Report on Special Approval for Emergency

August 17, 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 5 to 11 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran [JAN*])
Applicant	Pfizer Japan Inc.
Date of Application	June 22, 2022
Dosage Form/Strength	Injection: Each vial contains 0.130 mg of Tozinameran
Application Classification	Prescription drug (6) Drug with a new dosage
Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the 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 dosage and administration for the booster dose of the product has a certain level of efficacy in the prevention of disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) in children 5 to 11 years of age, and that the booster dose of the product has acceptable safety with no serious safety concern.

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)

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Dosage and Administration

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

(Underline denotes additions.)

Approval Conditions and Other Requirements

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

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

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

**Japanese Accepted Name (modified INN)*

Attachment

Report on Special Approval for Emergency

August 17, 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 5 to 11 years old
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	June 22, 2022
Dosage Form/Strength	Injection: Each vial contains 0.130 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 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).
For the primary series, 2 doses (0.2 mL each) are injected intramuscularly, usually 3 weeks apart.
For a booster dose, a single dose of 0.2 mL is injected intramuscularly.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

Comirnaty is a vaccine containing messenger RNA (mRNA) encoding spike protein of SARS-CoV-2 as the active ingredient. It is indicated for the prevention of disease caused by SARS-CoV-2 infection (COVID-19). In Japan, publicly funded SARS-CoV-2 vaccination was started since the approval of Comirnaty in February 2021, and 80.9% of the Japanese people have completed the second dose as of August 1, 2022. In children 5 to 11 years of age, primary series of vaccination was initiated in February 2022, and 18.2% of children of this age group have completed the second dose of the vaccination as of August 1, 2022 (website of the Prime Minister's Office: COVID-19 Vaccines).[1)]

Because clinical studies in adults and reports from various countries indicated that protective effect of the primary series wanes over time, and because variants that weaken the effect of vaccine emerged, necessity of a booster dose to individuals who have completed a primary series of a vaccine against SARS-CoV-2 was discussed (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated November 2, 2021]). As of August 1, 2022, SARS-CoV-2 vaccines available for use as a booster dose in Japan are Comirnaty (for ≥12 years old) and Spikevax Intramuscular Injection and Nuvaxovid Intramuscular Injection (both for ≥18 years old), while there is no vaccine available as a booster dose in children 5 to 11 years of age.

In the foreign phase I/II/III study (Study C4591007), the applicant investigated the immunogenicity and safety following the third dose of Comirnaty in children 5 to 11 years of age. Taking account of the study, Comirnaty was granted emergency use authorization for the booster dose in children 5 to 11 years of age on May 17, 2022, in the U.S., and application for partial change of the conditional marketing approval was submitted on May 13, 2022, in Europe, which is currently undergoing review process.

In Japan, the applicant has recently submitted an application for partial change for additional dosage and administration related to booster dose of Comirnaty in children 5 to 11 years of age, based on the result of Study C4591007.

This report contains the results 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).

2. Quality and Outline of the Review Conducted by PMDA

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

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.

1) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (last accessed on August 1, 2022)

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

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

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

The applicant submitted efficacy and safety evaluation data shown in Table 1. Study C4591007 was initiated as a study on the primary series in healthy children ≥6 months to <12 years of age, and a study on booster dose was added during the observation period after the primary series (protocol amendment, ver. 6, January 4, 2022). In the present application, an interim report on booster dose was submitted.

Table 1. Summary of data on efficacy and safety

Region	Study ID	Part	Population	No. of subjects enrolled	Dosage regimen	Main endpoints
Foreign	C4591007	Phase II/III	Healthy children 5-11 years of age who have received 2 doses of Comirnaty in phase II/III part of the study[a)]	401	Single dose of Comirnaty 10 μg or placebo administered intramuscularly.	Immunogenicity Safety Tolerability

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 II/III part, ongoing since June 2021 [data cutoff date, March 22, 2022])

An open-label, uncontrolled study was conducted to investigate the safety and immunogenicity of the third dose of Comirnaty in healthy children 5 to 11 years of age (including those with stable underlying disease) who received 2 doses of Comirnaty as the primary series in phase II/III part of Study C4591007. Participants were those who completed the primary series approximately ≥6 months before, were assessed eligible for receiving the third dose of Comirnaty by the investigator, and provided a consent of the guardian. The study is ongoing in 68 study sites in 4 foreign countries (the U.S., Finland, Poland, and Spain).

Comirnaty 10 μg was administered intramuscularly as a single dose.

The interim report submitted in the present application includes data from 425 subjects who received the third dose of Comirnaty on or before February 22, 2022.[2)] Of the 425 subjects, 401 were included in

[2)] The applicant explained that the applicant had proposed the following to FDA in late February 2022 and received approval: The interim report includes (a) data of safety analysis up to 1 month after the third dose in approximately 400 subjects and (b) descriptive assessment on immunogenicity in approximately 100 subjects.

the safety analysis set after excluding 24 who received 30 μg as the third dose (because they reached 12 years of age after the primary series). Of 123 subjects who completed blood sampling on or before March 15, 2022, for immunogenicity assessments at 1 month after the third dose, 115 who had no serious protocol deviation, received the second and third doses of Comirnaty within the pre-defined period, and showed effective immunogenicity assessed by the blood sample after the third dose collected within the pre-specified period were included in the population evaluable for immunogenicity of the third dose. Among them, 67 subjects with no history of SARS-CoV-2 infection (confirmed serologically or virologically) up to 1 month after the third dose were included in the primary population for immunogenicity analysis.

Among subjects in the population evaluable for immunogenicity of the third dose, only 30 subjects had blood sample at 1 month after the second dose. In order to ensure the number of subjects for the immunogenicity analysis at 1 month after the second dose, 67 subjects with no history of SARS-CoV-2 infection up to 1 month after the second dose were randomly extracted from the population evaluable for immunogenicity. Their data which had already been obtained in the investigation on the primary series were included in the analysis.

Table 2 shows the geometric mean titer (GMT) of neutralizing antibody in serum against SARS-CoV-2 (reference strain). Geometric mean ratio (GMR) (calculated as GMT at 1 month after the third dose/GMT at 1 month after the second dose) [2-sided 95% confidence interval (CI)] was 2.17 [1.76, 2.68] in the population with no history of SARS-CoV-2 infection and 2.53 [2.11, 3.04] in the population regardless of the history of infection. In the population evaluable for immunogenicity after the third dose, GMT [2-sided 95% CI] at 1 month after the second dose was 1659.4 [1385.1, 1988.0] in the population without history of SARS-CoV-2 infection (29 subjects) and 1743.2 [1425.3, 2132.0] in the population regardless of history of SARS-CoV-2 infection (30 subjects).

Table 2. Neutralizing antibody in serum against SARS-CoV-2 (reference strain) [a)]

History of SARS-CoV-2 infection	Blood sampling time point	n	GMT [2-sided 95% CI]
No history of infection	1 month after second dose	96	1253.9 [1116.0, 1408.9]
	Before third dose	67	271.0 [229.1, 320.6]
	1 month after third dose	67	2720.9 [2280.1, 3247.0]
Regardless of history of infection	1 month after second dose	97	1276.9 [1131.6, 1440.8]
	Before third dose	113	527.9 [420.9, 662.2]
	1 month after third dose	114	3235.6 [2814.6, 3719.6]

a) Determined by neutralization method using SARS-CoV-2 (reference strain).

The severity of adverse events was classified[3)] and evaluated by referring 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).[4)]

3) Injection site pain, fatigue, headache, chills, myalgia, and arthralgia: Grade 1, does not interfere with activity; Grade 2, interferes with activity; Grade 3, prevents daily activity; Grade 4, emergency room visit or hospitalization
Swelling and redness: Grade 1, >0.5-≤2.0 cm; Grade 2, >2.0-≤7.0 cm; Grade 3, >7.0 cm; Grade 4, necrosis
Diarrhoea: Grade 1, 2-3 stools/24 hours; Grade 2, 4-5 stools/24 hours; Grade 3, ≥6 stools/24 hours; Grade 4, emergency room visit or hospitalization
Vomiting: Grade 1, 1-2 episodes/24 hours; Grade 2, >2 episodes/24 hours; Grade 3, requires outpatient IV hydration; Grade 4, emergency room visit or hospitalization

4) 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 1, 2022)

The definition of observation periods:

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

In the safety analysis set, the median observation period from the third dose to data cut-off date (March 22, 2022) was 1.3 months (range: 1.0-1.8 months).

Table 3 shows reactogenicity events observed within 7 days after the third dose in 371 subjects who provided subject diary in the safety analysis set.

Table 3. Reactogenicity events within 7 days after the third dose of the study vaccine (safety analysis set)

Event terms	Comirnaty (N = 371[a)])
Local reactions (total)	278 (74.9)
Injection site pain	274 (73.9)
Swelling	61 (16.4)
Redness	58 (15.6)
Systemic reactions (total)	220 (59.3)
Fatigue	169 (45.6)
Headache	126 (34.0)
Myalgia	68 (18.3)
Chills	39 (10.5)
Arthralgia	25 (6.7)
Diarrhoea	18 (4.9)
Pyrexia	25 (6.7)
Vomiting	9 (2.4)

n (%)

a) Number of subjects who entered ≥1 event in the subject diary. Reactogenicity events on Day 1 of vaccination were not recorded in some subjects because technical trouble occurred during activation of subject diary (electronic diary), resulting in 244 subjects evaluated on Day 1 of vaccination (304 to 322 subjects evaluated on Day 2 to Day 7 after vaccination)

The incidence of adverse events and adverse reaction within 1 month after the third dose was 9.0% (36 of 401) and 4.7% (19 of 401) of subjects, respectively. Table 4 shows adverse events and adverse events observed in ≥2 subjects.

Table 4. Adverse events and adverse reactions observed in ≥2 subjects within 1 month after the third dose (safety analysis set)

Event terms (Preferred term: MedDRA ver.24.1)	Comirnaty (N = 401)	
	Adverse events	Adverse reactions
All events	36 (9.0)	19 (4.7)
Lymphadenopathy	8 (2.0)	8 (2.0)
Injection site pain	7 (1.7)	7 (1.7)
Headache	3 (0.7)	3 (0.7)
Diarrhoea	2 (0.5)	1 (0.2)
Vomiting	2 (0.5)	0
Fatigue	2 (0.5)	2 (0.5)
Upper respiratory tract infection	2 (0.5)	0
Nasal congestion	2 (0.5)	0
Oropharyngeal pain	2 (0.5)	0

n (%)

There were no serious adverse events, deaths, or adverse events leading to study discontinuation up to the data cut-off date (March 22, 2022).

After the data cut-off, serious adverse events (intestinal obstruction, asthma, and rhinovirus infection [1 subject had more than 1 event]) were observed in 2 subjects on or before June 8, 2022. The causal relationship to Comirnaty was denied, and the outcome was reported as "recovered" for all events.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Review Policy

The protective effect of Comirnaty against COVID-19 in adults was evaluated in the foreign phase III study (Study C4591001), which confirmed the efficacy after the primary series. In clinical studies of subsequent development processes (booster dose in adults, primary series in children 5 to 11 years of age), the efficacy was evaluated by confirming non-inferiority of immunogenicity, the primary endpoint, to the immunogenicity data in Study C4591001 which had demonstrated the efficacy.

In Study C4591007 submitted in the present application, the booster dose in children 5 to 11 years of age was investigated under open-label, uncontrolled conditions. Immunogenicity was evaluated in a descriptive manner without formulating a hypothesis in advance.

Given the following situations, PMDA considers that the booster dose should be promptly made available for children 5 to 11 years of age in preparation against the further prevalence of COVID-19 in the future. Although efficacy and immunogenicity were not evaluated based on pre-formulated hypothesis in the clinical study, the review is conducted based on the currently available findings and reports from various countries in addition to the Study C4591007 data.

- In Japan, COVID-19 continues to be prevalent, and the number of new SARS-CoV-2-positive children is on the increase in the prevalence of Omicron variant (MHLW website: The trends in COVID-19 occurrence in Japan, as of 24:00, August 2, 2022)[5])
- Vaccine effectiveness against COVID-19 wanes over time after the primary series but recovers by a booster dose in other age groups (*N Engl J Med.* 2022;386:1532-46).

[5] https://www.mhlw.go.jp/content/10906000/000972918.pdf (last accessed on August 1, 2022)

- Vaccine effectiveness was lower for the Omicron variant than for the Delta variant (*N Engl J Med*. 2022;386:1532-46).
- Comirnaty has been administered worldwide to individuals of wide age ranges as the primary series and as the booster dose, and its efficacy and safety have been investigated in many studies. Also, there are a multitude of reports on the efficacy of the booster dose in adults, etc. [see Section 7.R.1.2].
- In Japan, booster dose to individuals ≥12 years of age is ongoing, and Comirnaty has been administered as the third dose not less than 45 million times (website of the Prime Minister's Office: COVID-19 Vaccines: the third dose[6])
- In Japan, the primary series of Comirnaty in children 5 to 11 years of age was initiated from February 2022. The findings in other age ranges suggest that the efficacy is expected to wane over time after the primary series.

7.R.1.2 Efficacy

The applicant's explanation about the efficacy of the booster dose (the third dose) of Comirnaty in children 5 to 11 years of age:

In the development of the booster dose of Comirnaty in children 5 to 11 years of age, the protocol of Study C4591007, which was in the observation period after the primary series, was revised to include an investigation on safety and immunogenicity of the third dose of Comirnaty administered ≥6 months after the second dose in all subjects 5 to 11 years of age[7] who had received 2 doses of Comirnaty as the primary series in phase II/III part of Study C4591007. An interim analysis of this investigation showed that the neutralizing antibody titer against the reference strain (by neutralization method) was higher than the titer after the second dose, as assessed by GMT after the third dose, with GMR of titer after the third dose to that after the second dose (calculated as GMT at 1 month after the third dose/GMT at 1 month after the second dose) being 2.17 in subjects without history of infection and 2.53 in subjects regardless of history of infection [see Section 7.1]. Table 5 shows the result of exploratory evaluation of the neutralizing antibody titer (fluorescent focus reduction assay) against Omicron variant (B.1.1.529). GMT after the third dose was approximately 22 times higher than the titer after the second dose in the population without history of infection.

6) https://www.kantei.go.jp/jp/content/booster_data.pdf (last accessed on August 1, 2022)

7) In the primary series part for 5 to 11 years of age, subjects were unblinded after the 6-month observation period after the second dose. Subjects who had been assigned to the placebo group were provided with the opportunity of receiving 2 doses of Comirnaty in the study.

Table 5. Serum neutralizing antibody against Omicron variant (B.1.1.529) [a, b)]

History of SARS-CoV-2 infection	Blood sampling time point	No. of subjects analyzed	GMT against Omicron variant [2-sided 95% CI]	GMT against reference strain [2-sided 95% CI]	GMR [2-sided 95% CI] (Omicron variant/ reference strain)
None	1 month after second dose	29	27.6 [22.1, 34.5]	323.8 [267.5, 392.1]	0.09 [0.07, 0.10]
	1 month after third dose	17	614.4 [410.7, 919.2]	1702.8 [1282.6, 2260.7]	0.36 [0.28, 0.47]
Regardless of history of infection	1 month after second dose	30	27.3 [22.0, 33.9]	335.1 [275.1, 408.3]	0.08 [0.07, 0.10]
	1 month after third dose	30	992.7 [675.9, 1458.1]	2152.7 [1714.9, 2702.2]	0.46 [0.36, 0.58]

a) Measured by fluorescent focus reduction assay using SARS-CoV-2 (reference strain) and the recombinant virus generated by substituting the gene for spike protein of Omicron variant (B.1.1.529 lineage) for the gene of the reference strain.
b) Among subjects in the population evaluable for immunogenicity of the third dose, those available with blood sample at 1 month after the second dose were subjected to evaluation.

No clinical study was conducted to evaluate the efficacy of the third dose of Comirnaty in children 5 to 11 years of age. Instead, in the foreign phase III study (Study C4591031, ongoing since July 2021, data cut-off: October 2021), protective effect of the third dose of Comirnaty against COVID-19 was evaluated in subjects ≥16 years of age. The vaccine efficacy against COVID-19 onset ≥7 days after the third dose was 95.3% in subjects without history of SARS-CoV-2 infection and 94.6% in subjects regardless of history of SARS-CoV-2 infection (*N Engl J Med*. 2022;386:1910-21). While the above results were obtained before the prevalence of Omicron variant, the efficacy of the third dose of Comirnaty during the prevalence of Omicron variant is suggested by the following reports, among others.

- According to a survey in the U.S., the vaccine efficacy during the prevalence of Omicron variant was -3% ≥150 days after the second dose of Comirnaty and 81% ≥7 days after the third dose, as assessed based on the number of patients 16 to 17 years of age who developed COVID-19-like symptoms and visited, or were hospitalized in, emergency departments or urgent care units (*MMWR Morb Mortal Wkly Rep.* 2022;71:352-8).
- According to another survey in the U.S., the vaccine efficacy against symptomatic disease during the prevalence of Omicron variant in patients 12 to 15 years of age was 16.6% at 2 months after the second dose of Comirnaty and 71.1% at 2 to 6.5 weeks after the third dose (*JAMA.* 2022;327:2210-9).
- According to the report of the UK Health Security Agency, consensus estimates of vaccine effectiveness against Omicron variant-associated symptomatic disease (comparison with unvaccinated subjects), assessed by the UK Vaccine Effectiveness Expert Panel, was 10% to 15% at ≥6 months after the second dose of Comirnaty, 55% to 75% within 3 months after the third dose, 35% to 55% at 4 to 6 months after the third dose, and 0% to 20% at ≥6 months after the third dose. Vaccine efficacy against hospitalization was 55% to 90% at ≥6 months after the second dose of Comirnaty, 85% to 95% within 3 months after the third dose, 85% to 95% at 4 to 6 months after the third dose, and 50% to 85% at ≥6 months after the third dose (UK Health Security Agency. Covid-19 vaccine surveillance report. Week 27, 2022/7/7).
- A test-negative case-control design study comparing the efficacy of vaccine (not limited to Comirnaty) against Omicron BA.1 lineage and against BA.2 lineage showed that the efficacy against symptomatic disease and hospitalization after the second dose and after the third dose was similar for both lineages, with similar tendency of the change in efficacy over time after administration. (UK Health Security Agency. Covid-19 vaccine surveillance report. Week 27, 2022/7/7)

- The third dose of Comirnaty increased neutralizing antibody titer against Omicron variants BA.1, BA.2, BA.2.12.1, and BA.4 or BA.5. The neutralizing antibody titer against BA.2 was similar to that against BA.1, while the titer against BA.2.12.1 and BA.4 or BA.5 was lower than that against BA.1 (*N Engl J Med*. 2022;387:86-8).

Given the finding in Study C4591007 that immune response to the third dose of Comirnaty in children 5 to 11 years of age was 22 times higher than the response after the second dose, together with the report suggesting the efficacy of the third dose of Comirnaty during the prevalence of Omicron variant in individuals of other age groups, the third dose of Comirnaty administered to children 5 to 11 years of age is expected to enhance the protective effect against symptomatic disease and hospitalization caused by Omicron variants including BA.2 lineage. A vaccine against Omicron variant is currently under development. If a new variant becomes prevalent, development of a vaccine tailored to the variant will be considered, depending on the infection status and epidemiological situations.

PMDA's view:
Taking account of the immunogenicity results obtained in Study C4591007 and of the report suggesting the efficacy of the third dose of Comirnaty in other age groups during the prevalence of Omicron variant, administering the third dose of Comirnaty is expected to be effective in children 5 to 11 years of age as well. Although no data are available on the third dose of Comirnaty in Japanese children, the dose is expected to induce a high immune response in Japanese children 5 to 11 years of age as well, suggesting the efficacy of the third dose of Comirnaty, based on the following observations in addition to the results of Study C4591007: (a) During the development of the primary series in adults, similar or higher immune response was observed in the Japanese clinical study than in the foreign clinical study (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021]), and (b) During the development of the primary series in children 5 to 11 years of age, foreign clinical studies demonstrated that the immune response in this age group was similar to that observed in young adults (Comirnaty Intramuscular Injection for 5 to 11 years old: Report on Special Approval for Emergency [dated January 11, 2022]).

Because prevalent SARS-CoV-2 strain changes rapidly, other strains and variants may emerge at any time in the future. In addition, the efficacy of the booster dose wanes over time in other age groups (*MMWR Morb Mortal Wkly Rep*. 2022;71:255-63). Accordingly, information on the efficacy of the booster dose of Comirnaty in children 5 to 11 years of age should be collected in a timely manner from data and study reports accumulated in Japan and other countries, and necessary measures should be taken based on the information thus obtained. Also, attention should be paid to the emergence and epidemic situation of new variants, and necessary measures should be taken including the development of vaccines tailored to the new variants.

7.R.2 Safety

On the basis of the review in sections 7.R.2.1 through 7.R.2.3, PMDA concluded that there are no major concerns in the safety of the booster dose (the third dose) of Comirnaty in children 5 to 11 years of age.

Because of the limited information on the safety of the third dose of Comirnaty in children 5 to 11 years of age, however, information on the safety of Comirnaty in children of this age group in Japan and foreign countries should be collected continuously, and appropriate measures should be taken based on the information thus obtained.

Also, information on the following events should be provided as in the past to healthcare professionals, vaccine recipients, and their guardians, including the time of onset and duration: (a) Reactogenicity events that are observed in many vaccine recipients and may affect daily activities and (b) lymphadenopathy which occurred at a higher incidence after the third dose than after the primary series.

7.R.2.1 Safety profiles

The applicant's explanation about the safety of the third dose of Comirnaty in children 5 to 11 years of age in the phase II/III part of Study C4591007:

(a) Reactogenicity events

Table 6 shows the incidence of reactogenicity events observed within 7 days after Comirnaty administration compared between after the third dose and after the primary series. The incidences of headache, myalgia, and arthralgia were higher after the third dose than after the primary series (the first and second doses). The Grade ≥3 reactogenicity event with an incidence of ≥1% after the third dose was fatigue. No Grade ≥4 reactogenicity events occurred. Pyrexia was classified not by Grade but by body temperature. Thus, the incidence of pyrexia after the third dose classified by body temperature was as follows: 38.0 to 38.4℃ in 4.6% (17 of 371) of vaccine recipients, 38.5 to 38.9℃ in 1.3% (5 of 371), 39.0 to 40.0℃ in 0.8% (3 of 371), and >40.0℃ in none, showing no tendency of increase in the number of vaccine recipients with high fever than after the second dose (38.0 to 38.4℃ in 3.5% [14 of 399], 38.5 to 38.9℃ in 3.5% [14 of 399], 39.0 to 40.0℃ in 1.5% [6 of 399], and >40.0℃ in 0.3% [1 of 399]).

Table 6. Reactogenicity events within 7 days after each dose (phase II/III part: safety analysis set)

Dose No.	Booster dose		Primary series			
	Third (N = 371)		First (N = 398)		Second (N = 399)	
Event terms	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Local reactions (total)	278 (74.9)	-	315 (79.1)	-	296 (74.2)	-
Injection site pain	274 (73.9)	2 (0.5)	309 (77.6)	0	288 (72.2)	1 (0.3)
Swelling	61 (16.4)	0	38 (9.5)	0	56 (14.0)	0
Redness	58 (15.6)	1 (0.3)	46 (11.6)	0	66 (16.5)	1 (0.3)
Systemic reactions (total)	220 (59.3)	-	202 (50.8)	-	230 (57.6)	-
Fatigue	169 (45.6)	7 (1.9)	149 (37.4)	1 (0.3)	186 (46.6)	4 (1.0)
Headache	126 (34.0)	3 (0.8)	94 (23.6)	0	120 (30.1)	2 (0.5)
Myalgia	68 (18.3)	0	32 (8.0)	0	50 (12.5)	1 (0.3)
Chills	39 (10.5)	1 (0.3)	24 (6.0)	0	41 (10.3)	1 (0.3)
Arthralgia	25 (6.7)	0	15 (3.8)	0	22 (5.5)	0
Diarrhoea	18 (4.9)	1 (0.3)	27 (6.8)	0	26 (6.5)	0
Pyrexia[a)]	25 (6.7)	-	14 (3.5)	-	35 (8.8)	-
Vomiting	9 (2.4)	0	8 (2.0)	0	7 (1.8)	0

n (%), N = number of subjects analyzed (number of subjects who entered occurrence/non-occurrence of the event in the subject diary)
a) ≥38.0℃, not classified by Grade.

The median time to the onset of local reactions after the third dose was 1 to 2 days after the vaccination, and the median duration was 2 days. The median time to onset of systemic reactions was 2 to 5 days after the vaccination, and the median duration was 1 to 1.5 days. In several subjects, symptoms (injection site pain, pyrexia, and chills) lasted approximately 1 month.

The percentage of subjects who used an antipyretic analgesic at least once for the treatment of Comirnaty-associated symptoms was 30.7% (114 of 371) of subjects after the third dose which was higher than the percentage after the first dose (13.3% [53 of 398]) and after the second dose (21.8% [87 of 399]). In Study C4591007, prophylactic administration of antipyretic analgesics was not permitted.

During the conduct of Study C4591007, a problem occurred in the setting up of the subject diary (electronic diary) in 36 of 401 subjects in the safety analysis set, hindering the recording of reactogenicity events on Day 1 after the third dose, which resulted in no record of reactogenicity events up to Day 2 after the third dose in 25 of 36 subjects. Confirmation of these 25 subjects for the incidence of reactogenicity events revealed that there was no adverse event except in 1 subject who reported fatigue and injection site pain.

(b) Adverse events

The incidence of adverse events (except reactogenicity events within 7 days after the third dose) within 28 days after the third dose was 9.0% (36 of 401) of subjects [see Section 7.1]. The main adverse event was lymphadenopathy in 2.0% (8 of 401) of subjects (2.5% [10 of 401] if lymph node palpable and axillary mass are included). All of the adverse events were considered to be causally related to Comirnaty. They occurred 2 days after the third dose and disappeared after approximately 1 week. The incidence of lymphadenopathy after the third dose was higher than the incidence after the second dose (0.9% [13 of 1,518], Comirnaty Intramuscular Injection for 5 to 11 years old: Report on Special Approval for Emergency [dated January 11, 2022]), but similar to the tendency observed in the clinical study in adults ≥18 years of age (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated November 2, 2021]).

A severe adverse event (pyrexia) was reported in 1 subject and considered to be causally related to Comirnaty. The outcome was “recovered.”

Three serious adverse events were observed in 2 subjects (1 event each of asthma and rhinovirus infection in the same subject, and intestinal obstruction in 1 subject). Their causal relationship to Comirnaty was denied. Their outcome was “recovered.”

The above results show that the safety profiles after the third dose of Comirnaty in children 5 to 11 years of age observed in Study C4591007 are predictable from the safety profiles of Comirnaty confirmed in the primary series and the booster dose in other age groups as well as in the primary series in children 5 to 11 years of age. At present, no serious safety concerns are raised after the third dose in children 5 to 11 years of age, demonstrating the tolerability.

PMDA’s view:

After the third dose of Comirnaty in children 5 to 11 years of age in Study C4591007, reactogenicity events (local reactions and systemic reactions) were observed in many subjects. However, it was confirmed that most of these events were mild or moderate in severity and reversible, and that the incidence of adverse events other than reactogenicity events was low and most of them were mild or moderate. Lymphadenopathy occurred more frequently than after the second dose, but a similar

tendency had been observed in adults as well, indicating its predictability. On the basis of the above, PMDA concluded that results of Study C4591007 raise no serious safety concerns after the third dose of Comirnaty in children 5 to 11 years of age.

7.R.2.2 Postmarketing safety information of Comirnaty

The applicant's explanation about the postmarketing safety information of Comirnaty in children 5 to 11 years of age:

The booster dose of Comirnaty in children 5 to 11 years of age was first approved on May 17, 2022 (emergency use authorization in the U.S.). As of June 22, 2022, estimated 497,632 children 5 to 11 years of age had received the booster dose of Comirnaty in the U.S. (CDC website: COVID Data Tracker[8)]). According to the safety database of the applicant, a total of 24,947 adverse events were reported in 10,679 children 5 to 11 years of age in the postmarketing adverse events reports received on or before June 10, 2022. Most of them (10,560 subjects) developed adverse events after the primary series or after uncertain doses whereas 119 subjects developed adverse events after the booster dose. In the reports after the primary series or after uncertain doses, 3,842 serious adverse events occurred in 1,635 subjects. Serious adverse events (regardless of causal relationship) reported in ≥2% of subjects were COVID-19 (246 events), drug ineffective (224), syncope (206), pyrexia (144), seizure (108), headache (106), vomiting (100), loss of consciousness (74), abdominal pain (51), dizziness (47), chest pain (46), fatigue (46), dyspnoea (44), nausea (43), rash (43), myocarditis (42), urticaria (42), suspected COVID-19 (37), vaccination failure (37), pericarditis (35), and anaphylactic reaction (33). The outcome was death (58 events), not recovered (629), recovered with sequelae (38), recovered or recovering (1,909) and unknown (1,226). In the reports after the booster dose, 55 serious adverse events occurred in 22 subjects. Serious adverse events (regardless of causal relationship) reported twice or more were COVID-19 (7 events), drug ineffective (5), poor quality product administered (4), product administration error (4), dyspnoea (3), pyrexia (3), vaccination failure (3), chest pain (3), axillary pain (2), myocarditis (2), and swelling (2). The outcome was death (3 events), not recovered (5), recovered or recovering (20), and unknown (27). The outcome of myocarditis (2 events) was "recovered" or "recovering." Guillain-Barre syndrome, which is defined as a potential risk in the risk management plan of Comirnaty, was reported in 8 children 5 to 11 years of age. Assessment of these cases by the Brighton Collaboration for diagnostic accuracy criteria showed BC level 4 in all of them. It is considered unnecessary at present to change the risk minimization activities or to further revise the package insert. However, vaccine recipients in all age groups will be closely monitored continuously.

As a result of the review of the accumulated data in the postmarketing adverse event reports in children 5 to 11 years of age, literature search, and signal detection by statistical analysis method, etc., no new safety signals have been detected in children 5 to 11 years of age. Thus, no new or unknown Comirnaty-associated risk was detected at present, confirming the favorable risk benefit balance as has been observed.

PMDA's view:

Although there is limited postmarketing safety information on the booster dose of Comirnaty in children 5 to 11 years of age at present, PMDA has confirmed that the safety information on Comirnaty including

8) https://covid.cdc.gov/covid-data-tracker/#vaccinations/CDC COVID Data Tracker (last accessed on August 1, 2022).

the primary series does not pose new safety concerns in children 5 to 11 years of age. Review on myocarditis/pericarditis is described in section 7.R.2.3.

7.R.2.3 Myocarditis/pericarditis

Concerns on the risk of myocarditis/pericarditis after administration of mRNA vaccine have been raised from the postmarketing information on SARS-CoV-2 vaccines including Comirnaty; in particular, the events are frequently reported in young male vaccine recipients after the second dose. At the time of marketing approval for the primary series of Comirnaty in children 5 to 11 years of age, there were no findings suggestive of unacceptable risks, albeit based on the limited data in this age group (Comirnaty Intramuscular Injection for 5 to 11 years old: Report on Special Approval for Emergency [dated January 11, 2022]).

PMDA asked the applicant to explain the risk of myocarditis/pericarditis in children 5 to 11 years of age, based on the data in Study C4591007 and in the primary series as well.

The applicant's explanation:
Neither myocarditis nor pericarditis was observed in children 5 to 11 years of age after the third dose in Study C4591007.

According to the most updated, currently available postmarketing safety information on Comirnaty (Summary Bimonthly Safety Report 3: survey period from February 16, 2022, to April 15, 2022), myocarditis was reported in 18 children 5 to 11 years of age (8 after the first dose, 9 after the second dose, 1 after the third dose) and pericarditis in 13 children of the same year range (11 after the first dose, 2 after the second dose). Severity of these adverse events was assessed according to the Brighton Collaboration for diagnostic accuracy criteria in 7 vaccine recipients with myocarditis and 4 vaccine recipients with pericarditis who were available for the assessment. As a result, myocarditis and pericarditis in the same 1 vaccine recipient were classified as BC level 1. Although there was a temporal relationship between myocarditis/pericarditis and Comirnaty administration, possibility of symptoms due to simultaneous viral infection was also conceivable. No novel safety signal unique to children 5 to 11 years of age was observed in the reported cases of myocarditis/pericarditis.

The following reports in the U.S., although they contain only limited data in children 5 to 11 years of age receiving Comirnaty, suggest that (a) the incidence of myocarditis/pericarditis in children 5 to 11 years of age is lower than in those 12 to 18 years of age, according to the data after the primary series, and (b) the incidence is higher after the second dose than after the first dose, and in boys than in girls, as is the case with vaccine recipients in other age ranges.

- The Centers for Disease Control and Prevention (CDC) of the U.S. reported myocarditis/pericarditis after mRNA vaccination, using the data in the electronic health records from January 1, 2021, through January 31, 2022, of 40 U.S. medical institutions that participate in PCORnet (National Patient-Centered Clinical Research Network) (*MMWR Morb Mortal Wkly Rep*. 2022;71:517-23). In this study, myocarditis/pericarditis after the first or second dose was investigated while findings after the booster dose were excluded. The reporting rate (per 100,000 vaccine recipients) of "myocarditis" and "myocarditis or pericarditis" during the 7- and 21-day

observation period was 0 to 4 after the first dose, none after the second dose, and 12.6 to 17.6 after SARS-CoV-2 infection in boys 5 to 11 years of age. In girls 5 to 11 years of age, there was no report of either myocarditis or pericarditis in either of the observation period, with the reporting rate (per 100,000 vaccine recipients) after SARS-CoV-2 infection being 5.4 to 10.8. The reporting rate of "myocarditis" and "myocarditis or pericarditis" after vaccination was lower than the rate after SARS-CoV-2 infection, both in boys and girls 5 to 11 years of age.

- The U.S. CDC reported cases of myocarditis after mRNA vaccination based on the data of the "Vaccine adverse event reporting system" (VAERS) as of May 26, 2022 (Vaccines and Related Biological Products Advisory Committee [VRBPAC] 2022/6/14- Update on Myocarditis following mRNA COVID-19 vaccination[9]). In the U.S., Comirnaty has been administered 54.8 million times (including 3.8 million times as the third dose) to individuals 5 to 17 years of age. The reporting rate (per million doses) of myocarditis within 7 days after the second dose of Comirnaty in children 5 to 11 years of age was 2.6 in boys and 0.7 in girls, which was lower than the rate in adolescents 16 to 17 years of age (75.9 in boys, 7.5 in girls) and in adolescents 12 to 15 years of age (46.4 in boys, 4.1 in girls). The estimated background incidence rate in children 5 to 11 years of age during the 7-day observation period was 0.2 to 2.2/million person-days. Results of this analysis did not allow estimation of whether the incidence rate of myocarditis in children 5 to 11 years of age was statistically higher than the background incidence rate. The past analysis based on the data of VAERS on December 19, 2021 (ACIP 2022/1/5- COVID-19 vaccine safety updates: primary series in children and adolescent ages 5-11 and 12-15 years, and booster doses in adolescents ages 16-24 years[10]) also showed a higher reporting rate of myocarditis in boys after the second dose. The reporting rate (per million doses) of myocarditis in boys 5 to 11 years of age within 7 days after the second dose was 4.3, which was lower than the rate in boys of other age groups (45.7 in adolescents 12 to 15 years of age, 70.2 in adolescents 16 to 17 years of age), showing a similar tendency observed in the analysis based on the data on May 26, 2022.
- The U.S. CDC reported cases of myocarditis/pericarditis that required emergency care or hospitalized treatment within 0 to 7 days after Comirnaty administration, based on the data of the Vaccine Safety Datalink (VSD) as of May 28, 2022 (VRBPAC 2022/6/14- Update on Myocarditis following mRNA COVID-19 vaccination[9]). Comirnaty was administered approximately 0.8 million times to children 5 to 11 years of age, and 3 children (all were boys after the second dose) developed myocarditis/pericarditis requiring emergency care or hospitalized treatment. The reporting rate (per million doses) [95% CI] in boys within 7 days after the second dose was 15.2 [3.1, 44.5]. This rate was lower than that in boys in other age ranges (152.5 [103.6, 216.4] in adolescents 12 to 15 years of age, 138.7 [75.8, 232.8] in adolescents 16 to 17 years of age), but the range of 95% CI was wide, suggesting the low accuracy of the data.
- Hause, et. al., reported the safety of Comirnaty administration in children 5 to 11 years of age, using the data of the U.S. vaccine safety monitoring systems (*Pediatrics*. 2022;150:e2022057313). Estimated >16 million doses of Comirnaty had been administered to children 5 to 11 years of age as of February 27, 2022. The analysis based on VAERS data obtained from November 3, 2021, through February 27, 2022, showed that the reporting rate (per million doses) of myocarditis within 7 days after Comirnaty administration was <1 in both boys and girls after the first dose and 2.2 in

9) https://www.fda.gov/media/159228/download (last accessed on August 1, 2022)
10) https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/02-COVID-Su-508.pdf (last assessed on August 1, 2022)

boys and <1 in girls after the second dose. The weekly sequential analysis using the VSD data from October 31, 2021, through February 26, 2022, did not detect any signal suggestive of increased risk of myocarditis after Comirnaty administration.

Although data of myocarditis after the third dose of Comirnaty in children 5 to 11 years of age have not been accumulated, the following reports after the third dose in adolescents ≥12 years of age suggest that the risk of myocarditis/pericarditis after the third dose does not exceed the risk observed after the second dose.

- According to the above-mentioned VAERS report of the U.S. CDC on myocarditis after Comirnaty administration based on the data as of May 26, 2022 (VRBPAC 2022/6/14- Update on Myocarditis following mRNA COVID-19 vaccination[9)]), the reporting rate (per million doses) of myocarditis within 7 days after the third dose of mRNA vaccine in adolescents and adults 12 to 15 years of age, 16 to 17 years of age, 18 to 24 years of age, and 25 to 29 years of age was 15.3, 24.1, 9.9, and 4.8, respectively, in males and 0.0, 0.0, 0.6, and 2.0, respectively, in females, being lower than that after the second dose in all age groups (46.4, 75.9, 38.9, and 15.2, respectively, in males, 4.1, 7.5, 4.0, and 3.5, respectively, in females).
- According to the above-mentioned VSD report of the U.S. CDC on myocarditis/pericarditis requiring emergency care or hospitalized treatment within 7 days after Comirnaty administration based on the data as of May 28, 2022 (VRBPAC 2022/6/14- Update on Myocarditis following mRNA COVID-19 vaccination[9)]), the reporting rate (per million doses) [95% CI] within 7 days after the third dose of Comirnaty was 17.0 [0.4, 94.9] and 0.0 [0.0, 48.4], respectively, in boys and girls 12 to 15 years of age, and 200.3 [86.5, 394.7] and 44.0 [5.3, 159.0], respectively, in boys and girls 16 to 17 years of age. Thus, the rate in adolescents 12 to 15 years of age was lower than the rate after the second dose (152.5 [103.6, 216.4] in boys, 24.8 [8.1, 57.9] in girls) whereas, in adolescents 16 to 17 of age, the rate in boys was higher than the rate after the second dose (138.7 [75.8, 232.8] in boys, 9.4 [0.2, 52.6] in girls), but 95% CI was wide as was in the case described above. According to the VSD report based on the data as of April 9, 2022 (ACIP 2022/4/20- Safety update of 1st booster mRNA COVID-19 vaccination[11)]), the reporting rate (per million doses) [95% CI] of myocarditis/pericarditis requiring emergency care or hospitalized treatment within 7 days after Comirnaty administration in adolescents and adults 12 to 39 years of age was 41.4 [33.1, 51.1] after the second dose and 21.4 [12.7, 33.8] after the third dose, showing that the rate was lower after the third dose than after the second dose.

Thus, myocarditis after vaccination was observed more frequently after the second dose than after the third dose and in males than in females, in consistency with the results obtained so far. Although there are only limited data in children 5 to 11 years of age after Comirnaty administration, and there are no data on the booster dose, the currently available data suggest that the risk of myocarditis/pericarditis after Comirnaty administration in children 5 to 11 years of age is lower than the risk in adolescents 12 to 17 years of age and that the risk of myocarditis/pericarditis after the third dose tends to be no higher than the risk after the second dose. Thus, the benefit of the vaccination is considered to outweigh the risk, as is the case with the primary series.

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11) https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-04-20/03-COVID-Klein-Shimabukuro-508.pdf (last accessed on August 1, 2022).

PMDA's view:
In Japan, reports of myocarditis/pericarditis associated with vaccination are evaluated on a regular basis at the Working Group on Adverse Reactions of the Subcommittee on Immunization and Vaccines of the Health Sciences Council and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council. According to the documents 1-8[12)] presented on July 8, 2022 at a 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 reports (per million doses) of suspected myocarditis or pericarditis in Japan from the manufacturer of Comirnaty (reporting period from February 17, 2021 to June 12, 2022) was 1.5 and 0.6, respectively, after the first dose, 3.2 and 1.3, respectively, after the second dose, and 1.0 and 0.5, respectively, after the third dose in all age groups; 2.3 and 1.5, respectively after the first dose, and 2.6 and 0, respectively, after the second dose in children 5 to 11 years of age. Reports of suspected myocarditis/pericarditis in all age ranges after the third dose do not include reports from children 5 to 11 years of age, and comparison among age groups showed a tendency of higher reporting frequency in boys in their 10s, but the frequency tended to be lower after the third dose than after the second dose.

In Japan and other countries, there are reports of deaths due to suspected myocarditis or pericarditis after mRNA vaccination (documents 1-8[12)] presented on July 8, 2022 at a 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, VRBPAC 2022/6/14- Update on Myocarditis following mRNA COVID-19 vaccination[9)]). The U.S. CDC states that most of myocarditis after mRNA vaccination rapidly recovers after treatment or rest and the benefit of vaccination outweighs the risk of myocarditis/pericarditis, and continues to recommend vaccination in all individuals ≥5 years of age (CDC website: Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults[13)]). Information on children 5 to 11 years of age after Comirnaty administration is still limited in reports in Japan and in overseas information provided by the applicant. However, given the incidences of myocarditis/pericarditis by age group and the finding in other age groups that the risk after the third dose does not exceed the risk after the second dose, there is no information suggestive of unacceptable risk of the third dose in children 5 to 11 years of age at present, although it is necessary to collect information continuously and provide precautions.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of Comirnaty:
Despite the advance of SARS-CoV-2 vaccination program worldwide and the availability of multiple therapeutic agents, the COVID-19 epidemic is yet to be controlled due to the emergence of highly

12) https://www.mhlw.go.jp/stf/shingi2/0000208910_00044.html (last accessed on August 1, 2022)
13) https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html (last accessed on August 1, 2022)

transmissible variants. The vaccine efficacy wanes over time after administration (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated November 2, 2021]). The efficacy of 2 doses of a vaccine against the currently predominant Omicron variant wanes more rapidly than the efficacy against Delta variant, but the third dose is expected to be effective (*MMWR Morb Mortal Wkly Rep*. 2022;71:422-8), raising the necessity of a booster dose.

Symptoms of COVID-19 in children are mild, but require hospitalization or result in death in some cases. In rare cases, multisystem inflammatory syndrome in children/pediatric inflammatory multisystem syndrome (MIS-C/PIMS) accompanied by pyrexia and multi-organ disorder has been reported (CDC website: Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States[14]). Also, symptoms such as fatigue, headache, and shortness of breath may persist for a long time after SARS-CoV-2 infection *(Lancet Child Adolesc Health*. 2022;6:240-8). It is thus essential to prevent COVID-19 with vaccination in children as well.

Under the current prevalence of Omicron variant in Japan, younger generations account for a majority of new SARS-CoV-2-positive patients in weekly surveys, and the infection is reported also among many people in their 10s and younger (MHLW website: Visualizing the data: information on COVID-19 infections: Number of newly confirmed cases by sex and age (weekly)[15]), indicating the high need for vaccination with a booster dose in children 5 to 11 years of age. Taking account of the findings that a booster dose of Comirnaty is expected to show efficacy in children 5 to 11 years of age (see Section 7.R.1) and that there are no serious safety concerns (see Section 7.R.2), it is of clinical significance to allow a booster dose of Comirnaty in children 5 to 11 years of age.

PMDA's view:
In Japan, since Omicron variant has become prevalent in January 2022, the number of children <10 years of age who become newly infected with SARS-CoV-2 has increased (MHLW website: The trends in COVID-19 occurrence in Japan, as of 24:00, August 2, 2022).[16] According to the "The third interim report on the studies of clinical courses of Coronavirus Disease 2019 (COVID-19)-infected patients in Japan based on database"[17] of the Japanese Pediatric Society, although there are no tendencies of aggravation of pediatric COVID-19 in children during the prevalence of the Omicron variant, the incidence of symptoms such as pyrexia, convulsion, pharyngeal pain, and vomiting increased. The Committee of preventive vaccination/infection control of the Japanese Pediatric Society recommends, in the statement "On the vaccination of children 5 to 17 years of age against COVID-19 (August 10, 2022)",[18] that all children 5 to 17 years of age be vaccinated and that a booster dose (the third dose) be given to adolescents 12 to 17 years of age who received the second dose ≥5 months before.

As of August 1, 2022, Comirnaty is the only SARS-CoV-2 vaccine available for use in children 5 to 11 years of age and is currently used for the primary series, but there is no vaccine that can be used as a booster dose in this age group. Although the efficacy of the second dose against the currently prevalent

14) https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (last accessed on August 1, 2022)
15) https://covid19.mhlw.go.jp/ (last accessed on August 1, 2022)
16) https://www.mhlw.go.jp/content/10906000/000972918.pdf (last accessed on August 1, 2022)
17) http://www.jpeds.or.jp/uploads/files/20220328_tyukan_hokoku3.pdf (last accessed on August 1, 2022)
18) http://www.jpeds.or.jp/modules/activity/index.php?content_id=451 (last accessed on August 15, 2022)

Omicron variant is lower than against Delta variant, the third dose is expected to be effective against Omicron variant (*MMWR Morb Mortal Wkly Rep.* 2022;71:422-8) and SARS-CoV-2 may possibly cause further spread of infections in the future, there is a certain level of significance in making Comirnaty available for the booster dose in children 5 to 11 years of age based on studies on the efficacy (see Section 7.R.1) and safety (see Section 7.R.2) of the third dose of Comirnaty in children 5 to 11 years of age.

In vaccine recipients of other age groups, the efficacy of the booster dose wanes over time (*MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). Since the balance of benefit and risk of the booster dose varies depending on the epidemic status, and the presence of underlying disease in vaccine recipients, etc. sufficient information should be provided to medical professionals, vaccine recipients, and their guardians so that they can decide the necessity of the booster dose based on the understanding of the benefit and the risk (such as adverse reactions) of the booster dose in children.

7.R.4 Dosage and administration

7.R.4.1 Dosage and administration

In Study C4591007, the applicant evaluated the immunogenicity and safety of the booster dose of 10 μg, the same dose as in the primary series, in children 5 to 11 years of age. On the basis of the results obtained, the applicant determined the additional dosage and administration in the present application as follows: "For a booster dose, a single dose of 0.2 mL is injected intramuscularly."

PMDA accepted the proposed dosage and administration based on its reviews on efficacy [see Section 7.R.1] and safety [see Section 7.R.2].

7.R.4.2 Timing of booster dose (the third dose)

The applicant proposed that the timing of the booster dose is specified in section "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" of the package insert as follows based on the timing employed in Study C4591007: "Usually, the third dose may be given at least 6 months after the second dose."

PMDA's view:
Initially, the timing of the third dose of Comirnaty in those ≥12 years of age had been determined to be "at least 6 months after the second dose," but was shortened to "at least 5 months after," taking account of the results of foreign clinical studies, etc. (the Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, April 25, 2022). In order to avoid confusion at clinical practice, etc., the timing should be set as "at least 5 months after" in children 5 to 11 years of age as in those ≥12 years of age.

PMDA requested the applicant the above change, to which the applicant agreed to change to "at least 5 months after."

7.R.5 Post-marketing investigations and risk management plan (draft)

The applicant's explanation:

Study C4591007 revealed no serious safety concerns in the booster dose of Comirnaty in children 5 to 11 years of age, showing a similar safety profile as in the second dose (see Section 7.R.2). Accordingly, the applicant does not intend to plan a postmarketing surveillance, etc., to collect safety information related to the booster dose of Comirnaty in children 5 to 11 years of age.

PMDA's view:

Safety information related to the booster dose of Comirnaty in Japanese children 5 to 11 years of age should be promptly collected and provided to medical professionals, for the following reasons:

- Clinical studies and postmarketing reports after marketing in foreign countries have provided only limited information on the safety of the booster dose of Comirnaty in children 5 to 11 years of age.
- There is no safety information on the booster dose of Comirnaty in Japanese children 5 to 11 years of age.
- Safety information on the primary series is still being collected.

PMDA instructed the applicant to consider actions to be taken after market launch.

The applicant's response:

The applicant understands the importance of collecting safety information related to the booster dose of Comirnaty in Japanese children 5 to 11 years of age. Safety information of Comirnaty administered according to the approved dosage regimen has been collected promptly in the government-led health monitoring after COVID-19 vaccination. Supposing that a government-led surveillance is conducted for the booster dose of Comirnaty in a similar manner, an independent surveillance by the applicant may become redundant in its objective and the target population, possibly imposing unnecessary burdens on medical institutions. Accordingly, the applicant will continue to jointly discuss with PMDA the additional pharmacovigilance activities by taking account of the government policy. The applicant will stand ready to decide the conduct of the specified use-results survey on the booster dose of Comirnaty in Japanese children 5 to 11 years of age until it becomes clear whether a government-led surveillance will be conducted, and the outline of the surveillance plan is revealed. The applicant will then design the surveillance plan, as needed.

PMDA accepted the explanation of the applicant.

PMDA concluded that the risk management plan (draft) for Comirnaty at present should include the safety specification presented in Table 7, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 8. As explained above by the applicant, additional pharmacovigilance activities and additional risk minimization activities should be subjected to review as soon as it becomes clear whether a government-led surveillance will be conducted and the outline of the surveillance plan is revealed.

Table 7. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Myocarditis, pericarditis	• Vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD) • Guillain-Barre syndrome	• Safety in pregnant and lactating women
Efficacy specification		
Not applicable		

Table 8. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (child vaccine recipients 5 to 11 years of age)[a)] • Post-marketing clinical study (C4591005)[b)] • Use-results survey in post-approval early vaccine recipients (healthcare professionals) (follow-up study) (C4591006)[b)] • Specified use-results survey in individuals with underlying diseases who are at high risk of severe COVID-19 (C4591019)[b)] • Foreign phase II/III study (C4591001)[b)] • Foreign phase II/III study in pregnant women (C4591015)[b)]	• Disseminate data gathered during early post-marketing phase vigilance (child vaccine recipients 5 to 11 years of age)[a)] • Organize and disseminate information for healthcare professionals (a proper use guide for Comirnaty) • Organize and disseminate information (a brochure) for vaccine recipients and their family members • Organize and disseminate information (a brochure) for child vaccine recipients (for children receiving a COVID-19 vaccine Comirnaty and their guardians) • Periodical publication of the occurrence of adverse reactions (child vaccine recipients 5 to 11 years of age)[a)]

a) Pertaining to the primary series in child vaccine recipients 5 to 11 years of age
b) Pertaining to vaccine recipients ≥12 years of age

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

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

The new drug application data were subjected to a document-based 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.

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

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

9. Overall Evaluation

On the basis of the data submitted, PMDA has concluded that the booster dose of Comirnaty for 5 to 11 years old is expected to have a certain level of efficacy in preventing disease caused by SARS-CoV-2 infection (COVID-19) in children 5 to 11 years of age with acceptable safety without serious safety concerns. Making a booster dose of Comirnaty available for 5 to 11 years old has a certain clinical significance on the condition that the vaccine is used after assessing the benefit-risk balance based on the prevalence of SARS-CoV-2 and the characteristics of individual recipients. On the basis of the above

review, PMDA concluded that the booster dose of Comirnaty Intramuscular Injection may be approved for the following indication and dosage and administration. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until February 13, 2029).

Indication

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

Dosage and Administration

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

(no change from the proposed dosage and administration)

Approval Conditions and Other Requirements

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

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

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

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

Appendix

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
Comirnaty	Comirnaty Intramuscular Injection and/or Comirnaty Intramuscular Injection for 5 to 11 years old
COVID-19	Coronavirus disease 2019
FDA	Food and Drug Administration
GMR	Geometric mean ratio
GMT	Geometric mean titer
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C/PIMS	Multisystem inflammatory syndrome in children/Pediatric inflammatory multisystem syndrome
mRNA	Messenger RNA
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
Reference strain	Strain USA-WA1/2020
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
The product	Comirnaty Intramuscular Injection for 5 to 11 years old
VAERS	Vaccine adverse event reporting system
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink