.3]. The immune response against other sublineages including Omicron XBB.1.5 was confirmed [see Section 7.R.2.1, Table 11]. Moreover, during the prevalence of the Omicron variant, the bivalent mRNA vaccine (Original and Omicron BA.4-5) has higher protective effect against COVID-19 than the monovalent vaccine (Original) [see Section 7.R.2.1]. The monovalent vaccine (Original) does not provide sufficient protection against the currently prevalent Omicron strain which is genetically and antigenically different from the original strain (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63, etc.), suggesting the necessity of administering a vaccine targeted at the variant in order to achieve sufficient protective effect.

In March 2023, WHO recommended to consider the use of a bivalent mRNA vaccine targeted at BA.5 for the primary series (SAGE updates COVID-19 vaccination guidance, March 28, 2023).[17)] Given the immune responses, etc. of the monovalent vaccine (Original) and the bivalent vaccine (Original and Omicron BA.4-5), the primary series with the bivalent vaccine (Original and Omicron BA.4-5) is expected to demonstrate more efficacy than that with the monovalent vaccine (Original) at present.

PMDA's view:

Although results of a clinical study on the administration of primary series with the bivalent vaccine (Original and Omicron BA.4-5) are unavailable at present, a booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in subjects of Study C4591044 Cohort 2 induced neutralizing antibody against sublineages of Omicron. Results of the non-clinical study demonstrated that the primary series

with the bivalent vaccine (Original and Omicron BA.4-5) induced neutralizing antibodies against the sublineages of Omicron variant evaluated (BA.1, BA.2, BA.2.12.1, and BA.4/BA.5) as well as against the original strain, demonstrating a broad range of neutralizing antibodies [see Section 3.1]. Given the failure of the monovalent vaccine (Original) to provide sufficient protective effect against Omicron variant (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63, etc.), it is rational to make the bivalent vaccine (Original and Omicron BA.4-5) targeted at the Omicron variant available for the primary series. The prevalent SARS-CoV-2 variants mutate rapidly, and other Omicron sublineages and new variants may emerge in the future. Information should be collected from accrued data in each country and research reports, etc. as needed and, based on the information thus obtained, necessary measures should be examined. The applicant has also submitted an application for a Comirnaty vaccine targeted at Omicron variant XBB.1.5, which is currently undergoing review by PMDA.

7.R.3 Safety

The applicant's explanation about the safety of the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age, based on the results of the clinical studies and on the information obtained after the market launch in foreign countries:

(a) Safety profiles in clinical studies

In Study C4591048 Substudy B (Group 2) administering the fourth dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age (n = 60), the incidence of reactogenicity events (local reactions and systemic reactions [see Section 7.1, Table 4]) generally tended to be lower than the incidence reported in the clinical study administering the primary series (3 doses) of the monovalent vaccine (Original) in subjects of each age group (Report on Special Approval for Emergency for Comirnaty Intramuscular Injection for 6 months to 4 years old, dated September 15, 2022), with no Grade 3 or 4 events reported. The incidence of adverse events within 1 month after the vaccination was 12.5% (3 of 24) of subjects in children 6 months to 1 year of age and 2.8% (1 of 36) of subjects in children 2 to 4 years of age. There were no reports of severe adverse events, serious adverse events, immediate-type adverse events (events that occurred within 30 minutes after the study vaccine administration), clinically notable adverse events (lymphadenopathy, rash, anaphylaxis/hypersensitivity, appendicitis, Bell's palsy, myocarditis/pericarditis), or death, and there were no new safety concerns raised from the data obtained.

In addition to the above, results of clinical studies on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in subjects of other age groups [see Sections 7.2 and 7.3] showed safety profiles similar to those so far confirmed, posing no newly identified safety concerns.

(b) Post-marketing safety information

The applicant's safety database on Comirnaty (as of January 15, 2023) included post-marketing reports of 24,716 adverse events in 8,133 individuals that are related to the bivalent vaccine (Original and Omicron BA.4-5) in all age groups ≥6 months of age. Most of the adverse events associated with clinical events were reactogenicity events such as fatigue, headache, and pyrexia, and other commonly reported events were COVID-19, pain in extremity, lymphadenopathy, and dizziness among others. There were reports of adverse events in 54 children 6 months to 4 years of age, including 1 serious adverse event

(angioedema). The adverse event report related to the bivalent vaccine (Original and Omicron BA.4-5) in the latest Abbreviated Summary Monthly Safety Report (survey period March 16, 2023 to April 15, 2023) contains no new safety concerns.

