Review Report

February 6, 2025
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	Daichirona for Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 24, 2024
Dosage Form/Strength	Injection: Each vial contains 0.15 mg of mRNA encoding the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2.
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	None
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 aged 5 to 11 years, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

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

(No change)

Dosage and Administration

Individuals aged ≥12 years
A single dose of 0.6 mL is injected intramuscularly.
Children aged ≥5 and ≤11 years
A single dose of 0.2 mL is injected intramuscularly.

(Underline denotes additions.)

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

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

December 11, 2024

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	Daichirona for Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 24, 2024
Dosage Form/Strength	Injection: Each vial contains 0.15 mg of mRNA encoding the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2.

Proposed Indication

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

The indication applies to the following vaccine products:

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

(No change)

Proposed Dosage and Administration

Individuals aged ≥12 years

A single dose of 0.6 mL is injected intramuscularly as a booster dose.

Children aged ≥5 and ≤11 years

A single dose of 0.2 mL is injected intramuscularly as a booster dose.

The indication applies to the following vaccine products:

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

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

The global pandemic caused by the coronavirus disease (COVID-19) emerged in January 2020, and various preventive measures including vaccination have been taken since then. However, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants with altered infectivity, transmissibility, and antigenicity have emerged one after another, resulting multiple waves of spread of SARS-CoV-2 infection. On May 5, 2023, the World Health Organization (WHO) declared an end to COVID-19 as a Public Health Emergency of International Concern (PHEIC),[1)] but they still continue to recommend SARS-CoV-2 vaccination, collection and reporting of various data including epidemiologic information, and development of new vaccines and therapies.[2)]

In Japan, under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act), the category of COVID-19 was reclassified from "pandemic influenza (novel influenza or re-emerging influenza" (equivalent to Category 2 infectious diseases) to "Category 5 infectious diseases" on May 8, 2023, and the special temporary vaccination program under the Immunization Act was ended on March 31, 2024. However, SARS-CoV-2 variants with altered infectivity/transmissibility have been emerging so far, causing the intermittent resurgence of COVID-19 cases.

Although COVID-19 in children is relatively mild and rarely progresses to severe illness (https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Children_and_adolescents-2021.1 [last accessed on December 3, 2024]), a certain number of pediatric patients have required hospitalization for treatment (*J Pediatric Infect Dis Soc*. 2021;10:1097-100). In Japan, acute encephalitis or myocarditis have been reported in a certain number of pediatric patients infected with SARS-CoV-2 (*Front Neurosci*. 2023;27;17:1085082, etc.).

Daichirona for Intramuscular Injection (hereinafter referred to as Daichirona) is a vaccine containing messenger ribonucleic acid (mRNA) encoding receptor-binding domain (RBD) of the spike protein (S protein) of SARS-CoV-2 as the active substance. On August 2, 2023, Daichirona was approved for marketing as a monovalent vaccine against the Wuhan-Hu-1 strain (the original strain) in individuals aged ≥18 years (Daichirona [monovalent, Original]) for the indication of "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" in Japan. The Ministry of Health, Labour and Welfare (MHLW) presented their policy which stated that Omicron XBB.1.5-adapted monovalent SARS-CoV-2 vaccines should be basically used in the vaccination program in autumn and winter 2023 in Japan.[3)] In response to this policy, the applicant developed a monovalent vaccine adapted to the Omicron XBB.1.5 lineage (Daichirona [monovalent, Omicron XBB.1.5]) by modifying Daichirona (monovalent, Original). The applicant then submitted an application for partial change approval (partial change application) to change the target population to individuals aged ≥12 years and the antigen strain. Daichirona (monovalent, Omicron XBB.1.5) was then approved on November 28, 2023.

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1) https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic (last accessed on December 3, 2024)
2) https://cdn.who.int/media/docs/default-source/documents/ihr/covid-19_standing-recommendations_9-august-2023.pdf (last accessed on December 3, 2024)
3) Materials for the 49th meeting of the Subcommittee on Immunization and Vaccines of the Health Sciences Council: https://www.mhlw.go.jp/stf/newpage_34645.html (last accessed on December 3, 2024)

The present partial change application has been submitted to add the dosage regimen for children aged 5 to 11 years, based on data from a Japanese phase II/III study (Study DS5670-214 [Study 214]) of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years.

The MHLW's policy on the antigen composition of future COVID-19 vaccines was presented after submission of the present partial change application. The relevant subcommittee recommended that monovalent SARS-CoV-2 vaccines adapted to the Omicron JN.1 lineage and its sublineages should be basically used in the vaccination program in autumn and winter 2024 in Japan.[4)] To accommodate this policy, the applicant also developed a Daichirona monovalent vaccine adapted to the Omicron JN.1 lineage (Daichirona [monovalent, Omicron JN.1]) and submitted a partial change application to change the target strain, which was then approved on September 2, 2024. When the partial change application and minor change notification were submitted for the aforementioned change of the target strain,[5)] descriptions of the indication and dosage and administration for a booster dose in individuals aged ≥12 years were modified according to the "Modification of Dosage and Administration of COVID-19 Vaccines (in Japanese)" (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1 dated March 6, 2024).

Daichirona (monovalent, Omicron XBB.1.5) was developed as an mRNA vaccine to be manufactured in Japan, with support from the "Vaccine development project" of the Japan Agency for Medical Research and Development (AMED) and the "Urgent improvement project for vaccine manufacturing systems" of the MHLW.

As of November 2024, Daichirona is not approved in any country or region except Japan.

In this review report, vaccines adapted to specific SARS-CoV-2 strains are referred to as follows:

- Daichirona (monovalent, Original): Vaccine containing ufrenmeran (mRNA encoding RBD of the S protein of the original strain) as the active substance
- Daichirona (bivalent, Original and Omicron BA.4-5): Vaccine containing ufrenmeran and tegrenmeran (mRNA encoding RBD analog of the S protein of the Omicron BA.4-5 lineages) as the active substances
- Daichirona (monovalent, Omicron XBB.1.5): Vaccine containing bemremeran (mRNA encoding RBD analog of the S protein of the Omicron XBB.1.5 lineage) as the active substance
- Daichirona (monovalent, Omicron JN.1): Vaccine containing MAFB-6197a (mRNA encoding RBD analog of the S protein of the Omicron JN.1 lineage) as the active substance

2. Quality and Outline of the Review Conducted by PMDA

Since the present application has been filed for a new dosage, no data relating to quality have been submitted.

4) Materials for the discussion group for strains to be used in manufacture of seasonal influenza and COVID-19 vaccines, the second subcommittee meeting on the R&D and production and distribution working group of the Subcommittee on Immunization and Vaccine of the Health Sciences Council (in Japanese): https://www.mhlw.go.jp/stf/shingi2/newpage_00104.html (last accessed on December 3, 2024)

5) Dated on [redacted], 20[redacted]

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

Since the present application has been filed for a new dosage and the data relating to non-clinical pharmacology had been evaluated during the review process for the initial approval, no new data have been submitted.

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

Although the present application has been filed for a new dosage, no new data have been submitted because the data relating to non-clinical pharmacokinetics had been evaluated during the review process for the initial approval of Daichirona.

5. Toxicology and Outline of the Review Conducted by PMDA

Since the present application has been filed for a new dosage, no data relating to toxicology have been submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Blood anti-SARS-CoV-2 neutralizing antibody titers were determined by a cytopathic effect assay (lower limit of quantitation [LLOQ] = 10).

6.2 Clinical pharmacology

No data relating to clinical pharmacology have been submitted for the present application.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 1 study shown in Table 1.

Table 1. Clinical study for efficacy and safety evaluation

Region	Phase	Study ID	Study population	No. of subjects enrolled	Dosage regimen	Endpoint
Japan	II/III	Study 214	Children aged 5 to 11 years who completed the primary series of Comirnaty Intramuscular Injection for 5 to 11 years old[a)] (monovalent, Original)	Part 1: Daichirona (bivalent, Original and Omicron BA.4-5) 10 µg group: 4 Daichirona (bivalent, Original and Omicron BA.4-5) 20 µg group: 3 Part 2: Daichirona (bivalent, Original and Omicron BA.4-5) group: 76 Comirnaty (bivalent, Original and Omicron BA.4-5) group: 79	Part 1: A single intramuscular injection of Daichirona (bivalent, Original and Omicron BA.4-5) 10 µg or 20 µg Part 2: A single intramuscular injection of Daichirona (bivalent, Original and Omicron BA.4-5) 20 µg or Comirnaty Intramuscular Injection for 5 to 11 years old[a)] (bivalent, Original and Omicron BA.4-5)	Safety Immunogenicity

a) Each vaccine dose contained 10 µg of the active substance (mRNA encoding the S protein of SARS-CoV-2)

7.1 Japanese phase II/III study (CTD 5.3.5.1-1, Study DS5670-214, ongoing since May 2023 [data cut-off on December 2, 2023])

A multi-center, open-label, dose-escalation study (Part 1) and a multi-center, randomized, observer-blinded,[6)] active-controlled study (Part 2) were conducted at 42 study centers in Japan to evaluate the immunogenicity and safety of a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years who had received the primary series of Comirnaty Intramuscular Injection for 5 to 11 years old (monovalent, Original) and who had completed their second dose at least 3 months ago. Target sample size was 6 subjects (3 per group) in Part 1 and 204 subjects (102 per group) in Part 2.[7)]

Part 1:

The subjects received a single intramuscular administration of Daichirona (bivalent, Original and Omicron BA.4-5) 10 µg or 20 µg.

All of 7 enrolled subjects (4 in the Daichirona [bivalent, Original and Omicron BA.4-5] 10 µg group, 3 in the Daichirona [bivalent, Original and Omicron BA.4-5] 20 µg group) received study vaccine and were included in the safety analysis population. Based on the safety evaluation up to 72 hours after study vaccination in the Daichirona (bivalent, Original and Omicron BA.4-5) 10 µg group, vaccination was started in the Daichirona (bivalent, Original and Omicron BA.4-5) 20 µg group. Based on the safety evaluation up to 72 hours after study vaccination in the Daichirona (bivalent, Original and Omicron BA.4-5) 20 µg group, a decision was made on whether initiation of Part 2 was acceptable.[8)]

For immunogenicity, Table 2 shows data on blood anti-SARS-CoV-2 (Omicron BA.5.2.1 lineage) neutralizing antibody titer at Week 4 (Day 29) in the safety analysis population. In both groups, the neutralizing antibody titer increased.

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6) The following people were not blinded: Independent statisticians, study vaccine storage manager (or study vaccine storage assistant designated by the study vaccine storage manager), staff who prepared the study vaccine, staff who administered the study vaccine, unblinded sub-investigators (where necessary), unblinded study collaborators (where necessary), and unblinded sponsor staff.
The following people were blinded: Subjects, legally acceptable representatives, investigators, sub-investigators, study collaborators, nurses, monitors, sponsor, and staff who performed antibody titer assay.

7) Based on the results from a clinical study reviewed for the initial approval (Study 146), the following hypothesis was applied: the ratio of the geometric mean titer (GMT) with Daichirona to that with Comirnaty 4 weeks after study vaccination was 1.10; the standard deviations of common logarithms of neutralizing antibody titers in the 2 groups were both 0.490; and the antibody response rate was 97.5% in both groups. The power to demonstrate the non-inferiority of Daichirona to Comirnaty in the assumed sample size (on the assumption that the target sample size of 204 would be randomized in a 1:1 ratio and 10% of the subjects would not contribute to the immunogenicity evaluation) at a one-sided significance level of 0.025 was 83.4% for the GMT, 90.4% for the antibody response rate, and 75.4% for both measures.

8) The investigator collected safety data from subjects who had received study vaccine in each group at least up to 72 hours after study vaccination, and submitted the data with an opinion on whether the start of the next part was acceptable to the sponsor. The sponsor then submitted them to the advisory board (composed of advisors about development of Daichirona who gave guidance and advice on judgments for start of the next group or the next part and for continuation of the study from a medical viewpoint and provide medical advice upon request from the sponsor). The advisory board evaluated and investigated the safety data (severity, seriousness, outcome, etc.) in detail and decided whether to start the next group or the next part and informed the sponsor of their decision. The sponsor then informed the investigator of the decision on continuation or termination of the study or on discontinuation or interruption of study vaccination. The protocol specified that start of the next part should be held in the case where a serious adverse reaction occurred in at least 1 subject or more than 1 severe adverse reaction occurred in the majority of the subjects in the Daichirona bivalent(Original/Omicron BA.4-5) vaccine 10 µg group or 20 µg group within at least 72 hours after study vaccination or where the advisory board judged it necessary.

Table 2. Blood anti-SARS-CoV-2 (Omicron BA.5.2.1 lineage) neutralizing antibody titer at Week 4 (Part 1 of Study 214, safety analysis population)

	Neutralizing antibody titer	
	Daichirona (bivalent, Original and Omicron BA.4-5) 10 μg (N = 4)	Daichirona (bivalent, Original and Omicron BA.4-5) 20 μg (N = 3)
Baseline (Day 1)	48.3 (28.3, 320.0)	56.6 (7.1, 160.0)
Week 4 (Day 29)	1280.0 (226.3, 3620.4)	2560.0 (905.1, 5120.0)

Median (minimum, maximum)

For the safety, the subjects were followed up as described below. Severity of an adverse event was graded according to the criteria defined based on the U.S. Food and Drug Administration (FDA)'s guidance document (Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007). Solicited adverse events (except serious events and events leading to study discontinuation) were all deemed causally related to study vaccination.

- Solicited adverse events were collected for 7 days after study vaccination.[9)]
  - Adverse events at the injection site (redness, swelling, induration, pain, warmth, and pruritus)
  - Systemic adverse events (pyrexia [axillary temperature ≥37.5°C], malaise, headache, rash, and myalgia)
- Unsolicited adverse events were collected for 28 days after study vaccination.[9)]
- Serious adverse events were collected between the time of informed consent and Week 52 after study vaccination.[9)]

Table 3 shows solicited adverse events reported within 7 days after study vaccination.

Table 3. Solicited adverse events reported within 7 days after study vaccination (Part 1 of Study 214, safety analysis population)

Event	Daichirona (bivalent, Original and Omicron BA.4-5) 10 μg (N = 4)		Daichirona (bivalent, Original and Omicron BA.4-5) 20 μg (N = 3)	
	All	Severity	All	Severity
Adverse events at the injection site	100 (4)	0	100 (3)	0
Injection site erythema	0	0	0	0
Injection site swelling	50.0 (2)	0	0	0
Injection site induration	0	0	0	0
Injection site pain	100 (4)	0	100 (3)	0
Injection site warmth	50.0 (2)	0	33.3 (1)	0
Injection site pruritus	0	0	33.3 (1)	0
Systemic adverse events	50.0 (2)	0	33.3 (1)	33.3 (1)
Pyrexia	25.0 (1)	0	33.3 (1)	33.3 (1)
Malaise	50.0 (2)	0	33.3 (1)	0
Headache	0	0	0	0
Rash	0	0	0	0
Myalgia	0	0	0	0

Incidence % (number of subjects with events), Medical Dictionary for Regulatory Activities (MedDRA)/J Ver.26.1

Table 4 shows unsolicited adverse events and adverse reactions reported within 28 days after study vaccination in either group. No severe events occurred.

9) Legally acceptable representatives were required to record the status of solicited adverse events (yes/no and other information) in an electronic diary on a daily basis for 7 days (Days 1-8) after study vaccination. The status of unsolicited adverse events (including solicited adverse events occurring on and after Day 9), if any, had to be recorded in the electronic diary for 28 days (Days 1-29) after study vaccination. The investigator was required to identify and assess adverse events by checking the electronic diaries and interview sheets of the subjects or by examining the subjects.

Table 4. Unsolicited adverse events and adverse reactions reported within 28 days after study vaccination in either group
(Part 1 of Study 214, safety analysis population)

Event	Adverse events		Adverse reactions	
	Daichirona (bivalent, Original and Omicron BA.4-5) 10 μg (N = 4)	Daichirona (bivalent, Original and Omicron BA.4-5) 20 μg (N = 3)	Daichirona (bivalent, Original and Omicron BA.4-5) 10 μg (N = 4)	Daichirona (bivalent, Original and Omicron BA.4-5) 20 μg (N = 3)
Overall	50.0 (2)	66.7 (2)	50.0 (2)	0
Diarrhoea	50.0 (2)	0	50.0 (2)	0
Nausea	25.0 (1)	0	0	0
Pharyngitis	25.0 (1)	0	0	0
Upper respiratory tract inflammation	25.0 (1)	0	0	0
Conjunctivitis bacterial	25.0 (1)	0	0	0
Injection site erythema	25.0 (1)	0	25.0 (1)	0
Injection site swelling	25.0 (1)	0	25.0 (1)	0
Injection site pain	25.0 (1)	0	25.0 (1)	0
Injection site warmth	25.0 (1)	0	25.0 (1)	0
Injection site pruritus	25.0 (1)	0	25.0 (1)	0
Limb injury	25.0 (1)	0	0	0
Pyrexia	0	33.3 (1)	0	0
Influenza	0	33.3 (1)	0	0

Incidence % (number of subjects with events), MedDRA/J Ver.26.1

No serious adverse events, death, or adverse events leading to study discontinuation occurred.

Part 2:

Based on data on the immunogenicity and safety in Part 1, the optimal dose of Daichirona (bivalent, Original and Omicron BA.4-5) was determined to be 20 μg. The subjects received a single intramuscular administration of Daichirona (bivalent, Original and Omicron BA.4-5) 20 μg or Comirnaty Intramuscular Injection for 5 to 11 years old (bivalent, Original and Omicron BA.4-5).

Of the 155 randomized[10)] subjects (76 in the Daichirona [bivalent, Original and Omicron BA.4-5] group, 79 in the Comirnaty [bivalent, Original and Omicron BA.4-5] group),[11)] 154 subjects received study vaccine and were included in the safety analysis population and full analysis set (FAS). The remaining 1 subject in the Daichirona (bivalent, Original and Omicron BA.4-5) group was excluded. Of the FAS, 153 subjects (75 in the Daichirona [bivalent, Original and Omicron BA.4-5] group, 78 in the Comirnaty [bivalent, Original and Omicron BA.4-5]- group) were included in the immunogenicity-evaluable FAS. The remaining 1 subject in the Comirnaty(bivalent, Original and Omicron BA.4-5) group was excluded from the analysis because the immunogenicity data could not be obtained after study vaccination. Of the immunogenicity-evaluable FAS, 149 subjects (74 in the Daichirona [bivalent, Original and Omicron BA.4-5] group, 75 in the Comirnaty [bivalent, Original and Omicron BA.4-5] group) were included in the immunogenicity-evaluable per-protocol set (PPS) and handled as the primary analysis population for immunogenicity. The remaining 4 subjects comprised of 1 in the Daichirona (bivalent, Original and

10) The study center and prior SARS-CoV-2 infection were used as stratification factors. A subject with prior SARS-CoV-2 infection was defined as the person who had previously tested positive for SARS-CoV-2 infection (reverse transcription polymerase chain reaction [RT-PCR] testing, other nucleic acid amplification testing, or SARS-CoV-2 antigen testing), had a diagnosis of COVID-19 confirmed by a physician, or tested positive for SARS-CoV-2 antigen (anti-N protein antibody) at screening.

11) The number of subjects enrolled in this study did not reach the target sample size during the enrollment period. Because it could not be extended due to limitations of supply of study vaccines, the target sample size was not achieved.

Omicron BA.4-5) group and 3 in the Comirnaty (bivalent, Original and Omicron BA.4-5) group were excluded because they had serious protocol deviations affecting the immunogenicity evaluation.

The primary endpoints for immunogenicity were the geometric mean titer (GMT) and antibody response rate (percentage of subjects who had a ≥4-fold increase from baseline in neutralizing antibody titer) of blood anti-SARS-CoV-2 (Omicron BA.5.2.1 lineage) neutralizing antibody titer at Week 4 after study vaccination. The study protocol stated that Daichirona (bivalent, Original and Omicron BA.4-5) would be considered non-inferior to Comirnaty (bivalent, Original and Omicron BA.4-5) if the following 2 requirements were met:

- The lower limit of two-sided 95% confidence interval (CI) of the adjusted GMT ratio of Daichirona (bivalent, Original and Omicron BA.4-5) to Comirnaty (bivalent, Original and Omicron BA.4-5) exceeds 0.67.
- The lower limit of two-sided 95% CI of the difference in antibody response rate between the Daichirona (bivalent, Original and Omicron BA.4-5) and the Comirnaty (bivalent, Original and Omicron BA.4-5) vaccine groups exceeds −10%.

Table 5 shows the results of the primary endpoints for immunogenicity. The lower limit of two-sided 95% CI of the adjusted GMT ratio exceeded 0.67 (the pre-specified), and that of the difference in antibody response rate exceeded −10% (the pre-specified). The Daichirona (bivalent, Original and Omicron BA.4-5) was shown to be non-inferior to Comirnaty (bivalent, Original and Omicron BA.4-5).

Table 5. Blood anti-SARS-CoV-2 (Omicron BA.5.2.1 lineages) neutralizing antibody titer and antibody response rate at Week 4
(Part 2 of Study 214, immunogenicity-evaluable PPS)

	No. of subjects analyzed	Neutralizing antibody titer		Antibody response rate	
		Adjusted GMT [two-sided 95% CI][a)]	Adjusted GMT ratio [two-sided 95% CI][a)]	Antibody response rate [two-sided 95% CI][b)c)] (%)	Difference in antibody response rate [two-sided 95% CI][d)] (%)
Daichirona (bivalent, Original and Omicron BA.4-5) (N = 74)	67	1644.228 [1346.417, 2007.912]	1.636 [1.221, 2.190]	92.5 [83.4, 97.5]	2.6 [-7.8, 13.8]
Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 75)	59	1005.274 [812.690, 1243.494]		89.8 [79.2, 96.2]	

GMT and antibody response rate: The measured neutralizing antibody titer below the LLOQ (10) was handled as the product of 0.5 × the LLOQ in the analysis.

a) The adjusted GMT, adjusted GMT ratio, and respective two-sided 95% CI were calculated by analysis of covariance using common logarithm of neutralizing antibody titer as an explained variable, dose group as an explanatory variable, and common logarithm of baseline neutralizing antibody titer and presence or absence of prior SARS-CoV-2 infection as covariates.
b) Number of subjects who had a ≥4-fold increase from baseline in neutralizing antibody titer at Week 4/number of subjects analyzed
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.
d) The difference in antibody response rate was calculated according to the Mantel-Haenszel method using the status of prior SARS-CoV-2 infection as a stratification factor, and the two-sided 95% CI was calculated according to the Newcombe-Wilson score method using the status of prior SARS-CoV-2 infection as a stratification factor.

For safety, the subjects were followed up as described below. Severity of an adverse event was graded according to the criteria defined based on the U.S. FDA's guidance document (Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007). Solicited adverse events (except serious events and events leading to study discontinuation) were all deemed causally related to study vaccination.

- Solicited adverse events were collected for 7 days after study vaccination.[9)]
  - Adverse events at the injection site (redness [erythema], swelling, induration, pain, warmth, and pruritus)
  - Systemic adverse events (pyrexia [axillary temperature ≥37.5°C], malaise, headache, rash, and myalgia)
- Unsolicited adverse events were collected for 28 days after study vaccination.[9)]
- Serious adverse events were collected between the time of informed consent and Week 52 after study vaccination.[9)]

Table 6 shows solicited adverse events reported within 7 days after study vaccination.

Table 6. Solicited adverse events reported within 7 days after study vaccination (Part 2 of Study 214, safety analysis population)

	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 75)		Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 79)	
	All	Severity	All	Severity
Adverse events at the injection site	86.7 (65)	2.7 (2)	88.6 (70)	0
Injection site erythema	16.0 (12)	0	15.2 (12)	0
Injection site swelling	25.3 (19)	1.3 (1)	16.5 (13)	0
Injection site induration	20.0 (15)	0	10.1 (8)	0
Injection site pain	85.3 (64)	0	86.1 (68)	0
Injection site warmth	46.7 (35)	1.3 (1)	25.3 (20)	0
Injection site pruritus	10.7 (8)	0	11.4 (9)	0
Systemic adverse events	37.3 (28)	4.0 (3)	29.1 (23)	1.3 (1)
Pyrexia	16.0 (12)	4.0 (3)	12.7 (10)	1.3 (1)
Malaise	24.0 (18)	0	17.7 (14)	1.3 (1)
Headache	21.3 (16)	0	17.7 (14)	0
Rash	0	0	1.3 (1)	0
Myalgia	8.0 (6)	0	6.3 (5)	0

Incidence % (number of subjects with events), MedDRA/J Ver.26.1

Table 7 shows unsolicited adverse events and adverse reactions reported by ≥2 subjects in either group. No severe unsolicited adverse events occurred.

Table 7. Unsolicited adverse events and adverse reactions reported within 28 days after study vaccination by ≥2 subjects in either group
(Part 2 of Study 214, safety analysis population)

	Adverse events		Adverse reactions	
	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 75)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 79)	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 75)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 79)
Overall	48.0 (36)	41.8 (33)	10.7 (8)	10.1 (8)
Injection site erythema	10.7 (8)	1.3 (1)	8.0 (6)	1.3 (1)
Injection site pruritus	8.0 (6)	1.3 (1)	8.0 (6)	1.3 (1)
Injection site swelling	6.7 (5)	0	5.3 (4)	0
Pharyngitis	5.3 (4)	3.8 (3)	0	0
Nasopharyngitis	4.0 (3)	13.9 (11)	0	0
Cough	4.0 (3)	2.5 (2)	0	0
Influenza	2.7 (2)	2.5 (2)	0	0
Gastroenteritis	2.7 (2)	1.3 (1)	0	0
Oropharyngeal pain	2.7 (2)	0	0	0
Diarrhoea	2.7 (2)	0	0	0
Pyrexia	1.3 (1)	3.8 (3)	0	1.3 (1)
Headache	1.3 (1)	2.5 (2)	0	0
Vomiting	0	2.5 (2)	0	1.3 (1)
Pruritus	0	2.5 (2)	0	0

Incidence % (number of subjects with events), MedDRA/J Ver.26.1

Serious adverse events reported up to the data cut-off date were asthma in 1 subject in the Daichirona (bivalent, Original and Omicron BA.4-5) group and erythema multiforme in 1 subject in the Comirnaty (bivalent, Original and Omicron BA.4-5) group, but a causal relationship to the study vaccine was ruled out for both events.

Neither death nor adverse events leading to study discontinuation occurred up to the data cut-off date.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and data for review

The applicant's explanation about the clinical data package of Daichirona in children aged 5 to 11 years:
The applicant developed Daichirona to address the public health emergency of international concern for COVID-19 declared by the WHO and obtained an approval for marketing of Daichirona (monovalent, Original) for booster dose in individuals aged ≥18 years in Japan in August 2023. The WHO declared an end to COVID-19 as a public health emergency, and in Japan, the category of COVID-19 was reclassified from "pandemic influenza (novel influenza or re-emerging influenza" (equivalent to Category 2 infectious diseases) to "Category 5 infectious diseases" on May 8, 2023. However, SARS-CoV-2 variants with altered infectivity and transmissibility have been emerging so far, causing intermittent resurgence of COVID-19. COVID-19 thus remains as a public health concern.

Although COVID-19 in children is mostly mild, a certain number of pediatric patients experienced acute encephalopathy or myocarditis, some resulting in severe disease or death (*Front Neurosci.* 2023;17:1085082, etc.). In addition, because (1) vaccination in children is confirmed to be effective in preventing the onset of COVID-19 or progression to severe COVID-19 (hospitalization) in and outside Japan (*JAMA Pediatr.* 2023;177:384-94, etc.); and (2) potential spread of the infection with new variants remains as a concern, the applicant considers it meaningful to expand the indication of Daichirona to use in children, as has been done for other SARS-CoV-2 vaccines, and ensure supply to the expanded

population. In a development project to expand the indication to use in children, the applicant planned to evaluate the immunogenic non-inferiority of Daichirona to Comirnaty Intramuscular Injection for 5 to 11 years old approved in Japan utilizing the immunobridging approach according to the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" (Appendix 4).[12)]

While the development to expand the indication to use in children was ongoing, mutations of SARS-CoV-2 genes resulted in successive emergence of variants with altered infectivity, transmissibility, antigenicity, and pathogenicity and have caused the multiple waves of spread of SARS-CoV-2 infection. Development of vaccines adapted to SARS-CoV-2 variants was discussed at the "COVID-19 Omicron variant workshop"[13)] of the International Coalition of Medicines Regulatory Authorities (ICMRA) held on May 8, 2023, where the utilization of a platform approach was proposed. In this context, the development of Daichirona to be used for booster dose in individuals aged ≥12 years proceeded as follows: (1) Data relating to quality and results from non-clinical studies as well as results from clinical studies of Daichirona (bivalent, Original and Omicron BA.4-5) obtained by modifying Daichirona (monovalent, Original) were used to evaluate the efficacy and safety of Daichirona (monovalent, Omicron XBB.1.5); (2) a partial change application to change the antigen strains to reflect prevalent strains was submitted; and (3) Daichirona (monovalent, Omicron XBB.1.5) was approved for booster dose (see the Review Report of Daichirona for Intramuscular Injection dated November 17, 2023). The antigen strain of the vaccine in the present application intended to add a dosage for children aged 5 to 11 years is different from the virus strain prevalent at an early phase of the development for use in children and the antigen strain of the vaccine used in clinical studies. However, the applicant considered that the same principle as that applied to the change of the antigen strain in the vaccine for individuals aged ≥12 years might be applicable and therefore decided to evaluate the efficacy and safety of Daichirona (monovalent, Omicron XBB.1.5) in children aged 5 to 11 years by conducting a clinical study of Daichirona (bivalent, Original and Omicron BA.4-5).

During the review process, the indication for use in individuals aged ≥12 years was confirmed to meet the requirements provided in the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 5): Quality data required for the approval review of changing a strain in the vaccine for which the manufacturing process is well established (Early consideration)."[14)] In addition to the above, Daichirona (monovalent, Omicron JN.1) was approved. Given the above situation, the applicant also decided to evaluate the efficacy and safety of a booster dose of Daichirona (monovalent, Omicron JN.1) in children aged 5 to 11 years.

PMDA's view on its review policy:
In Japan, the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 4): Immunogenicity-based evaluation of variant vaccines modified from parent vaccines and booster vaccines with new active ingredients"[12)] indicates that (a) if a novel booster vaccine candidate has the mechanism of action similar to that of approved SARS-CoV-2 vaccines, its efficacy can be evaluated by utilizing an immunogenicity measures; and (b) the primary endpoints in a clinical study

12) Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, dated July 15, 2022
13) https://icmra.info/drupal/en/covid-19/8may2023 (last accessed on December 3, 2024)
14) Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, dated May 29, 2024

should be GMT of the neutralizing antibody titer against the target SARS-CoV-2 variant for development and immune response rate and the non-inferiority of the novel booster vaccine candidate to the appropriate active comparator vaccine should be tested. In view of the discussion at the COVID-19 Omicron variant workshop of ICMRA[13)] in addition to the above, PMDA considers the applicant's following opinion acceptable: Although no clinical studies of Daichirona (monovalent, Omicron XBB.1.5) have been conducted in children aged 5 to 11 years, (1) the dosage is selected based on the results from a Japanese phase II/III study (Study 214) in children aged 5 to 11 years; and (2) the efficacy and safety of Daichirona (monovalent, Omicron XBB.1.5) in children aged 5 to 11 years are explained by comparing the efficacy and safety of a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years with those of Comirnaty Intramuscular Injection for 5 to 11 years old (bivalent, Original and Omicron BA.4-5).

At the time of submission of a partial change application mainly intended to change the antigen strain of Daichirona for individuals aged ≥12 years from the original strain to the Omicron XBB.1.5 lineage, a clinical study of Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years was in the planning stage, and thus the application was reviewed based on the results from clinical studies of Daichirona (bivalent, Original and Omicron BA.4-5), as was done for the present application (see the Review Report of Daichirona for Intramuscular Injection dated November 17, 2023). Results from the clinical study of Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years are also reviewed in this report because they were obtained during this review.

Since the use of vaccines adapted to the Omicron JN.1 lineage and its sulineages was recommended for the regular vaccination program in autumn and winter 2024 in Japan, the principle of Appendix 5 was applied to Daichirona for Intramuscular Injection as well, and thus Daichirona (monovalent, Omicron JN.1) was approved for use in individuals aged ≥12 years. As a strategy to make Daichirona (monovalent, Omicron JN.1) available for not only individuals aged ≥12 years but also children aged 5 to 11 years, the applicant discussed the efficacy and safety of Daichirona (monovalent, Omicron JN.1) in children aged 5 to 11 years as well. PMDA considers the applicant's strategy acceptable. However, data on the safety of currently commercially available Daichirona (monovalent, Omicron JN.1) in children aged 5 to 11 years are not available. The applicant should therefore continue collecting the relevant information in post-marketing settings, provide the obtained information to healthcare professionals, and consider the necessity of raising additional caution.

7.R.2 Efficacy

PMDA's view:

Based on the results of the review in Sections 7.R.2.1 to 7.R.2.3, Daichirona (monovalent, Omicron XBB.1.5 or JN.1) is expected to have efficacy in the prevention of COVID-19 in children aged 5 to 11 years.

7.R.2.1 Immunogenicity of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years

The applicant's explanation about the immunogenicity of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years:

Study 214 was conducted with Daichirona (bivalent, Original and Omicron BA. 4-5) to evaluate the efficacy (immunogenicity) of Daichirona as a booster dose in children aged 5 to 11 years. Part 2 of Study 214 demonstrated the non-inferiority of Daichirona (bivalent, Original and Omicron BA. 4-5) to Comirnaty Intramuscular Injection for 5 to 11 years old (bivalent, Original and Omicron BA. 4-5) based on the results on the primary endpoints, which were the GMT and antibody response rate of anti-SARS-CoV-2 (Omicron BA.5.2.1 lineage) neutralizing antibody titer at Week 4 [see Section 7.1].

Table 8 shows the results on the immunogenicity of Daichirona against the Omicron BA.5.2.1 lineage or original strain before and after study vaccination in Part 2 of Study 214. Table 9 shows the results on the immunogenicity of Daichirona against the Omicron XBB.1 and BQ.1 lineages, which is an exploratory endpoint. Daichirona (bivalent, Original and Omicron BA.4-5) increased the neutralizing antibody titer and antibody response rate against the original strain and all the Omicron lineages. The increases in both groups had a generally similar trend.

In Part 2 of Study 214, no COVID-19 occurred between Day 8 and Week 4 after study vaccination.[15)]

Table 8. GMT, GMFR, and antibody response rate of blood anti-SARS-CoV-2 (Omicron BA.5.2.1 lineages and original strain) neutralizing antibody titer (Part 2 of Study 214, immunogenicity-evaluable PPS)

	Omicron BA.5.2.1 lineage		Original strain	
	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 74)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 75)	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 74)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 75)
Baseline (Day 1)				
Number of subjects analyzed	73	75	73	75
GMT [two-sided 95% CI][a)]	72.421 [50.366, 104.134]	79.274 [53.783, 116.845]	317.345 [226.872, 443.897]	368.174 [260.380, 520.595]
4 weeks after study vaccination (Day 29)				
Number of subjects analyzed	67	59	67	59
GMT [two-sided 95% CI][a)]	1692.483 [1310.447, 2185.893]	965.504 [729.071, 1278.609]	3316.202 [2607.950, 4216.798]	2874.621 [2310.323, 3576.750]
GMFR [two-sided 95% CI][a)]	26.421 [19.534, 35.736]	18.098 [13.184, 24.843]	11.732 [8.696, 15.828]	11.313 [8.457, 15.134]
Antibody response rate[b)] [two-sided 95% CI][c)] (%)	92.5 [83.4, 97.5]	89.8 [79.2, 96.2]	82.1 [70.8, 90.4]	86.4 [75.0, 94.0]

GMT and antibody response rate: The measured neutralizing antibody titer below the LLOQ (10) was handled as the product of 0.5 × LLOQ in the analysis.

a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the neutralizing antibody titer or fold rise in antibody titer.
b) Number of subjects who had a ≥4-fold increase from baseline in neutralizing antibody titer at Week 4/number of subjects analyzed
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

15) A patient with COVID-19 was defined as an individual who had at least 1 of "pyrexia of ≥37.5°C," "cough," "shortness of breath/suffocation," "fatigue/malaise," "myalgia/systemic pain," "headache," "new dysgeusia/dysosmia," and "pharyngeal pain" and tested positive for SARS-CoV-2 by RT-PCR or SARS--CoV-2 antigen testing, or other examination.

Table 9. GMT, GMFR, and antibody response rate of blood anti-SARS-CoV-2 (Omicron XBB.1.5.6 and BQ.1.1.3 lineages) neutralizing antibody titer (Part 2 of Study 214, immunogenicity-evaluable PPS)

	Omicron XBB.1.5.6 lineage		Omicron BQ.1.1.3 lineage	
	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 74)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 75)	Daichirona (bivalent, Original and Omicron BA.4-) (N = 74)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 75)
Baseline (Day 1)				
Number of subjects analyzed	73	75	73	75
GMT [two-sided 95% CI][a)]	37.073 [27.214, 50.504]	57.101 [37.874, 86.089]	65.233 [47.464, 89.654]	83.019 [57.820, 119.199]
4 weeks after study vaccination (Day 29)				
Number of subjects analyzed	67	59	67	59
GMT [two-sided 95% CI][a)]	783.048 [579.353, 1058.360]	488.448 [359.324, 663.971]	900.376 [662.739, 1223.222]	982.676 [746.611, 1293.380]
GMFR [two-sided 95% CI][a)]	24.581 [18.738, 32.244]	13.894 [10.103, 19.108]	15.191 [11.552, 19.977]	16.967 [12.396, 23.221]
Antibody response rate[b)] [two-sided 95% CI][c)] (%)	95.5 [87.5, 99.1]	86.4 [75.0, 94.0]	88.1 [77.8, 94.7]	89.8 [79.2, 96.2]

GMT and antibody response rate: The measured neutralizing antibody titer below the LLOQ (10) was handled as the product of 0.5 × LLOQ in the analysis.

a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the neutralizing antibody titer or fold rise in antibody titer.
b) Number of subjects who had a ≥4-fold increase from baseline in neutralizing antibody titer at Week 4/number of subjects analyzed
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

Table 10 shows the results on the immunogenicity of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years and individuals aged ≥12 years based on data from Part 2 of Study 214 and data from a Japanese phase III study (Study DS5670-212 [Study 212]),[16)] which supported the partial change application for changing the antigen strain for Daichirona (monovalent, Omicron XBB.1.5). Daichirona (bivalent, Original and Omicron BA.4-5) 20 μg in children aged 5 to 11 years increased the GMT as observed with Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg in individuals aged ≥12 years, demonstrating an immune response to Daichirona (bivalent, Original and Omicron BA.4-5) in children.

16) Modified from Table 9 in the Review Report of Daichirona for Intramuscular Injection dated November 17, 2023

Table 10. Immunogenicity of Daichirona against SARS-CoV-2 (Omicron BA.5.2.1 lineage) by age group (pooled data from Part 2 of Study 214 as well as the main part, Sub-part A, and Sub-part B of Study 212, immunogenicity-evaluable PPS)

	Daichirona (bivalent, Original and Omicron BA.4-5)			
	5 to 11 years (N = 74)	12 to 17 years (N = 33)	18 to 64 years (N = 656)	≥65 years (N = 132)
Baseline (Day 1)				
Number of subjects analyzed	73	33	656	132
GMT [two-sided 95% CI][a)]	72.421 [50.366, 104.134]	160.034 [85.085, 301.002]	67.558 [59.450, 76.771]	45.611 [35.325, 58.893]
Week 4 after study vaccination (Day 29)				
Number of subjects analyzed	67	30	603	126
GMT [two-sided 95% CI][a)]	1692.483 [1310.447, 2185.893]	1222.199 [842.632, 1772.744]	515.033 [464.219, 571.408]	362.173 [286.071, 458.521]
GMFR [two-sided 95% CI][a)]	26.421 [19.534, 35.736]	7.998 [4.964, 12.885]	8.276 [7.481, 9.155]	8.156 [6.700, 9.928]
Antibody response rate[b)] [two-sided 95% CI][c)] (%)	92.5 [83.4, 97.5]	73.3 [54.1, 87.7]	73.1 [69.4, 76.6]	76.2 [67.8, 83.3]

GMT and antibody response rate: The measured neutralizing antibody titer below the LLOQ (10) was handled as the product of 0.5 × LLOQ in the analysis.

a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the neutralizing antibody titer or fold rise in antibody titer.
b) Number of subjects who had a ≥4--fold increase from baseline in neutralizing antibody titer at Week 4/number of subjects analyzed
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

7.R.2.2 Efficacy of a booster dose of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in individuals aged ≥12 years

The applicant's explanation about efficacy of a booster dose of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in individuals aged ≥12 years in response to new results from a Japanese phase III study of Daichirona (monovalent, Omicron XBB.1.5) (Study DS5670-237 [Study 237]):

- Efficacy of Daichirona (monovalent, Omicron XBB.1.5)

In a Japanese phase I/II/III study (Study DS5670-146 [Study 146]) from which results were used to support the initial application for Daichirona (monovalent, Original), Daichirona induced anti-SARS-CoV-2 neutralizing antibody in blood and was demonstrated to be non-inferior to the control vaccine (approved vaccine) in terms of the immunogenicity (Review Report of Daichirona for Intramuscular Injection dated July 19, 2023). In addition, in a Japanese phase III study (Study 212) from which results were used to support the partial change application for changing the antigen strain for Daichirona (monovalent, Omicron XBB.1.5), Daichirona (bivalent, Original and Omicron BA.4-5) induced anti-SARS-CoV-2 neutralizing antibody in blood and was demonstrated to be non-inferior to the control vaccine (approved vaccine) in terms of the immunogenicity (Review Report of Daichirona for Intramuscular Injection dated November 17, 2023). The partial change application for changing the antigen strain for Daichirona (monovalent, Omicron XBB.1.5) was submitted with the supporting data comprised of data on quality attributes and non-clinical study results of Daichirona (monovalent, Omicron XBB.1.5) as well as results from a Japanese phase III study (Study 212) of Daichirona (bivalent, Original and Omicron BA.4-5), with reference to the discussion at the "COVID-19 Omicron variant workshop" of the ICMRA.[13)] At the time of the submission, a clinical study of Daichirona (monovalent, Omicron XBB.1.5) was in the planning stage.

Recently, results up to Day 28 after study vaccination (data cut-off on [redacted], 20[redacted]) were obtained from a Japanese phase III multi-center, randomized, observer-blinded,[7)] active-controlled study (Study 237) to evaluate the immunogenicity and safety of Daichirona (monovalent, Omicron XBB.1.5) in individuals

aged ≥12 years.[17] In this study, a single dose of Daichirona (monovalent, Omicron XBB.1.5) 60 μg or Comirnaty Intramuscular Injection (monovalent, Omicron XBB.1.5) was administered intramuscularly. The primary endpoints for immunogenicity were the GMT and antibody response rate (percentage of subjects who had a ≥4-fold increase from baseline in neutralizing antibody titer) of blood anti-SARS-CoV-2 (Omicron XBB.1.5.6 lineages) neutralizing antibody titer at Week 4 after study vaccination. The following 2 criteria had to be met to demonstrate the non-inferiority of Daichirona (monovalent, Omicron XBB.1.5) to Comirnaty Intramuscular Injection (monovalent, Omicron XBB.1.5):

- The lower limit of two-sided 95% CI of the adjusted GMT ratio of Daichirona (monovalent, Omicron XBB.1.5) to Comirnaty (monovalent, Omicron XBB.1.5) exceeds 0.67.
- The lower limit of two-sided 95% CI of the difference in antibody response rate between Daichirona (monovalent, Omicron XBB.1.5) and Comirnaty (monovalent, Omicron XBB.1.5) exceeds −10%.

Table 11 shows the results on the primary endpoints for immunogenicity. The lower limit of two-sided 95% CI of the adjusted GMT ratio and the lower limit of two-sided 95% CI of the difference in antibody response rate exceeded the pre-determined thresholds, demonstrating the non-inferiority of Daichirona (monovalent, Omicron XBB.1.5) to Comirnaty Intramuscular Injection (monovalent, Omicron XBB.1.5). COVID-19 occurred in 2 subjects in the Daichirona (monovalent, Omicron XBB.1.5) group and 3 subjects in the Comirnaty (monovalent, Omicron XBB.1.5) group between Day 8 and Week 4 after study vaccination. The incidence of COVID-19 did not differ between the dose groups. The above clinical study results also demonstrated the efficacy of Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years. Daichirona, irrespective of valency (monovalent or bivalent), is expected to have efficacy in the prevention of COVID-19.

Table 11. Blood anti-SARS-CoV-2 (Omicron XBB.1.5.6 lineage) neutralizing antibody titer and antibody response rate at Week 4
(Study 237, primary-series-completed, immunogenicity-evaluable PPS)

	No. of subjects analyzed	Neutralizing antibody titer		Antibody response rate	
		Adjusted GMT [two-sided 95% CI][a)]	Adjusted GMT ratio [two-sided 95% CI][a)]	Antibody response rate [two-sided 95% CI][b)c)] (%)	Difference in antibody response rate [two-sided 95% CI][d)] (%)
Daichirona (monovalent, Omicron XBB.1.5) (N = 362)	362	1691.877 [1527.122, 1874.405]	1.218 [1.059, 1.401]	87.3 [83.42, 90.54]	4.5 [-0.70, 9.71]
Comirnaty (monovalent, Omicron XBB.1.5) (N = 363)	363	1388.927 [1253.021, 1539.573]		82.9 [78.65, 86.65]	

GMT and antibody response rate: The measured neutralizing antibody titer below the LLOQ (10) was handled as the product of 0.5 × LLOQ in the analysis.

a) The adjusted GMT, adjusted GMT ratio, and respective two-sided 95% CI were calculated based on an analysis of covariance using common logarithm of neutralizing antibody titer as an explained variable, dose group as an explanatory variable, and common logarithm of baseline neutralizing antibody titer, prior SARS-CoV-2 infection, and prior vaccination against SARS-CoV-2 as covariates.
b) Number of subjects who had a ≥4-fold increase from baseline in neutralizing antibody titer at Week 4/number of subjects analyzed
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.
d) The difference in antibody response rate was calculated according to the Mantel-Haenszel method using presence or absence of prior SARS-CoV-2 infection and prior vaccination against SARS-CoV-2 as stratification factors. The two-sided 95% CI was calculated according to the Newcombe-Wilson score method using presence or absence of prior SARS-CoV-2 infection and prior vaccination against SARS-CoV-2 as stratification factors.

[17] Individuals with prior SARS-CoV-2 infection and/or prior vaccination against SARS-CoV-2

● Efficacy of Daichirona (monovalent, Omicron JN.1)

Based on the review of the initial application for Daichirona and the partial change application for changing the strain for Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years, Daichirona is deemed to be a vaccine in which a change of the antigen strain is very unlikely to affect the quality and safety of the vaccine and the post-change immunogenicity can be predicted from non-clinical studies. For Daichirona (monovalent, Omicron JN.1), a partial change application for changing the strain was submitted with data on the quality before and after the strain change as well as results from non-clinical studies for expedited review and then approved, in accordance with the "Handling of Changes to COVID-19 Vaccine Strains" (PSB/PED Notification No. 0523-1 and PSB/CND Notification No. 0523-3 dated May 23, 2024) and "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 5): Quality data required for the approval review of changing a strain in the vaccine for which the manufacturing process is well established (Early consideration)."[14)]

7.R.2.3 Efficacy of a booster dose of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in children aged 5 to 11 years

The applicant's explanation about the efficacy of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) as a booster dose in children aged ≥5 to 11 years:

In view of results from quality testing, mouse immunogenicity studies, and clinical studies (Studies 146, 212, 214, and 237) conducted to date and the review, the "discussion at the "COVID-19 Omicron variant workshop" of the ICMRA[13)] is considered applicable to Daichirona. Daichirona (monovalent, Omicron XBB.1.5 and JN.1) has been approved for use in individuals aged ≥12 years, and Daichirona (monovalent, Omicron XBB.1.5 or JN.1) is expected to have efficacy in children aged 5 to 11 years as well.

PMDA's view:

On the basis of the review policy described in Section 7.R.1, the following points has been confirmed in Sections 7.R.2.1 to 7.R.2.3. Daichirona (monovalent, Omicron XBB.1.5 or JN.1) is expected to have efficacy in the prevention of COVID-19 in children aged 5 to 11 years as well.

- Daichirona (monovalent, Omicron XBB.1.5 or JN.1) is a variant-adapted vaccine of which the antigen strain has been changed from Daichirona (monovalent, Original) approved in Japan.
- Daichirona (monovalent, Omicron XBB.1.5 or JN.1) is confirmed to have the same quality attributes as those of Daichirona (monovalent, Original), except the RNA sequence encoding RBD and potency, which are changed due to use of the different antigen strain (lineage).
- A non-clinical pharmacology study in mice showed that Daichirona (monovalent, Omicron XBB.1.5 or JN.1) induced an immune response to a virus corresponding to the antigen strain of the vaccine.
- A clinical study of Daichirona (bivalent, Original and Omicron BA.4-5) as a booster dose in children aged 5 to 11 years demonstrated the non-inferiority of Daichirona (bivalent, Original and Omicron BA.4-5) to Comirnaty Intramuscular Injection for 5 to 11 years old (bivalent, Original and Omicron BA.4-5) in terms of the GMT and antibody response rate of neutralizing antibody titer against SARS-CoV-2 (Omicron BA.5.2.1 lineage).
- The GMT and antibody response rate of neutralizing antibody titer against SARS-CoV-2 (Omicron BA.5.2.1 lineage) after dose of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years were similar to those in individuals aged ≥12 years.

- Daichirona (monovalent, Omicron XBB.1.5 and JN.1) has been already approved for use in individuals aged ≥12 years.
- A clinical study of Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years demonstrated the non-inferiority of Daichirona (monovalent, Omicron XBB.1.5) to Comirnaty Intramuscular Injection (monovalent, Omicron XBB.1.5) in terms of the GMT and antibody response rate of neutralizing antibody titer against SARS-CoV-2 (Omicron XBB.1.5.6 lineages).

7.R.3 Safety

PMDA's view:

Based on the results of the review in Sections 7.R.3.1 and 7.R.3.2, Daichirona (monovalent, Omicron XBB.1.5 or JN.1) as a booster dose in children aged 5 to 11 years has acceptable safety. However, the applicant should raise caution about myocarditis and pericarditis and collect information on the events, as has been done for the indication of Daichirona for use in individuals aged ≥12 years and with the same-class vaccines. The applicant should continue collecting information on the safety of Daichirona (monovalent, Omicron JN.1) in post-marketing settings, provide the obtained information to healthcare professionals, and consider the necessity of raising additional caution.

7.R.3.1 Safety profile

7.R.3.1.1 Safety of Daichirona (bivalent, Original and Omicron BA.4-5) as booster dose in children aged 5 to 11 years

The applicant's explanation about the safety of Daichirona (bivalent, Original and Omicron BA.4-5) as a booster dose in children aged 5 to 11 years:

Table 12 shows a summary of the safety in Part 2 of Study 214.

Table 12. Summary of safety (Part 2 of Study 214, safety analysis population)

	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 75)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 79)
Solicited adverse events at the injection site	86.7 (65)	88.6 (70)
Severe	2.7 (2)	0
Solicited systemic adverse events	37.3 (28)	29.1 (23)
Severe	4.0 (3)	1.3 (1)
Unsolicited adverse events	48.0 (36)	41.8 (33)
Severe	0	0
Unsolicited adverse reactions	10.7 (8)	10.1 (8)
Severe	0	0
Death	0	0
Serious adverse events	1.3 (1)	1.3 (1)
Adverse events leading to study discontinuation	0	0

Incidence % (number of subjects with events)

(a) Solicited adverse events

In Part 2 of Study 214, the incidence of solicited adverse events at the injection site was 86.7% in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 88.6% in the Comirnaty (bivalent, Original and Omicron BA.4-5) group, both of which were high, but most of the events were mild or moderate. Major solicited adverse events at the injection site were injection site pain (85.3% in the Daichirona [bivalent, Original and Omicron BA.4-5] group and 86.1% in the Comirnaty [bivalent, Original and Omicron BA.4-5] group) and injection site warmth (46.7% and 25.3%, respectively) (Table

6). Severe solicited adverse events at the injection site occurred in 2.7% (2 of 75) of subjects in the Daichirona (bivalent, Original and Omicron BA.4-5) group (injection site swelling and injection site warmth in 1 subject each), but both events resolved by the data cut-off date. The median (range) of time to onset of solicited adverse events at the injection site was 2 days (1-4 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 1.5 days (1-3 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group, and the median (range) of duration was 3 days (1-9 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 2 days (1-6 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. The incidences of injection site induration and injection site warmth tended to be higher in the Daichirona (bivalent, Original and Omicron BA.4-5) group than in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. However, no clear differences were observed in major subject characteristics, and the incidences of all solicited adverse events at the injection site and each of the other solicited adverse events at the injection site (injection site erythema, injection site pain, and injection site pruritus) did not differ between the 2 groups. Therefore, the difference in the incidences of injection site induration and injection site warmth is considered accidental and raise no safety concerns with Daichirona.

The incidence of systemic solicited adverse events was 37.3% (28 of 75 subjects) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 29.1% (23 of 79 subjects) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. The events occurred slightly more frequently in the Daichirona (bivalent, Original and Omicron BA.4-5) group, but most of them were mild or moderate. Major systemic solicited adverse events were malaise (24.0% and 17.7%) and headache (21.3% and 17.7%) (Table 6). Severe systemic solicited adverse events occurred in 4.0% (3 of 75) of subjects (pyrexia in 3 subjects) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 1.3% (1 of 79) of subjects (pyrexia and malaise in 1 subject each, 1 subject had more than 1 event) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group but all of them had resolved by the data cut-off date. The median (range) of time to onset of systemic solicited adverse events was 2 days (1-8 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 2 days (1-6 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group, and the median (range) of duration was 2 days (1-5 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 1 day (1-12 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. The incidence of all systemic solicited adverse events was slightly higher in the Daichirona (bivalent, Original and Omicron BA.4-5) group, but no clear difference was observed in the incidence of each event (pyrexia, malaise, headache, rash, and myalgia) between the 2 groups, and most of the events were mild or moderate. No safety concerns with Daichirona are indicated.

(b) Unsolicited adverse events

In Part 2 of Study 214, the incidence of unsolicited adverse events was 48.0% in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 41.8% in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. The major unsolicited adverse events were injection site erythema (10.7% in the Daichirona [bivalent, Original and Omicron BA.4-5] group and 1.3% in the Comirnaty [bivalent, Original and Omicron BA.4-5] group; the incidences are hereinafter presented in this order), injection site pruritus (8.0% and 1.3%), injection site swelling (6.7% and 0%), pharyngitis (5.3% and 3.8%), and nasopharyngitis (4.0% and 13.9%) (Table 7). All of the events were mild or moderate. The incidence of

unsolicited adverse reactions was 10.7% in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 10.1% in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. The major unsolicited adverse reactions were injection site erythema (8.0% and 1.3%), injection site pruritus (8.0% and 1.3%), and injection site swelling (5.3% and 0%), all of which were delayed adverse events at the injection site (occurring on Days 9-29).

The incidence of delayed adverse events at the injection site was 10.7% (8 of 75 subjects) in the Daichirona (bivalent, Original and Omicron BA.4-5) group (injection site erythema in 8 subjects, injection site pruritus and injection site swelling in 5 subjects each, and injection site induration and injection site warmth in 1 subject each; 1 subject had more than 1 event) and 1.3% (1 of 79 subjects) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group (injection site erythema and injection site pruritus in 1 subject each; 1 subject had more than 1 event). All of the delayed adverse events at the injection site were mild or moderate and resolved by the data cut-off date. The incidence of delayed systemic adverse events was 2.7% (2 of 75 subjects) in the Daichirona (bivalent, Original and Omicron BA.4-5) group (pyrexia and headache in 1 subject each) and 3.8% (3 of 79 subjects) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group (pyrexia in 2 subjects and headache in 1 subject). All of the above events were mild and resolved by the data cut-off date.

(c) Serious adverse events and death

In Part 2 of Study 214, no serious adverse events occurred during a period of 28 days after study vaccination. During a period from 29 days after study vaccination to the data cut-off date, serious adverse events occurred in 1 subject in the Daichirona (bivalent, Original and Omicron BA.4-5) group (asthma) and in 1 subject in the Comirnaty (bivalent, Original and Omicron BA.4-5) group (erythema multiforme), but a causal relationship to the study vaccine was ruled out for both events. No death occurred.

(d) Comparison of safety between populations aged 5 to 11 years and aged ≥12 years

Based on study results from Study 214 Part 2 and Study 212,[18)] the safety of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years was compared with that in individuals aged ≥12 years (Table 13). The incidences of solicited adverse events at the injection site, systemic solicited adverse events, and unsolicited adverse reactions were similar in these populations, but the incidence of unsolicited adverse events was higher in children aged 5 to 11 years.

[18)] Modified from Table 10 in the Review Report of Daichirona for Intramuscular Injection dated November 17, 2023

Table 13. Comparison of safety of Daichirona (bivalent, Original and Omicron BA.4-5) between children aged 5 to 11 years and individuals aged ≥12 years (Part 2 of Study 214, main part of Study 212, safety analysis population)

	5 to 11 years (N = 75)	≥12 years (N = 349)
Solicited adverse events at the injection site	86.7 (65)	89.4 (312)
Severe	2.7 (2)	2.3 (8)
Solicited systemic adverse events	37.3 (28)	43.0 (150)
Severe	4.0 (3)	2.3 (8)
Unsolicited adverse events	48.0 (36)	15.5 (54)
Severe	0	1.1 (4)
Unsolicited adverse reactions	10.7 (8)	6.3 (22)
Severe	0	0.9 (3)
Death	0	0
Serious adverse events	1.3 (1)	0.3 (1)
Adverse events leading to study discontinuation	0	0

Incidence % (number of subjects with events)

Although direct comparison using results from different studies has limitations, the higher incidence of unsolicited adverse events in children aged 5 to 11 years than in individuals aged ≥12 years is considered partially attributable to living environment specific to children, such as group activities, because events potentially associated with accidental infections (pharyngitis, nasopharyngitis, cough, influenza, etc.) more frequently occurred in children aged 5 to 11 years than in individuals aged ≥12 years. The incidence of delayed adverse events at the injection site was higher in children aged 5 to 11 years than in individuals aged ≥12 years. Delayed adverse events at the injection site in children aged 5 to 11 years tended to more frequently occur in the Daichirona (bivalent, Original and Omicron BA.4-5) group than in the Comirnaty (bivalent, Original and Omicron BA.4-5) group (Table 14). The incidences of delayed systemic adverse events and unsolicited adverse events in children aged 5 to 11 years did not clearly differ between the 2 groups, and differences in incidence between the 2 groups did not show a consistent trend. In individuals aged ≥12 years, the incidence of delayed adverse events at the injection site also tended to be slightly higher in the Daichirona (bivalent, Original and Omicron BA.4-5) group than in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. Delayed adverse events at the injection site were non-serious in either age group. Most of the delayed adverse events at the injection site observed in the Daichirona (bivalent, Original and Omicron BA.4-5) group resolved by the data cut-off date. The incidence of delayed systemic adverse events did not differ between the 2 groups. Accordingly, the incidences of delayed adverse events by age did not show any clinically meaningful difference.

Table 14. Incidence of delayed adverse events
(Part 2 of Study 214, main part of Study 212; safety analysis population)

Event	5 to 11 years		≥12 years	
	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 75)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 79)	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 349)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 352)
Adverse events at the injection site	10.7 (8)	1.3 (1)	1.4 (5)	0.3 (1)
Injection site erythema	10.7 (8)	1.3 (1)	0.9 (3)	0
Injection site pruritus	6.7 (5)	1.3 (1)	0	0
Injection site swelling	6.7 (5)	0	0.6 (2)	0
Injection site induration	1.3 (1)	0	0.3 (1)	0
Injection site warmth	1.3 (1)	0	0	0
Injection site pain	0	0	0.3 (1)	0.3 (1)
Systemic adverse events	2.7 (2)	3.8 (3)	0.6 (2)	0.9 (3)
Pyrexia	1.3 (1)	2.5 (2)	0.3 (1)	0
Headache	1.3 (1)	1.3 (1)	0.3 (1)	0.9 (3)

Incidence % (number of subjects with events)
MedDRA/J Ver.26.1 for children aged 5 to 11 years (Part 2 of Study 214); and MedDRA/J Ver.26.0 for individuals aged ≥12 years (main part of Study 212)

As shown above, the safety profile in children aged 5 to 11 years did not greatly differ between the Daichirona (bivalent, Original and Omicron BA.4-5) group and Comirnaty (bivalent, Original and Omicron BA.4-5) group and raised no safety concerns. In addition, the safety in children aged 5 to 11 years is largely similar to that in individuals aged ≥12 years. Daichirona (bivalent, Original and Omicron BA.4-5) is therefore considered to have acceptable safety.

7.R.3.1.2 Safety of a booster dose of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in individuals aged ≥12 years

The applicant's explanation about the safety of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) as a booster dose in individuals aged ≥12 years:

In a Japanese phase I/II/III study of Daichirona (monovalent, Original) as a booster dose in healthy adults aged ≥18 years (Study 146), which was included in the initial application of Daichirona, the safety did not greatly differ between Daichirona (monovalent, Original) and the control vaccine, i.e., Comirnaty Intramuscular Injection or Spikevax Intramuscular Injection (Review Report of Daichirona for Intramuscular Injection dated July 19, 2023). Study results included in the partial change application for Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years showed that the safety did not greatly differ between Daichirona (bivalent, Original and Omicron BA.4-5) and the control vaccine, i.e., Comirnaty Intramuscular Injection (bivalent, Original and Omicron BA.4-5) (Review Report of Daichirona for Intramuscular Injection dated November 17, 2023). Although clinical study results of Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years are not available, results from both studies showed that the safety profile of Daichirona (monovalent, Omicron XBB.1.5) as a booster dose was similar to those of Daichirona (monovalent, Original) and Daichirona (bivalent, Original and Omicron BA.4-5). In view of its acceptable safety, Daichirona (monovalent, Omicron XBB.1.5) was approved.

Recently, results up to Day 28 after study vaccination (data cut-off on [redacted], 20[redacted]) were obtained from a Japanese phase III study (Study 237) to evaluate the immunogenicity and safety of Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years. Table 15 shows a summary of the safety.

Table 15. Summary of the safety (Study 237, safety analysis population)

	Daichirona (monovalent, Omicron XBB.1.5) (N = 393)	Comirnaty (monovalent, Omicron XBB.1.5) (N = 384)
Solicited adverse events at the injection site	91.9 (361)	88.3 (339)
Severe	3.6 (14)	3.1 (12)
Solicited systemic adverse events	46.6 (183)	46.9 (180)
Severe	1.8 (7)	2.6 (10)
Unsolicited adverse events	19.6 (77)	19.3 (74)
Severe	0	0
Unsolicited adverse reactions	8.1 (32)	3.6 (14)
Severe	0	0
Death	0	0
Serious adverse events	0	0.5 (2)
Adverse events leading to study discontinuation	0	0

Incidence % (number of subjects with events)

Table 16 shows solicited adverse events reported within 7 days after study vaccination. Similar incidences were observed in both groups.

Table 16. Solicited adverse events reported within 7 days after study vaccination (Study 237, safety analysis population)

	Daichirona (monovalent, Omicron XBB.1.5) (N = 393)		Comirnaty (monovalent, Omicron XBB.1.5) (N = 384)	
	All	Severe	All	Severe
Adverse events at the injection site	91.9 (361)	3.6 (14)	88.3 (339)	3.1 (12)
Injection site erythema	14.0 (55)	1.5 (6)	9.9 (38)	2.1 (8)
Injection site swelling	17.8 (70)	1.8 (7)	14.6 (56)	1.3 (5)
Injection site induration	14.2 (56)	0.8 (3)	12.0 (46)	1.0 (4)
Injection site pain	89.3 (351)	0.5 (2)	85.7 (329)	0.5 (2)
Injection site warmth	29.3 (115)	0.3 (1)	31.5 (121)	0.3 (1)
Injection site pruritus	21.6 (85)	0	13.8 (53)	0
Systemic adverse events	46.6 (183)	1.8 (7)	46.9 (180)	2.6 (10)
Pyrexia	16.0 (63)	0.5 (2)	16.7 (64)	0.8 (3)
Malaise	30.5 (120)	0.8 (3)	35.9 (138)	1.3 (5)
Headache	17.8 (70)	0.8 (3)	24.7 (95)	0.8 (3)
Rash	1.0 (4)	0	1.0 (4)	0
Myalgia	17.3 (68)	0.3 (1)	19.0 (73)	0.3 (1)

Incidence % (number of subjects with events), MedDRA/J Ver.26.1

Table 17 shows unsolicited adverse events and adverse reactions reported within 28 days after study vaccination by ≥4 subjects in either group. Similar incidences were observed in both groups. No severe events occurred.

Table 17. Unsolicited adverse events and adverse reactions reported within 28 days after study vaccination by ≥4 subjects in either group (Study 237, safety analysis population)

Event	Unsolicited adverse events		Unsolicited adverse reactions	
	Daichirona (monovalent, Omicron XBB.1.5) (N = 393)	Comirnaty (monovalent, Omicron XBB.1.5) (N = 384)	Daichirona (monovalent, Omicron XBB.1.5) (N = 393)	Comirnaty (monovalent, Omicron XBB.1.5) (N = 384)
Overall	19.6 (77)	19.3 (74)	8.1 (32)	3.6 (14)
Nasopharyngitis	3.8 (15)	2.1 (8)	0.3 (1)	0
Injection site erythema	2.3 (9)	0.3 (1)	2.0 (8)	0.3 (1)
Injection site pain	1.5 (6)	0.3 (1)	1.5 (6)	0.3 (1)
Injection site pruritus	1.5 (6)	0	1.5 (6)	0
Headache	1.3 (5)	2.1 (8)	0.3 (1)	0.5 (2)
Pyrexia	1.3 (5)	0.5 (2)	0.5 (2)	0
COVID-19	1.0 (4)	1.0 (4)	0	0
Injection site induration	1.0 (4)	0.3 (1)	1.0 (4)	0.3 (1)
Injection site swelling	1.0 (4)	0.3 (1)	1.0 (4)	0.3 (1)

Incidence % (number of subjects with events), MedDRA/J Ver.26.1

No serious adverse events occurred in the Daichirona (monovalent, Omicron XBB.1.5) group until the data cut-off date. Serious adverse events occurred in 0.5% (2 of 384) of subjects in the Comirnaty (monovalent, Omicron XBB.1.5) group (anaemia megaloblastic and angina pectoris in 1 subject each), but a causal relationship to the study vaccine was ruled out for the events. Neither death nor adverse events leading to study discontinuation occurred.

The above results from Study 237 showed that the safety profile in individuals aged ≥12 years did not greatly differ between Daichirona (monovalent, Omicron XBB.1.5) and Comirnaty Intramuscular Injection (monovalent, Omicron XBB.1.5) and raised no additional safety concerns.

As described in Section 7.R.2, Daichirona (monovalent, Omicron JN.1) has been approved because the safety of Daichirona is considered very unlikely to be affected by the strain change, although clinical study results of Daichirona (monovalent, Omicron JN.1) are not available.

7.R.3.1.3 Safety of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) as booster dose in children aged 5 to 11 years

The applicant's explanation about safety of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) as a booster dose in children aged 5 to 11 years:

Based on study results and reviews described in Sections 7.R3.1.1 and 7.R3.1.2, the safety of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) as a booster dose in children aged 5 to 11 years is considered similar to that in individuals aged ≥12 years, as observed with Daichirona (bivalent, Original and Omicron BA.4-5), and thus considered acceptable, though no clinical study data of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in children aged 5 to 11 years are available.

PMDA's view:

There was no clinically relevant difference between the safety of Daichirona (bivalent, Original and Omicron BA.4-5) in children aged 5 to 11 years in Study 214 and that of Comirnaty Intramuscular Injection for 5 to 11 years old (bivalent, Original and Omicron BA.4-5), raising no serious safety concerns. The safety profile was also confirmed to be generally similar to the safety profile of Daichirona

(bivalent, Original and Omicron BA.4-5) in individuals aged ≥12 years in Study 212. Daichirona (bivalent, Original and Omicron BA.4-5) as a booster dose in children aged 5 to 11 years therefore have acceptable safety. The following applicant's explanation is acceptable: Although clinical study results of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in children aged 5 to 11 years are not available, in view of the formulation of Daichirona (monovalent, Omicron XBB.1.5 or JN.1), which is a modified version of Daichirona (monovalent, Original), and of the safety profiles in clinical studies of Daichirona (bivalent, Original and Omicron BA.4-5) and Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years, Daichirona (monovalent, Omicron XBB.1.5 or JN.1) as a booster dose have acceptable safety in children aged 5 to 11 years, as shown in individuals aged ≥12 years. However, since no data are available on the safety of Daichirona (monovalent, Omicron JN.1), the applicant should continue collecting the relevant information in post-marketing settings, provide the obtained information to healthcare professionals, and consider the necessity of raising additional caution.

7.R.3.2 Myocarditis and pericarditis

The applicant's view on the risk of myocarditis and pericarditis after Daichirona vaccination:
Data on the risk of myocarditis and pericarditis after vaccination with an approved SARS-CoV-2 RNA vaccine (Comirnaty Intramuscular Injection or Spikevax Intramuscular Injection), a same-class vaccine as Daichirona, do not show any clear difference between populations aged 5 to 11 years and ≥12 years (the joint meeting of the 104th meeting of the Adverse Reaction Working Group of the Subcommittee on Immunization and Vaccines of the Health Sciences Council and the 7th meeting of the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Council in FY2024[19]). In the clinical studies of Daichirona (monovalent, Original; bivalent, Original and Omicron BA.4-5; and monovalent, Omicron XBB.1.5) and post-marketing settings, neither myocarditis nor pericarditis has occurred.[20]

According to reports submitted to date, the risk of myocarditis and pericarditis after vaccination with Daichirona in the population aged 5 to 11 years is not considered to be clearly different from that in the population aged ≥12 years. However, the risk of myocarditis and pericarditis is included with a cautionary statement in the package inserts of the same-class vaccines (Comirnaty Intramuscular Injection and Spikevax Intramuscular Injection), and serious myocarditis or pericarditis, if it occurs, will require medical intervention and, otherwise, would rapidly lead to fatal outcome. This risk should be continuously listed as the important potential risk in the risk management plan (RMP) and subject to caution, as done with the same-class vaccines.

PMDA's view:
After vaccination with an approved SARS-CoV-2 RNA vaccine, a same-class vaccine, myocarditis and pericarditis occurred frequently in males aged ≥10 and ≤29 years (*MMWR.* 2022;71:517-23, *Vaccine*. 2022;40:5153-9, *J Infect Chemother.* 2024;S1341-321X(24)00209-5). However, the incidence of myocarditis after SARS-CoV-2 infection or vaccination with SARS-CoV-2 RNA vaccine is shown to be

[19] https://www.mhlw.go.jp/stf/shingi2/newpage_00109.html (last accessed on December 3, 2024)
[20] At the joint meeting of the 104th meeting of the Adverse Reaction Working Group of the Subcommittee on Immunization and Vaccines of the Health Sciences Council and the 7th meeting of the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Council in FY2024, myocarditis in 1 individual suspected to be related to Daichirona (monovalent, Omicron XBB.1.5) was reported. However, the investigation revealed that the individual had received a vaccine product different from Daichirona.

lower in the age group of 5 to 11 years than in the age group of ≥12 years (*MMWR.* 2022;71:517-23), but its onset has been reported (the joint meeting of the 104th meeting of the Adverse Reaction Working Group of the Subcommittee on Immunization and Vaccines of the Health Sciences Council and the 7th meeting of the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Council in FY2024[19)]).

In the clinical studies of Daichirona (monovalent, Original; bivalent, Original and Omicron BA.4-5; and monovalent, Omicron XBB.1.5) and post-marketing settings, neither myocarditis nor pericarditis has occurred, but Daichirona is classified as a SARS-CoV-2 RNA vaccine, and labeling of the same-class vaccines has raised caution about myocarditis and pericarditis. Therefore, as with the same-class vaccines, attention should be paid to myocarditis and pericarditis. The applicant is required to raise caution about myocarditis and pericarditis, as has been done for the indication of Daichirona for use in individuals aged ≥12 years and with the same-class vaccines, continue collecting information, and consider appropriate measures based on the obtained information.

7.R.4 Clinical positioning and indication

The applicant's explanation about the clinical positioning of Daichirona:
Since the WHO declared COVID-19 as a PHEIC in 2020, various measures have been taken against the global pandemic of COVID-19. Even after the end of the declaration on May 5, 2023, the WHO still continues to recommend SARS-CoV-2 vaccination, collection and reporting of various data including epidemiologic information, and development of new vaccines and therapies.[2)]

The proportion of children with anti-SARS-CoV-2 antibodies in Japan was approximately 91% for anti-N protein antibody and approximately 96% for anti-S protein antibody in the population aged 5 to 9 years and approximately 87% and 95%, respectively, in the population aged 10 to 14 years. Thus, most children possess these antibodies (the 85th meeting of the Infectious Diseases Working Group of the Health Sciences Council[21)]). However, while various measures are in place, the epidemic has not resolved due to the emergence of new variants. Although children are likely to have mild COVID-19 if infected with SARS-CoV-2, a certain number of pediatric patients experienced acute encephalopathy or myocarditis, some resulting in severe COVID-19 or death (*Front Neurosci.* 2023;17:1085082, etc.). Under such circumstances, SARS-CoV-2 vaccination in children is still recommended at present ("Principles for SARS-CoV-2 vaccination in children during the 2024/25 season [in Japanese]" dated October 27, 2024; Committee on Immunization and Infectious Diseases of the Japan Pediatric Society). To prevent the spread of SARS-CoV-2 infection at school or home, vaccination in children aged 5 to 11 years is important. Furthermore, development of Daichirona is considered meaningful because it will allow the establishment of the production of and supply system for variant-adapted vaccines in Japan, in addition to existing SARS-CoV-2 vaccines, to ensure prompt response to newly emerging variants in the future and provide preventive measures against COVID-19.

As described above, new SARS-CoV-2 variants have been emerging. Prevalent variants have changed from the time of Study 214 to the submission of the present application. The antigen strain of the vaccine in the present application (Omicron XBB.1.5 lineage) is different from the antigen strains (Original and

21) https://www.mhlw.go.jp/content/10906000/001257066.pdf (last accessed on December 3, 2024)

Omicron BA.4-5 lineages) of the vaccine used in Study 214, whose data are used to support the present application. Clinical study results of Daichirona (monovalent, Omicron XBB.1.5) in children aged 5 to 11 years are not available, but for use in individuals aged ≥12 years, the antigen strain of the vaccine has been changed through partial change applications. Taking also account of data from Study 214 [see Sections 7.R.2 and 7.R.3], a vaccine adapted to the currently prevalent strain may be used in children aged 5 to 11 years. Furthermore, since the use of vaccines adapted to the Omicron JN.1 lineage and its sublineages was recommended for the regular SARS-CoV-2 vaccination program in autumn and winter 2024 in Japan,[4)] the applicant developed an Omicron JN.1-adapted vaccine and obtained an approval of the vaccine for use in individuals aged ≥12 years (September 2024). Considering that children aged 5 to 11 years are also eligible for Daichirona (monovalent, Omicron JN.1) as with individuals aged ≥12 years, the applicant changed the plan of the present application to include Daichirona (monovalent, Omicron JN.1).

When the present application was submitted, the vaccine product to be used was specified in the Indication section. However, the statement specifying the vaccine product to be used was considered unnecessary and thus deleted based on the "Handling of Changes to COVID-19 Vaccine Strains" (PSB/PED Notification No. 0523-1 and PSB/CND Notification No. 0523-3 dated May 23, 2024) for the following reason: Daichirona is deemed as a vaccine in which a change of the antigen strain is very unlikely to affect the quality and safety and the post-change immunogenicity can be predicted from non-clinical study results.[22)]

Based on the above, the applicant considers that the indication for the present application should be the same as that for use in individuals aged ≥12 years, i.e., "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)."

PMDA's view:
Although most children in Japan have already acquired immunity to SARS-CoV-2, it is important to make a vaccine adapted to the prevalent virus available as a preventive measure against COVID-19, as it has been, under circumstances where the SARS-CoV-2 epidemic has not completely resolved even with various measures in place to date and new variants will continue to emerge in the future. In addition, SARS-CoV-2 vaccines available for children aged 5 to 11 years have been approved in Japan, but as the applicant explained, development of Daichirona is considered clinically meaningful because Daichirona is produced and supplied in Japan and its variant-adapted vaccines can be made available for children in Japan without delay.

In view of the emergence of SARS-CoV-2 variants and the speed of virus mutations observed to date, it is unavoidable to submit the application for the vaccine product with the antigen strain different from that of the vaccine product used in clinical studies. The previous review of Daichirona in individuals aged ≥12 years suggests an immune response to the target antigen strain, and the safety profile is also likely to remain unchanged irrespective of the antigen strain of the vaccine (Review Report of Daichirona for Intramuscular Injection dated November 17, 2023). The applicant's strategy is acceptable to obtain an approval of the indication of Daichirona (monovalent, Omicron XBB.1.5) based on the

22) Approved on September 2, 2024

results from Study 214 conducted using Daichirona (bivalent, Original and Omicron BA.4-5) [see Section 7.R.1].

During the review of the present application, the antigen strain of the vaccine to be used for the regular vaccination program in autumn and winter 2024 was determined to be the Omicron JN.1 lineage and its sublineages. A change in the antigen strain to the Omicron JN.1 lineage was approved for the use of Daichirona in individuals aged ≥12 years. Clinical study results of Daichirona (monovalent, Omicron JN.1) in children aged 5 to 11 years are not available. In view of study results of Daichirona available to date (Review Report of Daichirona for Intramuscular Injection dated July 19, 2023, Review Report of Daichirona for Intramuscular Injection dated November 17, 2023, and partial change approval for the change in the strain dated September 2, 2024) and the review of data from Study 214 [see Sections 7.R.2 and 7.R.3], an immune response to the target antigen strain is expected and the safety profile is likely to remain unchanged irrespective of the antigen strain of the vaccine. An approval of the indication of Daichirona (monovalent, Omicron JN.1) for use in children aged 5 to 11 years is expected to contribute to preventive measures against COVID-19 in Japan.

In conclusion, PMDA considers it possible to specify the same indication as that for use in individuals aged ≥12 years i.e., "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)," after deleting the statement specifying the vaccine product.

7.R.5 Dosage and administration

The applicant's explanation about the rationale for the dosage and administration:

The doses in children aged 5 to 11 years were investigated in Part 1 of Study 214. In Part 1 of Study 214, the doses investigated were determined to be 10 μg and 20 μg with reference to the dose of Comirnaty Intramuscular Injection planned to be used as the control vaccine and the dose of Spikevax Intramuscular Injection which was demonstrated to have immunogenicity similar to that of Daichirona in Study 146 included in the initial application for Daichirona. The immunogenicity and safety of Daichirona were investigated in Part 1 of Study 214. Since Daichirona 20 μg induced an immune response and was tolerable, the dose of 20 μg was selected for Part 2 of Study 214. In Part 2 of Study 214, Daichirona (bivalent, Original and Omicron BA.4-5) was demonstrated to be non-inferior to Comirnaty Intramuscular Injection (bivalent, Original and Omicron BA.4-5) in terms of the GMT and antibody response rate of neutralizing antibody titer against SARS-CoV-2 (Omicron BA.5.2.1 lineages) and shown to have acceptable safety. Clinical study results of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in children aged 5 to 11 years are not available, but Daichirona at the same dose, irrespective of valency, is expected to have efficacy and show a safety profile similar to that observed to date, in view of clinical study results of Daichirona (bivalent, Original and Omicron BA.4-5) and Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years.

Based on the above, the dosage and administration of Daichirona in children aged 5 to 11 years may be proposed as "A single dose of 0.2 mL is injected intramuscularly as a booster dose."

The approved dosage and administration of Daichirona in individuals aged ≥12 years at the time of submission of the present application was "A single dose of 0.6 mL is injected intramuscularly as a

booster dose." However, the "Modification of Dosage and Administration of COVID-19 Vaccines (in Japanese)" (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1 dated March 6, 2024) instructed that the "Dosage and Administration" of COVID-19 vaccines in individuals other than infants (those aged ≥5 years) should be described on the assumption that any vaccine is administered as a booster dose. The dosage and administration for use in individuals aged ≥12 years was changed to "A single dose of 0.6 mL is injected intramuscularly." through a minor change notification,[5)] and a statement specifying the vaccine product to be used was judged to be unnecessary and thus deleted as in the Indication section when a partial change application for changing the antigen strain of Daichirona (change from the Omicron XBB.1.5 lineage to the JN.1 lineage) was approved. The proposed dosage and administration of Daichirona in children aged 5 to 11 years was also changed to "A single dose of 0.2 mL is injected intramuscularly." as done for that in individuals aged ≥12 years.

PMDA's view:
The dosage and administration of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in children aged 5 to 11 years can be selected based on the results from clinical studies conducted using Daichirona (bivalent, Original and Omicron BA.4-5) in view of the review of the efficacy [see Section 7.R.2] and safety [see Section 7.R.3], and the applicant's explanation, although no clinical study of Daichirona (monovalent, Omicron XBB.1.5 or JN.1) in children aged 5 to 11 years has been conducted. In addition, the proposed dosage and administration in children aged 5 to 11 years in the present application may be revised to "A single dose of 0.2 mL is injected intramuscularly." as done for that in individuals aged ≥12 years according to the relevant notification.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigations of Daichirona:
The safety evaluation based on clinical study results [see Section 7.R.3] raised no particular safety concerns for use in children aged 5 to 11 years, who are added as a new population eligible for Daichirona.

According to reports from clinical studies conducted to date, the events listed in the safety specification in the risk management plan are expected to occur less frequently. Since post-marketing surveillance etc. does not allow identification of risk factors or assessment of a causal relationship between an event and Daichirona, additional pharmacovigilance activities will not include the post-marketing surveillance etc. In post-marketing settings, the applicant will conduct an early post-marketing phase vigilance and collect information from spontaneous reports, published literature and academic conferences, and reports on actions taken by foreign regulators as part of routine pharmacovigilance activities. Based on the evaluation results, the applicant will implement safety measures such as post-marketing surveillance, where necessary. If the general use-results survey being conducted in individuals aged ≥12 years raises any concern about the safety of Daichirona, the applicant will examine the relevant information including the information on use in children aged 5 to 11 years collected through the above routine pharmacovigilance activities, thereby implementing safety measures.

PMDA's view:

In view of the clinical study results and the applicant's explanation, the expansion of the age group eligible for Daichirona to children aged 5 to 11 years does not require any additional safety specification. All of the events listed in the safety specification have occurred less frequently, and thus the information on these events cannot be collected through post-marketing surveillance, etc. that only covers a portion of medical institutions and vaccine recipients. In addition, there are currently no critical concerns about the safety of Daichirona in children aged 5 to 11 years. The risk associated with Daichirona can be appropriately controlled if the applicant collects information through the routine pharmacovigilance activities and takes necessary actions, such as safety measures, based on the obtained information without conducting the post-marketing surveillance, etc. However, since Daichirona is expected to be administered to individuals with various characteristics, including those that have not been investigated in clinical studies, the applicant should analyze the safety information collected in post-marketing settings, including information on the development of myocarditis and pericarditis [see Section 7.R.3.2] and results from the general use-results survey being conducted in individuals aged ≥12 years, and continue to monitor whether the safety profile of the vaccine in children aged 5 to 11 years remains favorable. At the same time, the applicant should consider implementing further safety measures, where necessary.

The final decision on the appropriateness of the above PMDA's conclusion will be made, taking account of comments from the Expert Discussion.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Daichirona (monovalent, Omicron XBB.1.5 and JN.1) has efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in children aged 5 to 11 years to a certain extent, and that Daichirona is unlikely to raise critical safety concerns and therefore has acceptable safety. In view of the assessment of benefit-risk balance based on the prevalence of SARS-CoV-2 and characteristics of individual recipients, PMDA considers

that it is clinically meaningful to make Daichirona available for vaccination in children aged 5 to 11 years.

PMDA has concluded that Daichirona may be approved if Daichirona is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 5, 2025

Product Submitted for Approval

Brand Name	Daichirona for Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 24, 2024

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).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Sections "7.R.2 Efficacy," "7.R.3 Safety," "7.R.4 Clinical positioning and indication," "7.R.5 Dosage and administration," and "7.R.6 Post-marketing investigations" in the Review Report (1).

PMDA also discussed the following points and took action as necessary.

1.1 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA has concluded that the current risk management plan (draft) for Daichirona should include the safety specification presented in Table 18, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 19.

Table 18. 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 • Guillain Barre syndrome • Vaccine associated enhanced disease (VAED) and vaccine associated enhanced respiratory disease (VAERD)	• Safety in pregnant and nursing women
Efficacy specification		
None		

No change for the present application

Table 19. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (booster dose in individuals aged ≥12 years) [Omicron XBB.1.5] • Early post-marketing phase vigilance (booster dose in children aged ≥5 and ≤11 years) • General use-results survey	• Disseminate data collected through early post-marketing phase vigilance (booster dose in individuals aged ≥12 years) [Omicron XBB.1.5] • Disseminate data collected though early post-marketing phase vigilance (booster dose in children aged ≥5 and ≤11 years) • Organize and disseminate information material for healthcare professionals (a proper use guide) • Organize and disseminate information material for vaccine recipients (for individuals receiving Daichirona for Intramuscular Injection) • Organize and disseminate information material for vaccine recipients (for children receiving Daichirona for Intramuscular Injection and their guardians) • Periodical publication of the occurrence of adverse reactions (booster dose in individuals aged ≥12 years) [Omicron XBB.1.5]

Underline denotes changes associated with the present application.

2. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the proposed indication and the dosage and administration as shown below, with the following approval condition. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until August 1, 2031).

Indication

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

(No change)

Dosage and Administration

Individuals aged ≥12 years

A single dose of 0.6 mL is injected intramuscularly.

Children aged ≥5 and ≤11 years

A single dose of 0.2 mL is injected intramuscularly.

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

CI	Confidence interval
Comirnaty	Comirnaty Intramuscular Injection or Comirnaty RTU Intramuscular Injection
Comirnaty (bivalent, Original and Omicron BA.4-5)	Comirnaty RTU Intramuscular Injection (bivalent, Original and Omicron BA.4-5) or Comirnaty Intramuscular Injection (bivalent, Original and Omicron BA.4-5)
COVID-19	Coronavirus disease
Daichirona	Daichirona (monovalent, original) and its modified versions adapted to variants
Daichirona (monovalent, Original)	Vaccine containing ufrenmeran (mRNA encoding the RBD of the S protein of the original strain) as the active substance
Daichirona (monovalent, Omicron JN.1)	Vaccine containing MAFB-6197a (mRNA encoding the RBD analog of the S protein of the Omicron JN.1 lineage) as the active substance
Daichirona (monovalent, Omicron XBB.1.5)	Vaccine containing bemremeran (mRNA encoding the RBD analog of the S protein of the Omicron XBB.1.5 lineage) as the active substance
Daichirona (bivalent, Original and Omicron BA.4-5)	Vaccine containing ufrenmeran and tegrenmeran (mRNA encoding the RBD analog of the S protein of the Omicron BA.4/BA.5 lineages) as the active substances
DNA	Deoxyribonucleic acid
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
ICMRA	International Coalition of Medicines Regulatory Authorities
LNP	Lipid Nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
Original strain	Wuhan-Hu-1 strain
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-protocol set
RBD	Receptor-binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
S protein	Spike protein
Study 146	Study DS5670-146
Study 212	Study DS5670-212
Study 214	Study DS5670-214
Study 237	Study DS5670-237
WHO	World Health Organization