Report on the Deliberation Results

January 20, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

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	November 10, 2021

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 January 20, 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).

**Japanese Accepted Name (modified INN)*

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 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.
6. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 9 months after the approval.

Report on Special Approval for Emergency

January 11, 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)
Applicant	Pfizer Japan Inc.
Date of Application	November 10, 2021
Dosage Form/Strength	Injection: Each vial contains 0.130 mg of Tozinameran
Application Classification	Prescription drug, (6) Drug with a new dosage, (8) Drug in an additional dosage form (during the 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 1125-14, dated November 25, 2021]).
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 efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in children 5 to 11 years of age, and that the product has acceptable safety in view of its expected 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 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).
Two doses (0.2 mL each) are injected intramuscularly, usually 3 weeks apart.

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 2 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 patients (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 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.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 9 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)

December 15, 2021

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	November 10, 2021
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).
Usually, 2 doses (0.2 mL each) are injected intramuscularly, 3 weeks apart.

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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 of SARS-CoV-2 as the active ingredient. In Japan, "Comirnaty Intramuscular Injection" was granted marketing approval in February 2021 for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)." In Japan, vaccination with "Comirnaty Intramuscular Injection" and other SARS-CoV-2 vaccines has been administered in people ≥12 years of age and, as of December 10, 2021, ≥70% of all Japanese population have received 2 doses of SARS-CoV-2 vaccine (https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html [last accessed on December 10, 2021]). As a result, the number of newly infected people with COVID-19 remains low nationwide (https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html [last accessed on December 10, 2021]).

It is considered that COVID-19 is relatively mild and rarely becomes severe among children (https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Children_and_adolescents-2021.1 [last accessed on December 10, 2021]), while a certain number of pediatric patients have been reported to require inpatient treatment (*J Pediatric Infect Dis Soc.* 2021 Sep 6;piab085. doi: 10.1093/jpids/piab085). 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 multisystem inflammatory syndrome in children/pediatric inflammatory multisystem syndrome (MIS-C/PIMS) [in Japanese]" http://www.jpeds.or.jp/uploads/files/202109 16_mis-c_c_s.pdf [last accessed on December 10, 2021]), with fatal cases reported in foreign countries (*JAMA Pediatr.* 2021;175:837-45).

For the development of Comirnaty, the applicant conducted a foreign phase I/II/III study (Study C4591007) in children. On the basis of the immunogenicity and safety demonstrated in children 5 to 11 years of age in this study, emergency use authorization was granted in the US on October 29, 2021 for Comirnaty in children 5 to 11 years of age. As of December 8, 2021, Comirnaty is approved for marketing or authorized for emergency use in 15 countries and regions in the US and EU.

In Japan, the applicant has recently submitted an application for marketing approval of Comirnaty relating to (a) additional dosage and administration in children 5 through 11 years of age and (b) additional dosage form of vaccine product for children 5 through 11 years of age, based on the results of Study C4591007.

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 1125-14, dated November 25, 2021).

2. Data Relating to 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 multi-dose vial (1.3 mL) containing 0.130 mg of tozinameran. It is different from the approved vaccine product (Comirnaty Intramuscular Injection) in the content and concentration of the active ingredient, the content and concentration of lipid, and excipients. As a result of its review based on the submitted data, no particular problem was detected on the quality of Comirnaty. The shelf-life is currently under review and will be described in Review Report (2).

2.R.1 Number of doses that can be extracted from a single vial

The applicant's explanation about the number of doses that can be extracted from a single vial:
For use, Comirnaty (labeled volume 1.3 mL) is diluted with 1.3 mL of physiological saline, and 0.2 mL is used for each dose. Results of the test for extractable volume and the theoretical evaluation showed that each vial allows extraction of ten 0.2-mL doses when an injection syringe and needle with a small dead space was used. Information on the extractable doses from each vial will be provided to healthcare professionals.

PMDA accepted the explanation of the applicant.

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

6.1 Biopharmaceutic Studies and Associated Analytical Methods

Neutralizing antibody in serum was measured by a neutralization using SARS-CoV-2 (reference strain) transfected with fluorescent protein reporter gene (Study C4591007).

6.2 Clinical pharmacology

No data relating to clinical pharmacology were submitted in the present application.

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 months 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 5 through 11 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	Phase I	Healthy children 5 through 11 years of age[a)]	49 16 in 10 μg group 17 in 20 μg group 16[b)] in 30 μg group	Two doses of Comirnaty[c)] 10, 20, or 30 μg, administered intramuscularly 21 days apart.	Safety Tolerability Immunogenicity
		Phase II/III	Healthy children 5 through 11 years of age[a)]	Sentinel group: 2,285 (1,528 in Comirnaty group, 757 in placebo group) Additional group: 2,394 (1,598 in Comirnaty group, 796 in placebo group)	Two doses of Comirnaty[c)] 10 μg or placebo, administered intramuscularly 21 days apart.	Immunogenicity Safety Tolerability

a) Includes children with stable underlying disease.
b) Of 16 subjects who received 30 μg as the first dose, 4 subjects received the second 30-μg dose and developed pyrexia; the remaining 12 subjects received a 10-μg second dose.
c) Vaccine product (fill volume 0.2 mL) of the same composition with, but a different fill volume from, the approved vaccine product (Comirnaty Intramuscular Injection) (fill volume 0.45 mL)

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, September 6, 2021 in the sentinel group[1)]; October 8, 2021 in the additional group[2)]])

7.1.1 Phase I part

A multi-center, randomized, open-label study was conducted in 4 study sites in the US to investigate the safety, tolerability, and immunogenicity of Comirnaty and to determine the dose in healthy children 5 through 11 years of age (including those with stable underlying disease) (target sample size of 48 subjects [16 in each dose group]).

Two doses of Comirnaty 10 μg, 20 μg, or 30 μg was administered intramuscularly 21 days apart (Day 1 and Day 19-23).

Of 49 randomized subjects (16 in 10 μg group, 17 in 20 μg group, 16 in 30 μg group; hereinafter the same order shall apply), 48 (16, 16, 16) who received at least 1 dose of Comirnaty were included in the safety analysis set. All 16 subjects in the 30 μg group received the first 30-μg dose, and the first 4 subjects developed pyrexia after receiving the second 30-μg dose; therefore, the data evaluation committee[3)] decided to discontinue further 30 μg administrations, and the remaining 12 subjects received a second 10-μg dose. For this reason, immunogenicity was not evaluated in the 30 μg group. Of 32 subjects in the 10 μg or 20 μg group who received at least 1 dose of Comirnaty (16 in 10 μg group, 16 in 20 μg group; hereinafter the same order shall apply), 31 subjects (15, 16) were included in the all-available immunogenicity population, excluding 1 subject without immunogenicity data after Comirnaty administration. A total of 30 subjects (15, 15) were included in the evaluable immunogenicity population, excluding 1 subject without immunogenicity data within the specified period (Days 6 through 8) after the second dose.

1) See Section 7.1.2.1
2) See Section 7.1.2.2
3) A committee comprises internal members of Pfizer, but is independent of the Study C4591007 team. The committee is responsible for deciding the shift from low to high dose, discontinuation of vaccination, dose in the next phase, etc., based on the safety and immunogenicity data obtained from the phase I part.

The severity of adverse events was evaluated according to the Food and Drug Administration (FDA) Guidance "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).[4)]

The definition of observation periods:

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

Table 2 shows reactogenicity events that occurred within 7 days after each dose of Comirnaty.

Table 2. Reactogenicity events within 7 days after each dose of the study vaccine (safety analysis set)

Event terms	Dose #	Dose			
		10 μg (N = 16)	20 μg (N = 16)	30 μg (second 30 μg-dose) (N = 4)	30 μg (second 10 μg-dose) (N = 12)
		n (%)	n (%)	n (%)	n (%)
Local reaction					
Injection site pain	First	14 (87.5)	15 (93.8)	4 (100)	10 (83.3)
	Second	14 (87.5)	12 (75.0)	4 (100)	11 (91.7)
Redness	First	2 (12.5)	0	4 (100)	2 (16.7)
	Second	6 (37.5)	3 (18.8)	3 (75.0)	2 (16.7)
Swelling	First	3 (18.8)	1 (6.3)	2 (50.0)	1 (8.3)
	Second	5 (31.3)	3 (18.8)	2 (50.0)	0
Systemic reaction					
Pyrexia	First	1 (6.3)	1 (6.3)	0	4 (33.3)
	Second	2 (12.5)	3 (18.8)	4 (100)	0
Fatigue	First	8 (50.0)	11 (68.8)	4 (100)	6 (50.0)
	Second	11 (68.8)	10 (62.5)	4 (100)	9 (75.0)
Headache	First	4 (25.0)	5 (31.3)	3 (75.0)	4 (33.3)
	Second	8 (50.0)	9 (56.3)	3 (75.0)	4 (33.3)
Chills	First	0	4 (25.0)	2 (50.0)	2 (16.7)
	Second	5 (31.3)	7 (43.8)	3 (75.0)	4 (33.3)
Vomiting	First	0	1 (6.3)	0	1 (8.3)
	Second	0	0	1 (25.0)	1 (8.3)
Diarrhoea	First	1 (6.3)	1 (6.3)	0	0
	Second	1 (6.3)	0	2 (50.0)	0
Myalgia	First	2 (12.5)	4 (25.0)	4 (100)	0
	Second	0	3 (18.8)	2 (50.0)	1 (8.3)
Arthralgia	First	1 (6.3)	1 (6.3)	1 (25.0)	1 (8.3)
	Second	0	0	1 (25.0)	0

N = number of subjects analyzed. n = number of subjects with events (%)

Table 3 shows the incidences of adverse events and adverse reactions (i.e., adverse events for which a causal relationship to the study vaccine cannot be ruled out) within 1 month after the last dose of the study vaccine. Adverse events that occurred in ≥2 subjects were injection site pain (1 subject in the

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 December 10, 2021)

10 μg group, 2 subjects in the 30 μg group [second 10 μg-dose]) and arthralgia (1 each in the 10 μg group and the 30 μg group [second 30 μg-dose]), both of which were collected as reactogenicity events, lymphadenopathy (1 each in the 20 μg group and the 30 μg group [second 30 μg-dose]), and enterobiasis (2 in the 20 μg group). A causal relationship to Comirnaty could not be ruled out for lymphadenopathy in 1 subject (the 30 μg group); the outcome was "recovered."

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

	Dose			
	10 μg (N = 16)	20 μg (N = 16)	30 μg (second 30 μg-dose) (N = 4)	30 μg (second 10 μg-dose) (N = 12)
	n (%)	n (%)	n (%)	n (%)
Adverse events	7 (43.8)	5 (31.3)	2 (50.0)	3 (25.0)
Adverse reactions	4 (25.0)	2 (12.5)	2 (50.0)	3 (25.0)

N = number of subjects analyzed. n = number of subjects with events (%)

There were no deaths, serious adverse events, or adverse events leading to study discontinuation on or before the data cutoff date (July 16, 2021).

Geometric mean titer (GMT) [2-sided 95%CI] at 7 days after the second dose of Comirnaty in the evaluable immunogenicity population was 4,162.6 [2,584.7, 6,704.0] in the 10 μg group and 4,583.4 [2,802.9, 7,494.8] in the 20 μg group.

7.1.2 Phase II/III part

A multicenter, randomized, observer-blinded, placebo-controlled, parallel group study was conducted in 81 study sites in 4 countries (the US, Finland, Poland, and Spain) to investigate the immunogenicity, safety, and tolerability of Comirnaty in healthy children 5 through 11 years of age (including those with stable underlying disease). The subjects, the investigators, and other staff at the study sites (except for those who prepared or injected the study vaccine), and the sponsor (except for prespecified staff members independent of the study) were blinded to the study.

Two doses of the study vaccine (Comirnaty 10 μg or placebo) was administered intramuscularly 21 days apart (Day 1 and Day 19-23).

Initially, the planned target sample size of children 5 through 11 years of age was 2,250 (randomized to the Comirnaty group and the placebo group at 2:1 ratio; 1,500 in the Comirnaty group, 750 in the placebo group; hereinafter the same order shall apply). However, additional 2,250 subjects (1,500, 750) were

included to enlarge the size of the pediatric safety database at the request of the FDA during the study, and the sample size was revised to 4,500 (3,000, 1,500)[5], (protocol amendment, ver. 2, [redacted], 20[redacted]).

7.1.2.1 Sentinel group

Of 2,285 randomized subjects, 2,268 receiving at least 1 dose of the study vaccine (1,518 in the Comirnaty group, 750 in the placebo group; hereinafter the same order shall apply)[6] were included in the safety analysis set. In order to evaluate immunogenicity in 450 subjects, the first approximately 6 subjects in each study site in every participating country were extracted from among those randomized before the phase II/III part of the study, and 485 subjects (322, 163) were included in the immunogenicity population. Of these 485 subjects, 441 (294, 147) with at least 1 valid immunogenicity result after the second dose of the study vaccine were included in the evaluable immunogenicity population. Of these 441 subjects, 394 (264, 130) without history of SARSCoV-2 infection within 1 month after the second dose of the study vaccine were defined as the primary immunogenicity population.

The control population for immunobridging analysis [see Section 7.R.1 for immunobridging analysis plan] was defined as follows: Of 350 subjects (300, 50) who were randomly extracted from subjects 16 through 25 years of age receiving 2 doses of the study vaccine in Study C4591001, 320 subjects (273, 47) showing at least 1 valid immunogenicity result after the second dose of the study vaccine were defined as the evaluable immunogenicity population. Among them, 298 subjects (253, 45) without history of SARSCoV-2 infection within 1 month after the second dose of the study vaccine were defined as the control population in the primary immunogenicity analysis.

The primary immunogenicity endpoint was defined as the SARS-CoV-2-neutralizing antibody titer (50% neutralizing antibody titer) at 1 month after the second dose of the study vaccine in subjects without history of SARS-CoV-2 infection. The following parameters were calculated:

- Geometric mean ratio (GMR) which is the ratio of the GMTs in the primary immunogenicity population to those in the population 16 through 25 years of age in the phase II/III part of Study C4591001
- Difference in the neutralizing antibody response rate (the percentage of subjects who showed a ≥4-fold increase in the neutralizing antibody titer from the titer at baseline [the titer below the lower limit of quantitation (LLOQ) was regarded as the LLOQ]) in the primary immunogenicity population to those in the population 16 through 25 years of age in the phase II/III part of Study C4591001

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5) In the US, safety database of at least 3,000 subjects is required for marketing authorization. Accordingly, the applicant had planned to include 1,500 subjects in the Comirnaty group and 750 in the placebo group, with consideration given to the ongoing development in children of other age groups. Subsequently, in response to the FDA's request to collect safety data of at least 3,000 subjects in the Comirnaty group in children 5 through 11 years of age, the total sample size was changed to 4,500 (3,000 in the Comirnaty group, 1,500 in the placebo group). For the evaluation of immunogenicity, the number of subjects in the immunogenicity subset was assumed to be 225 both for the Comirnaty group in Study C4591007 (5 through 11 years of age) and for the Comirnaty group in Study C4591001 (16 through 25 years of age). By assuming the between-group difference of GMT (logarithmic value) to be -0.2, and the standard deviation (logarithmic value) to be 0.65, and GMR (the immunobridging criterion) to be 0.67, statistical power is 90.4%. When the antibody response rate in each group is assumed to be 90%, and the difference in antibody response rate to be 10% as the criterion for immunobridging success, the statistical power is 92.6%. In addition, by assuming the percentage of unevaluable cases to be 25%, the target sample size was set at 300 in the Comirnaty group of each study. For the placebo group in Study C4591007 (5 through 12 years of age), the target sample size was set at 150, the half of the target sample size in the Comirnaty group.

6) One subject who had been assigned to receive placebo but was administered Comirnaty in error was evaluated as a subject in the Comirnaty group.

Both primary endpoints were investigated sequentially: GMR was evaluated first and, if the prespecified success criteria were achieved, antibody response rate was evaluated.

Table 4 shows the neutralizing antibody titers at 1 month after the second dose of the study vaccine. GMR met the prespecified success criterion (the lower limit of 2-sided 95% CI is >0.67, and the point estimate is ≥0.8).

Table 4. Neutralizing antibody titer (evaluable immunogenicity population)

Study C4591007 (5 through 11 years of age)				Study C4591001 (16 through 25 years of age)				GMR [2-sided 95% CI] (5-11 years old in Comirnaty group/16-25 years old in Comirnaty group)
Comirnaty 10 μg		Placebo		Comirnaty 30 μg		Placebo		
N	GMT[a)] [2-sided 95%CI]	N	GMT[a)] [2-sided 95%CI]	N	GMT[a)] [2-sided 95%CI]	N	GMT[a)] [2-sided 95%CI]	
264	1197.6 [1106.1, 1296.6]	130	10.7 [9.7, 11.8]	253	1146.5 [1045.5, 1257.2]	45	10.0 [10.0, 10.0]	1.04 [0.93, 1.18]

N = number of subjects analyzed
a) When antibody titer is below LLOQ, the value 0.5×LLOQ is used for the analysis.

Table 5 shows the neutralizing antibody response rate at 1 month after the second dose of the study vaccine. The difference in antibody response rate met the prespecified success criterion (lower limit of 2-sided 95% CI >−10%).

Table 5. Neutralizing antibody response rate (evaluable immunogenicity population)

Study C4591007 (5 through 11 years of age)		Study C4591001 (16 through 25 years of age)		Difference in antibody response rate [2-sided 95% CI][a)] (5-11 years old in Comirnaty group – 16-25 years old in Comirnaty group)
Comirnaty 10 μg % (n/N)	Placebo % (n/N)	Comirnaty 30 μg % (n/N)	Placebo % (n/N)	
99.2% (262 of 264)	1.5% (2 of 130)	99.2% (251 of 253)	0% (0 of 45)	0.0% [-2.0, 2.2]

N = number of subjects analyzed, n = number of subjects achieving a ≥4-fold increase in antibody titer from baseline (LLOQ if baseline value is <LLOQ)
a) Miettinen and Nurminen method

The grading scale used for evaluating the severity of adverse events and each observation period were the same as those used in the phase I part [see Section 7.1.1].

In the safety analysis set, the median observation period from the second dose of the study vaccine to data cutoff date (September 6, 2021) was 2.3 months (range 0.0-2.5 months).

Table 6 shows reactogenicity events observed within 7 days after each dose of the study vaccine.

Table 6. Reactogenicity events within 7 days after each dose of the study vaccine (safety analysis set)

Event terms	Dose #	Comirnaty n/N (%)	Placebo n/N (%)
Local reaction			
Injection site pain	First	1,119/1,511 (74.1)	234/748 (31.3)
	Second	1,065/1,501 (71.0)	218/740 (29.5)
Redness	First	222/1,511 (14.7)	43/749 (5.7)
	Second	278/1,501 (18.5)	40/741 (5.4)
Swelling	First	158/1,511 (10.5)	20/749 (2.7)
	Second	229/1,501 (15.3)	20/741 (2.7)
Systemic reaction			
Pyrexia	First	38/1,511 (2.5)	10/749 (1.3)
	Second	98/1,501 (6.5)	9/741 (1.2)
Fatigue	First	508/1,511 (33.6)	234/748 (31.3)
	Second	592/1,501 (39.4)	180/740 (24.3)
Headache	First	339/1,511 (22.4)	180/748 (24.1)
	Second	420/1,501 (28.0)	138/740 (18.6)
Chills	First	70/1,511 (4.6)	35/748 (4.7)
	Second	147/1,501 (9.8)	32/740 (4.3)
Vomiting	First	33/1,511 (2.2)	11/748 (1.5)
	Second	28/1,501 (1.9)	6/740 (0.8)
Diarrhoea	First	89/1,511 (5.9)	31/748 (4.1)
	Second	79/1,501 (5.3)	35/740 (4.7)
Myalgia	First	137/1,511 (9.1)	51/748 (6.8)
	Second	175/1,501 (11.7)	55/740 (7.4)
Arthralgia	First	50/1,511 (3.3)	41/748 (5.5)
	Second	78/1,501 (5.2)	27/740 (3.6)

N = number of subjects analyzed (number of subjects who reported the presence or absence of event in subject diary), n = number of subjects with events (%)

The incidences of adverse events and adverse reactions within 1 month after the last dose of the study vaccine were 10.9% (166 of 1,518 subjects) and 3.0% (46 of 1,518 subjects), respectively, in the Comirnaty group and 9.2% (69 of 750 subjects) and 2.1% (16 of 750 subjects), respectively, in the placebo group. Table 7 shows adverse events and adverse reactions observed in ≥5 subjects in the Comirnaty group.

Table 7. Adverse events and adverse reactions observed in ≥5 subjects in the Comirnaty group within 1 month after the last dose of the study vaccine (safety analysis set)

Event terms	Adverse events		Adverse reactions	
	Comirnaty (N = 1,518)	Placebo (N = 750)	Comirnaty (N = 1,518)	Placebo (N = 750)
	n (%)	n (%)	n (%)	n (%)
Total	166 (10.9)	69 (9.2)	46 (3.0)	16 (2.1)
Lymphadenopathy	13 (0.9)	1 (0.1)	[redacted]	[redacted]
Injection site pain	11 (0.7)	3 (0.4)	11 (0.7)	3 (0.4)
Otitis externa	7 (0.5)	6 (0.8)	0	0
Nausea	6 (0.4)	2 (0.3)	5 (0.3)	1 (0.1)
Vomiting	6 (0.4)	2 (0.3)	0	0
Headache	6 (0.4)	2 (0.3)	[redacted]	[redacted]
Diarrhoea	5 (0.3)	1 (0.1)	0	0
Fall	5 (0.3)	1 (0.1)	0	0
Arthropod bite	[redacted]	[redacted]	0	0
Nasal congestion	5 (0.3)	4 (0.5)	[redacted]	[redacted]
Cough	5 (0.3)	2 (0.3)	0	0
Oropharyngeal pain	5 (0.3)	1 (0.1)	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]

N = number of subjects analyzed, n = number of subjects with events (%)

As of the data cutoff date (September 6, 2021), serious adverse events occurred in 1 subject in the Comirnaty group (upper limb fracture) and in 1 subject in the placebo group (abdominal pain and

pancreatitis). Causal relationship to the study vaccine was denied for both cases; the outcome was "recovered" or "recovering." There was no death or adverse event leading to study discontinuation.

7.1.2.2 Additional group

Of 2,394 randomized subjects, 2,379 (1,591 in the Comirnaty group, 788 in the placebo group) who received at least 1 dose of the study vaccine were included in the safety analysis set.

In the safety analysis set, the median observation period from the second dose of the study vaccine to the data cutoff date (October 8, 2021) was 2.4 weeks (range 0.0-3.7 weeks).

Reactogenicity events observed within 7 days after each dose of the study vaccine reported in subject diary were not tabulated.

The incidences of adverse events and adverse reactions from the first dose of the study vaccine to the data cutoff date (October 8, 2021) were 7.2% (115 of 1,591 subjects) and 3.5% (55 of 1,591 subjects), respectively, in the Comirnaty group and 6.3% (50 of 788 subjects) and 1.8% (14 of 788 subjects), respectively, in the placebo group. Table 8 shows adverse events observed in ≥5 subjects in the Comirnaty group.

Table 8. Adverse events observed in ≥5 subjects in the Comirnaty group from the first dose of the study vaccine to the data cutoff date (October 8, 2021) (safety analysis set)

Event terms	Adverse events		Adverse reactions	
	Comirnaty (N = 1,591)	Placebo (N = 788)	Comirnaty (N = 1,591)	Placebo (N = 788)
	n (%)	n (%)	n (%)	n (%)
Total	115 (7.2)	50 (6.3)	55 (3.5)	14 (1.8)
Injection site pain	18 (1.1)	2 (0.3)	18 (1.1)	2 (0.3)
Fatigue	7 (0.4)	3 (0.4)	7 (0.4)	2 (0.3)
Lymphadenopathy	6 (0.4)	3 (0.4)	5 (0.3)	3 (0.4)
Headache	6 (0.4)	3 (0.4)	5 (0.3)	2 (0.3)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Cough	5 (0.3)	3 (0.4)	0	0

N = number of subjects analyzed. n = number of subjects with events (%)

As of the data cutoff date (October 8, 2021), serious adverse events were observed in 3 subjects in the Comirnaty group (arthritis infective, foreign body ingestion, and epiphyseal fracture). A causal relationship to the study vaccine was denied for all of them. The outcome was "recovered" for arthritis infective and foreign body ingestion and "recovering" for epiphyseal fracture. No death occurred. Adverse events leading to study discontinuation were observed in 1 subject in the Comirnaty group (pyrexia and neutropenia). Both of the events were considered to have a causal relationship with the study vaccine; the outcome was "recovered" for pyrexia and "recovering" for neutropenia.

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 was confirmed in the phase II/III part of the foreign phase I/II/III study (Study C4591001) in subjects ≥16 years of age.[7)] In addition, a Japanese phase I/II study (Study C4591005) in subjects 20 through 85 years of age was conducted, and results confirmed that the immunogenicity in Japanese was similar to that observed 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 people ≥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]). Subsequently, the immunogenicity was evaluated in additionally enrolled subjects 12 through 15 years of age in Study C4591001 and was confirmed that the immunogenicity in this age group was similar to that observed in the population 16 through 25 years of age, without any particular safety concerns. On the basis of these results, the age of individuals who receive vaccinations were expanded to ≥12 years in May 2021 (revised package insert, dated May 31, 2021).

Among infection-preventing vaccines that have demonstrated their efficacy in adult population in clinical studies, some have actually been developed also for children and approved, using the immunobridging approach to assess clinical efficacy based on the similarity in immunogenicity between the adult and pediatric populations. In developing Comirnaty for children 12 through 15 years of age, the applicant explained the plan to demonstrate the efficacy of Comirnaty based on a similar approach, which each regulatory agency accepted, resulting in the expansion of the age range of individuals eligible to receive vaccination. Accordingly, the same immunobridging approach was employed in the development of Comirnaty for children 5 through 11 years of age to evaluate the clinical efficacy.

Comirnaty in children 5 through 11 years of age was developed according to the following procedures:

- A phase I/II/III study (Study C4591007) was conducted to evaluate the safety and immunogenicity of Comirnaty in children of this age group.
- A dose-finding study in phase I part selected 10 μg from the results of safety and immunogenicity data [see Section 7.1.1].
- In the succeeding phase II/III part, immunogenicity data in children 5 through 11 years of age was compared with those observed in the population 16 through 25 years of age in Study C4591001, using the immunobridging approach.
- The immunobridging success criteria (lower bound of 2-sided 95% CI of GMR, >0.67; point estimate, ≥0.8; and lower bound of 2-sided 95% CI of antibody response rate >−10%) were defined by referring to:
  (a) Guidelines on clinical evaluation of vaccines: regulatory expectations, WHO Technical Report Series 1004, Annex 9, 2017[8)]
  (b) Non-inferiority margin in many clinical studies on other infection-preventing vaccines (*Vaccine*. 2015;33:1426-32), and

7) During the study, the study protocol was amended to enroll subjects 12 through 15 years of age as well.
8) https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9 (last accessed on December 10, 2021)

(c) Immunogenicity success criteria[9] used in the clinical study for the development of 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, suggesting the expected efficacy of Comirnaty 10 μg in children 5 through 11 years of age [see Section 7.R.2]. The safety profile revealed no significant concerns, confirming the tolerability [see Section 7.R.3].

No Japanese clinical study was planned in children 5 through 11 years of age because the immunogenicity and safety in Japanese have been confirmed in the Japanese phase I/II study (Study C4591005) involving subjects 20 through 85 years of age, as described earlier.

Thus, a marketing application for "Comirnaty Intramuscular Injection for 5-to-11-year-old" has been filed based on the data of the immunogenicity and safety in 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"[10] 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 (addendum 3): Consideration for Evaluation of SARS-CoV-2 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 children using a similar immunobridging approach because Comirnaty has already been confirmed to be effective in the population ≥16 years of age.

On the basis of the above, PMDA concluded that, in the development of Comirnaty for children 5 through 11 years of age, it is acceptable to evaluate the efficacy according to the following procedures:

- To evaluate the neutralizing antibody titer in this age group in a clinical study, and

9) In accordance with the FDA Guidance "Guidance for Industry: Emergency Use Authorization for vaccines to Prevent COVID-19" (issued in May 2021) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19) (last accessed on December 10, 2021) and deliberation with FDA, the criteria were defined as follows: Lower bound of 2-sided 95% CI of GMR, >0.67; point estimate, ≥0.8; and lower bound of 2-sided 95% CI of antibody response rate >-10%

10) https://www.fda.gov/media/149935/download (last accessed on December 10, 2021)

- To evaluate the efficacy of Comirnaty in this age group by comparing the neutralizing antibody titer with that of an age group with confirmed efficacy.

PMDA also concluded that it is acceptable to evaluate the efficacy based on the specified immunobridging success criteria, taking account of the description in the above guidance, etc.

From July to August of 2021, the epidemic of Delta variant caused an increase in the number of patients with COVID-19 in foreign countries including the US and EU. The number then temporarily decreased from September to October of the same year, but again tended to increase thereafter (https://covid19.who.int/ [last accessed on December 10, 2021]). In Japan, the number of those who become newly infected with SARS-CoV-2 remains low as of December 10, 2021 (https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html [last accessed on December 10, 2021]), but there is a possibility of resurgence, necessitating the SARSCoV-2 vaccination in children as well, as soon as possible. Although no Japanese clinical study was conducted in children, PMDA decided to evaluate the immunogenicity and safety of Comirnaty based on the results of Study C4591007 submitted, taking account of the following:

- The immunogenicity and safety in Japanese have been confirmed in a Japanese clinical study in subjects ≥20 years of age,
- After the approval of Comirnaty, vaccination in the population ≥12 years of age has progressed, resulting in the accumulation of use experiences in Japan, and
- Development of Comirnaty intramuscular injection for 5 through 11 years of age is urgently needed.

7.R.2 Efficacy

The applicant's explanation about the efficacy of Comirnaty in children 5 through 11 years of age:

The efficacy of Comirnaty in children 5 through 11 years of age was evaluated according to the following procedures:

- As the primary endpoint in phase II/III part of Study C4591007, the neutralizing antibody titer (GMT and antibody response rate) against SARS-CoV-2 (reference strain) at 1 month after the second dose of Comirnaty (10 μg) was evaluated.
- The neutralizing antibody titer was compared with that observed in the population randomly extracted from subjects 16 through 25 years of age who received 2 doses of Comirnaty (30 μg) in Study C4591001 conducted to confirm COVID-19-preventive effect of Comirnaty.

To compare the immunogenicity, the upper limit of age range was set at 25 years to allow comparison between the populations of closer ages, by taking into consideration the effect of age on immunogenicity. Participating countries are partly different between the two studies (US, Finland, Poland, and Spain in Study C4591007; US, Germany, Turkey, Brazil, Argentina, and South Africa in Study C4591001), but the main inclusion and exclusion criteria were the same except for age criterion. Using serum samples obtained from subjects without history of SARS-CoV-2 infection in both studies, the neutralizing antibody titer was measured at the same time by the same method. This allows the comparison of immunogenicity data between the two studies.

After the phase II/III part of Study C4591007, data were compared with those obtained from the population 16 through 25 years of age in Study C4591001, using the primary efficacy endpoint of neutralizing antibody titer at 1 month after the second dose of Comirnaty as the index. Results showed

that both GMR and the difference in antibody response rate met the pre-defined success criteria [see Section 7.1.2.1].

Table 9 shows the demographic characteristics of subjects in phase II/III part of Study C4591007 and in the evaluable immunogenicity population within the population 16 through 25 years of age in Study C4591001.

Table 9. Comparison of demographic characteristics (phase II/III part, evaluable immunogenicity population)

		Study C4591007 5-11 years old, Comirnaty 10 µg N = 294	Study C4591001 16-25 years old, Comirnaty 30 µg N = 273
		n (%)	n (%)
Sex	Male	153 (52.0)	133 (48.7)
	Female	141 (48.0)	140 (51.3)
Race	White	232 (78.9)	205 (75.1)
	Black, African-American	18 (6.1)	32 (11.7)
	Asian	23 (7.8)	17 (6.2)
	Multiracial	17 (5.8)	12 (4.4)
	Others[a)] or not reported	4 (1.3)	7 (2.6)
Ethnicity	Hispanic or Latino	46 (15.6)	98 (35.9)
	Non-Hispanic or non-Latino	246 (83.7)	175 (64.1)
	Not reported	2 (0.7)	0
Obesity[b)]	Yes	25 (8.5)	44 (16.1)
	No	269 (91.5)	229 (83.9)
Baseline SARS-CoV-2 infection status[c)]	Positive	21 (7.1)	13 (4.8)
	Negative	273 (92.9)	259 (94.9)
	Not reported	0	1 (0.4)

N = number of subjects analyzed, n = number of corresponding subjects (%)

a) American Indians, Alaska natives, Native Hawaiians, other Pacific Islanders

b) Study C4591007, BMI ≥95 percentile; Study C4591001, BMI ≥30 kg/m^2

c) Determined based on SARS-CoV-2 N-binding antibody test, nucleic acid amplification test, or history of COVID-19 at visit 1 ("positive" if the subject was positive for any of the tests or had a history of COVID-19; "negative" if the subject was negative for all tests and had no history of COVID-19).

Table 10 shows the neutralizing antibody titer 1 month after the second dose of Comirnaty, by subpopulation. The antibody response rate was high at 98.6% to 100% regardless of population or age range. 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 analyzed in some subpopulations. The neutralizing antibody titer in the population with past SARS-CoV-2 infection at baseline was higher than the titer in those without past SARS-CoV-2 infection at baseline, but the antibody response rate was high in both subpopulations.

Table 10. Neutralizing antibody titer at 1 month after the second dose of Comirnaty, by subpopulation (phase II/III part, evaluable immunogenicity population)

		Study C4591007 5-10 years old, Comirnaty 10 μg		Study C4591001 16-25 years old, Comirnaty 30 μg	
		N	GMT [2-sided 95% CI]	N	GMT [2-sided 95% CI]
All subjects		294	1300.3 [1195.9, 1413.8]	273	1192.6 [1089.7, 1305.2]
Sex	Male	153	1218.5 [1102.8, 1346.3]	133	1081.8 [939.2, 1245.9]
	Female	141	1395.3 [1216.4, 1600.6]	140	1308.3 [1168.1, 1465.5]
Race	White	232	1299.4 [1178.8, 1432.4]	205	1225.6 [1120.7, 1340.3]
	Black, African-American	18	1171.2 [823.7, 1665.4]	32	1010.3 [657.3, 1552.9]
	Asian	23	1219.4 [918.6, 1618.6]	17	967.9 [641.0, 1461.3]
	Multiracial	17	1435.8 [1086.7, 1896.9]	12	1236.8 [649.5, 2354.8]
Ethnicity	Hispanic or Latino	46	1412.3 [1118.1, 1783.9]	98	1179.2 [1046.6, 1328.6]
	Non-Hispanic or non-Latino	246	1276.9 [1166.4, 1397.9]	175	1200.2 [1059.4, 1359.6]
Baseline SARS-CoV-2 infection status[a)]	Positive	21	3270.0 [2032.1, 5261.8]	13	2253.8 [1497.7, 3391.5]
	Negative	273	1211.3 [1211.1, 1308.7]	259	1151.2 [1050.5, 1261.5]

a) Determined based on SARS-CoV-2 N-binding antibody test, nucleic acid amplification test, or history of COVID-19 at visit 1 ("positive" if the subject was positive for any of the tests or had a history of COVID-19; "negative" if the subject was negative for all tests and had no history of COVID-19).

Because of the difference in the definition of risk factors for severe COVID-19[11)] between Study C4591007 and Study C4591001, efficacy results in the subpopulation with or without the risk factors were not compared between these studies. In phase II/III part of Study C4591007, the neutralizing antibody titer (GMT [2-sided 95% CI]) was 1,364.0 [1,170.8, 1,589.1] in the subpopulation with risk factors for severe COVID-19 and 1,158.2 [1,056.6, 1,269.6] in the subpopulation without the risk factors, showing no effect of the risk factors on the neutralizing antibody titer.

The immunogenicity against Delta variant in children 5 through 11 years of age in phase II/III part of Study C4591007 was evaluated in an exploratory manner. The neutralizing antibody titer (GMT [2-sided 95% CI]) against Delta variant at 28 days after the second dose of Comirnaty was 294.9 [214.6, 405.3], which was lower than that against the reference strain (365.3 [279.0, 478.4]). A similar tendency was observed in adults. Thus, the neutralizing antibody titer (GMT [2-sided 95% CI]) at 28 days after the second dose of Comirnaty was 241.0 [180.1, 322.4] against Delta variant and 310.1 [203.3, 473.0] against the reference strain (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated November 2, 2021]).

In phase II/III part of Study C4591007, it had been planned to evaluate the COVID-19-preventive effect based on vaccine efficacy (VE) at the time point when data were accumulated from at least 21 confirmed COVID-19 cases as the secondary endpoint. However, in order to provide efficacy data in children 5 through 11 years of age to FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss emergency use authorization of "Comirnaty Intramuscular Injection for 5 to 11 years old," unscheduled VE analysis was conducted upon confirmation of the fulfillment of the success criteria by the immunobridging analysis. The analysis was conducted by a statistician and a

11) In each study, the following underlying diseases and obesity were defined as risk factors for severe COVID-19:
Study C4591007:
Underlying diseases: Asthma, blood disorder, cardiovascular disease, chronic lung disease, chronic metabolic disease, congenital heart disease, diabetes mellitus, patients on tube feeding, immunodeficiency, neurological disorder, sickle cell disease, etc.
Obesity: ≥95th percentile BMI value in CDC growth chart (https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm [last accessed on December 10, 2021])
Study C4591001:
Underlying diseases: Diseases included in Charlson Comorbidity Index
Obesity: BMI ≥30 kg/m^2

programmer[12] who were unblinded but not directly involved in the study conduct, based on the cutoff data on October 8, 2021. As of the data cutoff date, data were collected from 19 confirmed COVID-19 cases[13] (3 of 1,450 in the Comirnaty group, 16 of 736 in the placebo group) from ≥7 days after the second dose of the study vaccine in the evaluable efficacy population.[14] In the subpopulation without SARS-CoV-2 infection before the first dose until 7 days after the second dose of study vaccine (1,305 in the Comirnaty group, 663 in the placebo group), VE [2-sided 95% CI] was 90.7% [67.4, 98.3]. There were no confirmed COVID-19 cases among subjects with history of SARSCoV-2 infection. Among confirmed COVID-19 cases, no severe cases[15] were reported from either Comirnaty group or placebo group. No MIS-C was reported either.

Thus, results of phase II/III part of Study C4591007 demonstrated the following:

- Immunobridging success criteria were met with the population 16 through 25 years of age in Study C4591001.
- A preliminary data showed a high VE in this study which was conducted during the Delta variant epidemic, with an increase in neutralizing antibody titer against Delta variant.

Given the COVID-19-preventive effect of Comirnaty confirmed in Study C4591001, these results suggest that Comirnaty is expected to have a certain level of efficacy in children 5 through 11 years of age.

The currently available immunogenicity data in children 5 through 11 years of age are only those obtained at 1 month after the second dose of Comirnaty. It is planned to collect additional immunogenicity data in Study C4591007, including those at 6 months after the second dose of Comirnaty.

PMDA's view:

Comparison of the immunogenicity data between the subjects in phase II/III part of Study C4591007 and the population 16 through 25 years of age in Study C4591001 confirmed a high COVID-19-preventive effect of Comirnaty and an increase in the neutralizing antibody titer, albeit differences in the distribution of some demographic characteristics between the two populations (Table 9). The subpopulation analysis also confirmed a high COVID-19-preventive effect regardless of the demographic characteristics (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021], *N Engl J Med*. 2021;384:1576-7). On the basis of the above, PMDA concluded that demographic characteristics are unlikely to cause clinically significant difference

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12) The statistician and the programmer different from blinded persons in charge of study conduct

13) A confirmed COVID-19 case was defined as a subject who has at least 1 symptom suggestive of 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 onset of loss of taste or smell, sore throat, diarrhoea, and vomiting) with a positive SARSCoV-2 result by nasopharyngeal swab nucleic acid amplification testing.

14) Of 2,285 randomized subjects, 1,450 in the Comirnaty group and 736 in the placebo group were included in the evaluable efficacy population, excluding the following:
- Those in whom the interval between the first dose and the second dose of the study drug was outside the defined range of Day 19 to 42 (31 in the Comirnaty group, 18 in the placebo group)
- Those with important protocol deviations within 7 days after the second dose of the study drug (47 in the Comirnaty group, 4 in the placebo group)

15) Confirmed COVID-19 cases with at least 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

in immune response and that it is acceptable to compare immunogenicity data between the two populations.

Comirnaty is expected to have a certain level of efficacy in children 5 through 11 years of age, given the following observations:

- In phase II/III part of Study C4591007, GMR of neutralizing antibody titer and the difference in antibody response rate at 1 month after the second dose of Comirnaty met the immunobridging success criteria.
- Subpopulation analysis of neutralizing antibody titer did not detect significant difference among subjects with different demographic characteristics.
- Study C4591001 confirmed COVID-19-preventive effect of Comirnaty.

The immunogenicity data submitted in the present application are those obtained up to 1 month after the second dose of Comirnaty. It is unknown how the neutralizing antibody titer changes over time after the vaccination in children 5 through 11 years of age. It has been confirmed in Study C4591001, etc., that the neutralizing titer decreases over time after vaccination with Comirnaty (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated November 2, 2021]). The applicant should continue to collect information on the change in the immunogenicity over time in children 5 through 11 years of age and take appropriate measures based on the information obtained. In addition, the applicant should continue to pay attention to the emergence and spread of new variants in order to collect information on the efficacy and immunogenicity of Comirnaty on such variants and take appropriate measures depending on the situations.

7.R.3 Safety

7.R.3.1 Safety profile

The applicant's explanation of safety in Study C4591007:

(a) Reactogenicity events

Table 11 shows reactogenicity events observed within 7 days after the study vaccine administration (either the first or the second dose) in phase II/III part (sentinel group). Local reactions and systemic reactions were observed in large numbers of subjects in the Comirnaty group. The incidence of each event was similar between the Comirnaty group and the placebo group for vomiting, diarrhoea, and arthralgia, while the incidences of other adverse events were higher in the Comirnaty group than in the placebo group. There were no Grade ≥3 events with incidence of ≥1%. No Grade 4 events occurred. Pyrexia was not classified by Grade. The incidence of pyrexia in the Comirnaty group, classified by temperature range, was as follows: 38.0°C to 38.4°C, 4.4% (66 subjects) (1.5% [23 subjects] after the first dose, 3.4% [51 subjects] after the second dose; hereinafter the same order shall apply); 38.5°C to 38.9°C, 3.2% (48 subjects) (0.8% [12], 2.5% [38]); 39.0°C to 40.0°C, 0.7% (11 subjects) (0.2% [3], 0.5% [8]); and >40.0°C, 0.1% (1 subject) (0% [0], 0.1% [1]). In the subject with pyrexia of >40°C, the pyrexia occurred on Day 2 after the second dose and resolved on the next day.

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

	Event term	Total		Grade ≥3	
		Comirnaty (N = 1,517) n/N (%)	Placebo (N = 750) n/N (%)	Comirnaty (N = 1,517) n/N (%)	Placebo (N = 750) n/N (%)
Local reaction	Total	1,308/1,517 (86.2)	349/750 (46.5)	—	—
	Injection site pain	1,279/1,517 (84.3)	322/749 (43.0)	9/1,517 (0.6)	0/749
	Redness	401/1,517 (26.4)	72/750 (9.6)	3/1,517 (0.2)	0/749
	Swelling	309/1,517 (20.4)	35/750 (4.7)	1/1,517 (0.1)	0/749
Systemic reaction	Total	1,011/1,517 (66.6)	418/750 (55.7)	—	—
	Pyrexia[a)]	126/1,517 (8.3)	19/750 (2.5)	—	—
	Fatigue	785/1,517 (51.7)	299/749 (39.9)	13/1,517 (0.9)	2/749 (0.3)
	Headache	579/1,517 (38.2)	242/749 (32.3)	5/1,517 (0.3)	4/749 (0.5)
	Chills	188/1,517 (12.4)	58/749 (7.7)	2/1,517 (0.1)	1/749 (0.1)
	Vomiting	60/1,517 (4.0)	17/749 (2.3)	0/1,517	0/749
	Diarrhoea	146/1,517 (9.6)	61/749 (8.1)	0/1,517	0/749
	Myalgia	266/1,517 (17.5)	85/749 (11.3)	2/1,517 (0.1)	0/749
	Arthralgia	115/1,517 (7.6)	58/749 (7.7)	0/1,517	0/749

N = number of subjects analyzed (number of subjects who reported the presence or absence of event in subject diary), n = number of subjects with events (%)
a) ≥38.0°C, not classified by Grade.

The median time to the onset of local reaction was 1 to 2 days both after the first and the second doses of Comirnaty, and the median duration was 1 to 2 days. The median time to the onset of systemic reactions was 2 to 4 days both after the first and the second doses of Comirnaty with the median duration of 1 day, but symptoms persisted for ≥1 month for some events.

The incidence of reactogenicity events by each dose was as shown in Table 6 [see Section 7.1.2.1]. In the placebo group, the incidences of most of events were similar between after the first dose and after the second dose, whereas in the Comirnaty group, the incidences of redness, swelling, pyrexia, fatigue, headache, chills, myalgia, and arthralgia were higher after the second dose than after the first dose.

The percentage of subjects who used at least 1 dose of an antipyretic analgesic for the treatment of symptoms associated with the study vaccination was 14.4% (217 of 1,511 subjects) in the Comirnaty group and 8.3% (62 of 749 subjects) in the placebo group after the first dose and 19.7% (296 of 1,501 subjects) in the Comirnaty group and 8.1% (60 of 741 subjects) in the placebo group after the second dose. Prophylactic administration of antipyretic analgesic was not allowed in Study C4591007.

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

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

		Local reaction		Systemic reaction	
		Comirnaty n/N (%)	Placebo n/N (%)	Comirnaty n/N (%)	Placebo n/N (%)
Total		1,308/1,517 (86.2)	349/750 (46.5)	1,011/1,517 (66.6)	418/750 (55.7)
Sex	Male	674/799 (84.4)	165/383 (43.1)	533/799 (66.7)	206/383 (53.8)
	Female	634/718 (88.3)	184/367 (50.1)	478/718 (66.6)	212/367 (57.8)
Race	White	1,047/1,204 (87.0)	267/586 (45.6)	797/1,204 (66.2)	320/586 (54.6)
	Black, African-American	69/88 (78.4)	24/58 (41.4)	60/88 (68.2)	31/58 (53.4)
	Others[a)]	192/225 (85.3)	58/106 (54.7)	154/225 (68.4)	67/106 (63.2)
Ethnicity	Hispanic or Latino	271/318 (85.2)	79/159 (49.7)	212/318 (66.7)	89/159 (56.0)
	Non-Hispanic or non-Latino	1,034/1,196 (86.5)	270/591 (45.7)	797/1,196 (66.6)	591/329 (55.7)
	Not reported	3/3 (100)	0/0	2/3 (66.7)	0/0
Baseline SARS-CoV-2 infection status[a)]	Positive	112/133 (84.2)	22/65 (33.8)	81/133 (60.9)	28/65 (43.1)
	Negative	1,196/1,384 (86.4)	327/685 (47.7)	930/1,384 (67.2)	390/685 (56.9)
Obesity[c)]	Yes	151/173 (87.3)	42/92 (45.7)	118/173 (68.2)	57/92 (62.0)
	No	1,157/1,343 (86.2)	307/658 (46.7)	893/1,343 (66.5)	361/658 (54.9)
Risk factors for severe COVID-19[d)]	Yes	269/311 (86.5)	69/152 (45.4)	211/311 (67.8)	85/152 (55.9)
	No	1,039/1,206 (86.2)	280/598 (46.8)	800/1,206 (66.3)	333/598 (55.7)

N = number of subjects analyzed, n = number of subjects with events (%)

a) 109 Multiracials, 90 Asians, 12 American Indians or Alaska natives, 5 Native Hawaiians or other Pacific Islanders, and 9 with ethnicity not reported

b) Determined based on SARS-CoV-2 N-binding antibody test, nucleic acid amplification test, or history of COVID-19 at visit 1 ("positive" if the subject was positive for any of the tests or had a history of COVID-19; "negative" if the subject was negative for all tests and had no history of COVID-19).

c) ≥95 percentile BMI value in CDC growth chart (https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm [last accessed on December 10, 2021])

d) Underlying diseases (asthma, blood disorder, cardiovascular disease, chronic lung disease, chronic metabolic disease, congenital heart disease, diabetes mellitus, patients on tube feeding, immunodeficiency, neurological disorder, sickle cell disease, etc.) and obesity (see Note c) were defined as risk factors.

(b) Adverse events

In phase II/III part (sentinel group), the incidence of adverse events (except reactogenicity events within 7 days after each dose of the study vaccine) within 1 month after the last dose of the study vaccine was 10.9% (166 of 1,518 subjects) in the Comirnaty group and 9.2% (69 of 750 subjects) in the placebo group. There were no events with an incidence of ≥1%. The event with the highest incidence in the Comirnaty group was lymphadenopathy (0.9%; 13 of 1,518 subjects) [see Table 7 in Section 7.1.2.1].

In the additional group, the incidence of adverse events observed up to the data cutoff date (October 8, 2021) was 7.2% (115 of 1,591 subjects) in the Comirnaty group and 6.3% (50 of 788 subjects) in the placebo group (the median observation period after the second dose of the study vaccine was 2.4 weeks). The adverse event with an incidence of ≥1% in the Comirnaty group was injection site pain (1.1%; 18 of 1,591 subjects) [see Table 8 in Section 7.1.2.2]. The occurrences of adverse events in the additional group were generally similar to those in the sentinel group.

There was no report of anaphylaxis, myocarditis, pericarditis, or Bell's palsy in either group. There was neither report of severe COVID-19 nor evidence suggestive of vaccine-associated enhanced disease or (VAED) or vaccine-associated enhanced respiratory disease (VAERD).

(c) Serious adverse events

No serious adverse events were observed in phase I part (data cutoff date July 16, 2021).

In the Comirnaty group of phase II/III part, serious adverse events were observed in 1 subject (upper limb fracture) in the sentinel group (data cutoff September 6, 2021) and in 3 subjects (arthritis infective,

foreign body ingestion, and epiphyseal fracture in 1 each) in the additional group (data cutoff date October 8, 2021). The causal relationship to Comirnaty was denied for all of the events, and their outcome was "recovered" or "recovering."

No death occurred in either part.

As shown in (a) to (c) above, reactogenicity events (local and systemic reactions) were observed in many subjects receiving Comirnaty in Study C4591007, but most of them were mild or moderate in severity, resolving within a short time after the onset. Thus, the symptom profile was similar to that observed in those ≥12 years of age. For adverse events other than reactogenicity events, the incidence was low, and the most of them were mild or moderate in severity, with no serious adverse events for which a causal relationship to Comirnaty is possibly related. To date, Comirnaty has posed no serious safety concerns in children 5 through 11 years of age, confirming the tolerability.

In Study C4591007, none of the subjects received the study vaccine simultaneously with any other prophylactic vaccine.[16)] After the first dose of the study vaccine, a prophylactic vaccine against other infection was administered to 10 of 1,518 subjects in the Comirnaty group and 6 of 750 subjects in the placebo group.[17)] Within 1 month after the last dose of the study vaccine, adverse events were observed in none of the subjects in the Comirnaty group and in 2 subjects in the placebo group.

PMDA's view:
PMDA confirmed the following in Study C4591007:

- Reactogenicity events (local reactions and systemic reactions) were observed in many of the subjects, but the most cases were mild or moderate in severity and reversible.
- For adverse events other than reactogenicity events, the incidence was low, and most of them were mild or moderate in severity.

On the basis of the currently available information, PMDA concluded that there are no serious safety concerns with Comirnaty in children 5 through 11 years of age. However, because of the limited safety information available in children 5 through 11 years of age, the safety information on Comirnaty in children of this age group should be collected after the market launch, and appropriate measures should be taken based on the information obtained. In addition, the following information should be provided appropriately to healthcare professionals, vaccine recipients, and their caregivers:

- Local reactions and systemic reactions were observed in many subjects.
- Some events were observed with a higher incidence after the second dose than after the first dose of vaccination.
- The timing of occurrence and duration of events with a high incidence.

16) The clinical study protocol specified that the study vaccination should be postponed in subjects who received a nonlive vaccine, influenza vaccine, or rotavirus vaccine within 14 days and subjects who received other live vaccines (excluding live influenza and rotavirus vaccines) within 28 days.

17) The interval from the study vaccination to the administration of vaccine for other infections was 10 to 34 days in the Comirnaty group and 6 to 42 days in the placebo group. The breakdown of vaccines against other infections was diphtheria-pertussis (acellular)-tetanus vaccine (5 subjects in the Comirnaty group, 3 in the placebo group; hereinafter the same order shall apply), diphtheria-pertussis (5-component acellular)-tetanus vaccine (0, 1), diphtheria-tetanus vaccine (0, 1), human papillomavirus vaccine (3, 4), human papillomavirus-like particle-based tetravalent vaccine (1, 1), meningococcal vaccine (2, 0), tetravalent meningococcal vaccine (1, 2), tetravalent meningococcal vaccine (diphtheria toxoid conjugate) (1, 0), tick-borne encephalitis vaccine (1, 0), and inactivated tick-borne encephalitis vaccine (2, 0).

7.R.3.2 Safety in children with underlying diseases

The applicant's explanation about the safety in children with underlying diseases:

It is considered that some children with underlying disease or obesity have a high risk of severe COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html [last accessed on December 10, 2021]). In Study C4591007, children with stable underlying disease were eligible for enrollment. The following underlying diseases (asthma, blood disorder, cardiovascular disease, chronic lung disease, chronic metabolic disease, congenital heart disease, diabetes mellitus, patients on tube feeding, immunodeficiency, neurological disorder, sickle cell disease, etc.) and obesity[18)] were defined as the risk factors for severe COVID-19, and subjected to analysis. In the safety analysis set of the sentinel group in phase II/III part, 20.6% (312 of 1,518 subjects) in the Comirnaty group and 20.3% (152 of 750 subjects) in the placebo group had risk factors for severe COVID-19 at baseline. The main underlying diseases or conditions were obesity (11.5% [174 of 1,518 subjects] in the Comirnaty group, 12.3% [92 of 750 subjects] in the placebo group; hereinafter the same order shall apply), asthma (7.8% [119 of 1,518 subjects], 8.3% [62 of 750 subjects]), neurological disorder (1.3% [19 of 1,518 subjects], 0.4% [3 of 750 subjects]), and congenital heart disease (1.0% [15 of 1,518 subjects], 0.7% [5 of 750 subjects]). In the population with risk factors for severe COVID-19, the incidence of reactogenicity events within 7 days after administration of the study vaccine (either the first or second dose) was 86.5% (269 of 311 subjects) in the Comirnaty group and 45.4% (69 of 152 subjects) in the placebo group for local reactions and 67.8% (211 of 311 subjects) in the Comirnaty group and 55.9% (85 of 152 subjects) in the placebo group for systemic reactions. The incidence of adverse events and adverse reactions within 1 month after the last dose of study vaccination was 13.1% (41 of 312 subjects) and 4.8% (15 of 312 subjects), respectively, in the Comirnaty group and 11.8% (18 of 152 subjects) and 4.6% (7 of 152 subjects), respectively, in the placebo group. Adverse events with an incidence of ≥1% in the Comirnaty group were injection site pain (1.3% [4 of 312 subjects]), lymphadenopathy (1.0% [3 of 312 subjects]), and rash (1.0% [3 of 312 subjects]).

The above results were not significantly different from the safety results in the entire population of Study C4591007 [see Section 7.R.3.1], posing no safety concerns unique to the population with risk factors for severe COVID-19.

PMDA's view:

PMDA confirmed that the safety in subjects with risk factors for severe COVID-19 enrolled in phase II/III part of Study C4591007 was similar to that in the entire population. However, only a limited number of subjects were evaluated in the above study. In addition, children with underlying diseases were eligible for the study only if their conditions were stable. After the market launch, however, children with underlying diseases of various conditions also are expected to receive the vaccination. Therefore, information on the safety of Comirnaty should be collected from children with underlying diseases after the market launch, and appropriate measures should be taken based on the information thus obtained.

[18)] ≥95th percentile BMI value in CDC growth chart (https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm [last accessed on December 10, 2021])

7.R.3.3 Myocarditis or pericarditis

Concerns about the risk of myocarditis and pericarditis after administration of mRNA vaccine against SARS-CoV-2 have been raised from the post-marketing information, etc., of the approved product (for those ≥12 years of age).

The applicant's explanation about myocarditis and pericarditis in children:
Neither myocarditis nor pericarditis was observed in Study C4591007.

The safety database of the applicant includes a report of 1 case of myocarditis or pericarditis[19)] in children 5 through 11 years of age during the period from December 19, 2020 through October 28, 2021. According to the report, the patient developed myocarditis 4 days after the second administration of Comirnaty (vaccination dose unknown) and was hospitalized for 8 days, with unknown outcome (as of December 8, 2021). The case did not meet the criteria for definite diagnosis (level 1) in the classification based on the Brighton Collaboration case definition criteria (v.1.5.0).

Among 1,861 cases of myocarditis or pericarditis (myocarditis in 934, pericarditis in 927) (regardless of age) reported in the above database during the period from October 1, 2021 through October 28, 2021, 83 cases of myocarditis (9 cases in Japan) and 38 cases of pericarditis (3 in Japan) were reported in children 12 through 15 years of age (approved dose, 30 μg). The breakdown of reports by gender in children 12 through 15 years of age was 68 boys, 13 girls, and 2 with unknown sex for myocarditis and 25 boys and 13 girls for pericarditis. Myocarditis occurred in 18 subjects after the first dose, in 47 subjects after the second dose, and in 18 subjects after unknown dose number of vaccination, and pericarditis occurred in 11 subjects after the first dose, in 11 subjects after the second dose, and in 16 after unknown dose number of vaccination. Myocarditis occurred on the day of vaccination in 3 subjects, from 1 through 5 days after vaccination in 50 subjects, from 7 through 14 days after vaccination in 7 subjects, and from 19 through 48 days after vaccination in 5 subjects. Pericarditis occurred on the day of vaccination in 3 subjects, from 1 through 3 days after vaccination in 8 subjects, from 6 through 15 days after vaccination in 5 subjects, from 17 through 24 days after vaccination in 5 subjects, and the day of the onset unknown in 17 subjects. The outcome for myocarditis was "recovered" or "recovering" in 39 subjects, "not recovered" in 20 subjects, and "unknown" in 24 subjects. The outcome for pericarditis was "recovered" or "recovering" in 15 subjects, "not recovered" in 13 subjects, and "unknown" in 10 subjects. No fatal outcome was reported either for myocarditis or for pericarditis. The median time (range) to recovery was 5 (1-10) days in 8 subjects with myocarditis from whom information was available, and 25 days in 1 subject with pericarditis from whom information was available. Among these reports, clinically determined cases (10 cases of myocarditis, 12 cases of pericarditis) were subjected to classification using the Brighton Collaboration case definition criteria (v.1.5.0). Results showed that myocarditis was level 1 (definite diagnosis) in 1 subject (overseas report, boy, outcome was "recovering") and level 4 in 9 subjects; and pericarditis was level 2 in 2 subjects and level 4 in 10 subjects. There were no cases of level 1 pericarditis (definite diagnosis). It was difficult to evaluate the causal relationship between administration of Comirnaty and myocarditis or pericarditis because of (a) the limited number of subjects with definite diagnosis of myocarditis or pericarditis and (b) the

[19)] Preferred terms of MedDRA: Myocarditis, eosinophilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, autoimmune myocarditis, immune myocarditis, pericarditis, autoimmune pericarditis, pericarditis adhesive, pericarditis constrictive, pleuropericarditis

insufficient information available for evaluating the causal relationship (information for excluding viral infection and other factors, disease history, etc.). However, (a) the timing of the onset after Comirnaty administration and (b) the larger number of reports after the second dose than after the first dose were consistent with post-vaccination myocarditis so far reported.

The results of survey based on the pharmacovigilance database in Israel showed that the incidence of myocarditis after the vaccination (per 100,000 doses) in the age group of 12 through 29 years was 0.63 after the first dose and 8.20 after the second dose in male subjects 12 through 15 years of age; and 1.21 after the first dose and 16.47 after the second dose in male subjects 16 through 19 years of age, being the highest. Thus, the incidence showed no tendency to increase in the younger age group (Vaccines and Related Biological Products Advisory Committee October 26, 2021 Meeting Document [https://www.fda.gov/media/153409/download (last accessed on December 10, 2021)]).

Comirnaty was granted the initial marketing approval or the emergency use authorization for children 5 through 11 years of age on October 29, 2021. To date, no sufficient information is available for evaluating the risk of myocarditis or pericarditis in children 5 through 11 years of age. However, by considering the following observations, the benefits of Comirnaty administration are great, suggesting the favorable benefit-risk profile of Comirnaty:

- The incidence of myocarditis or pericarditis after administration of mRNA vaccine is low in subjects of other age groups (*Circulation*. 2021;144:471-84, etc.).
- Myocarditis or pericarditis, even if it occurs, is asymptomatic or mild in most of cases (ibid.).
- Risks of myocarditis associated with COVID-19, MIS-C/PIMS, and sequelae of COVID-19, etc.

The information material for vaccine recipients and caregivers will include the following:

- Specific information on symptoms suggesting the possibility of myocarditis or pericarditis
- That the caregiver is requested to monitor the physical conditions of the child for several days from immediately after the vaccination, and
- In case the child complains of symptoms or any change is noted in the child's physical conditions, the caregiver should promptly notify the physician.

PMDA's view:

According to the information from foreign countries, myocarditis or pericarditis is reported more frequently after the second dose than after the first dose, primarily in young males after the second dose of mRNA vaccine, including Comirnaty (*N Engl J Med*. 2021;385:2140-9, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf [last accessed on December 10, 2021]).

In Japan, a joint meeting of the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 72nd meeting), and the 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (the 22nd meeting) (hereinafter referred to as "the meeting on November 12, 2021")[20] observed that, of the 210 cases of suspected myocarditis-related events reported

[20] https://www.mhlw.go.jp/stf/shingi2/0000208910_00034.html, document 2-6-1 (last accessed on December 10, 2021)

by the marketing authorization holder in Japan (reporting period February 17, 2021 through October 24, 2021), many were events occurring after the second dose, particularly in males in their 10s or 20s. During the above reporting period, there were 13 deaths among patients with suspected myocarditis-related events after Comirnaty vaccination. Although none of them is concluded to be causally related to mRNA vaccine at the current moment, they are considered to reflect situations requiring cautions for possible causal relationship between mRNA vaccination and death caused by myocarditis-related events. On the other hand, since the incidence of post-vaccination myocarditis is lower than that of COVID-19-associated myocarditis-related events, it is considered acceptable to continue administration of SARS-CoV-2 vaccine in males of 10s and 20s as well.

To date, only limited information is available on children 5 through 11 year of age who have received Comirnaty. As described above, post-vaccination myocarditis or pericarditis in young individuals occurs less frequently than COVID-19-associated myocarditis-related events and, even if it occurs, remains asymptomatic or mild in most cases (*Circulation*. 2021;144:471-84, etc.). In addition, analysis of the occurrences by age group provides no information that suggests unacceptable risk in children 5 through 11 years of age. Although COVID-19 in children is considered relatively mild, there are possibility that severe COVID-19 may develop. Given the risk of complications of COVID-19 (myocarditis, MIS-C/PIMS, etc.), Comirnaty should be available for children 5 through 11 of age as well.

Children of this age group may not be able to notice myocarditis or pericarditis and complain of the symptoms (chest pain and shortness of breath). The applicant should include specific symptoms in the information material and provide caution to consult the physician if the child complains of symptoms or any change is noted in the child's physical conditions.

The applicant should continue to collect information on myocarditis or pericarditis in children in and out of Japan and take appropriate measures based on the information thus obtained.

7.R.3.4 Post-marketing safety information

The applicant's explanation about post-marketing safety information on Comirnaty in children:
The safety database of the applicant collected during the period from December 19, 2020 through September 30, 2021 contains 309 reports[21)] in 140 children 5 through 11 years of age. The reports were on events without clinical results[22)] in 92 children and on 124 clinical events in the remaining 48 children. Events reported ≥3 times were pyrexia (12 events), pain in extremity (11), headache (9), vaccination site pain (6), fatigue (5), pain (4), diarrhoea, nausea, oropharyngeal pain, peripheral swelling and pruritus (3 each). A total of 20 serious events were reported in 8 children. They were headache (3 events), pyrexia and peripheral swelling (2 each), cardiac flutter, myocarditis, aphthous ulcer, diarrhoea, stomatitis, vomiting, swelling, herpes virus infection, mastitis, pain in extremity, seizure, product administered to patient of inappropriate age, and pruritus (1 each). The outcome was "recovered" or "recovering" with 8 events (pyrexia and headache [2 events each], swelling, seizure, vomiting, and diarrhoea [1 each]) and

21) Reports before marketing approval or use authorization of Comirnaty in children 5 through 11 years of age. The vaccination dose was 0.1 mL (1 child), 0.15 mL (2), or 0.3 mL (10) in 13 children with known vaccination dose.
22) Accidental exposure to product by child, accidental underdose, circumstance or information capable of leading to medication error, inappropriate schedule of product administration, incorrect dose administered, incorrect route of product administration, off label use, product administered to patient of inappropriate age, product use issue, therapeutic response unexpected, underdose, vaccination error, wrong patient received product.

"not recovered" with 6 events (cardiac flutter, peripheral swelling, aphthous ulcer, stomatitis, mastitis, and pruritus [1 each]). The outcome was unknown with other events. During the period from October 1, 2021 through October 28, 2021, 132 events were reported in 62 children <12 years of age. Events reported ≥3 times were product administered to patient of inappropriate age (44 events), off label use (13), product use issue (10), pyrexia (5), wrong product administered (5), headache (4), and pain in extremity (3). The outcome was "recovered" or "recovering" in 10 children, "not recovered" in 3, and "unknown" in others.

For children 5 through 11 years of age, Comirnaty was granted the initial marketing approval or the emergency use authorization on October 29, 2021. Since the information available to date in this age group is still limited, reports in children 12 through 15 years of age (approved dose 30 μg) were also reviewed for evaluating the safety profile in children. During the period from October 1, 2021 through October 28, 2021, there were reports of 5,069 events in 1,502 children 12 through 15 years of age. Events reported ≥100 times were headache (317 events), pyrexia (292), fatigue (170), nausea (169), syncope (138), malaise (137), chest pain (122), dizziness (121), and vomiting (107) [see Section 7.R.3.3 Myocarditis or pericarditis].

In summary, no new safety concerns unique to children have been detected within the limited safety information available in children 5 through 11 years of age after the market launch; the same holds among children 12 through 15 years of age.

PMDA's view:
At the current moment, only limited information is available on the safety of Comirnaty in children 5 through 11 years of age, and the post-marketing safety information contains no data suggestive of safety concerns unique to children. The applicant should continue to collect information in and out of Japan and take appropriate measures based on the information thus obtained.

7.R.4 Clinical positioning

PMDA's view on the clinical positioning of Comirnaty:
From September 2021, the number of people who became newly infected with SARS-CoV-2 started to decrease in Japan, and remains at a low level as of December 10. However, during the period from July through August of 2021 when highly infective and transmissive Delta variant became prevalent, there was an upsurge in the number of those newly infected with SARS-CoV-2, with approximately 20% of them being children in their 10s or below. (Current Situation of SARS-CoV-2 Infection in Japan [in Japanese] [as of December 7, 2021], https://www.mhlw.go.jp/content/10906000/000864405.pdf [last accessed on December 10, 2021]). A new type of variant may arise at any time in future, possibly spreading and causing severe COVID-19 in children.

Although it is said that COVID-19 in children is mild and rarely severe, children with underlying diseases or obesity are considered to have a high risk of severe COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html [last accessed on December 10, 2021]) and, in the US and Europe, severe or fatal cases

are reported in a certain percentage of children with COVID-19 (*Lancet Child Adolesc Health*. 2020;4:653-61).

Apart from severe COVID-19, many cases of MIS-C/PIMS have been reported in foreign countries that occurs 2 to 6 weeks after SARS-CoV-2 infection and is accompanied by pyrexia and multiple organ failure (*Eur J Pediatr*. 2020;180:2019-34, *JAMA Pediatr*. 2021;175:837-45, etc.). Similar cases are reported in Japan. MIS-C/PIM develops with or without COVID-19 symptoms, and rapidly worsens even if the symptoms do not meet the diagnostic criteria at the disease onset, requiring treatment in intensive care unit or emergency care facilities. Outside Japan, fatal cases have been reported, albeit at a low frequency (Consensus Statement on the diagnosis and treatment of multisystem inflammatory syndrome in children (MIS-C)/pediatric inflammatory multisystem syndrome (PIMS) [in Japanese] (http://www.jpeds.or.jp/uploads/files/20210916_mis-c_c_s.pdf [last accessed on December 10, 2021]).

As of December 10, 2021, there is no SARS-CoV-2 vaccine available for administration to children ≤11 years of age in Japan. As of December 8, 2021, Comirnaty is granted marketing approval or use authorization in children 5 through 11 years of age in 15 countries or regions including the US and EU. The Centers for Disease Control and Prevention (CDC) in the US recommends vaccination in all children ≥5 years of age because preventing COVID-19 of children by vaccination helps (a) to avoid risks of COVID-19-caused hospitalization, death, MIS-C/PIMS, sequelae in children and (b) to prevent children becoming the source of the spread of infection at home and school (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/children-teens.html [last accessed on December 10, 2021]).

On the basis of the Study C4591007 data submitted in this application, PMDA concluded that Comirnaty is effective to a certain extent in children 5 through 11 years of age [see Section 7.R.2], with no serious safety concerns detected to date [see Section 7.R.3]. Although the number of children newly infected with SARS-CoV-2 remains at a low level as of December 10, 2021 (https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html [last accessed on December 10, 2021]), PMDA considers that there is a certain significance to make Comirnaty available for vaccination in children, taking account of the following: (a) Children with underlying disease have a high risk of severe COVID-19, (b) there are reports of severe complications such as MIS-C/PIMS in pediatric patients with COVID-19, and (c) there is a possibility of resurgence at any time in future. On the other hand, given the current epidemic status in Japan, it is unnecessary to prompt SARS-CoV-2 vaccination in all children because symptoms are mostly mild when healthy children are infected with COVID-19. The expected benefit vs. risk balance of SARS-CoV-2 vaccination differs depending on the status of the spread of infection, presence or absence of underlying diseases in vaccine recipients, and other factors. Sufficient information should be provided to help healthcare professionals, vaccine recipients, and their caregivers decide the necessity of vaccination after understanding the benefits and risks such as adverse reactions expected in children.

7.R.5 Dosage and administration

Comirnaty Intramuscular Injection for 5 to 11 years old was developed as a vaccine product for children 5 through 11 years of age, and the proposed dosage and administration is 2 doses of 0.2 mL administered intramuscularly 21 days apart.

The applicant's explanation about the defining of dose and eligible age range:
In phase I part of Study C4591007 conducted as a dose-finding study [see Section 7.1.1], safety, tolerability, and immunogenicity were investigated following 2 doses of Comirnaty 10 μg, 20 μg, or 30 μg administered intramuscularly 21 days apart to children 5 through 11 years of age. The number of doses and the interval between the doses were the same as those in the approved dosage regimen in people ≥12 years of age. Results confirmed the tolerability in Comirnaty 10 μg group, whereas the incidence and severity of reactogenicity events tended to increase in higher dose groups, and neutralizing antibody titer following Comirnaty administration was similar between Comirnaty 10 μg group and 20 μg group. On the basis of the results, the dosage regimen for Comirnaty in children 5 through 11 years of age in phase II/III part was defined as 2 doses of 10 μg administered 21 days apart (allowable period: Days 19 to 23). The immunogenicity results in phase II/III part suggested the efficacy in children 5 through 11 years of age [see Section 7.R.2], and safety and tolerability were considered to be acceptable [see Section 7.R.3]. Therefore, the dosage regimen of Comirnaty in children 5 through 11 years of age was determined to be 2 doses of 10 μg administered 21 days apart.

A clinical study on children <5 years of age is currently ongoing, with the vaccine product for this age range undergoing development.

PMDA's view:
On the basis of the above explanation of the applicant and on the reviews in Sections 7.R.2 and 7.R.3, PMDA concluded that it is acceptable to determine the individuals eligible to receive vaccination to be children 5 through 11 years of age and the dosage regimen as proposed by the applicant.

7.R.6 Post-marketing investigations

7.R.6.1 Post-marketing surveillance

The applicant's explanation about the post-marketing surveillance on Comirnaty:
No serious safety concerns of Comirnaty has been observed in children 5 through 11 years of age in Study C4591007 [see Section 7.R.3]. However, the applicant plans to conduct a specified use-results survey (survey period from the first dose up to 28 days after the second dose) to promptly collect and publish safety information of Comirnaty in children 5 through 11 years of age in routine clinical practice as no safety information on Comirnaty is available in Japanese children of this age range.

PMDA's view:
In the post-marketing surveillance, etc., safety information of Comirnaty in routine clinical practice should be promptly collected from children 5 through 11 years of age, including those with underlying diseases, and provided to healthcare professionals without delay.

7.R.6.2 Measures to avoid potential vaccination error due to mix-up of Comirnaty Intramuscular Injection, the approved vaccine product, and Comirnaty Intramuscular Injection for 5 to 11 years old

Comirnaty Intramuscular Injection for 5 to 11 years old used in children 5 through 11 years of age is different from the approved product of Comirnaty Intramuscular Injection for those ≥12 years of age in the diluting method, vaccination dose, and the maximum storage period after dilution.

The applicant's explanation about the method to avoid vaccination error due to mix-up:
To avoid potential vaccination error due to mix-up of Comirnaty Intramuscular Injection for 5 to 11 years old and the approved product of Comirnaty Intramuscular Injection, the applicant plans to use vial caps and labels of different color for easy identification, and also to prepare and supply identification sticker that can be affixed to syringes containing the extracted drug solution. In addition, in order to facilitate the appropriate use of Comirnaty in preparation procedure, vaccination dose, etc., the applicant plans to provide information to healthcare professionals appropriately by the following methods:

- To prepare materials for providing information on the difference of each product in their appearance, filled volume, preparation procedure (from thawing to vaccination), dosage and administration, etc.
- To hold explanatory sessions for healthcare professionals

PMDA's view:
Errors have been reported in the preparation, storage, and control of the approved product. "Notification regarding proper use" has been issued multiple times (Information on errors in the use of COVID-19 vaccines, No. 1 and No. 2 [dated August 3, 2021, Administrative Notice of the Office of Vaccination, Health Service Division, Health Service Bureau]), "Comirnaty Intramuscular Injection: Request for Proper Use" (May 2021, Pfizer Japan Inc.).[23)] It is necessary and important that the vaccination error-avoiding measures to be taken in the introduction of Comirnaty Intramuscular Injection for 5 to 11 years old should be widely known to all medical institutions to which Comirnaty (either the vaccine product of this application or the approved vaccine product) is supplied and should be understood by the healthcare professionals. Also, after the conduct of the activities as planned, the applicant should promptly collect and evaluate information on the proper use of Comirnaty Intramuscular Injection for 5 to 11 years old and take further safety measures, as necessary.

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).

23) https://www.pmda.go.jp/files/000240928.pdf (last accessed on December 10, 2021)

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 5 to 11 years old has a certain level of efficacy in preventing disease caused by SARS-CoV-2 infection (COVID-19) in children 5 through 11 years of age with acceptable tolerability and without serious safety concerns. Comirnaty Intramuscular Injection for 5 to 11 years old is the first COVID-19 preventive vaccine for children 5 through 11 years of age applied for marketing approval in Japan. Making Comirnaty Intramuscular Injection for 5 to 11 years old available for vaccination has a clinical significance in view of its expected benefits.

PMDA has concluded that Comirnaty Intramuscular Injection for 5 to 11 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)

January 11, 2022

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	November 10, 2021

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

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.2 Efficacy" of Report (1).

The applicant's explanation about the efficacy against Omicron variant:
Although data in children 5 through 11 years of age have not been available to date, the preventive effect of 2 doses of Comirnaty against severe COVID-19 is expected according to the preliminary results of the study in those 18 through 85 years (https://www.businesswire.com/news/home/20211208005542/en/Pfizer-and-BioNTech-Provide-Update-on-Omicron-Variant (last accessed on January 11, 2022).

PMDA instructed the applicant to continue to collect information on variants including Omicron and to consider appropriate measures based on the information thus obtained. The applicant agreed to take appropriate actions.

1.2 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.3 Safety" of Report (1).

PMDA asked the applicant to explain again the risk of myocarditis or pericarditis in children 5 through 11 years of age based on the most updated post-marketing information or after emergency use authorization in foreign countries.

The applicant's explanation:
In the safety database possessed by the applicant, there are 12 suspected cases of myocarditis or pericarditis[24] among children 5 through 11 years of age during the period from the marketing approval or emergency use authorization through December 5, 2021. They were 9 boys and 3 girls, and 7 of them developed myocarditis or pericarditis after the second dose. No sufficient information is available on laboratory test results, clinical course, etc., in any of them, and all 7 cases were assessed as level 4 according to the Brighton Collaboration case definition criteria (v.1.5.0). It remains difficult to draw conclusions on the risk of myocarditis or pericarditis in children 5 through 11 years of age based on these reports.

PMDA's view:
At the current moment, there is no information requiring additional measures other than those advised by PMDA in Report (1). As described in the Report (1), PMDA instructed the applicant to continue to collect information on the occurrences and risk of myocarditis or pericarditis in and out of Japan, analyze the information, and consider the necessity of providing additional cautions and information. The applicant agreed to take appropriate actions.

1.3 Clinical positioning

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.4 Clinical positioning" of Report (1).

1.4 Dosage and administration

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

1.5 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.6 Post-marketing investigations" of Report (1).

PMDA has concluded that the risk management plan (draft) for Comirnaty should include the safety specifications presented in Table 13, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 14.

[24] Preferred terms of MedDRA: Myocarditis, eosinophilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, autoimmune myocarditis, immune-mediated myocarditis, pericarditis, autoimmune pericarditis, pericarditis adhesive, pericarditis constrictive, pleuropericarditis

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)	• Safety in pregnant and lactating women
Efficacy specification		
Not applicable		

Table 14. Summary of additional pharmacovigilance activities and 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 through 11 years of age) • Post-marketing clinical study (Study C4591005) • Use-results survey on post-approval early vaccine recipients (healthcare professionals) (follow-up study) (C4591006) • Specified use-results survey on vaccine recipients with underlying diseases who are at high risk of severe COVID-19 (C4591019) • Specified use-results survey on child vaccine recipients 5 through 11 years of age (C4591032)[a)] • Foreign phase II/III study (C4591001) • Foreign phase II/III study in pregnant women (C4591015)	• Disseminate data gathered during early post-marketing phase vigilance (child vaccine recipients 5 through 11 years of age) • 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 through 11 years of age)

The underlined parts are changes made according to the present application

a) To be determined based on the presence or absence of the government-led surveillance and its survey items

After the approval of Comirnaty Intramuscular Injection, "Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan" (Health, Labor and Welfare Policy Research Grants, Research on Emerging and Re-emerging Infectious Diseases and Immunization, 2020) and other government-led surveillance were conducted. Accordingly, PMDA instructed that, if another government-led surveillance is initiated for Comirnaty in children 5 through 11 years of age in a similar manner, the applicant should plan a specified use-results survey on child vaccine recipients 5 through 11 years of age (C4591032), with consideration given to said surveillance plan. The applicant agreed to take appropriate actions.

1.6 Quality

1.6.1 Shelf-life of the vaccine product

As of January 11, 2022, the long-term testing is still ongoing, and the test results up to 9 months, the shelf-life for Comirnaty Intramuscular Injection for 5 to 11 years old proposed by the applicant, are yet to be submitted.

The applicant explained that it is acceptable to set the shelf-life of Comirnaty Intramuscular Injection for 5 to 11 years old to be 9 months as is the case with the approved vaccine product, for the following reasons:

- The difference in the fill volume does not affect the stability, based on the results, at Month 6, of the long-term testing on vaccine products of the same composition but different fill volumes between the approved vaccine product (fill volume 2.25 mL in 2 batches and 0.48 mL in 1 batch) and the proposed vaccine product (fill volume 1.3 mL).
- The comparability between the approved vaccine product and the proposed vaccine product has been confirmed.

PMDA's view:

Although results of the long-term test of Comirnaty Intramuscular Injection for 5 to 11 years old (fill volume 1.3 mL) are yet to be submitted, PMDA confirmed that vaccine products with the same composition but different fill volume met the specifications for the long-term test at Month 6 and showed no significant change over time. Comirnaty is manufactured as a vaccine product common to countries around the world, and its shelf-life is defined as 9 months in countries outside Japan. Defining a different shelf life of the vaccine product from that in other countries may have an adverse impact on manufacturing and distribution control, and may affect the batches and quantity supplied to Japan. Given the social need for Comirnaty in Japan, there is no choice but to define the shelf life of the vaccine product as 9 months. Results of the long-term storage test on the proposed vaccine product should be submitted to PMDA as soon as they become available in order to confirm its stability throughout the shelf-life.

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 the above review, PMDA has concluded that the product may be approved for the following indication and dosage and administration as proposed, with approval conditions shown below. Although this is an application for a drug with a new dosage, the re-examination period for the present application is the remainder of the re-examination period for the initial approval (until February 13, 2029) because it has more than 4 years left. The product is not classified as a biological product or a specified biological product. The vaccine 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 1.3 mL of physiological saline (Japanese Pharmacopoeia grade).
Two doses (0.2 mL each) are injected intramuscularly, usually 3 weeks apart.

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 2 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 patients (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 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.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 9 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
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of 1961)
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
Comirnaty	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
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
Ministerial Ordinance for Enforcement for Pharmaceuticals and Medical Devices Act	Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance of the Ministry of Health and Welfare No. 1 of 1961)
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 August 10, 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
Reference strain	Strain USA-WA1/2020
Report (1)/(2)	Report on Special Approval for Emergency (1)/(2)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Tozinameran	Tozinameran
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine Efficacy
WHO	World Health Organization