Thus, with the pharmacovigilance activities on the bivalent vaccine (Original and Omicron BA.4-5) identifying no new safety concerns other than those known with the monovalent vaccine (Original), the applicant considers that safety profiles of the bivalent vaccine (Original and Omicron BA.4-5) continue to be favorable.

PMDA's view:
The safety profile of the bivalent vaccine (Original and Omicron BA.4-5) is considered to be similar to those confirmed in clinical studies and the post-marketing safety information obtained so far. No new safety concern was identified at present, and the safety profile with bivalent vaccine (Original and Omicron BA.4-5) is acceptable. Because of the limited experience with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age, information should continue to be collected and the safety should be evaluated promptly based on the information thus obtained, and appropriate measures including provision of necessary information to healthcare professionals should be taken.

7.R.4 Dosage and administration

The proposed dosage and administration were as follows. (Strikethrough denotes deletions. Underline denotes additions.)

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person

~~• Vaccine product containing mRNA encoding spike protein of SARS-CoV-2 (the original strain)~~
~~For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.~~
~~For a booster dose, a single dose of 0.3 mL is injected intramuscularly.~~

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

<u>For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.</u>
For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

(c) Comirnaty Intramuscular Injection for 5 to 11 years old

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

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

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old

The product is diluted with 2.2 mL of physiological saline (Japanese Pharmacopoeia grade).

For the primary series, 3 doses (0.2 mL each) are injected intramuscularly. The second dose is administered 3 weeks apart usually. The third dose is administered at least 8 weeks after the second dose.
For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

The applicant's explanation about the rationale for the dosing regimen:
The dose of vaccine against variant was investigated in the clinical study conducted during the development of booster dose with the bivalent vaccine (Original/Omicron BA.1) in subjects ≥12 years of age, and the same dose (30 μg) as that for the monovalent vaccine (Original) was selected (Report on Special Approval for Emergency for Comirnaty RTU Intramuscular Injection, dated September 7, 2022). The same dose was approved for the booster dose with the bivalent vaccine (Original and Omicron BA.4-5). For the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 5 to 11 years of age, the same dose (10 μg) as that for the monovalent vaccine (Original) was approved (Report on Special Approval for Emergency for Comirnaty Intramuscular Injection for 5 to 11 years old, dated February 7, 2023).

As with the case for other age groups, in the clinical study on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) of Comirnaty Intramuscular Injection for 6 months to 4 years old (Study C4591048 Substudy B [Group 2]), the same dose (3 μg) as that for the monovalent vaccine (Original) was used. Evaluation of immunogenicity and safety showed that the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) was expected to show efficacy [see Section 7.R.2.1], with the similar safety profile as that observed in preceding clinical studies [see Section 7.R.3].

Clinical study data on the primary series with the bivalent vaccine (Original and Omicron BA.4-5) are unavailable for any age group. However, given the experience of Comirnaty so far, the primary series with the bivalent vaccine (Original and Omicron BA.4-5) using the same dosage regimen as with the monovalent vaccine (Original) is expected to show efficacy [see Section 7.R.2.2] with the similar safety profile as has been obtained.

PMDA's view:
For the dosage regimen of the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age and of the primary series with the bivalent vaccine (Original and Omicron BA.4-5) in individuals of all age groups ≥6 months of age, based on the review on the efficacy and safety [see Sections 7.R.2 and 7.R.3] and on the applicant's explanation, it is acceptable to determine the same dosage regimen as that for the monovalent vaccine (Original), as proposed by the applicant. The currently approved range of the dosage regimen differs between the monovalent vaccine (Original) and the bivalent vaccine targeted at the Omicron variant; i.e., the monovalent vaccine was for the primary series and booster dose (only primary series in children 6 months to 4 years of age) and the bivalent vaccine was only for the booster dose (yet to be approved for children 6 months to 4 years of age), thus necessitating description of the dosage regimen for the monovalent vaccine (Original) and for the bivalent vaccine targeted at the Omicron variant separately from each other in the approval document. In the present review, the following dosage regimens were added: (1) Booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age; and (2) primary series

with the bivalent vaccine (Original and Omicron BA.4-5) in all age groups ≥6 months of age, which makes it possible to use both the monovalent vaccine (Original) and the bivalent vaccine (Original and Omicron BA.4-5) for both the primary series and the booster dose for each age group. PMDA concluded that it is acceptable to specify the dosage regimen as proposed instead of specifying the dosage regimen of these vaccines separately, taking account of the following: (1) The content of approval is identical between the monovalent vaccine (Original) and the bivalent vaccine targeted at the Omicron variant; and (2) the experience of Comirnaty shows the similarity of the safety profile between the monovalent vaccine (Original) and the bivalent vaccine targeted at the Omicron variant.

7.R.5 Indication

On the basis of the reviews on the efficacy and safety [see Sections 7.R.2 and 7.R.3], PMDA concludes that it is acceptable to define the indication as "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as before. PMDA also concluded that it is acceptable to spare the separate description of the monovalent vaccine (Original) and the bivalent vaccine targeted at the Omicron variant in the Indication section of the approval document, as mentioned in Section 7.R.4.

7.R.6 Post-marketing investigations

The applicant's explanation:

Results of the foreign clinical studies submitted for this application showed that the safety profile of the bivalent vaccine (Original and Omicron BA.4-5) is similarly favorable to that of the monovalent vaccine (Original) and that the safety profile did not differ among different age groups or among vaccine products. Results of clinical studies on Comirnaty thus far suggest that the safety profile of Comirnaty does not significantly differ among races or among age groups. In Japan, a government-led cohort surveillance of Comirnaty was conducted on each age group, which did not detect any new concern and neither the spontaneous reports showed serious safety concerns, precluding the necessity of additions or changes of safety specifications. On the other hand, there are only a limited number of children 6 months to 4 years of age who are assessed in clinical studies for the booster dose with the bivalent vaccine (Original and Omicron BA.4-5). There is only limited post-marketing information in Japan on the primary series with the monovalent vaccine (Original) in this age group. It is therefore important to collect information on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age. At present, it is unclear whether a government-led cohort surveillance will be conducted on the booster dose with the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age. If no such cohort surveillance is conducted, the applicant plans to conduct a specified use-results survey to investigate the safety of the bivalent vaccine (Original and Omicron BA.4-5) in children 6 months to 4 years of age in clinical practice as additional pharmacovigilance activities. The applicant will continue to jointly discuss the additional pharmacovigilance activities by taking account of the government policy.

PMDA's view:

Post-marketing information in children 6 months to 4 years of age should continue to be collected for the following reasons: (1) There is limited experience with administration of vaccines including the primary series with monovalent vaccine (Original) in this age group in Japan and (2) available

information on the booster dose in clinical studies is limited. The plan for the specified use-results survey should be discussed further, taking account of the government's policy on the vaccination in the future.

PMDA has concluded that the risk management plan (draft) should include the safety specifications presented in Table 12, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 13.

Table 12. 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) 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, Comirnaty RTU Intramuscular Injection, and Comirnaty RTU Intramuscular Injection for 1 person)
Efficacy specification		
None		

No change pertaining to the present application.

Table 13. 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 to 4 years of age: Comirnaty Intramuscular Injection for 6 months to 4 years old [monovalent: Original]) • Early post-marketing phase vigilance (child vaccine recipients 6 months to 4 years of age: Comirnaty Intramuscular Injection for 6 months to 4 years old [bivalent: Original and Omicron BA.4-5]) • Early post-marketing phase vigilance (vaccine recipients ≥12 years of age: Comirnaty RTU Intramuscular Injection [bivalent: Original/Omicron BA.1]), [bivalent: Original and Omicron BA.4-5]) • Early post-marketing phase vigilance (vaccine recipients 5-11 years of age: Comirnaty Intramuscular Injection for 5-11 years old [bivalent: Original and Omicron BA.4-5]) • Post-marketing clinical study (C4591005) (Comirnaty Intramuscular Injection [monovalent: Original]) • Use-results survey on post-approval early vaccine recipients (healthcare professionals) (follow-up study) (C4591006) (Comirnaty Intramuscular Injection [monovalent: Original]) • Specified use-results survey on booster dose in children 6 months to 4 years of age (C4591057) (Comirnaty Intramuscular Injection for 6 months to 4 years old [bivalent: Original and Omicron BA.4-5])) • Foreign phase II/III study (C4591001) (Comirnaty Intramuscular Injection [monovalent: Original]) • Foreign phase II/III study in pregnant women (C4591015) (Comirnaty Intramuscular Injection [monovalent: Original])	• Disseminate data gathered during early post-marketing phase vigilance (child vaccine recipients 6 months to 4 years of age: Comirnaty Intramuscular Injection for 6 months to 4 years old [monovalent: Original], [bivalent: Original and Omicron BA.4-5]) • Disseminate data gathered during early post-marketing phase vigilance (vaccine recipients ≥12 years of age: Comirnaty RTU Intramuscular Injection [bivalent: Original/Omicron BA.1], [bivalent: Original and Omicron BA.4-5]) • 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 and Omicron BA.4-5]) • 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 to 4 years of age: Comirnaty Intramuscular Injection for 6 months to 4 years old [monovalent: Original], [bivalent: Original and Omicron BA.4-5]) • Periodical publication of the occurrence of adverse reactions (vaccine recipients ≥12 years of age: Comirnaty RTU Intramuscular Injection [bivalent: Original and Omicron BA.1], [bivalent: Original and Omicron BA.4-5]) • 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 and Omicron BA.4-5])

Underline denotes additions pertaining to the present application.

Under the current circumstances where multiple Comirnaty 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 and Omicron BA.4-5) in children 6 months to 4 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

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old

The new drug application data (CTD 5.3.5.1.3) 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.

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old

The new drug application data (CTD 5.3.5.1.1 to 5.3.5.1.3) 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 and the findings available so far, PMDA has concluded that the bivalent vaccine (Original and Omicron BA.4-5) administered as the booster dose in children 6 months to 4 years of age and as the primary series in individuals of all age groups ≥6 months 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 an acceptable safety profile as that observed with the approved products of Comirnaty. In view of its benefit/risk balance by considering the status of COVID-19 outbreaks and the background factors in individuals, PMDA considers that it is clinically significant to make the bivalent vaccine (Original and Omicron BA.4-5) available for use as the booster dose for children 6 months to 4 years of age and as the primary series for individuals of all age groups ≥6 months 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

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old

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 (the original strain)~~

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

(Strikethrough denotes deletions.)

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old

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

(No change)

Dosage and Administration

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person

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

~~For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.~~

~~For a booster dose, a single dose of 0.3 mL is injected intramuscularly.~~

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

For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.

For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

(c) Comirnaty Intramuscular Injection for 5 to 11 years old

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

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.

(d) Comirnaty Intramuscular Injection for 6 months to 4 years old

The product is diluted with 2.2 mL of physiological saline (Japanese Pharmacopoeia grade).

For the primary series, 3 doses (0.2 mL each) are injected intramuscularly. The second dose is administered 3 weeks apart usually. The third dose is administered at least 8 weeks after the second dose.

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

(Strikethrough denotes deletions. Underline denotes additions.)

Approval Conditions

(a) Comirnaty RTU Intramuscular Injection, (b) Comirnaty RTU Intramuscular Injection for 1 person, (c) Comirnaty Intramuscular Injection for 5 to 11 years old, (d) Comirnaty Intramuscular Injection for 6 months to 4 years old

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 the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.
   (4) The efficacy and safety data of the product will be accrued with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of

the product in written form and 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
Bivalent vaccine (Original and Omicron BA.1)	Bivalent vaccine containing tozinameran and riltozinameran (at an RNA mass ratio of 1:1)
Bivalent vaccine (Original and Omicron BA.4-5)	Bivalent vaccine containing tozinameran and famtozinameran (at an RNA mass ratio of 1:1)
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11, 1961)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
FDA	Food and Drug Administration
GMFR	Geometric mean-fold rise
GMT	Geometric mean titer
Infectious Diseases Control Act	Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Act No. 114 of 1998)
LLOQ	Lower limit of quantitation
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
Monovalent vaccine (Original)	Monovalent vaccine containing tozinameran
mRNA	Messenger RNA
Original strain	Wuhan-Hu-1 strain; USA-WA1/2020
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
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization