Report on the Deliberation Results

October 5, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Comirnaty Intramuscular Injection for 6 months to 4 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran [JAN*])
Applicant	Pfizer Japan Inc.
Date of Application	July 14, 2022

Results of Deliberation

Under the current pandemic of disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on October 5, 2022, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product is the remainder of the re-examination period for the initial approval of the product (until February 13, 2029).

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
3. 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.
4. 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.
5. The efficacy and safety data of the product will be accrued with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and who have provided written informed consent through the vaccine screening questionnaire in advance.
6. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 12 months after the approval.

**Japanese Accepted Name (modified INN)*

Report on Special Approval for Emergency

September 15, 2022
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Comirnaty Intramuscular Injection for 6 months to 4 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	July 14, 2022
Dosage Form/Strength	Injection: Each vial contains 0.040 mg of Tozinameran
Application Classification	Prescription drug, (6) Drug with a new dosage, (8) Drug in an additional dosage form (drug in a reexamination period)
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 0721-6, dated July 21, 2022]).
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has expected efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in children 6 months through 4 years of age, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

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

(No change)

Dosage and Administration

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

Approval Conditions

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 1
   The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
   (2) 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.
   (3) 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.
   (4) 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) The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14- 3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
   (3) 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.
   (4) 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.

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

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 12 months after the approval.

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.

Attachment

Report on Special Approval for Emergency (1)

August 15, 2022

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

Product Submitted for Approval

Brand Name	Comirnaty Intramuscular Injection for 6 months to 4 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	July 14, 2022
Dosage Form/Strength	Injection: Each vial contains 0.040 mg of Tozinameran

Proposed Indication

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

(No change)

Proposed Dosage and Administration

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

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List of Abbreviations

See Appendix.

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

Comirnaty is a vaccine containing messenger RNA (mRNA) encoding the spike protein (S-protein) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the active ingredient. In Japan, "Comirnaty Intramuscular Injection" and "Comirnaty Intramuscular Injection for 5 to 11 years old," both containing the same active ingredient as that of Comirnaty in the present application, were granted marketing approval in February 2021 and in January 2022, respectively, for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)." In Japan, vaccination with SARS-CoV-2 vaccines including the above two products has proceeded in individuals ≥5 years of age. As of August 8, 2022, ≥80% of all Japanese people, including 18.5% of children 5 through 11 years of age, have completed 2 doses of SARS-CoV-2 vaccine.[1)] In order to cope with a COVID-19 epidemic which is prolonged by SARS-CoV-2 viral mutations, the third dose as a booster is administered to individuals ≥12 years of age, and even the fourth dose is administered to the elderly ≥60 years of age and others.

It is considered that COVID-19 is relatively mild and rarely becomes severe among children,[2)] while a certain number of pediatric patients have been reported to require inpatient treatment, with fatal cases reported (*J Pediatric Infect Dis Soc.* 2021 Sep 6;piab085. doi:10.1093/jpids/piab085, COVID-19 Advisory Board [No. 86][3)]). Also, some of SARS-CoV-2-infected children have been reported to develop multisystem inflammatory syndrome in children/pediatric inflammatory multisystem syndrome (MIS-C/PIMS) accompanied by pyrexia and multi-organ disorder ("Consensus statement on the clinical practice of MIS-C/PIMS")[4)], with fatal cases reported in foreign countries (*JAMA Pediatr.* 2021;175:837-45).

The applicant conducted a foreign phase I/II/III study (Study C4591007) in children 6 months through 11 years of age to investigate the immunogenicity and safety of Comirnaty in children 6 months through 4 years of age. Emergency use authorization of Comirnaty in children of this age group was granted in June 2022 in the US based on the results of the above study. In the EU, application for partial change of the conditional marketing approval was submitted in July 2022, which is currently under review. The Centers for Disease Control and Prevention (CDC) in the US recommends that children in this age group should receive a COVID-19 vaccine (including Comirnaty).[5)]

In Japan, the applicant has recently submitted an application for marketing approval of Comirnaty relating to (a) additional dosage and administration in children 6 months through 4 years of age and (b) additional dosage form of vaccine product for children 6 months through 4 years of age, based on the results of StudyC4591007.

This report contains the result of 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 0721-6, dated July 21, 2022).

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1) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (last accessed on August 9, 2022)
2) https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Children_and_adolescents-2021.1 (last accessed on August 9, 2022)
3) Document 3-8: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00348.html (last accessed on August 9, 2022)
4) http://www.jpeds.or.jp/uploads/files/20210916_mis-c_c_s.pdf(last accessed on August 9, 2022)
5) https://www.cdc.gov/media/releases/2022/s0618-children-vaccine.html (last accessed on August 9, 2022)

2. Quality and Outline of the Review Conducted by PMDA

Since the new vaccine product, tailored to the new dosage, is used for vaccine recipients, this application also includes that of an additional dosage form, with submission of data relating to quality.

2.R Outline of the review conducted by PMDA

Comirnaty comes as a multiple-dose vial (0.4 mL) containing 0.040 mg of tozinameran. It is similar in composition to the approved Comirnaty Intramuscular Injection for 5 through 11 years old which contains tozinameran as the active ingredient and is different only in fill volume of the vaccine product per vial. As a result of its review based on the submitted data, no particular problem was detected on the quality of Comirnaty.

2.R.1 Shelf-life of vaccine product

As of July 14, 2022, the long-term testing for Comirnaty Intramuscular Injection for 6 months through 4 years old is still ongoing. The test results up to 12 months, the shelf-life proposed by the applicant, are yet to be submitted.

The applicant's explanation about the stability of Comirnaty:

- No stability concern has been identified based on the results, at Month 12, of the long-term testing, etc. on vaccine products of the same composition as, but different fill volume from, those of the proposed vaccine product (fill volumes, 2.25 mL and 0.48 mL).
- The difference in the fill volume is confirmed not to affect the stability profile among multiple vaccine products of the same composition as, but different fill volume from, those of the proposed vaccine product.
- No stability concern has been identified based on the results, up to Month 12, of the long-term testing on the approved Comirnaty Intramuscular Injection, albeit the composition and fill volumes are different from those of the proposed vaccine product.

On the basis of the above, the applicant considers that the shelf-life of the vaccine product can be proposed as 12 months as is the case with approved vaccine products.

PMDA's view:

Although the data from the long-term testing on Comirnaty (fill volume, 0.4 mL) have not been submitted, PMDA confirmed that there are no stability concerns with the vaccine product of the same composition as, but different fill volume from, those of the proposed vaccine product, as assessed based on the results of long-term testing at Month 12, and that the difference in the fill volume does not significantly affect the safety profile. In foreign countries, it is accepted to determine the shelf-life of the product as 12 months. Since Comirnaty is manufactured as a vaccine product common to all countries, setting a shelf-life different from that in other countries may possibly cause problems in production control and distribution management, hindering stable supply of Comirnaty to Japan. In addition, given the societal need for Comirnaty, it is inevitable to determine the shelf-life of the product as 12 months based on the above results. Results of the long-term testing on Comirnaty should be submitted to PMDA as soon as results become available, and the stability of Comirnaty within the shelf-life should be confirmed.

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

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

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

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

5. Toxicity and Outline of the Review Conducted by PMDA

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

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

Since the present application relates to a new dosage, no data relating to biopharmaceutic studies and associated analytical methods, and clinical pharmacology were submitted.

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

The applicant submitted the results of a foreign phase I/II/III study (Study C4591007) as the efficacy and safety evaluation data. The study has been planned to evaluate the efficacy and safety in healthy children of multiple age ranges (6 month through 1-year-old, 2- through 4-years-old, 5- through 11-years-old, and others). For the present application, the applicant submitted results in children 6 months through 1 year and 2 through 4 years of age, as shown in Table 1.

Table 1. Summary of data on efficacy and safety

Region	Study ID	Part	Population	No. of subjects enrolled	Dosage regimen	Main endpoints
Foreign	C4591007	I	Children 6 months-4 years of age	6 months-1 year old 16 in Comirnaty 3 μg group 2-4 years old 16 in Comirnaty 3 μg group 32 in Comirnaty 10 μg group	Two doses of Comirnaty 3 or 10 μg, administered intramuscularly 21 days apart	Safety Immunogenicity
		II/III	Children 6 months-4 years of age[a)]	3,013 in Comirnaty 3 μg group 1,513 in placebo group	Two doses of Comirnaty 3 μg or placebo, administered intramuscularly 21 days apart, followed by an additional intramuscular dose ≥8 weeks after the second dose	Safety Immunogenicity Efficacy

a) Includes children with stable underlying disease

7.1 Foreign phase I/II/III study (CTD 5.3.5.1.1: Study C4591007; study period - phase I part, ongoing since March 2021 [data cutoff date, July 16, 2021]; phase II/III part, ongoing since March 2021 [data cutoff date, April 29, 2022])

7.1.1 Phase I part

A multi-center, randomized, open-label study was conducted in 7 study sites in the US to investigate the safety, tolerability, and immunogenicity of Comirnaty and to determine the dose in healthy children 6 months through 4 years of age (target sample size of 64 subjects).

Two doses of Comirnaty containing tozinameran 3 μg or 10 μg was administered intramuscularly 21 days apart (Day 1 and Day 19-23). For children 6 months through 1 year of age, only the dose of tozinameran 3 μg was administered, based on the results of evaluation of the safety data obtained from the preceding study in children 2 through 4 years of age.

A total of 48 subjects 2 through 4 years of age (16 in 3 μg group, 32 in 10 μg group; hereinafter the same order shall apply) out of 49 randomized subjects and all 16 subjects 6 months through 1 year of age (3 μg group) received ≥1 doses of Comirnaty and were included in the safety analysis group. Among them, 46 subjects 2 through 4 years of age (15, 31) and 13 subjects 6 months through 1 year of age were included in the evaluable immunogenicity population, excluding 2 subjects 2 through 4 years of age and 3 subjects 6 months through 1 year of age without immunogenicity data during the specified period and 1 subject 2 through 4 years of age who did not receive the second dose.

The severity of adverse events was defined and evaluated with reference 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)[6].

The definition of observation periods:

(a) Reactogenicity events (local reactions and systemic reactions) were collected by the subject diary for 7 days after each dose of the study vaccine.
- Local reactions (injection site pain, redness, and swelling in subjects 2 through 4 years old; injection site tenderness, redness, and swelling in subjects 6 months through 1 year old)
- Systemic reactions (pyrexia [≥38°C[7]]), fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia in subjects 2 through 4 years old; pyrexia [≥38°C[7]], decreased appetite, drowsiness, and irritability in subjects 6 months through 1 year old)

(b) Adverse events (excluding reactogenicity events) were collected from the first dose through 1 month after the last dose of the study vaccine.

(c) Serious adverse events were collected from the first dose through 6 months after the last dose of the study vaccine.

6) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (last accessed on August 9, 2022)

7) Pyrexia was evaluated according to the following 4 classifications: ≥38.0°C to 38.4°C, >38.4°C to 38.9°C, >38.9°C to 40.0°C, and >40.0°C.

(a) Reactogenicity events

Table 2 shows reactogenicity events observed within 7 days after each dose of the study vaccine.

Table 2. Reactogenicity events within 7 days after vaccination (safety analysis set)

Subjects 2-4 years of age				Subjects 6 months-1 year of age		
Event terms	Dose #	3 μg (N = 16)	10 μg (N = 32)	Event terms	Dose #	3 μg (N = 16)
		n (%)	n (%)			n (%)
Local reactions						
Local reactions (total)	First	5 (31.3)	23 (71.9)	Local reactions (total)	First	3 (18.8)
	Second	6 (37.5)	20 (62.5)		Second	1 (6.3)
Injection site pain	First	5 (31.3)	20 (62.5)	Injection site tenderness	First	0
	Second	6 (37.5)	17 (53.1)		Second	1 (6.3)
Redness	First	0	9 (28.1)	Redness	First	3 (18.8)
	Second	0	5 (15.6)		Second	0
Swelling	First	0	3 (9.4)	Swelling	First	1 (6.3)
	Second	0	1 (3.1)		Second	0
Systemic reactions						
Systemic reactions (total)	First	6 (37.5)	18 (56.3)	Systemic reactions (total)	First	8 (50.0)
	Second	4 (25.0)	23 (71.9)		Second	7 (43.8)
Pyrexia	First	0	6 (18.8)	Pyrexia	First	1 (6.3)
	Second	1 (6.3)	6 (18.8)		Second	2 (12.5)
Fatigue	First	4 (25.0)	15 (46.9)	Decreased appetite	First	1 (6.3)
	Second	4 (25.0)	19 (59.4)		Second	2 (12.5)
Headache	First	2 (12.5)	3 (9.4)	Drowsiness	First	4 (25.0)
	Second	2 (12.5)	5 (15.6)		Second	1 (6.3)
Chills	First	1 (6.3)	2 (6.3)	Irritability	First	7 (43.8)
	Second	1 (6.3)	2 (6.3)		Second	5 (31.3)
Vomiting	First	0	1 (3.1)			
	Second	1 (6.3)	2 (6.3)			
Diarrhoea	First	1 (6.3)	2 (6.3)			
	Second	1 (6.3)	4 (12.5)			
Myalgia	First	0	2 (6.3)			
	Second	0	3 (9.4)			
Arthralgia	First	1 (6.3)	0			
	Second	0	1 (3.1)			

N = number of subjects analyzed (number of subjects who entered occurrence/non-occurrence of the event in the subject diary), n = number of subjects with events

(b) Adverse events (excluding reactogenicity events)

Table 3 shows the incidence of adverse events and adverse reactions. Adverse events observed in ≥2 subjects were abdominal pain (2-4 years old, 2 in 10 μg group) and injection site pain (2-4 years old, 2 in 3 μg group, 3 in 10 μg group). Among them, adverse reactions were abdominal pain and injection site pain in 1 subject each. The outcome was “recovered” in both of them.

Table 3. Adverse events and adverse reactions within 1 month after the last dose of the study vaccine (safety analysis set)

	Subjects 2-4 years of age		Subjects 6 months-1 year of age
	3 μg (N = 16)	10 μg (N = 32)	3 μg (N = 16)
	n (%)	n (%)	n (%)
Adverse events	4 (25.0)	12 (37.5)	2 (12.5)
Adverse reactions	2 (12.5)	7 (21.9)	1 (6.3)

N = number of subjects analyzed, n = number of subjects with events

(c) Serious adverse events

Neither serious adverse events nor adverse events leading to death or study discontinuation were observed up to the data cut-off date (July 16, 2021).

Geometric mean titer (GMT) [2-sided 95% CI] on 7 days after the second dose of Comirnaty in the evaluable immunogenicity population was 1350.4 [973.1, 1873.9] in 3 μg group and 2059.5 [1679.1, 2526.0] in 10 μg group of 2 to 4 years of age and 1643.8 [1151.3, 2347.1] in 3 μg group of 6 months to 1 year of age.

High GMT of neutralizing antibody was observed in both dose groups of subjects 2 through 4 years of age, whereas the safety assessment showed a tendency of lower incidence and lower severity of reactogenicity events in the 3 μg group than in the 10 μg group. Immunogenicity and tolerability were also confirmed in subjects 6 months through 1 year of age (3 μg group). Accordingly, the dose 3 μg was selected in both age groups of phase II/III part.

7.1.2 Phase II/III part

A multicenter, randomized, observer-blind study was conducted in 65 foreign study sites to investigate the safety, tolerability, and immunogenicity of Comirnaty in children 6 months through 4 years of age (target sample size 4,500[8)]: 3,000 in Comirnaty group, 1,500 in placebo group). The study was blinded to subjects, investigator, the staff of the study site (except those who prepared or injected the study vaccine) and the sponsor (except some of the pre-designated staff independent from the study).

Two doses of the study vaccine (3 μg Comirnaty or placebo) were administered intramuscularly 21 days apart (Day 1 and Day 19-23), followed by the third dose ≥8 weeks after the second dose.

Results of the immunogenicity evaluation 1 month after the second dose revealed the failure to achieve immunobridging (explained later) in children 2 through 4 years of age (Table 6). In addition, the most recent infection status suggested that vaccination with the third dose of SARS-CoV-2 vaccine was necessary to ensure efficacy against Omicron variant in all age groups. Accordingly, the third vaccination was added to phase II/III part (protocol, ver. 6 revised on January 4, 2022). The study on the third dose was conducted while the blindness in phase II/III part was preserved.

A total of 2,750 randomized subjects 2 through 4 years of age (1,835 in Comirnaty group, 915 in placebo group; hereinafter the same order shall apply) and 1,776 randomized subjects 6 months through 1 year of age (1,178, 598) received ≥1 dose of the study vaccine and were included in the safety analysis set. More than 99% of subjects in both age groups received the second dose of the vaccine, whereas the percentage of subjects who received the third dose before unblinding was 32.2% in those 2 through 4 years of age and 32.1% in those 6 months through 1 year of age.

Severity of adverse events was evaluated in the same manner and during the same observation period as in phase I part [see Section 7.1.1]. In the safety analysis set, the median observation period from the third dose of the study vaccine to the data cut-off date (April 29, 2022) was 1.4 months (range 0.0-3.2 months) in those 2 through 4 years of age and 1.3 months (range 0.0-3.2 months) in those 6 months through 1 year of age.

8) The number was determined to ensure the database size sufficient for approval application in future.

(a) Reactogenicity events

Table 4 shows reactogenicity events observed within 7 days after each dose of the study vaccine.

Table 4. Reactogenicity events within 7 days after vaccination (safety analysis set)

Subjects 2-4 years of age				Subjects 6 months-1 year of age			
Event terms	Dose #	Comirnaty n/N (%)	Placebo n/N (%)	Event terms	Dose #	Comirnaty n/N (%)	Placebo n/N (%)
Local reactions				Local reactions			
Local reactions (total)	First	648/1,825 (35.5)	229/909 (25.2)	Local reactions (total)	First	279/1,173 (23.8)	104/595 (17.5)
	Second	645/1,779 (36.3)	205/878 (23.3)		Second	248/1,147 (21.6)	79/591 (13.4)
	Third	174/ 552 (31.5)	41/262 (15.6)		Third	75/ 365 (20.5)	26/170 (15.3)
Injection site pain	First	559/1,814 (30.8)	186/905 (20.6)	Injection site tenderness	First	192/1,159 (16.6)	66/591 (11.2)
	Second	550/1,772 (31.0)	178/877 (20.3)		Second	171/1,137 (15.0)	50/590 (8.5)
	Third	146/ 547 (26.7)	35/262 (13.4)		Third	58/ 362 (16.0)	20/170 (11.8)
Redness	First	160/1,825 (8.8)	77/909 (8.5)	Redness	First	124/1,173 (10.6)	44/595 (7.4)
	Second	202/1,779 (11.4)	50/878 (5.7)		Second	107/1,147 (9.3)	39/591 (6.6)
	Third	60/ 552 (10.9)	9/262 (3.4)		Third	26/ 365 (7.1)	9/170 (5.3)
Swelling	First	67/1,825 (3.7)	26/909 (2.9)	Swelling	First	46/1,173 (3.9)	15/595 (2.5)
	Second	102/1,779 (5.7)	18/878 (2.1)		Second	45/1,147 (3.9)	9/591 (1.5)
	Third	17/ 552 (3.1)	3/262 (1.1)		Third	10/ 365 (2.7)	3/170 (1.8)
Systemic reactions				Systemic reactions			
Systemic reactions (total)	First	693/1,825 (38.0)	354/909 (38.9)	Systemic reactions (total)	First	715/1,173 (61.0)	346/595 (58.2)
	Second	599/1,779 (33.7)	283/878 (32.2)		Second	640/1,147 (55.8)	298/591 (50.4)
	Third	170/ 552 (30.8)	77/262 (29.4)		Third	188/ 365 (51.5)	77/170 (45.3)
Pyrexia	First	95/1,824 (5.2)	48/909 (5.3)	Pyrexia	First	85/1,173 (7.2)	43/595 (7.2)
	Second	88/1,779 (4.9)	46/878 (5.2)		Second	85/1,147 (7.4)	36/591 (6.1)
	Third	28/ 552 (5.1)	11/262 (4.2)		Third	25/ 365 (6.8)	10/170 (5.9)
Fatigue	First	539/1,813 (29.7)	277/905 (30.6)	Decreased appetite	First	257/1,159 (22.2)	125/591 (21.2)
	Second	456/1,772 (25.7)	201/877 (22.9)		Second	252/1,137 (22.2)	106/590 (18.0)
	Third	134/ 547 (24.5)	57/262 (21.8)		Third	73/ 362 (20.2)	23/170 (13.5)
Headache	First	81/1,813 (4.5)	44/905 (4.9)	Drowsiness	First	313/1,159 (27.0)	173/591 (29.3)
	Second	81/1,772 (4.6)	36/877 (4.1)		Second	271/1,137 (23.8)	125/590 (21.2)
	Third	27/ 547 (4.9)	11/262 (4.2)		Third	72/ 362 (19.9)	22/170 (12.9)
Chills	First	41/1,813 (2.3)	22/905 (2.4)	Irritability	First	593/1,159 (51.2)	279/591 (47.2)
	Second	53/1,772 (3.0)	23/877 (2.6)		Second	539/1,137 (47.4)	240/590 (40.7)
	Third	18/ 547 (3.3)	7/262 (2.7)		Third	158/ 362 (43.6)	64/170 (37.6)
Vomiting	First	54/1,813 (3.0)	24/905 (2.7)				
	Second	61/1,772 (3.4)	29/877 (3.3)				
	Third	9/ 547 (1.6)	10/262 (3.8)				
Diarrhoea	First	139/1,813 (7.7)	72/905 (8.0)				
	Second	118/1,772 (6.7)	64/877 (7.3)				
	Third	28/ 547 (5.1)	13/262 (5.0)				
Myalgia	First	43/1,813 (2.4)	15/905 (1.7)				
	Second	46/1,772 (2.6)	21/877 (2.4)				
	Third	11/ 547 (2.0)	4/262 (1.5)				
Arthralgia	First	14/1,813 (0.8)	18/905 (2.0)				
	Second	24/1,772 (1.4)	9/877 (1.0)				
	Third	7/ 547 (1.3)	2/262 (0.8)				

N = number of subjects analyzed (number of subjects who entered occurrence/non-occurrence of the event in the subject diary), n = number of subjects with events

(b) Adverse events (excluding reactogenicity events)

The incidence of adverse events was 18.7% (344 of 1,835) of subjects in the Comirnaty group and 18.7% (171 of 915) of subjects in the placebo group among those 2 through 4 years of age; and 30.1% (355 of 1,178) of subjects in the Comirnaty group and 27.1% (162 of 598) of subjects in the placebo group among those 6 months through 1 year of age. Table 5 shows adverse events and adverse reactions observed in ≥5 subjects in the Comirnaty group within 1 month after the third dose.

Table 5. Adverse events and adverse reactions observed in ≥5 subjects of Comirnaty group (safety analysis set)

Subjects 2-4 years of age				
	Comirnaty (N = 1,835)		Placebo (N = 915)	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions
	n (%)	n (%)	n (%)	n (%)
All events	344 (18.7)	37 (2.0)	171 (18.7)	18 (2.0)
Vomiting	50 (2.7)	2 (0.1)	30 (3.3)	2 (0.2)
Diarrhoea	26 (1.4)	4 (0.2)	18 (2.0)	4 (0.4)
Pyrexia	55 (3.0)	9 (0.5)	27 (3.0)	3 (0.3)
Injection site pain	11 (0.6)	10 (0.5)	5 (0.5)	5 (0.5)
Fatigue	12 (0.7)	7 (0.4)	3 (0.3)	2 (0.2)
Seasonal allergy	5 (0.3)	0	1 (0.1)	0
Rhinitis	21 (1.1)	0	13 (1.4)	0
Ear infection	12 (0.7)	0	2 (0.2)	0
Otitis media	8 (0.4)	0	4 (0.4)	0
Conjunctivitis	5 (0.3)	0	3 (0.3)	0
Hand-foot-and-mouth disease	6 (0.3)	0	1 (0.1)	0
Fall	6 (0.3)	0	5 (0.5)	0
Skin laceration	4 (0.2)	0	5 (0.5)	0
Cough	32 (1.7)	1 (0.1)	12 (1.3)	0
Rhinorrhoea	19 (1.0)	1 (0.1)	11 (1.2)	0
Nasal congestion	9 (0.5)	0	1 (0.1)	0
Tonsillar hypertrophy	5 (0.3)	0	0	0
Urticaria	6 (0.3)	0	3 (0.3)	0
Subjects 6 months-1 year of age				
	Comirnaty (N = 1,178)		Placebo (N = 598)	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions
	n (%)	n (%)	n (%)	n (%)
All events	355 (30.1)	55 (4.7)	162 (27.1)	21 (3.5)
Vomiting	47 (4.0)	8 (0.7)	29 (4.8)	4 (0.7)
Diarrhoea	39 (3.3)	9 (0.8)	17 (2.8)	5 (0.8)
Teething	12 (1.0)	0	8 (1.3)	0
Pyrexia	54 (4.6)	6 (0.5)	28 (4.7)	0
Fatigue	8 (0.7)	6 (0.5)	2 (0.3)	2 (0.3)
Injection site erythema	9 (0.8)	9 (0.8)	1 (0.2)	1 (0.2)
Otitis media	19 (1.6)	0	13 (2.2)	0
Hand-foot-and-mouth disease	18 (1.5)	0	13 (2.2)	0
Ear infection	12 (1.0)	0	8 (1.3)	0
Rhinitis	10 (0.8)	0	5 (0.8)	0
Conjunctivitis	11 (0.9)	0	2 (0.3)	0
Otitis media acute	6 (0.5)	0	3 (0.5)	0
Gastroenteritis	5 (0.4)	0	0	0
Fall	5 (0.4)	0	4 (0.7)	0
Somnolence	5 (0.4)	5 (0.4)	1 (0.2)	1 (0.2)
Irritability	16 (1.4)	11 (0.9)	5 (0.8)	4 (0.7)
Rhinorrhoea	26 (2.2)	0	10 (1.7)	1 (0.2)
Cough	19 (1.6)	2 (0.2)	6 (1.0)	1 (0.2)
Nasal congestion	12 (1.0)	0	3 (0.5)	0
Rash	8 (0.7)	3 (0.3)	3 (0.5)	0
Urticaria	8 (0.7)	1 (0.1)	3 (0.5)	1 (0.2)
Eczema	5 (0.4)	0	4 (0.7)	1 (0.3)

N = number of subjects analyzed, n = number of subjects with events

(c) Serious adverse events

The incidence of serious adverse events observed on or before the data cut-off date (April 29, 2022) was 0.7% (12 of 1,835) of subjects in the Comirnaty group and 0.9% (8 of 915) of subjects in the placebo group among those 2 through 4 years of age; and 1.4% (17 of 1,178) of subjects in the Comirnaty group and 2.3% (14 of 598) of subjects in the placebo group among those 6 months through 1 year of age. Serious adverse events observed in each age group were as follows (some subjects had more than 1 event):

Subjects 2 through 4 years of age

Comirnaty group: Appendicitis and dehydration in 2 subjects each, diarrhoea, pyrexia, focal peritonitis, gastroenteritis rotavirus, gastroenteritis viral, lower respiratory tract infection, upper respiratory tract infection, pain in extremity, epilepsy, febrile convulsion, and status epilepticus in 1 subject each.

Placebo group: Papilloedema, gastroenteritis, gastroenteritis adenovirus, gastroenteritis rotavirus, foreign body, epilepsy, febrile convulsion, and bronchial hyperreactivity in 1 subject each.

Subjects 6 months through 1 year of age

Comirnaty group: Respiratory syncytial virus bronchiolitis in 4 subjects, gastroenteritis and pneumonia in 2 subjects each, and anaphylactic reaction, anal abscess, enterovirus infection, gastroenteritis rotavirus, gastroenteritis viral, large intestine infection, lower respiratory tract infection, lower respiratory tract infection viral, metapneumovirus infection, respiratory syncytial virus infection, rhinovirus infection, accidental overdose, febrile convulsion, and seizure in 1 subject each.

Placebo group: Bronchiolitis and cyanosis in 2 subjects each, vomiting, anaphylactic reaction, gastroenteritis norovirus, gastroenteritis rotavirus, respiratory syncytial virus bronchiolitis, tonsillitis, viral infection, burns second degree, head injury, thermal burn, feeding intolerance, hypoglycaemia, pneumomediastinum, and respiratory distress in 1 subject each.

A causal relationship to the study vaccine was denied for all events except pyrexia and pain in extremity in the Comirnaty group of subjects 2 through 4 years of age and cyanosis in the placebo group of subjects 6 months through 1 year of age. The outcome was “recovering” or “recovered.”

Adverse events leading to treatment discontinuation were observed in 3 subjects in the Comirnaty group (pyrexia, status epilepticus, and urticaria in 1 subject each) and in 1 subject in the placebo group (swelling face and rash macular) among those 2 to 4 years of age; and in 2 subjects in the Comirnaty group (pyrexia in 2 subjects and rash in 1 subject [1 subject had more than 1 event]) among those 6 months through 1 year of age. Except status epilepticus, all other events were considered to be causally related to Comirnaty. The outcome was “recovered” in all subjects.

Immunogenicity was evaluated by geometric mean ratio (GMR) and neutralizing antibody response rate, and the success of immunobridging was evaluated based on the comparison of the results of Study C4591007 and those of C4591001 according to the following criteria:

- GMR: Immunobridging success based on GMR was declared if the lower limit of the 2-sided 95% confidence interval for the GMR is >0.67 and the point estimate of the GMR is ≥0.8 (predefined in the protocol) or ≥1 (definition of FDA).
- Neutralizing antibody response rate: Immunobridging success based on the neutralizing antibody response rate was declared if, under the condition of immunobridging success based on GMR, the lower limit of the 2-sided 95% confidence interval for the difference in percentage of subjects with

neutralizing antibody response is >−10% where the neutralizing antibody response rate is defined as the proportion of subjects who showed ≥4-fold increase in neutralizing antibody titer against SARS-CoV-2 from the baseline (before the first dose). If the baseline level was below the lower limit of quantitation (LLOQ), the titer ≥4 times the LLOQ was regarded as antibody response.

In order to achieve the criteria for GMR and neutralizing antibody response rate with the statistical power of ≥90%, immunobridging analysis set requires approximately 225 subjects in the Comirnaty group of each age group. Accordingly, 200 to 300 subjects in the Comirnaty group and 50 to 150 subjects in the placebo group were randomly extracted from each of 3 age groups (Study C4591007; 6 months through 1 year old, 2 through 4 years old: Study C4591001 [control]; 16 through 25 years old), and those without serologically or virologically confirmed history of SARS-CoV-2 infection were subjected to analysis.

A total of 317 subjects 2 through 4 years of age (218 in Comirnaty group, 99 in placebo group; hereinafter the same order shall apply) and 222 subjects 6 months through 1 year of age (148, 74) were randomly extracted, but 21 subjects 2 through 4 years of age (14, 7) and 23 subjects 6 months through 1 year of age (16, 7) were excluded because of no immunogenicity data during the specified vaccination period, failure to receive the third dose, or serious protocol deviation, and the remaining 296 subjects 2 through 4 years of age (204, 92) and 199 subjects 6 months through 1 year of age (132, 67) were included in the evaluable immunogenicity population after the third dose. A total of 202 subjects 2 through 4 years of age (143, 59) and 131 subjects 6 months through 1 year of age (82, 49) without history of SARS-CoV-2 infection within 1 month after the third dose were subjected to immunobridging analysis.

Table 6. GMT and response rate of neutralizing antibody 1 month after the second dose (evaluable immunogenicity population after the second dose[a])

	GMT			Antibody response rate		
Age group	N	GMT	2-sided 95% CI	N	n (%)	2-sided 95% CI
2-4 years old[a]	243	763.9	[688.5, 847.5]	243	235 (96.7)	[93.6, 98.6]
16-25 years old (1)[b]	252	1255.4	[1131.2, 1393.3]	251	245 (97.6)	[94.9, 99.1]
Comparison between 2-4 years old and 16-25 years old (1)	GMR	0.61	[0.53, 0.70]	Difference	-0.9	[-4.3, 2.3]
6 months-1 year old[a]	245	979.7	[893.2, 1074.6]	245	240 (98.0)	[95.3, 99.3]
16-25 years old (2)[b]	238	946.8	[850.8, 1053.7]	238	229 (96.2)	[92.9, 98.3]
Comparison between 6 months-1 year old and 16-25 years old (2)	GMR	1.03	[0.90, 1.19]	Difference	1.7	[-1.4, 5.2]

N = number of subjects analyzed, n = number of subjects with antibody response
Shaded region: Failure to achieve immunobridging
a) Subjects without history of SARS-CoV-2 infection among the evaluable immunogenicity population after the second dose were subjected to analysis.
b) The population of 16-25 years of age (1) and the population of 16-25 years of age (2) are mutually exclusive.

Table 7. GMT and response rate of neutralizing antibody 1 month after the third dose (evaluable immunogenicity population after the third dose[a])

Age group	GMT			Antibody response rate		
	N	GMT	2-sided 95% CI	N	n (%)	2-sided 95% CI
2-4 years old[a]	143	1535.2	[1388.2, 1697.8]	141	141 (100.0)	[97.4, 100.0]
16-25 years old (3)[b]	170	1180.0	[1066.6, 1305.4]	170	168 (98.8)	[95.8, 99.9]
Comparison between 2-4 years old and 16-25 years old (3)	GMR	1.30	[1.13, 1.50]	Difference	1.2	[-1.5, 4.2]
6 month-1 year old[a]	82	1406.5	[1211.3, 1633.1]	80	80 (100.0)	[95.5, 100.0]
16-25 years old (3)[b]	170	1180.0	[1066.6, 1305.4]	170	168 (98.8)	[95.8, 99.9]
Comparison between 6 months-1 year old and 16-25 years old (3)	GMR	1.19	[1.00, 1.42]	Difference	1.2	[-3.4, 4.2]

N = number of subjects analyzed, n = number of subjects with antibody response

a) Population not overlapping with the evaluable immunogenicity population after the second dose in Table 6

b) Population not overlapping with the population of 16-25 years of age (1) or (2) in Table 6. Subjects 2-4 years of age and those 6 months-1 year of age were compared with the same population of 16-25 years old (3), respectively.

As for immunogenicity 1 month after the second dose (Table 6), the difference in the neutralizing antibody response rate met the pre-defined criteria in those 2 through 4 years of age and in those 16 through 25 years of age, whereas GMR did not meet the pre-defined criteria, failing to achieve the immunobridging.

In contrast, the immunogenicity 1 month after the third dose (Table 7) fulfilled the pre-defined criteria in both age groups, achieving the immunobridging.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical Data Package and Review Policy

The applicant's explanation about the clinical data package:

The COVID-19-preventive effect and safety of Comirnaty Intramuscular Injection, the vaccine which contains the same active ingredient as that of Comirnay in the present application, was confirmed in phase II/III part of the foreign phase I/II/III study (Study C4591001) in subjects mainly ≥16 years of age. In addition, a Japanese phase I/II study (Study C4591005) was conducted in subjects 20 through 85 years of age, and results confirmed that the immunogenicity in Japanese was similar to that in the subjects of Study C4591001 and that there were no particular safety concerns. In Japan, "Comirnaty Intramuscular Injection" was granted marketing approval in February 2021 for individuals ≥16 years of age based on the results of these 2 studies (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021]).

For the development of Comirnaty in children, the applicant decided to evaluate the clinical efficacy based on the demonstration of the similar extent of immunogenicity between the study population and the population with confirmed clinical efficacy, using the immunobridging technique. This technique has been used in the evaluation of vaccines for other infectious diseases, leading to actual regulatory approvals. In a similar manner, lower age indication (revision of the package insert, dated May 31, 2021) and Comirnaty Intramuscular Injection for 5 through 11 years old (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated January 20, 2022]) have been approved based on the following observations: (a) The immunogenicity in subjects 12 through 15 years of age and 5 through 11 years of age was similar to that in subjects 16 through 25 years of age in Study C4591001 which confirmed COVID-19-preventive effect, and (b) there were no particular safety concerns in any of the

age groups. In the development of Comirnaty for children 6 months through 4 years of age, the applicant decided to evaluate the clinical efficacy using the immunobridging technique as was the case in other age groups.

For the development of Comirnaty in children 6 months through 4 years of age, the foreign phase I/II/III study (Study C4591007) was conducted to investigate the immunogenicity and safety in 2 separate groups: subjects 6 months through 1 year of age and subjects 2 through 4 years of age. Phase I part was conducted to find the appropriate dose, and the dose 3 μg was selected in both age groups from the safety and immunogenicity results after the second dose of Comirnaty [see Section 7.1.1]. The subsequent phase II/III part was planned to compare immunogenicity data of children 6 months through 1 year of age and children 2 through 4 years of age with those obtained in the population of subjects 16 through 25 years of age in Study C4591001. The immunobridging success criteria (lower limit of 2-sided 95% CI of GMR of neutralizing antibody titer, >0.67; point estimate, ≥0.8; and lower limit of 2-sided 95% CI of the difference in antibody response rate, >−10%) were defined by referring to:

(a) Guidelines on clinical evaluation of vaccines: regulatory expectations, World Health Organization (WHO) Technical Report Series 1004, Annex 9, 2017[9)]
(b) Non-inferiority margin in many clinical studies on other infection-preventing vaccines (*Vaccine*. 2015;33:1426-32), and
(c) Immunogenicity success criteria used in clinical studies for the development of a booster dose of Comirnaty (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated November 2, 2021]).

Results of phase II/III part demonstrated that the data met the immunobridging success criteria in both subjects 6 months through 1 year of age and 2 through 4 years of age, suggesting the expected efficacy of Comirnaty in children 6 months through 4 years of age [see Section 7.R.2]. No serious safety concerns were noted with Comirnaty, demonstrating the tolerability [see Section 7.R.3].

Thus, the applicant filed a marketing application for Comirnaty in pediatric population 6 months through 4 years of age based on the immunogenicity and safety results of Study C4591007.

PMDA's view:

In general, children rarely develop COVID-19 and become seriously ill, possibly making it difficult to conduct a clinical study with enough statistical power to demonstrate the efficacy of SARS-CoV-2 vaccines in pediatric population. However, it has been demonstrated that the neutralizing antibody titer serves as a biomarker for estimating the efficacy of SARS-CoV-2 vaccines (*Nat Med*. 2021;27:1205-11). Taking account of the above findings, the FDA's "Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19 for Use in Pediatric Populations" states that if the efficacy of a vaccine has been demonstrated in any other population such as adults, it is possible to estimate the efficacy in children by the immunobridging approach using GMT of neutralizing antibody titer and antibody response rate. It has gradually become clear that there is a correlation between the neutralizing antibody titer after SARS-CoV-2 vaccination and the COVID-19-preventing effect (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11). Against this background, PMDA indicates, in the "Consideration for Evaluation of SARS-CoV-2 vaccine (Appendix 3): Consideration for Evaluation of SARS-CoV-2

9) https://www.who.int/publications/m/item/clinical-evaluation-of-vaccines-annex-9-trs-no-1004 (last accessed on August 9, 2022)

vaccine based on immunogenicity" (October 22, 2021, Office of Vaccines and Blood Products, PMDA), that in the development of a novel SARS-CoV-2 vaccine, it is acceptable to employ the immunobridging approach of evaluating the efficacy based on an immunogenicity index, using an approved SARS-CoV-2 vaccine as the control. Thus, it is acceptable to evaluate the efficacy of Comirnaty in population 6 months through 4 years of age, using the same immunobridging technique because Comirnaty has already been confirmed to be effective in the population ≥5 years of age.

On the basis of the above, PMDA concluded that the following evaluation policies of the applicant are acceptable: (1) The neutralizing antibody titer in subjects 6 months through 1 year of age and in subjects 2 through 4 years of age is evaluated in clinical studies, and the efficacy of Comirnaty in children 6 months through 4 years of age is evaluated by comparing the titer in the age group with established efficacy, and (2) the efficacy is evaluated based on the prespecified criteria for immunobridging success. During the conduct of phase II/III part of Study C4591007, the number of vaccinations with the study vaccine was changed pursuant to the results of the immunogenicity evaluation 1 month after the second dose, the originally defined evaluation time point and, as a result, it was decided to evaluate the immunogenicity after the third dose [see Section 7.1.2]. The above protocol change in evaluating the immunogenicity after the third dose is acceptable given the following: (a) Recent epidemic status suggests the necessity of 3 doses of SARS-CoV-2 vaccine in all age groups in order to ensure efficacy against Omicron variant, (b) the third dose is highly likely to be effective in the population of the present study, and (c) the urgent need for the efficacy assessment. It is considered acceptable to evaluate the efficacy of Comirnaty based on the results of the present study, taking account of the objectivity of the immunogenicity index and the fact that subjects and observers were preserved blinded to the study until the completion of post third dose assessment after the protocol change.

From December 2021, the epidemic of Omicron variant caused an increase in the number of patients with COVID-19 throughout the world. The number temporarily decreased from April to June of 2022 but shifted towards the rise again in July.[10)] In Japan also, the number of people newly infected with SARS-CoV-2 has rapidly risen again in July of the same year,[11)] indicating the necessity of making SARS-CoV-2 vaccine available to children <5 years of age as soon as possible. Although no Japanese clinical study has been conducted in Japanese children 6 months through 4 years of age, the age indication of the present application, it was decided to evaluate the immunogenicity and safety of Comirnaty in children 6 months through 4 years of age based on the results of the foreign study C4591007 submitted, taking account of the following: (a) Immunogenicity and safety in Japanese people have been confirmed in the Japanese clinical study in subjects ≥20 years of age, (b) use experience in individuals ≥5 years of age has been accrued in Japan as well, and (c) urgent need for vaccines in children <5 years of age.

10) https://covid19.who.int/ (last accessed on August 9, 2022)
11) https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html (last accessed on August 9, 2022)

7.R.2 Efficacy

The applicant's explanation about the efficacy of Comirnaty in children 6 months through 1 year of age and 2 through 4 years of age:

Originally, the applicant had planned to evaluate the efficacy of Comirnaty in children 6 months through 1 year of age and 2 through 4 years of age with the primary endpoint in phase II/III part of Study C4591007: "neutralizing antibody titer (GMT and antibody response rate) against SARS-CoV-2 (reference strain [strain USA-WA1/2020]) 1 month after the second dose of Comirnaty (3 μg)." However, with the addition of the third dose in Study C4591007, the plan for the efficacy assessment was changed as follows (protocol amendment, ver. 6, January 4, 2022): (a) To evaluate the neutralizing antibody titer (GMT and antibody response rate) against SARS-CoV-2 (reference strain) at 1 month after the third dose of Comirnaty (3 μg), and then (b) to compare the data with the immunogenicity data of the population randomly extracted from subjects 16 through 25 years of age who had received 2 doses of Comirnaty (30 μg) in Study C4591001 which had confirmed COVID-19-preventive effect.

For the immunogenicity control data, those obtained from subjects ≤25 years of age were used to allow comparison with the population of a closer age group, by considering the effect of age on immunogenicity. Although the participating countries of these studies are partially different from each other,[12)] the main inclusion and exclusion criteria were the same except for age. It was considered appropriate to compare the immunogenicity data between both studies by simultaneously measuring neutralizing antibody titer, using the same assay method, in serum samples obtained from subjects without history of SARS-CoV-2 infection.

GMR and antibody response rate obtained in phase II/III part of Study C4591007 were compared with those in the population of 16 through 25 years of age in Study C4591001 which evaluated the neutralizing antibody titer at 1 month after the third dose of Comirnaty as the primary endpoint. Results showed that the difference in both GMR and antibody response rate fulfilled the pre-defined success criteria [see Section 7.1.2, Table 7]. Table 8 shows subject characteristics of the evaluable immunogenicity populations in phase II/III part of Study C4591007 and in the reference population, i.e., population of 16 through 25 years of age in Study C4591001.

[12)] Study C4591007: The US, Finland, Poland, and Spain
Study C4591001: The US, Germany, Turkey, Brazil, Argentina, and South Africa

Table 8. Subject characteristics (evaluable immunogenicity population in phase II/III part) (without SARS-CoV-2 infection at baseline)

		Study C4591007		Study C4591001
		6 months-1 year old (Comirnaty 3 μg) N = 204	2-4 years old (Comirnaty 3 μg) N = 132	16-25 years old (Comirnaty 30 μg*) N = 183
		n (%)	n (%)	n (%)
Sex	Male	94 (46.1)	73 (55.3)	89 (48.6)
	Female	110 (53.9)	59 (44.7)	94 (51.4)
Race	Caucasian	151 (74.0)	102 (77.3)	138 (75.4)
	Black, African-American	9 (4.4)	2 (1.5)	18 (9.8)
	Asian	20 (9.8)	14 (10.6)	15 (8.2)
	Multiracial	21 (10.3)	13 (9.8)	7 (3.8)
	Other[a)] or unknown	3 (1.5)	1 (0.8)	5 (2.7)
Ethnicity	Hispanic or Latino	24 (11.8)	18 (13.6)	56 (30.6)
	Non-Hispanic or non-Latino	179 (87.7)	114 (86.4)	127 (69.4)
	Unknown	1 (0.5)	0	0
Obesity[b)]	Yes	11 (5.4)	—	34 (18.6)
	No	193 (94.6)	—	149 (81.4)
Baseline SARS-CoV-2 infection status[c)]	Positive	11 (5.4)	6 (4.5)	7 (3.8)
	Negative	193 (94.6)	125 (94.7)	176 (96.2)
	Not reported	0	1 (0.8)	0

N = number of subjects analyzed, n = number of corresponding subjects
* One month after administration of 2 doses of Comirnaty 30 μg, 3 weeks apart
a) American Indians, Alaska natives, Native Hawaiians, other Pacific Islanders
b) Study C4591007: BMI ≥95 percentile; Study C4591001: BMI ≥30 kg/m^2
c) Baseline SARS-CoV-2 infection status: "Yes" if positive for SARS-CoV-2 N-binding antibody test, nucleic acid amplification test, or history of COVID-19 infection at Visit 1; "No" if both tests are negative and without history of COVID-19 infection.

Table 9 shows the neutralizing antibody titer at 1 month after the third dose of Comirnaty in each subpopulation. GMT was generally similar regardless of sex, race, or ethnicity, although caution is required in the interpretation of the results of neutralizing antibody titer because of the limited number of subjects in certain subpopulations. A high antibody response rate was observed both in the subpopulation with SARS-CoV-2 infection at baseline and in the subpopulation without the infection, although the neutralizing antibody tier was higher in the former subpopulation.

Table 9. Neutralizing antibody titer at 1 month after the third dose of Comirnaty by subpopulations (evaluable immunogenicity population in phase II/III part)

		Study C4591007				Study C4591001	
		6 months-1 year old (Comirnaty 3 μg)		2-4 years old (Comirnaty 3 μg)		16-25 years old (Comirnaty 30 μg*)	
		n	GMT [2-sided 95% CI]	n	GMT [2-sided 95% CI]	n	GMT [2-sided 95% CI]
All		132	1724.0 [1523.4, 1951.0]	204	1636.3 [1482.4, 1806.3]	183	1210.9 [1095.6, 1338.4]
Sex	Male	73	1673.5 [1429.8, 1958.7]	94	1537.5 [1301.3, 1816.6]	89	1275.9 [1117.5, 1456.8]
	Female	59	1788.6 [1462.0, 2188.2]	110	1725.8 [1535.5, 1939.7]	94	1152.4 [991.2, 1339.8]
Race	Caucasian	102	1765.6 [1530.3, 2037.1]	151	1703.7 [1533.6, 1892.6]	138	1240.5 [1104.2, 1393.6]
	Black, African-American	2	777.0 [30.3, 19904.9]	9	1726.2 [989.4, 3011.5]	18	1156.7 [836.2, 1600.1]
	Asian	14	1994.1 [1461.4, 2720.9]	20	1229.5 [705.3, 2143.2]	15	914.8 [573.3, 1459.8]
	Multiracial	13	1334.4 [828.3, 2149.6]	21	1711.3 [1351.1, 2167.4]	7	1213.5 [878.3, 1676.7]
Ethnicity	Hispanic or Latino	18	1719.0 [1161.5, 2543.9]	24	1904.0 [1501.4, 2414.6]	56	1088.7 [879.7, 1347.3]
	Non-Hispanic or non-Latino	114	1724.8 [1511.7, 1967.9]	179	1604.0 [1439.2, 1787.6]	127	1269.1 [1136.3, 1417.4]
Baseline SARS-CoV-2 infection status[a)]	Positive	6	3794.8 [2669.6, 5394.3]	11	3474.9 [2515.2, 4800.8]	7	2468.4 [1214.9, 5015.0]
	Negative	125	1656.0 [1459.6, 1878.7]	193	1567.6 [1418.5, 1732.3]	176	1177.1 [1065.5, 1300.4]

* One month after administration of 2 doses of Comirnaty 30 μg, 3 weeks apart
a) Same as note c) in Table 8

In phase II/III part of Study C4591007, neutralizing antibody titer against Delta variant and Omicron variant (BA.1) was evaluated by comparing the titer before the third dose of Comirnaty with the titer 1

month after the third dose. Table 10 shows the results in children 2 through 4 years of age and 6 months through 1 year of age. Neutralizing antibody titer increased after the third dose in both age groups.

Table 10. Neutralizing antibody titer (GMT [2-sided 95% CI]) against SARS-CoV-2 variants before the third dose of Comirnaty and at 1 month after the third dose (evaluable immunogenicity population in phase II/III part)

		Study C4591007		Study C4591001
		2-4 years old (Comirnaty 3 μg) N = 34	6 months-1 year old (Comirnaty 3 μg) N = 32	18-55 years old (Comirnaty 30 μg) N = 40
Reference strain	Before the third dose	70.1 [51.1, 96.0]	103.7 [78.4, 137.3]	33.9 [26.1, 44.1]
	One month after the third dose	471.4 [344.6, 644.8]	640.0 [502.6, 815.0]	1067.1 [834.4, 1364.5]
Delta variant	Before the third dose	68.0 [49.5, 93.3]	94.1 [67.9, 130.5]	36.4 [26.5, 49.9]
	One month after the third dose	471.4 [341.2, 651.1]	606.3 [455.5, 806.9]	1153.6 [886.4, 1501.4]
Omicron variant (BA.1)	Before the third dose	14.0 [10.6, 18.5]	16.3 [12.8, 20.8]	12.7 [11.0, 14.8]
	One month after the third dose	82.5 [55.4, 122.9]	127.5 [90.2, 180.1]	340.0 [253.8, 455.6]

N = number of subjects analyzed

In phase II/III part of Study C4591007, COVID-19-preventive effect based on vaccine efficacy (VE) was evaluated in an exploratory manner. According to the data available at the cut-off date of April 29, 2022, the number of subjects with COVID-19[13)] confirmed ≥Day 7 after the third dose of the study vaccine was 3 in the Comirnaty group and 7 in the placebo group among the efficacy analysis set 6 months through 4 years of age (992 in Comirnaty group, 464 in placebo group), with VE [2-sided 95% CI] adjusted for the observation period being 80.3 [13.9, 96.7]. Relative vaccine efficacy (RVE) of 3 doses of Comirnaty relative to 2 doses was evaluated in an exploratory manner, based on the data obtained during the period from February 7, 2022 to April 29 of the same year from 1,212 subjects who received 3 doses of Comirnaty ≥7 days earlier under blinded conditions and from 516 subjects in the placebo group who received 2 doses of Comirnaty ≥7 days after unblinding. COVID-19 was confirmed in 4 subjects ≥7 days after the third dose of Comirnaty and in 6 subjects ≥7 days after the second dose, with RVE [2-sided 95% CI] adjusted for duration of observation period being 76.2 [-0.5, 95.1]. VE by age group was 82.3 [-8.0, 98.3] in subjects 2 through 4 years of age and 75.5 [-370.1, 99.6] in subjects 6 months through 1 year of age; RVE by age group was 84.0 [-11.8, 98.6] in subjects 2 through 4 years of age and 59.4 [-459.5, 97.1] in subjects 6 months through 1 year of age. The following investigations on COVID-19-preventive effect are planned in Study C4591007: (a) Analysis when data of ≥21 subjects with confirmed COVID-19 have been accrued, and (b) ≥12-month follow-up after the third dose.

Thus, results of phase II/III part of Study C4591007 met the criteria for successful immunobridging with the population 16 through 25 years of age in Study C4591001. The preliminary data showed a high VE in the study conducted over a period that includes prevalence of Omicron variant, coupled with an increase in neutralizing antibody titer against Omicron variant (BA.1). These findings, together with the COVID-19-preventive effect confirmed in Study C4591001, suggest that Comirnaty is expected to have certain level of efficacy in children 6 months through 4 years of age.

13) Defined as individuals with ≥1 of the symptoms of suspected COVID-19 (pyrexia, new onset or worsening of cough, new onset or worsening of shortness of breath, chills, new onset or worsening of myalgia, new loss of taste or smell, sore throat, diarrhoea, vomiting, poor or no food intake) and with a positive SARSCoV-2 result confirmed by nasopharyngeal swab nucleic acid amplification testing.

PMDA's view:
It is acceptable to compare the immunogenicity data between pediatric populations 2 through 4 years of age or 6 months through 1 year of age in phase II/III part of Study C4591007 and the population 16 through 25 years of age in Study C4591001, taking account of the following observations: (a) Study C4591001 demonstrated a marked increase in neutralizing antibody titer and COVID-19-preventive effect, and (b) subpopulation analysis showed a significant COVID-19-preventive effect regardless of the subject characteristics (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021], *N Engl J Med*. 2021;384:1576-7).

In phase II/III part of Study C4591007, the difference in both GMR of neutralizing antibody titer and antibody response rate at 1 month after the third dose of Comirnaty achieved the immunobridging success criteria. In addition, no significant difference was observed in subject characteristics in the subpopulation analysis of neutralizing antibody titer. These findings, coupled with the COVID-19-preventive effect confirmed in Study C4591001, suggest that Comirnaty is expected to have certain level of efficacy in children 6 months through 4 years of age.

The immunogenicity data submitted in the present application are those obtained up to 1 month after the third dose of Comirnaty, and changes over time in neutralizing antibody titer in children 6 months through 4 years of age are unknown. Further information on COVID-19-preventive effect in Study C4591007, which is planned to be evaluated continuously, and efficacy information on variants from epidemiological studies, should be provided in an appropriate manner when they become available.

It has been confirmed in Study C4591001 and other studies that neutralizing antibody titer decreases over time after vaccination (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated November 2, 2021]). Information on changes in the immunogenicity data over time in children 6 months through 4 years should be collected continuously and, when new information is obtained, necessity of an additional booster dose should be investigated. It is necessary to pay attention to emergence of variants and epidemic status, to collect information on the efficacy and immunogenicity of Comirnaty against variants, and to consider taking appropriate measures against the situations.

7.R.3 Safety

7.R.3.1 Safety profile

The applicant's explanation about the safety in Study C4591007:

(a) Reactogenicity events

Subjects 2 through 4 years of age

Table 4 shows reactogenicity events observed within 7 days after the study vaccine administration in subjects 2 through 4 years of age in phase II/III part. Localized reactions and systemic reactions were observed in many subjects in the Comirnaty group. The incidence of each event was similar between the Comirnaty group and the placebo group for systemic reactions, whereas the incidence was higher in the Comirnaty group than in the placebo group for local reactions. There were no Grade ≥3 events with an incidence of ≥1%, whereas no grade 4 event was observed.

The incidence of pyrexia in the Comirnaty group classified by body temperature was as follows: 38.0 to 38.4℃, 5.3% (97 subjects) (3.1% [57] of subjects after the first dose, 2.3% [41] of subjects after the second dose, 2.9% [16] of subjects after the third dose; hereinafter the same order shall apply); 38.5 to 38.9℃, 3.1% (56) (1.3% [24], 1.5% [26], 1.4% [8]); 39.0 to 40.0℃, 2.0% (36) (0.7% [13], 1.1% [19], 0.7% [4]); and >40.0℃, 0.2% (3) (0.1% [1], 0.1% [2], 0). Pyrexia of >40.0℃ was observed in 3 subjects: 1 subject after the first dose and the other 2 subjects after the second dose. Pyrexia occurred 2 to 5 days after study vaccine administration and persisted for 1 to 5 days, whereas pyrexia of ≥40.0℃ persisted for 1 to 3 days. Two of them used antipyretic or pain medication. The outcome was "recovered" in all subjects.

The incidence of local reactions after the third dose was similar to, or lower than, the incidence after the first and second dose. After each dose, the median time to the onset of local reactions was 1 to 2 days and the median duration was 1 day. The incidence of systemic reactions tended to decrease in the order of the first, second, and third dose. The median time to the onset of systemic reactions was 2 days after each dose, with the median duration of 1 day.

At least 1 dose of antipyretic or pain medication was used to treat the study vaccine-associated symptoms in 10.8% (197 of 1,825) of subjects in the Comirnaty group and in 9.1% (83 of 909) of subjects in the placebo group after the first dose; 9.9% (177 of 1,779) of subjects in the Comirnaty group and in 8.4% (74 of 878) of subjects in the placebo group after the second dose; and 8.5% (47 of 552) of subjects in the Comirnaty group and in 6.9% (18 of 262) of subjects in the placebo group after the third dose. In Study C4591007, prophylactic administration of antipyretic or pain medication was not allowed.

Table 11 shows the incidence of reactogenicity events in each subpopulation. No clear difference in the incidence was observed among subpopulations with different subject characteristics.

Table 11. Subpopulation analysis of reactogenicity events within 7 days after each dose of study vaccine (first, second, or third dose) (phase II/III part, safety analysis set)

		Local reactions		Systemic reactions	
		Comirnaty n/N (%)	Placebo n/N (%)	Comirnaty n/N (%)	Placebo n/N (%)
All subjects		981/1,833 (53.5)	348/913 (38.1)	1,044/1,833 (57.0)	493/913 (54.0)
Sex	Male	444/899 (49.4)	164/469 (35.0)	476/899 (52.9)	248/469 (52.9)
	Female	537/934 (57.5)	184/444 (41.4)	539/934 (57.7)	245/444 (55.2)
Race	Caucasian	795/1,469 (54.1)	274/719 (38.1)	828/1,469 (56.4)	399/719 (55.5)
	Black, African-American	43/92 (46.7)	13/40 (32.5)	36/92 (39.1)	18/40 (45.0)
	Asian	59/127 (46.5)	33/76 (43.4)	69/127 (54.3)	38/76 (50.0)
	Multiracial	79/131 (60.3)	24/69 (34.8)	75/131 (57.3)	32/69 (46.4)
Ethnicity	Hispanic or Latino	122/264 (46.2)	32/120 (26.7)	118/264 (44.7)	51/120 (42.5)
	Non-Hispanic or non-Latino	857/1,566 (54.7)	316/793 (39.8)	895/1,566 (57.2)	442/793 (55.7)
Baseline SARS-CoV-2 infection status[a)]	Yes	118/231 (51.1)	37/124 (29.8)	110/231 (47.6)	62/124 (50.0)
	No	860/1,597 (53.9)	310/782 (39.6)	900/1,597 (56.4)	426/782 (54.5)

N = number of subjects analyzed, n = number of subjects with events

a) Baseline SARS-CoV-2 infection status: "Yes" if positive for SARS-CoV-2 N-binding antibody test, nucleic acid amplification test, or history of COVID-19 infection at Visit 1; "No" if both tests are negative and without history of COVID-19 infection.

Subjects 6 months through 1 year of age

Table 4 shows reactogenicity events observed within 7 days after the study vaccine administration to subjects 6 months through 1 year of age in phase II/III part. Local and systemic reactions were observed in many subjects of the Comirnaty group.

The incidence of pyrexia was similar between the Comirnaty group and the placebo group, whereas the incidence of other events was higher in the Comirnaty group than in the placebo group. The only Grade ≥3 events with ≥1% incidence was decreased appetite in 1.1% (4 of 362) of subjects after the third dose of Comirnaty. There was no Grade 4 event.

The incidence of pyrexia in the Comirnaty group classified by body temperature was as follows: 38.0 to 38.4℃, 6.7% (79 subjects) (3.6% [42] of subjects after the first dose, 3.6% [41] of subjects after the second dose, 3.8% [14] of subjects after the third dose; hereinafter the same order shall apply); 38.5 to 38.9℃, 3.7% (43) (2.0% [23], 1.7% [20], 1.4% [5]); 39.0 to 40.0℃, 3.7% (44) (1.6% [19], 2.0% [23], 1.4% [5]); and >40.0℃, 0.3% (3) (0.1% [1], 0.1% [1], 0.1% [1]). Pyrexia of >40.0℃ was observed in 3 subjects: 1 subject each after the first, second, and third dose. Pyrexia occurred 1 to 3 days after the vaccination and persisted for 2 to 5 days, whereas pyrexia of >40.0℃ persisted only for 1 day. Two of them used antipyretic or pain medication. The outcome was “recovered” in all subjects.

The incidence of local reactions was lower after the third dose than after the first or second dose. After each dose, the median time to the onset of local reactions was 1 to 2 days and the median duration was 1 day. The incidence of systemic reactions tended to decrease in the order of the first, second, and third dose. The median time to the onset of systemic reactions was 2 days after each dose, with the median duration of 1 to 2 days.

The incidence of reactogenicity events decreased in the order of the first, second, third dose, except injection site pain in the placebo group, and except injection site pain and decreased appetite in the Comirnaty group.

At least 1 dose of antipyretic or pain medication was used to treat the study vaccine-associated symptoms in 24.0% (281 of 1,173) of subjects in the Comirnaty group and in 19.7% (117 of 595) of subjects in the placebo group after the first dose; 21.2% (243 of 1,147) of subjects in the Comirnaty group and in 18.8% (111 of 591) of subjects in the placebo group after the second dose; and 19.2% (70 of 365) of subjects in the Comirnaty group and in 16.5% (28 of 170) of subjects in the placebo group after the third dose. In Study C4591007, prophylactic administration of antipyretic or pain medication was not allowed.

Table 12 shows the incidence of reactogenicity events in each subpopulation. No clear difference in the incidence was observed among subpopulations with different subject characteristics.

Table 12. Subpopulation analysis of reactogenicity events within 7 days after each dose of study vaccine (first, second, or third dose) (phase II/III part, safety analysis set)

		Local reactions		Systemic reactions	
		Comirnaty n/N (%)	Placebo n/N (%)	Comirnaty n/N (%)	Placebo n/N (%)
All subjects		434/1,177 (36.9)	161/597 (27.0)	906/1,177 (77.0)	435/597 (72.9)
Sex	Male	214/588 (36.4)	79/291 (27.1)	459/588 (78.1)	208/291 (71.5)
	Female	220/589 (37.4)	82/306 (26.8)	447/589 (75.9)	227/306 (74.2)
Race	Caucasian	352/921 (38.2)	131/480 (27.3)	722/921 (78.4)	354/480 (73.8)
	Black, African-American	13/42 (31.0)	6/23 (26.1)	25/42 (59.5)	15/23 (65.2)
	Asian	24/91 (26.4)	10/40 (25.0)	64/91 (70.3)	26/40 (65.0)
	Multiracial	44/117 (37.6)	12/49 (24.5)	91/117 (77.8)	35/49 (71.4)
Ethnicity	Hispanic or Latino	55/160 (34.4)	17/64 (26.6)	124/160 (77.5)	48/64 (75.0)
	Non-Hispanic or non-Latino	376/1,014 (37.1)	142/529 (26.8)	779/1,014 (76.8)	385/529 (72.8)
Baseline SARS-CoV-2 infection status[a)]	Yes	31/88 (35.2)	6/43 (14.0)	69/88 (78.4)	30/43 (69.8)
	No	398/1,078 (36.9)	152/541 (28.1)	827/1,078 (76.7)	396/541 (73.2)

N = number of subjects analyzed, n = number of subjects with events

a) Baseline SARS-CoV-2 infection status: "Yes" if positive for SARS-CoV-2 N-binding antibody test, nucleic acid amplification test, or history of COVID-19 infection at Visit 1; "No" if both tests are negative and without history of COVID-19 infection.

(b) Adverse events

Subjects 2 through 4 years of age

In phase II/III part, the incidence of adverse events from the first dose of the study vaccine up to 1 month after the last dose was 18.7% (344 of 1,835) of subjects in the Comirnaty group and 18.7% (171 of 915) of subjects in the placebo group, showing no difference between the groups [see Section 7.1.2, Table 5]. The incidence of adverse events observed from the first dose of the study vaccine up to the data cut-off date (April 29, 2022) was 18.8% (345 of 1,835) of subjects in the Comirnaty group and 18.9% (173 of 915) of subjects in the placebo group, and reported events were generally the same as those reported during 1 month after the last dose of the study vaccine.

There were no reports of important identified risks (shock, anaphylaxis, myocarditis, pericarditis) or important potential risk (Guillain-Barre syndrome) for approved Comirnaty Intramuscular Injection and Comirnaty Intramuscular Injection for 5 through 11 years old.

Severe COVID-19[14)] was reported in 6 subjects in the Comirnaty group and in 1 subject in the placebo group. All of the events occurred after the second dose of Comirnaty, with symptoms occurring at 32 to 208 days after the last dose. Of the 6 subjects in the Comirnaty group, 5 were diagnosed with severe COVID-19 based on a single symptom (heart rate increased in 2 subjects, respiratory rate increased in 3 subjects). One subject diagnosed with severe COVID-19 based on increased heart rate had contracted COVID-19 twice in the past. The remaining 1 subject was diagnosed with severe COVID-19 based on multiple symptoms (heart rate increased, respiratory rate increased, and oxygen saturation as measured by pulse oximetry [SpO_2] decreased) and found to be co-infected with parainfluenza virus infection. One subject in the placebo group was diagnosed with severe COVID-19 based on decreased SpO_2. This

14) Confirmed COVID-19 cases with ≥1 of the following conditions:
- Clinical signs at rest suggesting severe systemic disease (respiratory rate increased, heart rate increased, SpO_2 decreased, or PaO_2/FiO_2 decreased)
- Respiratory failure (defined as requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation)
- Shock or cardiac failure, acute renal failure, hepatic failure, or neurological disorder, admission to an intensive care unit, death.

subject had been serologically confirmed to have a history of SARS-CoV-2 at baseline. There was no evidence suggestive of MIS-C or vaccine-associated enhanced disease (VAED)/vaccine-associated enhanced respiratory disease (VAERD), an important potential risk with approved Comirnaty.

Subjects 6 months through 1 year of age:
In phase II/III part, the incidence of adverse events from the first dose of the study vaccine up to 1 month after the last dose was 30.1% (355 of 1,178) of subjects in the Comirnaty group and 27.1% (162 of 598) of subjects in the placebo group [see Section 7.1.2, Table 5]. The incidence of adverse events observed from the first dose of the study vaccine up to the data cut-off date (April 29, 2022) was 30.3% (357 of 1,178) of subjects in the Comirnaty group and 27.3% (163 of 598) of subjects in the placebo group. Most of adverse events additionally reported from the last dose of the study vaccine up to the data cut-off date were those observed in general population of the same age group (viral infection, pyrexia, and other rare diseases and injuries).

There were no reports of important identified risks (shock, anaphylaxis, myocarditis, pericarditis) or important potential risk (Guillain-Barre syndrome) for approved Comirnaty Intramuscular Injection and Comirnaty Intramuscular Injection for 5 through 11 years old.

Severe COVID-19 was reported in none of the subjects in the Comirnaty group and in 1 subject in the placebo group. This subject was diagnosed with severe COVID-19 because of increased heart rate and was found to be co-infected with enterovirus. There was no evidence suggestive of MIS-C or VAED/VAERD, an important potential risk with approved Comirnaty.

(c) Serious adverse events and adverse events requiring particular attention
Subjects 2 through 4 years of age:
In phase I part (data cut-off date of July 16, 2021), no serious adverse events were observed.

In phase II/III part, the incidence of serious adverse events observed on or before the data cut-off date (April 29, 2022) was 0.7% (12 of 1,835) of subjects in the Comirnaty group and 0.9% (8 of 915) of subjects in the placebo group [see Section 7.1.2]. No death occurred in either part.

The following events were evaluated as adverse events requiring particular attention: (i) Autoimmune or neuroinflammatory events, (ii) events theoretically related to vaccine administration, and (iii) events supposed to occur in patients with COVID-19. No myocarditis, pericarditis, Bell's palsy (or facial paralysis/facial paresis), or anaphylaxis was observed in either part. In the Comirnaty group of phase II/III part, lymphadenopathy and appendicitis were reported in 1 and 2 subjects, respectively. Causal relationship of lymphadenopathy to the study vaccination could not be ruled out. The outcome was "recovered."

Subjects 6 months through 1 year of age:
In phase I part (data cut-off date of July 16, 2021), no serious adverse event was observed.

In phase II/III part, serious adverse events were observed in 1.4% (17 of 1,178) of subjects in the Comirnaty group and in 2.3% (14 of 598) of subjects in the placebo group up to the data cut-off date (April 29, 2022) [see Section 7.1.2]. No death occurred in either part.

Adverse events requiring particular attention were evaluated in the same manner as in the population 2 through 4 years of age. No myocarditis, pericarditis, Bell's palsy (or facial paralysis/facial paresis), appendicitis, or anaphylaxis was observed in either part. Lymphadenopathy was reported in 2 subjects of the Comirnaty group in phase II/III part, and the causal relationship to Comirnaty was not ruled out for lymphadenopathy in 1 subject. The outcome in this subject was "recovered."

As shown in (a) to (c) above, reactogenicity events (local reactions and systemic reactions) were observed in many subjects receiving Comirnaty among the population 6 months through 4 years of age in Study C4591007, but most of the events were mild or moderate in severity and resolved within a short time after the onset of symptoms, showing the profile similar to that confirmed in subjects ≥5 years of age. Adverse events other than reactogenicity events were only seldom observed, and most of them were mild or moderate in severity. The incidences of serious adverse events and adverse events leading to study discontinuation were low as well. Adverse events requiring particular attention were observed in a small number of subjects, but there were no cases of anaphylaxis, myocarditis, or pericarditis suspected to be related to Comirnaty. Thus, there are no serious safety concerns with Comirnaty in children 6 months through 4 years of age at present, confirming the tolerability of Comirnaty.

PMDA's view:
Most of reactogenicity events (local reactions and systemic reactions) observed in many subjects in Study C4591007 were mild or moderate in severity, and all of them have resolved. The incidence of adverse events other than reactogenicity events was low, and most of them were mild or moderate in severity. Accordingly, PMDA concluded that Comirnaty poses no serious safety concerns in children 6 months through 4 years of age, at present.

Because of the limited safety information in children 6 months through 4 years of age, safety information on Comirnaty in children in this age group should be collected after marketing, and safety measures should be re-evaluated in an appropriate manner and timing, based on the information thus obtained. The finding that local reactions and systemic reactions were observed in many subjects, together with the timing and duration of events with a higher incidence, should be explained appropriately to healthcare professionals, vaccine recipients, and their guardians.

7.R.3.2 Post-marketing safety information

The applicant's explanation about safety information in children 6 months through 4 years of age obtained after use authorization, etc., in foreign countries:
Use of Comirnaty in children 6 months through 4 years of age was started from June 17, 2022 (the date of emergency use authorization in the US), and there is only limited use experience at present. Post-marketing safety information in foreign countries is being collected and evaluated. Spontaneous reports collected up to July 15, 2022 do not include shock, anaphylaxis, myocarditis, etc., that are identified as risks of approved SARS-CoV-2 vaccines as well. No adverse events specific to children 6 months

through 4 years of age have been observed either. Children 6 months through 4 years of age will be monitored for possible new safety concerns based on the information to be obtained after marketing as well as during the follow-up period or Study C4591007, by continued case evaluation, literature search, and signal detection. Taking into account that it is difficult for children 6 months through 4 years of age to complain subjective symptoms (including those of myocarditis and pericarditis), information materials will be distributed in the same manner as for children ≥5 years so that the guardians of vaccine recipients will notice adverse events at the early stage from changes in physical conditions, etc., of their children, and take appropriate measures such as bringing their children to hospitals.

PMDA's view:
In countries outside Japan, there are many reports of myocarditis and pericarditis after the second dose of mRNA vaccine against SARS-CoV-2, particularly in young male vaccine recipients after the second dose (*N Engl J Med*. 2021;385:2140-9, Myopericarditis following COVID-19 vaccination: Updates from the Vaccine Adverse Event Reporting System (VAERS)[15)]). In Japan, on the basis of accrued reports from manufacturers on suspected myocarditis-related events, myocarditis and pericarditis were included in the Reporting Criteria for suspected adverse reactions on December 6, 2021 and have been assessed on a regular basis. At the joint meeting of the 81st Meeting of the Working Group on Adverse Reactions of the Subcommittee on Immunization and Vaccines of the Health Sciences Council and the 6th meeting of FY 2022 Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council, the number of suspected myocarditis or pericarditis (per million doses) reported by the manufacturer (the number of all reported cases including those of Brighton level 4 and 5) was 0.6 to 3.2 for myocarditis and 0.4 to 1.3 for pericarditis in all age group after administration of Comirnaty Intramuscular Injection (reporting period from February 17, 2021 to June 12, 2022) and 2.3 to 2.6 for myocarditis and 0 to 1.7 for pericarditis after administration of Comirnaty Intramuscular Injection for 5 through 11 years old (reporting period from February 21, 2022 to June 12, 2022). It was concluded that there are no serious safety concerns affecting the vaccination system at present, including vaccination in children ≥5 years of age.

In young people, the frequency of myocarditis/pericarditis after vaccination is lower than the frequency of myocarditis-related events associated with COVID-19, and most of them, if any, are asymptomatic or mild in severity (*Circulation*. 2021;144:471-84, etc.). In addition, given the occurrence after administration of Comirnaty Intramuscular Injection for 5 through 11 years old, there are no information, at present, suggestive of unacceptable risk in children 6 months through 4 years of age.

As for adverse reactions other than myocarditis/pericarditis, there are no reports so far of shock or anaphylaxis in children 6 months through 4 years of age, nor are there reports suggesting risks unique to this age group. Nevertheless, it is essential to continuously collect safety information in children 6 months through 4 years of age, including overseas information, and to devise appropriate measures based on the information thus obtained. The applicant's proposal to distribute information materials to guardians of vaccine recipients describing specific symptoms, necessity of consulting doctors, etc., is

[15)] ACIP Presentation Slides: October 20-21, 2021 Meeting, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf (last accessed on August 9, 2022)

appropriate because children 6 months through 4 years of age are hardly able to notice or complain symptoms of adverse reactions.

7.R.4 Clinical positioning

PMDA's view on clinical positioning of Comirnaty:

In Japan, the number of COVID-19 patients which increased during the period from December 2021 to March 2022 due to the epidemic of Omicron variant turned to decrease temporarily from April to June, 2022, but the number of people newly infected with SARS-CoV-2 rapidly increased again in July of the same year,[11)] accompanied by an increase in COVID-19 patients in all age groups including children <5 years of age (the 92nd Advisory Board Meeting for COVID-19 Measures[16)]). Depending on the trend of the current epidemic and on the emergence of novel variants, there are possibilities of further expansion of the infection.

Pediatric COVID-19 is reported to be relatively mild and rarely becomes severe but, with the increase in the number of infected individuals, complications with febrile convulsion, croup, etc., are observed. Hospitalized or fatal cases are also reported.[3)] Children with underlying diseases or obesity have a high risk of severe COVID-19,[17)] and, in the US and Europe, severe cases and deaths are reported to occur at a constant rate among such children (*Lancet Child Adolesc Health.* 2020;4:653-61).

Apart from severe COVID-19, there are many reports in foreign countries of MISC/PIMS that occurs 2 to 6 weeks after SARS-CoV-2 infection and are accompanied by pyrexia and multi-organ disorder (*Eur J Pediatr.* 2020;180:2019-34, *JAMA Pediatr.* 2021;175:837-45, etc.). Similar cases are reported in Japan as well (*Modern Rheumatology Case Reports.* 2021;5:442-447, *IDCases.* 2022;28:e01493, etc.). MIS-C/PIMS occurs regardless of presence or absence of COVID-19 symptoms, sometimes rapidly resulting in symptom aggravation even if the diagnostic criteria are not met at the onset, necessitating control in the intensive care unit. Deaths are also reported in foreign countries, albeit at a low frequency (multisystem inflammatory syndrome in children associated with COVID-19 [MIS-C/PIMS] diagnosis consensus statement[4)]).

In Japan, as of August 9, 2022, there is no SARS-CoV-2 vaccine that can be used in children ≤4 years of age. In the US, in contrast, Comirnaty is granted marketing approval or authorized for use in children 6 months through 4 years of age as of June 2022. The US CDC recommends COVID-19 vaccines for all children ≥6 months of age for the following reasons[18)]: Preventing COVID-19 in children by vaccination is expected not only to protect children from risks such as COVID-19-associated hospitalization, death, MIS-C/PIMS, and sequelae, but also to prevent the spread of infection in houses and schools mediated by children.

On the basis of the results of Study C4591007 submitted in the present application, PMDA has concluded that Comirnaty is effective in children 6 months to 4 years of age [see Section 7.R.2] with no serious safety concerns at present [see Section 7.R.3].

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16) Document 3-2: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00348.html (last accessed on August 9, 2022)
17) https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (last accessed on August 9, 2022)
18) https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/children-teens.html (last accessed on August 9, 2022)

Accordingly, Comirnaty should be made available for administration in children 6 months through 4 years of age as soon as possible. The benefit-risk balance expected of SARS-CoV-2 vaccination differs depending on the infection epidemic status, presence or absence of underlying disease in vaccine recipients, etc. Sufficient information should be provided so that healthcare professionals, vaccine recipients, and their guardians decide the necessity of vaccination after understanding the benefits expected in children receiving Comirnaty and risks such as adverse reactions.

7.R.5 Dosage and administration

Comirnaty, in this application, was developed as a formulation for children 6 months through 4 years of age. The proposed dosage and administration instructions are as follows: "Three doses of 0.2 mL each (containing 3 μg of tozinameran) 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."

The applicant's explanation about the selection of dose levels and age indication:
In phase I part of Study C4591007 which was conducted as a dose-finding study, 2 doses of Comirnaty (3 or 10 μg) were administered to children 2 through 4 years of age 21 days apart to investigate the safety, tolerability, and immunogenicity. The number and interval of vaccination were determined based on the approved dosage regimen for vaccine recipients 5 through 11 years of age and above. Results showed that the incidence and severity of reactogenicity events tended to be high in the 10 μg group, and that the neutralizing antibody titer after Comirnaty administration was similar between 3 μg group and 10 μg. Accordingly, the dosage regimen in children 2 through 4 years of age in phase II/III part was decided to be 2 doses of 3 μg of Comirnaty administered21 days apart (allowance: 19-23 days) [see Section 7.1.1].

The third dose was considered necessary for children 2 through 4 years of age for the following reasons [see Section 7.1.2]: (a) Results of immunogenicity assessment at 1 month after the second dose in phase II/III part (Table 6) failed to meet the criteria for immunobridging success in children 2 through 4 years of age, and (b) the most recent epidemic status suggested that vaccination with the third dose was necessary to ensure disease-preventive effect against Omicron variant in adolescents and adults (*MMWR*. 2022;71:139-45, UK Health Security Agency. COVID-19 vaccine surveillance report- Week 27, 7 July 2022[19)], etc.).

The third dose is to be administered ≥8 weeks after the second dose to acquire immunity swiftly. No upper limit for the dosing interval is set by referring to the generalities in immunology that longer dosing interval may lead to better immune response and to the dosing interval for other vaccines. The same dosage regimen of Comirnaty is applied to children 6 months through 1 year of age as that of 2 through 4 years of age.

The immunogenicity results of phase II/III part indicated that Comirnaty is expected to have efficacy in children 6 months through 4 years of age [see Section 7.R.2], and the safety and tolerability of 3 doses of Comirnaty are acceptable [see Section 7.R.3]. Accordingly, the dosage regimen of Comirnaty in

19) https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports (last accessed on August 9, 2022)

children 6 months through 4 years of age is proposed as follows: “Three doses of tozinameran 3 μg 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.”

PMDA’s view:
On the basis of the above explanation of the applicant and reviews in 7.R.2 and 7.R.3, PMDA concluded that it is acceptable to determine the dosage regimen of Comirnaty in children 6 months through 4 years of age as proposed.

7.R.6 Post-marketing investigations

7.R.6.1 Post-marketing surveillance

The applicant’s explanation about the post-marketing surveillance:
Although no serious safety concerns for Comirnaty were noted in children 6 months through 4 years of age in Study C4591007 [see Section 7.R.3], no safety information on Comirnaty is available in Japanese children of this age group. It is therefore important to collect, evaluate, and provide safety information following Comirnaty administration in routine clinical use after the marketing. However, a government-led surveillance may be conducted to collect safety information on Comirnaty in routine clinical use, as is the case with approved Comirnaty Intramuscular Injection, etc. Since conducting a surveillance redundant in its objective and the target population should be avoided, discussion on the need to conduct pharmacovigilance activities such as post-marketing surveillance will be continued with PMDA, taking account of whether a government-led surveillance is conducted on Comirnaty administration in children 6 months through 4 years of age. When conduct/non-conduct of the government-led surveillance is decided together with its detailed plan, if any, the applicant will promptly consider a specified use-results survey to collect safety information such as adverse events and reactogenicity (local reactions and systemic reactions) after administering Comirnaty to children 6 months through 4 years of age and plan the detail of the study as necessary.

PMDA’s view:
After the marketing approval, a surveillance should be conducted to collect safety information in children 6 months through 4 years of age, and results should be promptly provided for the following reasons: (a) No information is currently available on Comirnaty administration in Japanese children of this age group, and (b) there is only limited information on the safety of Comirnaty administration in this age group. It is acceptable to plan the surveillance after the government’s policy on the surveillance is decided. It is imperative, however, to lay out the framework to allow assessment of the necessity and details of the post-marketing investigation on Comirnaty once the government’s policy is announced and to promptly start the surveillance.

7.R.6.2 Measures to prevent vaccine administration errors resulting from differences between Comirnaty Intramuscular Injection for 6 months through 4 years old and approved vaccines

Comirnaty Intramuscular Injection for 6 months through 4 years old is different from the approved vaccines (“Comirnaty Intramuscular Injection for 5 through 11 years old” for individuals 5 through 11

years of age, “Comirnaty Intramuscular Injection” for individuals ≥12 years of age) in the diluting method, vaccination dose, number of administrations, and other aspects.

The applicant’s explanation about the measures to prevent vaccine administration errors:
In order to prevent vaccine administration errors caused by the differences between the proposed vaccine and the approved vaccines, the following preventive measures will be continued, as have been employed currently.

- To prevent product mix-up, color-coded vial caps and labels are used to help differentiate products, and identification stickers that can be attached to a syringe after withdrawing the vaccine dose are prepared and distributed.
- To ensure the proper preparation method and administration volume of the vaccine, information will be prepared and provided appropriately to healthcare professionals. For this purpose, (a) information material on the appearance of each vaccine, filling volume, preparation method (handling procedure from thawing to administration), dosage regimen, and their differences will be prepared, and (b) briefing sessions will be held for healthcare professionals.

In order to further facilitate the above measures, the applicant plans to prepare and distribute information material containing examples of vaccination errors and their preventive measures.

PMDA’s view:
Errors related to preparation of vaccine, storage management, and wrong vaccination have been reported with approved SARS-CoV-2 vaccines, and several administrative notices on the proper use of vaccines have been issued (“Information on SARS-CoV-2 vaccine administration error: No. 1 and No. 2” [Administrative Notice dated August 3, 2021, issued by the Immunization Office, Health Service Division, Health Service Bureau, Ministry of Health, Labour and Welfare], “Request on the proper use of Comirnaty Intramuscular Injection” [Pfizer Japan Inc., dated May 2021]),[20)] “Request to prevent vaccine administration errors with Comirnaty Intramuscular Injection for 5 through 11 years old and Comirnaty Intramuscular Injection” [Pfizer Japan Inc., dated April 2022][21)]). In order to facilitate the preventive measures proposed by the applicant, it is mandatory to make sure that all facilities delivered with Comirnaty Intramuscular Injection for 6 months through 4 years old and approved vaccines are informed of the preventive measures and to facilitate the understanding of healthcare professionals on the measures. In the present application, enhanced measures for preventing vaccination errors are discussed. Since the new vaccine is added to the existing vaccines, careful attention is required more than ever. In addition to the activities planned by the applicant, it is required to collect information on proper use continuously and to consider further safety measures as necessary.

[20)] https://www.pmda.go.jp/files/000240928.pdf (last accessed on August 9, 2022)
[21)] https://www.pmda.go.jp/files/000246187.pdf (last accessed on August 9, 2022)

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 inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Report on Special Approval for Emergency (1)

On the basis of the data submitted, PMDA has concluded that Comirnaty Intramuscular Injection for 6 months through 4 years old has a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in this age group and that it has acceptable safety with no significant safety concerns. Comirnaty is the first COVID-19 preventive vaccine in Japan for children 6 months through 4 years old. PMDA considers that Comirnaty has a clinical significance in view of its expected benefits.

PMDA has concluded that Comirnaty Intramuscular Injection for 6 months through 4 years old may be approved if it is not considered to have any particular problems based on comments from the Expert Discussion.

Report on Special Approval for Emergency (2)

September 14, 2022

Product Submitted for Approval

Brand Name	Comirnaty Intramuscular Injection for 6 months to 4 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	July 14, 2022

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and clinical positioning

The PMDA's conclusions on "7.R.2 Efficacy" and "7.R.4 Clinical positioning" in Report on Special Approval for Emergency (1) were supported by the expert advisors, with the following comment: With the increase in the number of patients with COVID-19, there are increased reports of complications such as febrile convulsion, croup, pneumonia, and encephalopathy in children <5 years of age, accompanied by an increase in the number of hospitalizations (*J Infect Chemother*. 2022 Aug, https://doi.org/10.1016/j.jiac.2022.08.004, the 36th meeting of the Subcommittee on Immunization and Vaccines of the Health Sciences Council[22], etc.). Given the current infection status, it is extremely important to provide vaccine to children 6 months through 4 years of age, the population with no available vaccine.

After the expert discussion, the pre-planned vaccine efficacy (VE) analysis was conducted in ≥21 accrued cases of COVID-19 in Study C4591007, and the following results were reported by the applicant.

In the efficacy analysis set (794 subjects in Comirnaty group, 351 subjects in placebo group) in phase II/III part of Study C4591007 (data at cut-off point of June 17, 2022),[23] there were 13 and 21 cases, respectively, of confirmed COVID-19[13] in the Comirnaty group and in the placebo group ≥7 days after

[22] Document 7: https://www.mhlw.go.jp/stf/newpage_27763.html (last accessed on September 5, 2022)

[23] The number of subjects contributing to the follow-up study among those in the efficacy evaluable population after the third dose without history of SARS-CoV-2 infection within 7 days after the third dose

the third dose of the study vaccine, with the observation period-adjusted VE [2-sided 95% CI] of 73.2 [43.8, 87.6]. SARS-CoV-2 detected was Omicron variant in all subjects with confirmed COVID-19 except in 1 subject infected with unknown variant of SARS-CoV-2: The lineage of Omicron variant detected was BA.2 lineage in 27 subjects, BA.4 lineage in 3, BA.5 lineage in 2, and BA.1 lineage in 1. VE in each age group was as follows:

- Subjects 6 months through 1 year of age (296 in Comirnaty group, 147 in placebo group)[23)]: There were 4 and 8 cases of confirmed COVID-19 in the Comirnaty group and in the placebo group, respectively, with VE of 75.8 [9.7, 94.7].
- Subjects 2 through 4 years of age (498 in Comirnaty group, 204 in placebo group)[23)]: There were 9 and 13 cases of confirmed COVID-19 in the Comirnaty group and in the placebo group, respectively, with VE of 71.8 [28.6, 89.4].

1.2 Safety

The PMDA's conclusion on "7.R.3 Safety" in Report on Special Approval for Emergency (1) was supported by the expert advisors. The following was reported by the applicant regarding the evaluation of reactogenicity events associated with Comirnaty in Study C4591007, but PMDA confirmed that they do not affect the conclusion in Report on Special Approval for Emergency (1).

Due to a technical trouble in updating the subject diary (electronic diary) during the conduct of Study C4591007, reactogenicity events on Day 1 after the third dose in 151 of 1,456 subjects (64 of 570 subjects 6 months through 1 year of age, 87 of 886 subjects 2 through 4 years of age) were not recorded. A total of 93 subjects without entry in the electronic diary for 2 days after vaccination were confirmed for the occurrence of reactogenicity events. A total of 6 adverse events were observed in 5 subjects (1 event of injection site erythema, 2 events of fatigue, 2 events of diarrhoea, and 1 event of pyrexia). No other adverse events were reported.

1.3 Dosage and administration

The PMDA's conclusion on "7.R.5 Dosage and administration" in Report on Special Approval for Emergency (1) was supported by the expert advisors. The following comments were raised from the expert advisors: Injection site may be either the middle part of deltoid muscle or the anterolateral thigh in children 1 through 2 years of age but, in infants 6 months through <1 year of age, the vaccine should be administered to the anterolateral thigh. This should be made absolutely clear.

PMDA requested the applicant to clearly state the above cautions on the intramuscular injection site in each age group in the "PRECAUTIONS CONCERNING USE" and provide the information to healthcare professionals. The applicant responded that they would include appropriate precautions in the package insert and information materials, by referring to "Intramuscular injection of vaccines in children (2nd revision)" (Committee on Immunization and Prevention of Infectious Diseases, Japan Pediatric Society, 2nd revision, January 2022) published by the Japan Pediatric Society.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors commented that because of no safety information of Comirnaty available in Japanese children 6 months to 4 years of age, a post-marketing surveillance plan

should be planned promptly in order to quickly collect the above safety information, and the PMDA's conclusion on "7.R.6 Post-marketing investigations" in Report on Special Approval for Emergency (1) was supported by the expert advisors.

PMDA has concluded that the risk management plan (draft) for Comirnaty should include the safety specification presented in Table 13, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 14. At present, a plan for the post-marketing surveillance on Comirnaty is not included in the additional pharmacovigilance activities. However, as described in "7.R.6 Post-marketing investigations," the post-marketing surveillance should be started promptly in order to rapidly collect safety information of Comirnaty, should it become necessary to conduct the surveillance depending on the direction of the government-led surveillance, etc.

Table 13. 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
Efficacy specification		
Not applicable		

No change arises from the present application.

Table 14. 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 (vaccine recipients≥12 years of age: RTU intramuscular injection (bivalent; original strain/Omicron BA.1 lineage) • Early post-marketing phase vigilance (pediatric vaccine recipients 5 through 11 years of age) • <u>Early post-marketing phase vigilance (pediatric vaccine recipients 6 months through 4 years of age)</u> • Post-marketing clinical study (C4591005) (Comirnaty Intravenous Injection) • Use-results survey on post-approval early vaccine recipients (healthcare professionals) (follow-up study) (C4591006) (Comirnaty Intravenous Injection) • Specified use-results survey on individuals with underlying diseases who are at high risk of severe COVID19 (C4591019) (Comirnaty Intravenous Injection) • Foreign phase II/III study (C4591001) (Comirnaty Intravenous Injection) • Foreign phase II/III study in pregnant women (C4591015) (Comirnaty Intravenous Injection)	• Disseminate data gathered during early post-marketing phase vigilance (vaccine recipients ≥12 years of age: RTU intramuscular injection [bivalent: original strain/Omicron BA.1 lineage]) • Disseminate data gathered during early post-marketing phase vigilance (pediatric vaccine recipients 5 through 11 years of age) • <u>Disseminate data gathered during early post-marketing phase vigilance (pediatric vaccine recipients 6 months through 4 years of age)</u> • Organize and disseminate information for healthcare professionals • Organize and disseminate information (a brochure) for vaccine recipients • Organize and disseminate information (a brochure) for pediatric vaccine recipients • Periodical publication of the occurrence of adverse reactions (vaccine recipients ≥12 years of age: RTU intramuscular injection [bivalent: original strain/Omicron BA.1 lineage]) • Periodical publication of the occurrence of adverse reactions (pediatric vaccine recipients 5 through 11 years of age) • <u>Periodical publication of the occurrence of adverse reactions (pediatric vaccine recipients 6 months through 4 years of age)</u>

Underline denotes additions arising from the present application.

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

2.1 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 compliance 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.

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

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

3. Overall Evaluation

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. Although this is an application for a drug with a new dosage, as 4 or more years remain before the expiration of the previously granted re-examination period, 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). The product is classified as a biological product. The product is classified as a powerful drug.

Indication

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

(No change)

Dosage and Administration

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

Approval Conditions

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 1
   The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
   (2) 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.

(3) 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.

(4) 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) The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
   (3) 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.
   (4) 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.
   (5) The efficacy and safety data of the product will be accrued with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and who have provided written informed consent through the vaccine screening questionnaire in advance.
   (6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 12 months after the approval.

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

BMI	Body mass index
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
Comirnaty	Comirnaty Intramuscular Injection for 6 months through 4 years old
COVID-19	Coronavirus disease 2019
CTD	Common technical document
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good clinical practice
GMR	Geometric mean ratio
GMT	Geometric mean titer
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C/PIMS	Multisystem inflammatory syndrome in children/Pediatric inflammatory multisystem syndrome
mRNA	Messenger RNA
PaO_2	Partial pressure of oxygen, arterial
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Device
PMDA	Pharmaceuticals and Medical Devices Agency
Reference strain	Strain USA-WA1/2020
RVE	Relative vaccine efficacy
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO_2	Oxygen saturation as measured by pulse oximetry
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine Efficacy
WHO	World Health Organization