Review Report

November 17, 2023
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Daichirona for Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine (Active ingredients: (a) Ufrenmeran [JAN*], (b) MAFB-7256a)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	September 7, 2023
Dosage Form/Strength	(a) Injection: Each vial contains 0.15 mg of Ufrenmeran. (b) Injection: Each vial contains 0.15 mg of MAFB-7256a.
Application Classification	Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage, (10-2) Other drugs (among drugs classified as [10], those pertaining to change of manufacturing method of biological products, etc.)
Items Warranting Special Mention	Application and expedited review based on "Handling of application for partial change approval of a drug and the review and investigation pertaining to the concerned application" (PSB/PED Notification No. 0905-3 dated September 5, 2023 by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare) and "Expedited processing of the review and investigation of drugs (Request)" (PSB/PED Notification No. 1023-2 dated October 23, 2023 by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product is expected to have efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety with no critical concerns (see Attachment).

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

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)

(Underline denotes additions.)

Dosage and Administration

A single dose of 0.6 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.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information on the product at the current moment, the applicant is required to (a) promptly collect the safety data of the product, such as information on adverse reactions after the market launch based on the pre-designed schedule, (b) submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and (c) take necessary actions to ensure the proper use of the product.
3. The applicant is required to submit results of the ongoing or planned Japanese clinical studies of the product to PMDA as soon as they become available and take necessary actions to make the latest efficacy and safety data of the product easily accessible to healthcare professionals and vaccine recipients.
4. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the latest efficacy and safety data of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

November 16, 2023

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

Product Submitted for Approval

Brand Name	Daichirona for Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine (Active ingredients: (a) Ufrenmeran, (b) MAFB-7256a)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	September 7, 2023
Dosage Form/Strength	(a) Injection: Each vial contains 0.15 mg of Ufrenmeran. (b) Injection: Each vial contains 0.15 mg of MAFB-7256a.

Proposed Indication

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

Proposed Dosage and Administration

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

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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 in multiple waves of SARS-CoV-2 infection. On May 5, 2023, World Health Organization (WHO) declared an end to COVID-19 as a public health emergency of international concern,[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, but under the Immunization Act, SARS-CoV-2 vaccines are still included in the temporary vaccination program.

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 Wuhan-Hu-1 variant (the original strain) (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 that SARS-CoV-2 vaccines to be used in the vaccination program in autumn and winter 2023 in Japan should be basically monovalent vaccine against the Omicron XBB.1.5 lineage.[3)] In response to this policy, the applicant developed a monovalent vaccine against 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 of Daichirona (monovalent, Omicron XBB.1.5) based on (a) the quality data and the non-clinical study results of Daichirona (monovalent, Omicron XBB.1.5) and (b) the clinical study results of bivalent vaccine of Daichirona against the original strain and Omicron BA.4-5 lineage (Daichirona [bivalent, Original and Omicron BA.4-5]) administered as a booster dose. 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 2023, 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

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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 November 1, 2023)

2) https://cdn.who.int/media/docs/default-source/documents/ihr/covid-19_standing-recommendations_9-august-2023.pdf (last accessed on November 1, 2023)

3) Material for the 49th meeting of the Subcommittee on Immunization and Vaccines of the Health Sciences Council: https://www.mhlw.go.jp/stf/shingi/shingi-kousei_127713.html (last accessed on November 1, 2023)

- Daichirona (monovalent, Omicron XBB.1.5): Vaccine containing MAFB-7256a (mRNA encoding RBD analog of S protein of Omicron XBB.1.5 lineage) as the active substance (to be added through the present application)
- Daichirona (monovalent, Omicron BA.4-5): Vaccine containing MAFB-6282a (mRNA encoding RBD analog of the S protein of Omicron BA.4/BA.5 lineages) as the active substance
- Daichirona (bivalent, Original and Omicron BA.4-5): Vaccine containing ufrenmeran and MAFB-6282a (mRNA encoding RBD analog of the S protein of Omicron BA.4/BA.5 lineages) as the active substances

2. Quality and Outline of the Review Conducted by PMDA

Daichirona (monovalent, Omicron XBB.1.5), the product proposed in the present application, is a vaccine containing MAFB-7256a (i.e., mRNA encoding RBD analog of the S protein of the SARS-CoV-2 Omicron XBB.1.5 lineage) encapsulated in lipid nanoparticles (LNPs).

2.1 Active substance

The active substances of the proposed Daichirona (monovalent, Omicron XBB.1.5) and the approved Daichirona (monovalent, Original) are MAFB-7256a and ufrenmeran, respectively. The mRNA sequence encoding RBD partially differs between MAFB-7256a and ufrenmeran, but these active substances are the same in that (a) both include the 5' cap structure and poly A tail and (b) all original cytidine and uridine residues have been replaced by 5-methylcytidine and 5-methyluridine residues, respectively.

2.1.1 Generation and control of cell substrate used in manufacture of raw materials

A cell bank of *Escherichia coli* (*E. coli*) is used to prepare the template deoxyribonucleic acid (DNA), one of the raw materials. The cell bank of *E. coli* for MAFB-7256a is prepared in the same manner as that for ufrenmeran, except that a plasmid DNA encoding MAFB-7256a is used to prepare the former. The cell bank for MAFB-7256a is controlled in the same manner as that for ufrenmeran, except that the former is subject to identification of the DNA sequence specific to RBD analog of the Omicron XBB.1.5 lineage.

2.1.2 Manufacturing process of active substance and manufacturing process development

The active substance of Daichirona (monovalent, Omicron XBB.1.5) and the ufrenmeran active substance are made through the same manufacturing process, except that template DNA encoding MAFB-7256a is used in *in vitro* transcription in the manufacturing process of the former.

The ufrenmeran and MAFB-7256a active substances underwent comparability exercises and were demonstrated to have comparable quality attributes, except the RNA sequence.

2.1.3 Characterization and control of active substance

Characterization of the active substance of Daichirona (monovalent, Omicron XBB.1.5) included RNA sequence (Sanger sequencing), 5'-cap structure (reverse-phase chromatography and mass spectrometry after RNase H digestion), Poly A tail length ([redacted]), tertiary structure (circular dichroism spectroscopy), [redacted] ([redacted] electrophoresis),

ultraviolet absorption (ultraviolet-visible spectrophotometry) and *in vitro* biological activity (cell-based assay [ ]).

The specifications for the active substance of Daichirona (monovalent, Omicron XBB.1.5) are the same as those for the ufrenmeran active substance, except for identification. The identification test was changed from (a) sequencing by polymerase chain reaction (PCR) and by electrophoresis and determination of electrophoresis time by electrophoresis to (b) sequencing by Sanger sequencing.

2.1.4 Stability of active substance

Table 1 shows a summary of the main stability studies for the active substance of Daichirona (monovalent, Omicron XBB.1.5). For the present application, the applicant submitted the long-term testing plan and baseline data.

Table 1. Summary of main stability studies for active substance

Study	Number of batches	Storage condition	Period	Storage form
Long-term	3	−70 ± 10°C	0 months[a)]	bag

a) Baseline. The long-term testing is ongoing and continued until Month 24.

The shelf life of the ufrenmeran active substance is 12 months (Review Report on Daichirona for Intramuscular Injection dated July 19, 2023). The same shelf life (12 months) was proposed for the MAFB-7256a active substance. Both active substances are manufactured by the same process (except template DNA) and were demonstrated to have comparable quality attributes (except RNA sequence).

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

The proposed Daichirona (monovalent, Omicron XBB.1.5) vaccine product is an aqueous injection, and each vial (1.5 mL) contains 150 µg of RNA as the MAFB-7256a active substance for 2 doses (0.6 mL per dose). Except for the active substance, the proposed vaccine product has the same formulation as Daichirona (monovalent, Original) vaccine product, which contains the ufrenmeran active substance instead.

2.2.2 Manufacturing process of vaccine product and manufacturing process development

The manufacturing process of Daichirona (monovalent, Omicron XBB.1.5) vaccine product is comprised of , , , liquid preparation, sterile filtration, filling, clamping, testing, and labeling/packaging/storage, and is the same as that of Daichirona (monovalent, Original) vaccine product, except that a change has been made to a part of procedures of the liquid preparation process. In the pre-change process of liquid preparation, , while in the post-change process, . The post-change manufacturing process has been validated at a commercial scale.

In response to the strain change, Daichirona (monovalent, Original) and Daichirona (monovalent, Omicron XBB.1.5) underwent comparability exercises and were demonstrated to have comparable quality attributes, except the RNA sequence and potency. Of note, the applicant submitted results from

a Japanese phase III clinical study (Study DS5670-212 [Study 212]) of Daichirona (bivalent, Original and Omicron BA.4-5) for the present application. This vaccine product (Daichirona [bivalent, Original and Omicron BA.4-5]) was also demonstrated to have comparable quality attributes to those of Daichirona (monovalent, Original) and Daichirona (monovalent, Omicron XBB.1.5), except RNA sequence and potency.

2.2.3 Control of vaccine product

The specifications for Daichirona (monovalent, Omicron XBB.1.5) vaccine product are the same as those for Daichirona (monovalent, Original) vaccine product, except for identification, [redacted], and potency assay. The identification test was changed from determination of electrophoresis time by [redacted] electrophoresis to sequencing by Sanger sequencing. [redacted] was changed from [redacted] to [redacted]. In the potency assay, [redacted] remains unchanged, but minor changes were made to the acceptance criteria and test methods [see Section 2.R.1].

2.2.4 Stability of vaccine product

Table 2 shows a summary of the main stability studies for Daichirona (monovalent, Omicron XBB.1.5) vaccine product. For the present application, the applicant submitted the long-term testing plan and baseline data.

Table 2. Summary of main stability studies for vaccine product

Study	Number of batches	Storage condition	Period	Storage form
Long-term	4	5 ± 3°C	0 months[a)]	Glass vial and [redacted] rubber stopper

a) Baseline. The long-term testing is ongoing and continued until Month 12.

The shelf life of Daichirona (monovalent, Original) vaccine product is 7 months (Review Report on Daichirona for Intramuscular Injection dated July 19, 2023). The same shelf life (7 months) was proposed for Daichirona (monovalent, Omicron XBB.1.5) vaccine product. Both vaccine products are manufactured by the same process and were demonstrated to have comparable quality attributes except RNA sequence and potency.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that the active substance and vaccine product have no particular problems in quality.

2.R.1 Potency assay of vaccine product

The potency assay is a test for [redacted].
The potency assay for Daichirona (monovalent, Original) vaccine product was based on [redacted], but the applicant proposed potency assay based on [redacted] for Daichirona (monovalent, Omicron XBB.1.5) vaccine product, because the change of mRNA-encoded vaccine antigen [redacted].

Potency assay acceptance criteria for Daichirona (monovalent, Omicron XBB.1.5) vaccine product were defined based on precision of the analytical procedure and batch-to-batch variations, which were obtained from the potency assay of Daichirona (monovalent, Original) vaccine product. PMDA asked the applicant to explain the appropriateness of such defined potency assay acceptance criteria.

The applicant's explanation:
In view of potency assay data obtained from Daichirona (monovalent, Original) and Daichirona (bivalent, Original and Omicron BA.4-5) vaccine products to date through development, changes made to the mRNA-encoded vaccine antigen and test procedures are considered to have only a limited impact on [redacted] of the potency assay. Both Daichirona (monovalent, Original) and Daichirona (monovalent, Omicron XBB.1.5) vaccine products are made by the same manufacturing process, except that changes have been made to the sequence of template DNA and to a part of procedures in the liquid preparation process. There are currently limited manufacturing experience (data) with Daichirona (monovalent, Omicron XBB.1.5) vaccine product, but Daichirona (monovalent, Original) and Daichirona (monovalent, Omicron XBB.1.5) vaccine products were demonstrated to be comparable, and both are presumed to have similar batch-to-batch variations. In view of the above supporting information, the applicant considered it possible to establish potency assay acceptance criteria for Daichirona (monovalent, Omicron XBB.1.5) vaccine product based on potency assay data (precision of the analytical procedure and batch-to-batch variations) obtained from Daichirona (monovalent, Original) vaccine product.

PMDA's view:
Potency assay acceptance criteria for Daichirona (monovalent, Omicron XBB.1.5) vaccine product should be established based on its manufacturing experience (data). However, it is unavoidable to establish potency assay acceptance criteria for Daichirona (monovalent, Omicron XBB.1.5) vaccine product based on precision of the analytical procedure and batch-to-batch variations obtained from potency assay of Daichirona (monovalent, Original) vaccine product, in view of the following:

(a) The Japanese government's vaccination policy demands early commercialization of Daichirona (monovalent, Omicron XBB.1.5)
(b) Potency assay data obtained from Daichirona (monovalent, Original) and Daichirona (bivalent, Original and Omicron BA.4-5) vaccine products
(c) Comparability data between the vaccine products and between the active substances of Daichirona (monovalent, Original) and Daichirona (monovalent, Omicron XBB.1.5).

In the future, however, appropriateness of the potency assay acceptance criteria should be verified based on the manufacturing experience (data) of Daichirona (monovalent, Omicron XBB.1.5) vaccine product. PMDA asked the applicant to submit verification results of the potency assay acceptance criteria as soon as the results become available. The applicant agreed.

2.R.2 Stability of active substance and vaccine product

The proposed shelf lives of the active substance and vaccine product of Daichirona (monovalent, Omicron XBB.1.5) should be supported by their long-term test results, but no data are available from the tests. PMDA asked the applicant to explain the stability of the active substance and vaccine product of Daichirona (monovalent, Omicron XBB.1.5).

The applicant's explanation:
MAFB-7256a active substance and ufrenmeran active substance have comparable quality attributes, except RNA sequence encoding RBD, and are therefore considered to have comparable stability profiles. Thus the shelf life of MAFB-7256a active substance can be the same (i.e., 12 months) as that of ufrenmeran active substance.

Daichirona (monovalent, Omicron XBB.1.5) vaccine product and Daichirona (monovalent, Original) vaccine product have comparable quality attributes, except RNA sequence encoding RBD and potency, and are therefore considered to have comparable stability profiles. Thus the shelf life of Daichirona (monovalent, Omicron XBB.1.5) vaccine product can be the same (i.e., 7 months) as that of Daichirona (monovalent, Original) vaccine product.

PMDA's view:
The following applicant's explanation is acceptable:

> The comparability exercises showed that the active substances of Daichirona (monovalent, Omicron XBB.1.5) and Daichirona (monovalent, Original) had similar quality attributes and their vaccine products also had similar quality attributes. This means that the active substances, as well as the vaccine products, are presumed to have similar stability profiles. Thus the shelf lives of the active substance and the vaccine product of Daichirona (monovalent, Omicron XBB.1.5) can be the same as those of Daichirona (monovalent, Original).

However, the applicant should confirm the stability of MAFB-7256a active substance and Daichirona (monovalent, Omicron XBB.1.5) vaccine product by the ongoing long-term testing of these active substance and vaccine product. PMDA asked the applicant to submit results from the ongoing stability studies of MAFB-7256a active substance and Daichirona (monovalent, Omicron XBB.1.5) vaccine product as soon as they become available. The applicant agreed.

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

The applicant submitted data on primary pharmacodynamics of Daichirona (bivalent, Original and Omicron BA.4-5) and Daichirona (monovalent, Omicron XBB.1.5) as non-clinical pharmacology data.

3.1 Primary pharmacodynamics

3.1.1 Immunogenicity (CTD 4.2.1.1-2)

BALB/c mice (8 females/group) received 2 doses of Daichirona (monovalent, Original)[4)] 2 weeks apart as the primary series and then a booster dose of Daichirona (monovalent, Original),[4)] Daichirona (bivalent, Original and Omicron BA.4-5),[4)] or Daichirona (monovalent, Omicron XBB.1.5)[4)] 2 weeks after the second dose. Immunogenicity of these vaccine products was then investigated.

Serum samples from blood collected 2 weeks after the booster dose were subjected to a luciferase reporter assay using pseudo-virus to measure blood neutralization activity. The booster dose of any vaccine product induced neutralizing antibodies against the corresponding strain or variant. In addition,

4) The dose is 2 μg of mRNA.

the booster dose of Daichirona (monovalent, Original) scarcely induced neutralizing antibodies against the Omicron XBB.1.5 lineage, but that of Daichirona (bivalent, Original and Omicron BA.4-5; or monovalent, Omicron XBB.1.5) induced them. Furthermore, the booster dose of Daichirona (bivalent, Original and Omicron BA.4-5; or monovalent, Omicron XBB.1.5) induced neutralizing antibodies against Omicron XBB.1.16 and XBB.2.3 lineages.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that the applicant's explanation about non-clinical pharmacology of Daichirona is acceptable.

3.R.1 Immunogenicity for production of antibodies against other variants

The applicant's explanation about Daichirona-induced immunogenicity against variants:

Since the start of the COVID-19 pandemic, various SARS-CoV-2 variants have emerged. In Japan, Omicron EG.5.1 and EG.5.1.1 lineages are predominant as of September 2023 (COVID-19 weekly surveillance update: epidemiologic situational awareness Week 36, 2023 [September 4-10], National Institute of Infectious Diseases[5]; Currently Prevalent SARS-CoV-2 Variants Worldwide [in Japanese] [October 11, 2023], Tokyo Metropolitan Institute of Public Health[6]). In view of this situation, the immune response to the Omicron EG.5.1 lineage was investigated in the mouse immunogenicity study [see Section 3.1.1]. Neutralizing antibodies against the Omicron EG.5.1 lineage was induced in mice that received the primary series consisting of 2 doses of Daichirona (monovalent, Original) and a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5; or monovalent, Omicron XBB.1.5), which was administered 2 weeks after the second dose of primary series.

PMDA accepted the applicant's explanation.

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

Although the present application relates to a new indication and 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. Toxicity and Outline of the Review Conducted by PMDA

Since the present application relates to a new indication and a new dosage, no data relating to toxicity 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 quantification, 10).

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5) https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/12015-covid19-surveillance-report.html (last accessed on November 1, 2023)
6) https://www.tmiph.metro.tokyo.lg.jp/lb_virus/worldmutation/ (last accessed on November 1, 2023)

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 results from 1 study as the efficacy and safety evaluation data (Table 3). Although Study 212 is comprised of 3 parts, the main part only is outlined in Section 7.1.

Table 3. Clinical study for efficacy and safety evaluation

Data category	Region	Study ID	Phase	Study population	No. of subjects enrolled	Dosage regimen	Objective
Evaluation	Japan	Study 212	III	**Main part and Sub-A part:** Individuals aged ≥12 years who had received the primary series and a booster(s) of Comirnaty (At least 3 months had passed since the last Comirnaty dose.) **Sub-B part:** Individuals aged ≥12 years who had received the primary series of an approved vaccine and a booster(s) of an approved vaccine (At least 3 months had passed since the last dose of an approved vaccine)	Main part: 701 Sub-A part: 301 Sub-B part: 401	**Main part:** A single intramuscular injection of Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg[a)] or Comirnaty (bivalent, Original and Omicron BA.4-5) 30 μg[b)] **Sub-A part:** A single intramuscular injection of Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg[a)] Daichirona (monovalent, Original) 60 μg, or Daichirona (monovalent, Omicron BA.4-5) 30 or 60 μg **Sub-B part:** A single intramuscular injection of Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg[a)]	Immunogenicity Safety

a) Containing 30 μg each of ufrenmeran and MAFB-6282a RNA (mRNA encoding RBD analog of the S protein of Omicron BA.4/BA.5 lineages)
b) Containing equal RNA amounts of tozinameran and famtozinameran

7.1 Japanese phase III study (CTD 5.3.5.1-1-1 to 5.3.5.1-1-33, main part of Study 212, ongoing since May 2023 [data cut-off on ■■, 20■])

A multi-center, randomized, observer-blind,[7)] active-controlled study was conducted at 5 study centers in Japan, to evaluate the immunogenicity and safety of a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) in healthy individuals aged ≥12 years with no history of SARS-CoV-2 infection who had received the primary series and a booster dose(s) of Comirnaty (the last booster dose was with Comirnaty [bivalent, Original and Omicron BA.4-5]) (At least 3 months had passed since the last Comirnaty booster dose.) The target sample size was 700 subjects (350 per group[8)]).

7) The following people were not blinded: independent statistics experts, 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.

8) The primary objective of this study was to demonstrate non-inferiority of Daichirona (bivalent, Original and Omicron BA.4-5) to Comirnaty (bivalent, Original and Omicron BA.4-5). Both of the following criteria were required to be met to demonstrate the non-inferiority:
(a) The lower limit of 2-sided 95% CI of GMT ratio (Daichirona [bivalent, Original and Omicron BA.4-5] / Comirnaty [bivalent, Original and Omicron BA.4-5]) of blood anti-SARS-CoV-2 neutralizing antibody titer at Week 4 after study vaccination exceeds 0.67, the non-inferiority margin.
(b) The lower limit of 2-sided 95% CI of difference (Daichirona [bivalent, Original and Omicron BA.4-5] – Comirnaty [bivalent, Original and Omicron BA.4-5]) in antibody response of blood anti-SARS-CoV-2 neutralizing antibody titer at Week 4 exceeds –10%, the non-inferiority margin.

The subjects received a intramuscular administration of Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg or Comirnaty (bivalent, Original and Omicron BA.4-5) 30 μg.

All of 701 randomized subjects[9] (349 in the Daichirona [bivalent, Original and Omicron BA.4-5] group, 352 in the Comirnaty [bivalent, Original and Omicron BA.4-5] group) received study vaccine and were included in the safety analysis and full analysis set (FAS). Of the 701 subjects in the FAS, 700 (348 in the Daichirona [bivalent, Original and Omicron BA.4-5] group, 352 in the Comirnaty [bivalent, Original and Omicron BA.4-5] group) were included in the per-protocol set (PPS). The remaining 1 subject in the Daichirona (bivalent, Original and Omicron BA.4-5) group was excluded because of a critical protocol deviation that would affect efficacy evaluation. Of the 701 subjects in the FAS, 699 (349 in the Daichirona [bivalent, Original and Omicron BA.4-5] group, 350 in the Comirnaty [bivalent, Original and Omicron BA.4-5] group) were included in the immunogenicity-evaluable FAS. The remaining 2 subjects in the Comirnaty (bivalent, Original and Omicron BA.4-5) group were excluded because their immunogenicity data could not be obtained after study vaccination. Of the 699 subjects in the immunogenicity-evaluable FAS, 698 (348 in the Daichirona [bivalent, Original and Omicron BA.4-5] group, 350 in the Comirnaty [bivalent, Original and Omicron BA.4-5] group) were included in the immunogenicity-evaluable PPS. The remaining 1 subject in the Daichirona (bivalent, Original and Omicron BA.4-5) group was excluded because of a critical protocol deviation that would affect immunogenicity evaluation. The immunogenicity-evaluable PPS was the primary analysis population for immunogenicity.

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 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 both of the following requirements were met:

- The lower limit of 2-sided 95% confidence interval (CI) of the adjusted GMT ratio (Daichirona [bivalent, Original and Omicron BA.4-5] group/Comirnaty [bivalent, Original and Omicron BA.4-5] group) exceeds 0.67.
- The lower limit of 2-sided 95% CI of the difference in the antibody response rate between the Daichirona (bivalent, Original and Omicron BA.4-5) and Comirnaty (bivalent, Original and Omicron BA.4-5) groups exceeds −10%.

Table 4 shows the results of the primary endpoints for immunogenicity. The lower limit of 2-sided 95% CI of the adjusted GMT ratio exceeded 0.67 (the predefined value), and that of the difference in the antibody response rate exceeded −10% (the predefined value). Thus Daichirona (bivalent, Original

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In a study where the target sample size of 700 subjects are randomized in a 1:1 ratio, 10% of them would not contribute to immunogenicity evaluation, and a one-sided significance level of 0.025 is applied, on the assumption that GMT ratio (Daichirona [bivalent, Original and Omicron BA.4-5] /Comirnaty [bivalent, Original and Omicron BA.4-5]) is 1.00, and pooled standard deviation of common logarithm of neutralization activity is 0.490, the power to demonstrate the non-inferiority in terms of GMT is 99.4%; and on the assumption that the antibody response rate in both Daichirona (bivalent, Original and Omicron BA.4-5) and Comirnaty [bivalent, Original and Omicron BA.4-5] groups is 90.0%, the power to demonstrate the non-inferiority in terms of the antibody response rate is 98.2%.

9) Stratification factors were study center, age (≥12 and <18 years; ≥18 and <65 years; or ≥65 years), and interval from the last SARS-CoV-2 vaccination (≥3 and <5 months; or ≥5 months).

and Omicron BA.4-5) was shown to be non-inferior to Comirnaty (bivalent, Original and Omicron BA.4-5).

Table 4. Blood anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibody titer and antibody response rate at Week 4 (main part of Study 212, immunogenicity-evaluable PPS)

	Serum neutralizing antibody titer			Serum neutralizing antibody response rate		
	n	Adjusted GMT [2-sided 95% CI][a)]	Adjusted GMT ratio [2-sided 95% CI][a)]	n2/n1	Antibody response rate (%) [2-sided 95% CI][b)]	Difference in antibody response rate (%) [2-sided 95% CI][c)]
Daichirona (bivalent, Original and Omicron BA.4-5) (N = 348)	328	390.741 [353.627, 431.751]	1.720 [1.516, 1.952]	221/328	67.4 [62.0, 72.4]	21.6 [14.0, 28.8]
Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 350)	321	227.113 [205.169, 251.405]		147/321	45.8 [40.2, 51.4]	

N = Number of subjects analyzed
n or n1 = Number of subjects with immunogenicity data available
n2 = Number of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
When the antibody titer was below the lower limit of quantification, the value of "0.5 × the lower limit of quantification" was used in analyses of GMT and antibody response rate.
a) The adjusted GMT, adjusted GMT ratio, and their 2-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, age (≥12 and <65 years, or ≥65 years), and interval from the last SARS-CoV-2 vaccination (≥3 and <6 months, or ≥6 months) as covariates.
b) The 2-sided 95% CI was calculated according to the Clopper-Pearson method.
c) The 2-sided 95% CI was calculated according to the Newcombe-Wilson score method.

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) guidance (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[10)]
  - Adverse events at the injection site (redness [erythema], swelling, induration, pain, warmth, and pruritus)
  - Systemic adverse events (fever [axillary temperature ≥37.5°C], malaise, headache, rash, myalgia)
- Unsolicited adverse events were collected for 28 days after study vaccination[10)]
- Serious adverse events were collected between the time of informed consent and Week 52 after study vaccination.[10)]

Table 5 shows solicited adverse events occurring within 7 days after study vaccination.

[10)] Subjects (or legally acceptable representatives, in principle, if subjects were aged ≥12 and <18 years) were required to record in an electronic diary (a) the status of solicited adverse events (yes/no and other information) on a daily basis for 7 days (Day 1-8) after study vaccination and (b) the description of unsolicited adverse events (including solicited adverse events that occurred on and after Day 9), if occurred, for 28 days (Day 1-29) after study vaccination. The investigators or sub-investigators were required to identify and assess adverse events by checking entries in the electronic diaries and interview sheets of the subjects or by examining the subjects.

Table 5. Solicited adverse events (main part of Study 212, safety analysis population)

Event	Daichirona (bivalent, Original and Omicron BA.4-5) N = 349		Comirnaty (bivalent, Original and Omicron BA.4-5) N = 352	
	All	Severity	All	Severity
	n (%)	n (%)	n (%)	n (%)
Adverse events at the injection site	312 (89.4)	8 (2.3)	306 (86.9)	5 (1.4)
Injection site erythema	28 (8.0)	0	19 (5.4)	0
Injection site swelling	57 (16.3)	2 (0.6)	36 (10.2)	0
Injection site induration	54 (15.5)	0	35 (9.9)	1 (0.3)
Injection site pain	300 (86.0)	4 (1.1)	300 (85.2)	2 (0.6)
Injection site warmth	133 (38.1)	2 (0.6)	128 (36.4)	2 (0.6)
Injection site pruritus	52 (14.9)	0	36 (10.2)	1 (0.3)
Systemic adverse events	150 (43.0)	8 (2.3)	170 (48.3)	3 (0.9)
Fever	46 (13.2)	5 (1.4)	44 (12.5)	1 (0.3)
Malaise	115 (33.0)	3 (0.9)	137 (38.9)	2 (0.6)
Headache	64 (18.3)	0	78 (22.2)	0
Rash	5 (1.4)	0	3 (0.9)	0
Myalgia	44 (12.6)	1 (0.3)	41 (11.6)	1 (0.3)

N = Number of subjects analyzed, n = Number of subjects with events, Medical Dictionary for Regulatory Activities (MedDRA)/J Ver.26.0

Table 6 shows unsolicited adverse events and adverse reactions reported by ≥2 subjects in either group. Severe unsolicited adverse events occurred in 4 subjects (1.1%) in the Daichirona (bivalent, Original and Omicron BA.4-5) group only (diarrhoea, inguinal hernia, injection site erythema, and injection site swelling in 1 subject each). A causal relationship to Daichirona (bivalent, Original and Omicron BA.4-5) could not be ruled out for diarrhoea, injection site erythema, and injection site swelling.

Table 6. Unsolicited adverse events and adverse reactions occurring in ≥2 subjects in either group by Day 28 (main part of Study 212, safety analysis population)

Event	Adverse events		Adverse reactions	
	Daichirona (bivalent, Original and Omicron BA.4-5) N = 349	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 352	Daichirona (bivalent, Original and Omicron BA.4-5) N = 349	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 352
	n (%)	n (%)	n (%)	n (%)
Overall	54 (15.5)	42 (11.9)	22 (6.3)	15 (4.3)
Nasopharyngitis	8 (2.3)	5 (1.4)	0	0
Fever	4 (1.1)	0	3 (0.9)	0
COVID-19	3 (0.9)	3 (0.9)	0	0
Diarrhoea	3 (0.9)	1 (0.3)	1 (0.3)	1 (0.3)
Injection site erythema	3 (0.9)	0	3 (0.9)	0
Headache	2 (0.6)	4 (1.1)	2 (0.6)	1 (0.3)
Injection site pain	2 (0.6)	3 (0.9)	2 (0.6)	3 (0.9)
Rhinorrhoea	2 (0.6)	2 (0.6)	0	0
Dental caries	2 (0.6)	1 (0.3)	0	0
Nausea	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Urticaria	2 (0.6)	1 (0.3)	0	0
Injection site swelling	2 (0.6)	0	2 (0.6)	0
Chills	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)
Oropharyngeal pain	0	3 (0.9)	0	0

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver.26.0

Serious adverse events occurred in 1 subject (inguinal hernia) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and in 1 subject (appendicitis) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. As for the outcome at the time of data cut-off, inguinal hernia in the Daichirona (bivalent, Original and Omicron BA.4-5) group was resolving (eventually resolved according to the subsequent follow-up), and appendicitis in the Comirnaty (bivalent, Original and

Omicron BA.4-5) group resolved. A causal relationship to the study vaccine was ruled out for both events.

Neither deaths nor adverse events leading to study discontinuation occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

On May 5, 2023, WHO declared an end to COVID-19 as a public health emergency of international concern.[11] In Japan, under the 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, but public health concerns for the spread of infection have not completely disappeared. Since January 2020, several therapeutic agents and preventive vaccines against COVID-19 have been developed, and various preventive measures including vaccination have been taken. However, mutations of SARS-CoV-2 genes resulted in successive emergence of variants with altered infectivity, transmissibility, antigenicity, and pathogenicity and have caused the multiple waves of SARS-CoV-2 infection. The Omicron variant, which has become dominant SARS-CoV-2 strain worldwide since 2022, evades immunity induced by already available vaccines due to its changed antigenicity; this may result in decreased efficacy and durability of vaccines against the Omicron variant (*N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). The primary series alone of a SARS-CoV-2 vaccine for original strain has reduced efficacy against the Omicron variant, but a booster dose restores neutralization activity against the variant (*Nat Med.* 2022;28:1063-71, *Nat Commun.* 2022;13:3082). In preparation for the next COVID-19 waves in autumn 2023 or later, the regulatory authorities in Japan and other countries recommend that the Omicron XBB.1 lineage be used as the antigen strain for SARS-CoV-2 vaccines. The Japanese regulatory authority announced the policy that monovalent vaccines against the Omicron XBB.1.5 lineage should be basically used for the SARS-CoV-2 vaccination program in autumn and winter 2023 in Japan.[12]

Development of vaccines against SARS-CoV-2 variants was discussed at the COVID-19 Omicron variant workshop of the International Coalition of Medicines Regulatory Authorities (ICMRA) held on May 8, 2023. The workshop presented an approach for authorization/approval of antigen strain changes for vaccines already authorized or approved as of May 8, 2023; this approach would only require confirmatory quality and non-clinical study data at time of authorization or approval, provided that post-approval data on the quality, efficacy, immunogenicity, and safety are collected.[13]

In view of the above circumstances, the applicant developed Daichirona (monovalent, Omicron XBB.1.5) using the Omicron XBB.1.5 lineage as the antigen strain instead of the original strain, which was used in Daichirona (monovalent, Original) approved for marketing in Japan on August 2, 2023. Although clinical study results of Daichirona (monovalent, Omicron XBB.1.5) were not available, the applicant considered that the approach for authorization/approval of variant-adapted vaccines

[11] 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 November 1, 2023)
[12] Material for the 49th meeting of the Subcommittee on Immunization and Vaccines of the Health Sciences Council: https://www.mhlw.go.jp/stf/shingi/shingi-kousei_127713.html (last accessed on November 1, 2023)
[13] https://icmra.info/drupal/en/covid-19/8may2023 (last accessed on November 1, 2023)

presented by the ICMRA COVID-19 Omicron variant workshop, was applicable to development of Daichirona (monovalent, Omicron XBB.1.5), because it was a variant-adapted vaccine with antigen strain that has been changed from that of Daichirona (monovalent, Original), an already approved vaccine in Japan. The applicant, therefore, submitted an application for partial change approval of Daichirona (monovalent, Omicron XBB.1.5) based on its quality and non-clinical data and results from a Japanese phase III study (Study 212) of Daichirona (bivalent, Original and Omicron BA.4-5), which was a modified version of Daichirona (monovalent, Original). Further, the applicant is planning a clinical study of Daichirona (monovalent, Omicron XBB.1.5) to collect data on its efficacy, immunogenicity, and safety.

PMDA's review policy for the present application:
Data on quality submitted for the present application demonstrated that quality attributes of Daichirona (monovalent, Omicron XBB.1.5) were comparable to those of Daichirona (monovalent, Original), except RNA sequence encoding RBD and potency [see Section 2]. Further, a non-clinical pharmacology study demonstrated that Daichirona (monovalent, Omicron XBB.1.5) induced an immune response in mice [see Section 3]. In view of limited clinical experience with Daichirona including the monovalent vaccine (Original) currently, data from the Japanese phase III study (Study 212) of Daichirona (bivalent, Original and Omicron BA.4-5) are considered useful in discussing the efficacy and safety of Daichirona (monovalent, Omicron XBB.1.5), although the antigen strains of these vaccines are different. PMDA therefore considered that the approach for authorization/approval of variant-adapted vaccines presented at the ICMRA COVID-19 Omicron variant workshop held on May 8, 2023, was applicable to Daichirona, and decided to conduct a review for Daichirona (monovalent, Omicron XBB.1.5) based on its quality and non-clinical data and the clinical study results of Daichirona (bivalent, Original and Omicron BA.4-5), on condition that the applicant plans to conduct a clinical study of Daichirona (monovalent, Omicron XBB.1.5). The applicant should conduct the planned clinical study of Daichirona (monovalent, Omicron XBB.1.5) promptly and thereby evaluate its efficacy (immunogenicity) and safety. The applicant should promptly submit efficacy (immunogenicity) and safety data obtained from clinical studies, etc. after the market launch of Daichirona (monovalent, Omicron XBB.1.5) and take necessary actions, such as appropriately providing the data to healthcare professionals.

7.R.2 Efficacy

The applicant's explanation about immunogenicity of the booster dose with Daichirona (bivalent, Original and Omicron BA.4-5) in the Japanese phase III study (Study 212) submitted for the present application:
Data from the approved SARS-CoV-2 vaccines show that blood anti-SARS-CoV-2 neutralizing antibody titer can predict vaccine efficacy (*Nat Med.* 2021;27:1205-11). In addition, "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" (Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, dated July 15, 2022) includes the following statements:

> If a new vaccine for booster dose has a mechanism of action similar to that of an approved SARS-CoV-2 vaccine, the efficacy of the new vaccine can be evaluated based on immunogenicity.

The primary endpoints of a clinical study of the new vaccine should be the GMT and immune response rate of neutralizing antibody titer against the target SARS-CoV-2 strain. The non-inferiority of the new vaccine to an appropriate active comparator should be demonstrated using these primary endpoints.

Based on the above, the main part of Study 212 was conducted in order to demonstrate the non-inferiority of a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) to a booster dose of Comirnaty (bivalent, Original and Omicron BA.4-5) using the following primary endpoints: the GMT and antibody response rate of neutralizing antibody titer against the SARS-CoV-2 strain (Omicron BA.5 lineage) at Week 4. The study demonstrated non-inferiority of Daichirona (bivalent, Original and Omicron BA.4-5) to Comirnaty (bivalent, Original and Omicron BA.4-5) [see Section 7.1]. Table 7 shows immunogenicity results of the study vaccines against the Omicron BA.5 lineage or original strain before and after study vaccination in the main part of Study 212. Table 8 shows immunogenicity results against the Omicron XBB.1 and BQ.1 lineages, which were assessed for an exploratory purpose. The booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) increased neutralizing antibody titers against any strain or lineage assessed.

Table 7. Blood anti-SARS-CoV-2 (Omicron BA.5 lineage and original strain) neutralizing antibody titer: GMT, GMFR, and antibody response rate (main part of Study 212, immunogenicity-evaluable PPS)

	Omicron BA.5 lineage		Original strain	
	Daichirona (bivalent, Original and Omicron BA.4-5) N = 348	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 350	Daichirona (bivalent, Original and Omicron BA.4-5) N = 348	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 350
Baseline (Day 1)				
n	348	349	348	349
GMT [2-sided 95% CI][a)]	73.286 [62.084, 86.510]	74.492 [63.156, 87.861]	470.556 [410.490, 539.412]	469.818 [411.229, 536.755]
Week 4 (Day 29)				
n	328	321	328	321
GMT [2-sided 95% CI][a)]	405.458 [351.356, 467.891]	235.502 [203.819, 272.109]	1933.583 [1752.908, 2132.880]	1015.538 [907.077, 1136.967]
GMFR [2-sided 95% CI][a)]	5.852 [5.209, 6.574]	3.398 [3.092, 3.733]	4.298 [3.866, 4.777]	2.291 [2.102, 2.498]
Antibody response rate[b)]				
n2/n1	221/328	147/321	178/328	75/321
Antibody response rate (%) [2-sided 95% CI][c)]	67.4 [62.0, 72.4]	45.8 [40.2, 51.4]	54.3 [48.7, 59.8]	23.4 [18.8, 28.4]

N = Number of subjects analyzed
n or n1 = Number of subjects with immunogenicity data available
n2 = Number of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
When the antibody titer was below the lower limit of quantification, the value of "0.5 × the lower limit of quantification" was used in analyses of GMT and antibody response rate.
a) The 2-sided 95% CI was calculated using the assumed t-distribution for common logarithm of the antibody titer or antibody fold-rise.
b) Percentage of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
c) The 2-sided 95% CI was calculated according to the Clopper-Pearson method.

Table 8. Blood anti-SARS-CoV-2 (Omicron XBB.1.5.6 and BQ.1.1.3 lineages) neutralizing antibody titer: GMT, GMFR, and antibody response rate (main part of Study 212, immunogenicity-evaluable PPS)

	Omicron XBB.1.5.6 lineage		Omicron variant BQ.1.1.3 lineage	
	Daichirona (bivalent, Original and Omicron BA.4-5) N = 348	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 350	Daichirona (bivalent, Original and Omicron BA.4-5) N = 348	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 350
Baseline (Day 1)				
n	348	349	348	349
GMT [2-sided 95% CI][a)]	25.503 [22.333, 29.124]	26.597 [23.178, 30.521]	46.914 [40.007, 55.013]	49.722 [42.503, 58.168]
Week 4 (Day 29)				
n	328	321	328	321
GMT [2-sided 95% CI][a)]	148.283 [130.808, 168.092]	84.257 [74.511, 95.278]	184.337 [159.247, 213.380]	157.255 [136.272, 181.469]
GMFR [2-sided 95% CI][a)]	6.155 [5.592, 6.776]	3.461 [3.186, 3.760]	4.115 [3.741, 4.527]	3.427 [3.140, 3.741]
Antibody response rate[b)]				
n2/n1	237/328	138/321	172/328	143/321
Antibody response rate (%) [2-sided 95% CI][c)]	72.3 [67.1, 77.0]	43.0 [37.5, 48.6]	52.4 [46.9, 58.0]	44.5 [39.0, 50.2]

N = Number of subjects analyzed
n or n1 = Number of subjects with immunogenicity data available
n2 = Number of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
When the antibody titer was below the lower limit of quantification, the value of "0.5 × the lower limit of quantification" was used in analyses of GMT and antibody response rate.
a) The 2-sided 95% CI was calculated using the assumed t-distribution for common logarithm of the antibody titer or antibody fold-rise.
b) Percentage of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
c) The 2-sided 95% CI was calculated according to the Clopper-Pearson method.

The eligible age for the approved Daichirona (monovalent, Original) is ≥18 years, but Study 212 was conducted in a wider age population (i.e., ≥12 years of age). Immunogenicity analysis by age group used data from not only the main part but also Sub-A and Sub-B parts of Study 212, because the main part included only 6 subjects aged ≥12 years and <18 years. As shown in Table 9, GMTs in subjects aged ≥12 years and <18 years before and after study vaccination were higher than those in the other age groups, and the geometric mean fold rise (GMFR) and antibody response rate in this age group had similar trends to those in the other age groups.

Table 9. Immunogenicity against SARS-CoV-2 (Omicron BA.5 lineage) by age group (pooled data from the main, Sub-A, and Sub-B parts of Study 212, immunogenicity-evaluable PPS)

	≥12 years and <18 years		≥18 years and <65 years		≥65 years	
	Daichirona (bivalent, Original and Omicron BA.4-5) N = 33	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 4	Daichirona (bivalent, Original and Omicron BA.4-5) N = 656	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 276	Daichirona (bivalent, Original and Omicron BA.4-5) N = 132	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 70
Baseline (Day 1)						
n	33	4	656	276	132	69
GMT [2-sided 95% CI][a)]	160.034 [85.085, 301.002]	134.447 [11.626, 1554.834]	67.558 [59.450, 76.771]	77.929 [64.489, 94.172]	45.611 [35.325, 58.893]	60.098 [42.502, 84.978]
Week 4 (Day 29)						
n	30	4	603	253	126	64
GMT [2-sided 95% CI][a)]	1222.199 [842.632, 1772.744]	452.487 [74.696, 2741.028]	515.033 [464.219, 571.408]	246.677 [210.044, 289.699]	362.173 [286.071, 458.521]	188.225 [133.364, 265.653]
GMFR [2-sided 95% CI][a)]	7.998 [4.964, 12.885]	3.366 [0.643, 17.623]	8.276 [7.481, 9.155]	3.356 [3.009, 3.743]	8.156 [6.700, 9.928]	3.569 [2.953, 4.314]
Antibody response rate[b)]						
n2/n1	22/30	2/4	441/603	114/253	96/126	31/64
Antibody response rate (%) [2-sided 95% CI][c)]	73.3 [54.1, 87.7]	50.0 [6.8, 93.2]	73.1 [69.4, 76.6]	45.1 [38.8, 51.4]	76.2 [67.8, 83.3]	48.4 [35.8, 61.3]

N = Number of subjects analyzed
n or n1 = Number of subjects with immunogenicity data available
n2 = Number of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
When the antibody titer was below the lower limit of quantification, the value of "0.5 × the lower limit of quantification" was used in analyses of GMT and antibody response rate.
a) The 2-sided 95% CI was calculated using the assumed t-distribution for common logarithm of the antibody titer or antibody fold-rise.
b) Percentage of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
c) The 2-sided 95% CI was calculated according to the Clopper-Pearson method.

For COVID-19 occurring on Day 8 or later,[14)] the data up to Week 4 in the main part of Study 212 are available. COVID-19 occurred in 2 subjects in the Daichirona (bivalent, Original and Omicron BA.4-5) group, while it did not occur in the Comirnaty (bivalent, Original and Omicron BA.4-5) group.

The applicant's explanation about the efficacy of Daichirona (monovalent, Omicron XBB.1.5):
Study results submitted for the initial application of Daichirona showed that Daichirona (monovalent, Original) increased blood anti-SARS-CoV2 neutralizing antibody titers in both mouse immunogenicity and clinical studies (Review Report on Daichirona for Intramuscular Injection dated July 19, 2023). Study results submitted for the present application showed that Daichirona (bivalent, Original and Omicron BA.4-5) increased (a) blood anti-SARS-CoV-2 (Omicron BA.4-5 lineage) neutralization activity in the mouse immunogenicity study [see Section 3.1] and (b) neutralizing antibody titer in the clinical study, as described above. Clinical study results of Daichirona (monovalent, Omicron XBB.1.5) are not available, but Daichirona (monovalent, Omicron XBB.1.5) induced blood anti-SARS-CoV-2 neutralization activity (Omicron XBB.1.5, XBB.1.16, XBB.2.3 lineages, etc.) in a mouse immunogenicity study [see Section 3.1]. As described in Section 7.R.1, the applicant considers that the approach for authorization/approval of variant-adapted vaccines presented

14) A patient with COVID-19 was defined as an individual who had at least 1 of "fever 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 reverse transcription polymerase chain reaction (RT-PCR), SARS-CoV-2 antigen testing, or other examinations.

at the ICMRA COVID-19 Omicron variant workshop held on May 8, 2023, is applicable to development of Daichirona (monovalent, Omicron XBB.1.5). A booster dose of Daichirona (monovalent, Omicron XBB.1.5) is expected to increase blood anti-SARS-CoV-2 neutralizing antibody titers against the Omicron variant and have efficacy against the Omicron variant, in view of the following:

(a) The quality attributes of Daichirona (monovalent, Omicron XBB.1.5) are comparable to those of Daichirona (monovalent, Original), except RNA sequence encoding RBD and potency [see Section 2].
(b) The non-clinical and clinical study results presented above.

PMDA's view:
Based on the policy for review described in Section 7.R.1, PMDA considers that a booster dose of Daichirona (monovalent, Omicron XBB.1.5) is expected to have efficacy against the Omicron variant, because the following points have been confirmed by the data submitted for the present application:

- Daichirona (monovalent, Omicron XBB.1.5) is a variant-adapted vaccine with antigen strain modified from that of Daichirona (monovalent, Original), an already approved vaccine in Japan.
- Quality attributes of Daichirona (monovalent, Omicron XBB.1.5) were demonstrated to be comparable to those of Daichirona (monovalent, Original), except RNA sequence encoding RBD and potency [see Section 2].
- In a non-clinical pharmacology study in mice, Daichirona (monovalent, Omicron XBB.1.5) induced an immune response [see Section 3].
- The clinical study of a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) demonstrated the non-inferiority of Daichirona (bivalent, Original and Omicron BA.4-5) to Comirnaty (bivalent, Original and Omicron BA.4-5) in terms of the GMT and antibody response rate of anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibody titer. The analysis by age group showed that immune response was induced in all age groups including individuals aged 12 to 18 years.

The applicant, however, should conduct a clinical study of Daichirona (monovalent, Omicron XBB.1.5) promptly and then submit the obtained results to PMDA and provide relevant information to healthcare professionals appropriately.

7.R.3 Safety

Based on the following review, PMDA considers that a booster dose of Daichirona (monovalent, Omicron XBB.1.5) in individuals aged ≥12 years has acceptable safety. However, the applicant should raise caution about myocarditis and pericarditis and collect information on the evens, as has been done with the same-class vaccines. The applicant should continue collecting the safety information of Daichirona (monovalent, Omicron XBB.1.5) through clinical studies, post-marketing surveillance, etc., provide the obtained information to healthcare professionals, and consider the necessity of raising additional caution.

7.R.3.1 Safety profile

The applicant's explanation about safety in Study 212:

Table 10 shows a summary of the safety data in the main part of Study 212.

Table 10. Summary of safety (main part of Study 212, safety analysis population)

	Daichirona (bivalent, Original and Omicron BA.4-5) (N = 349) % (n)	Comirnaty (bivalent, Original and Omicron BA.4-5) (N = 352) % (n)
Solicited adverse events at the injection site	89.4 (312)	86.9 (306)
Severe events	2.3 (8)	1.4 (5)
Solicited systemic adverse events	43.0 (150)	48.3 (170)
Severe events	2.3 (8)	0.9 (3)
Unsolicited adverse events	15.5 (54)	11.9 (42)
Severe events	1.1 (4)	- (0)
Unsolicited adverse reactions	6.3 (22)	4.3 (15)
Severe events	0.9 (3)	- (0)
Death	- (0)	- (0)
Serious adverse events	0.3 (1)	0.3 (1)

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

(a) Solicited adverse events

In the main part of Study 212, solicited adverse events at the injection site and solicited systemic adverse events occurred frequently in both Daichirona (bivalent, Original and Omicron BA.4-5) and Comirnaty (bivalent, Original and Omicron BA.4-5) groups, but most of them were mild or moderate. Main solicited adverse events were injection site pain (86.0% in the Daichirona [bivalent, Original and Omicron BA.4-5] group and 85.2% in the Comirnaty [bivalent, Original and BA.4-5] group), injection site warmth (38.1% and 36.4%), malaise (33.0% and 38.9%), and headache (18.3% and 22.2%) [see Table 5, Section 7.1].

Median time to onset of solicited adverse events at the injection site (range) was 2 days (1-4 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 2 days (1-5 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. Median duration of the events was 2 days (1-10 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 2 days (1-7 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. Median time to onset of solicited systemic adverse events was 2 days (1-8 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 2 days (1-8 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. Median duration of the events was 1 day (1-10 days) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 1 day (1-10 days) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group.

(b) Unsolicited adverse events

In the main part of Study 212, main unsolicited adverse events were nasopharyngitis (2.3% in the Daichirona [bivalent, Original and Omicron BA.4-5] group and 1.4% in the Comirnaty [bivalent, Original and Omicron BA.4-5] group), fever (1.1% and 0%), COVID-19 (0.9% and 0.9%), diarrhoea (0.9% and 0.3%), and injection site erythema (0.9% and 0%), but most of them in both groups were mild or moderate. Severe unsolicited adverse events in the Daichirona group were diarrhoea, inguinal hernia, injection site erythema, and injection site swelling in 1 subject each, and all of them except

inguinal hernia were considered causally related to Daichirona; all of these events resolved or were resolving at the time of data cut-off ([redacted], 20[redacted]). Neither shock nor anaphylaxis occurred in any of the main, Sub-A, and Sub-B parts of Study 212. Adverse events related to shock and anaphylaxis (adverse events coded to Standardised Medical Dictionary for Regulatory Activities [MedDRA] queries "Anaphylactic reaction [narrow and broad]" and "Hypersensitivity [narrow]") occurred in 2.3% (19 of 824) of subjects in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 1.1% (4 of 352) of subjects in the Comirnaty (bivalent, Original and Omicron BA.4-5) group (according to pooled data from the main, Sub-A, and Sub-B parts of Study 212); all of these events were mild or moderate.

(c) Serious adverse events

In Study 212, serious adverse events occurred in 1 subject (inguinal hernia) in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 1 subject (appendicitis) in the Comirnaty (bivalent, Original and Omicron BA.4-5) group in the main part, and in 1 subject (clavicle fracture) in the Sub-B part (in the Daichirona [bivalent, Original and Omicron BA.4-5] group only), but a causal relationship to study vaccination was ruled out for all of them. All of these events were resolving or resolved. No deaths occurred in any of the main, Sub-A, and Sub-B parts.

(d) Safety by age group

Table 11 shows incidences of solicited adverse events by age group in pooled data from the main, Sub-A, and Sub-B parts of Study 212. Incidences of solicited adverse events at the injection site did not clearly differ among age groups. The incidence of solicited systemic adverse events tended to be lower in the age group ≥65 years than in the other age groups, but did not clearly differ between the age group ≥12 years and <18 years and the age group ≥18 years and <65 years.

Table 11. Solicited adverse events by age group
(pooled data from the main, Sub-A, and Sub-B parts of Study 212, safety analysis population)

Event	≥12 years and <18 years		≥18 years and <65 years		≥65 years	
	Daichirona (bivalent, Original and Omicron BA.4-5) N = 33	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 4	Daichirona (bivalent, Original and Omicron BA.4-5) N = 658	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 277	Daichirona (bivalent, Original and Omicron BA.4-5) N = 132	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 71
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Adverse events at the injection site	97.0 (32)	100 (4)	91.6 (603)	89.2 (247)	84.8 (112)	77.5 (55)
Severe events	3.0 (1)	- (0)	2.6 (17)	1.4 (4)	0.8 (1)	1.4 (1)
Injection site erythema	9.1 (3)	- (0)	6.4 (42)	4.3 (12)	3.0 (4)	9.9 (7)
Severe events	3.0 (1)	- (0)	- (0)	- (0)	- (0)	- (0)
Injection site swelling	24.2 (8)	- (0)	11.9 (78)	9.4 (26)	11.4 (15)	14.1 (10)
Severe events	3.0 (1)	- (0)	0.5 (3)	- (0)	- (0)	- (0)
Injection site induration	15.2 (5)	- (0)	9.9 (65)	10.1 (28)	12.9 (17)	9.9 (7)
Severe events	3.0 (1)	- (0)	0.2 (1)	0.4 (1)	- (0)	- (0)
Injection site pain	93.9 (31)	100 (4)	89.8 (591)	88.1 (244)	79.5 (105)	73.2 (52)
Severe events	- (0)	- (0)	0.9 (6)	0.4 (1)	0.8 (1)	1.4 (1)
Injection site warmth	48.5 (16)	50.0 (2)	40.6 (267)	36.5 (101)	27.3 (36)	35.2 (25)
Severe events	- (0)	- (0)	1.2 (8)	0.4 (1)	- (0)	1.4 (1)
Injection site pruritus	15.2 (5)	- (0)	12.5 (82)	10.5 (29)	9.1 (12)	9.9 (7)
Severe events	- (0)	- (0)	- (0)	0.4 (1)	- (0)	- (0)
Systemic adverse events	60.6 (20)	50.0 (2)	51.1 (336)	52.7 (146)	27.3 (36)	31.0 (22)
Severe events	- (0)	- (0)	2.3 (15)	1.1 (3)	2.3 (3)	- (0)
Fever	30.3 (10)	50.0 (2)	17.0 (112)	13.7 (38)	9.1 (12)	5.6 (4)
Severe events	- (0)	- (0)	1.5 (10)	0.4 (1)	0.8 (1)	- (0)
Malaise	51.5 (17)	50.0 (2)	39.5 (260)	42.6 (118)	21.2 (28)	23.9 (17)
Severe events	- (0)	- (0)	0.6 (4)	0.7 (2)	1.5 (2)	- (0)
Headache	30.3 (10)	50.0 (2)	24.0 (158)	25.3 (70)	7.6 (10)	8.5 (6)
Severe events	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Rash	- (0)	- (0)	1.5 (10)	1.1 (3)	- (0)	- (0)
Severe events	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Myalgia	24.2 (8)	- (0)	15.5 (102)	12.6 (35)	15.9 (21)	8.5 (6)
Severe events	- (0)	- (0)	0.5 (3)	0.4 (1)	- (0)	- (0)

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver.26.0

As shown above, adverse events in Study 212 did not markedly differ between the Daichirona (bivalent, Original and Omicron BA.4-5) and Comirnaty (bivalent, Original and Omicron BA.4-5) groups. A booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) in individuals aged ≥12 years was considered to have acceptable safety.

The applicant's explanation about the safety of Daichirona (monovalent, Omicron XBB.1.5):
The safety profile of a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) in Study 212 do not largely differ from the safety results of a booster dose of Daichirona (monovalent, Original) obtained from a Japanese phase I/II/III study (Study 146), which was submitted for the initial application of Daichirona (Review Report on Daichirona for Intramuscular Injection dated July 19, 2023). Thus no additional safety concerns have been identified. The target SARS-CoV-2 strain/variant and valency (monovalent or bivalent) are considered to have little impact on the safety profile of Daichirona. Accordingly, although clinical study results of Daichirona (monovalent, Omicron

XBB.1.5) are not available, the safety profile of a booster dose of Daichirona (monovalent, Omicron XBB.1.5) is considered similar to those of a booster dose of Daichirona (monovalent, Original) or Daichirona (bivalent, Original and Omicron BA.4-5), and is thus acceptable.

PMDA's view:
The safety profile of a booster dose of Daichirona (bivalent, Original and Omicron BA.4-5) is not largely different from that of a booster dose of Comirnaty (bivalent, Original and Omicron BA.4-5) in Study 212, and is almost similar to safety profile of a booster dose of Daichirona (monovalent, Original) obtained from the clinical study reviewed for the initial approval. Daichirona (bivalent, Original and Omicron BA.4-5) has acceptable safety in individuals aged ≥12 years. Clinical study results of Daichirona (monovalent, Omicron XBB.1.5) are not available, but Daichirona (monovalent, Omicron XBB.1.5) is a modified version of Daichirona (monovalent, Original), and Daichirona (monovalent, Original) and Daichirona (bivalent, Original and Omicron BA.4-5) were shown to have similar safety profiles in clinical studies. Based on the above, the applicant's explanation that the booster dose of Daichirona (monovalent, Omicron XBB.1.5) has acceptable safety is acceptable. However, since safety data of Daichirona (monovalent, Omicron XBB.1.5) are not available, the applicant should continue collecting the safety information of Daichirona (monovalent, Omicron XBB.1.5) through clinical studies, post-marketing surveillance, etc., provide the obtained information to healthcare professionals, and consider the necessity of raising additional caution.

7.R.3.2 Myocarditis and pericarditis

PMDA's view on a risk of myocarditis and pericarditis after a dose of Daichirona:
After administration of an approved SARS-CoV-2 RNA vaccine, a same-class vaccine as Daichirona, myocarditis and pericarditis occurred frequently in males aged ≥10 and <30 years (*MMWR Morb Mortal Wkly Rep.* 2022;71:517-23, the joint meeting of [a] the 82nd meeting of the Adverse Reaction Working Group of the Subcommittee on Immunization and Vaccines of the Health Sciences Council and [b] the 8th meeting of the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council in FY2022[15]). In the clinical studies of Daichirona (monovalent, Original) and Daichirona (bivalent, Original and Omicron BA.4-5), neither myocarditis nor pericarditis occurred, but caution should be exercised about onset of myocarditis and pericarditis, as has been done with the same-class vaccines, for the following reasons:

(1) Vaccination experience with Daichirona is limited.
(2) Daichirona is a SARS-CoV-2 RNA vaccine.
(3) The eligible age for vaccination with Daichirona will be expanded from ≥18 to ≥12 years [see Section 7.R.5.2].

The applicant is required to raise caution about myocarditis and pericarditis, as has been done with the same-class vaccines, continue collecting information, and consider appropriate measures based on the obtained information.

[15] https://www.mhlw.go.jp/stf/shingi2/0000208910_00046.html (last accessed on November 1, 2023)

7.R.4 Clinical positioning and indication

PMDA's view on clinical positioning and indication of Daichirona (monovalent, Omicron XBB.1.5):
As of November 2023, Comirnaty and Spikevax Intramuscular Injection are marketed as SARS-CoV-2 vaccines against Omicron XBB.1.5 lineage in Japan. Based on review on the efficacy and safety, a booster dose of Daichirona (monovalent, Omicron XBB.1.5) is expected to have efficacy in individuals aged ≥12 years [see Section 7.R.2] and is considered to have acceptable safety [see Section 7.R.3]. Daichirona (monovalent, Omicron XBB.1.5), therefore, can be an option among other SARS-CoV-2 vaccines against the Omicron XBB.1.5 lineage. Various SARS-CoV-2 variants have emerged so far. If infection with a new variant spreads in the future, prompt development of a new vaccine against the variant may be required. Compared with conventional vaccines, mRNA vaccines can be developed and produced quickly, and thus establishing a production and supply system of variant-adapted Daichirona vaccine in Japan can be meaningful because this enables prompt measures to be taken to control COVID-19.

The indication of Daichirona (monovalent, Omicron XBB.1.5) can be specified as "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as with that of initially approved Daichirona (monovalent, Original).

7.R.5 Dosage and administration

Based on the following review, PMDA has concluded that the following dosage and administration of Daichirona (monovalent, Omicron XBB.1.5) is acceptable: "A single dose of 0.6 mL is injected intramuscularly as a booster dose." The eligible age of "≥12 years" and the interval from the last SARS-CoV-2 vaccination of "at least 3 months" are both acceptable. (The eligible age and interval will be specified in Precautions Concerning Dosage and Administration section of the package insert.)

7.R.5.1 Dosage

The applicant's e rationale for the dosage of Daichirona (monovalent, Omicron XBB.1.5):
The approved dosage and administration of Daichirona (monovalent, Original) is "A single dose of 0.6 mL is injected intramuscularly as a booster dose." Daichirona (monovalent, Original) 0.6 mL contains 60 μg of ufrenmeran as the active substance.

The main part of Study 212 enrolled subjects who had received the primary series and a booster dose(s) of Comirnaty. In the main part, Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg (containing equal amounts of ufrenmeran and MAFB-6282a [mRNA encoding RBD analog of the S protein of Omicron BA.4/BA.5 lineages]) was shown to be non-inferior to the active comparator Comirnaty (bivalent, Original and Omicron BA.4-5) in terms of the GMT and antibody response rate of blood anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibody titer at Week 4 [see Section 7.R.2], and was shown to have acceptable safety [see Section 7.R.3]. Sub-A part of Study 212 evaluated the immunogenicity of Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg, Daichirona (monovalent, Original) 60 μg, and Daichirona (monovalent, Omicron BA.4-5) 30 or 60 μg to confirm the appropriateness of the selected dosage of Daichirona (bivalent, Original and Omicron BA.4-5). At Week 4, GMT of blood anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibody

titer in the Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg group was higher than those in the Daichirona (monovalent, Original) 60 μg group and Daichirona (monovalent, Omicron BA.4-5) 30 μg group and similar to that in the Daichirona (monovalent, Omicron BA.4-5) 60 μg group. GMT of blood anti-SARS-CoV-2 (original strain) neutralizing antibody titer in the Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg group was similar to that in the Daichirona (monovalent, Original) 60 μg group and higher than that in the Daichirona (monovalent, Omicron BA.4-5) 30 or 60 μg. In Sub-B part, immunogenicity of Daichirona (bivalent, Original and Omicron BA.4-5) 60 μg was evaluated in subjects who had received various SARS-CoV-2 vaccines approved in Japan.[16)] The observed immunogenicity was not affected by previously received SARS-CoV-2 vaccines.

According to the results from Study 212, Daichirona monovalent vaccine 60 μg is expected to yield higher neutralizing antibody titer against a SARS-CoV-2 strain, the target antigen, than Daichirona monovalent vaccine 30 μg. In addition, Daichirona 60 μg, irrespective of valency (monovalent or bivalent), is expected to have efficacy against a SARS-CoV-2 strain(s), the target antigen(s), and the safety profile of Daichirona is not affected by the target SARS-CoV-2 strain/variant or valency (monovalent or bivalent) [see Section 7.R.3].

Thus the appropriate dosage of Daichirona (monovalent, Omicron XBB.1.5) is considered to be 60 μg, the same dosage as with the already approved Daichirona (monovalent, Original) and Daichirona (bivalent, Original and Omicron BA.4-5) used in Study 212. The applicant therefore has proposed the following dosage and administration for Daichirona (monovalent, Omicron XBB.1.5): "A single dose of 0.6 mL is injected intramuscularly as a booster dose."

PMDA's conclusion:
In view of review on the efficacy and safety of Daichirona (monovalent, Omicron XBB.1.5) [see Sections 7.R.2 and 7.R.3] and the above applicant's explanation, the following dosage and administration of Daichirona (monovalent, Omicron XBB.1.5) for a booster dose is acceptable: "a single intramuscular dose of 0.6 mL (60 μg of MAFB-7256a)" (which is the same dosage as with Daichirona [monovalent, Original]).

7.R.5.2 Eligible age

Daichirona (monovalent, Original) was approved based on results from clinical studies in subjects aged ≥18 years (Review Report on Daichirona for Intramuscular Injection dated July 19, 2023). The eligible age for Daichirona (monovalent, Original) is therefore ≥18 years.

The applicant has proposed the eligible age of ≥12 years for Daichirona for the following reasons:

(a) Study 212 investigated the immunogenicity and safety of Daichirona (bivalent, Original and Omicron BA.4-5) in subjects ≥12 years, and analyses on the immunogenicity [see Section 7.R.2] and safety [see Section 7.R.3] by age group raised no particular concerns.

[16)] The study included subjects aged ≥12 years who had received the primary series of Comirnaty (monovalent, Original) or Spikevax Intramuscular Injection (monovalent, Original) and a booster dose(s) of Comirnaty (monovalent, Original; bivalent, Original and Omicron BA.1; bivalent, Original and Omicron BA.4-5), Spikevax Intramuscular Injection (monovalent, Original; bivalent, Original and Omicron BA.1; bivalent, Original and Omicron BA.4-5), Daichirona (monovalent, Original), or Nuvaxovid Intramuscular Injection.

(b) The efficacy and safety of same-class vaccines (Comirnaty and Spikevax Intramuscular Injection) do not differ between individuals aged ≥12 years and <18 years and individuals aged ≥18 years (*MMWR Morb Mortal Wkly Rep.* 2022;71:1401-6, *Advisory Committee on Immunization Practices. Updates to COVID-19 vaccine effectiveness (VE) in the U.S* [September 12, 2023], etc.).

PMDA's view:
Caution should be raised about the risk of myocarditis and pericarditis associated with Daichirona, as has been done with the same-class vaccines, in view of the following:

(a) The review of efficacy [see Section 7.R.2] and safety [see Section 7.R.3] of Daichirona (monovalent, Omicron XBB.1.5)
(c) Analyses results of immunogenicity [see Section 7.R.2] and safety [see Section 7.R.3] by age group in Study 212
(d) Clinical experience with the approved SARS-CoV-2 vaccines

Currently, however, benefit-and-risk balance of Daichirona in the age group of ≥12 years and <18 years presented no additional concerns potentially affecting the eligibility for vaccination, compared with that in the age group of ≥18 years. Accordingly, the eligible age of ≥12 years is acceptable for Daichirona.

7.R.5.3 Interval from the last SARS-CoV-2 vaccination

The applicant's explanation about the interval from the last SARS-CoV-2 vaccination:
Study 212 was planned to include individuals who had received the last SARS-CoV-2 vaccination ≥3 months before. In subjects of the main part of Study 212, the median interval (range) between the last SARS-CoV-2 vaccination and study vaccination was 6.10 (3.1-7.8) months in the Daichirona (bivalent, Original and Omicron BA.4-5) group and 6.00 (3.0-7.6) months in the Comirnaty (bivalent, Original and Omicron BA.4-5) group. As shown in Table 12, immunogenicity results by the interval did not largely differ from the immunogenicity results in the overall population.

Table 12. Blood neutralizing antibody titer and antibody response rate against SARS-CoV-2 Omicron BA.5 lineage by interval from the last SARS-CoV-2 vaccination (main part of Study 212, immunogenicity-evaluable PPS)

	<6 months		≥6 months	
	Daichirona (bivalent, Original and Omicron BA.4-5) N = 158	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 160	Daichirona (bivalent, Original and Omicron BA.4-5) N = 190	Comirnaty (bivalent, Original and Omicron BA.4-5) N = 190
Baseline (Day 1)				
n	158	159	190	190
GMT [2-sided 95% CI][a)]	87.725 [68.378, 112.547]	91.994 [71.892, 117.715]	63.107 [50.542, 78.795]	62.432 [50.049, 77.880]
Week 4 (Day 29)				
n	146	149	182	172
GMT [2-sided 95% CI][a)]	442.999 [356.775, 550.061]	253.591 [204.334, 314.722]	377.657 [311.630, 457.673]	220.878 [181.619, 268.624]
GMFR [2-sided 95% CI][a)]	5.343 [4.503, 6.341]	2.782 [2.444, 3.167]	6.294 [5.367, 7.380]	4.040 [3.544, 4.606]
Antibody response rate[b)]				
n2/n1	95/146	54/149	126/182	93/172
Antibody response rate (%) [2-sided 95% CI][c)]	65.1 [56.7, 72.8]	36.2 [28.5, 44.5]	69.2 [62.0, 75.8]	54.1 [46.3, 61.7]

N = Number of subjects analyzed
n or n1 = Number of subjects with immunogenicity data available
n2 = Number of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
When the antibody titer was below the lower limit of quantification, the value of "0.5 × the lower limit of quantification" was used in analyses of GMT and antibody response rate.
a) The 2-sided 95% CI was calculated using the assumed t-distribution for common logarithm of the antibody titer or antibody fold-rise.
b) Percentage of subjects who showed a ≥4-fold increase in neutralizing antibody titer from baseline to Week 4
c) The 2-sided 95% CI was calculated according to the Clopper-Pearson method.

Table 13 shows solicited adverse events in the main part of Study 212 by interval between the last SARS-CoV-2 vaccination and as study vaccination.

Severe solicited adverse events at the injection site were as follows:

Subjects with an interval <6 months

The Daichirona (bivalent, Original and Omicron BA.4-5) group: 1.9% (3 of 158) of subjects (injection site swelling, injection site pain, and injection site warmth in 1 subject each)

The Comirnaty (bivalent, Original and Omicron BA.4-5) group: 2.5% (4 of 161) of subjects (injection site pain in 2 subjects; injection site induration, injection site warmth, and injection site pruritus in 1 subject each [1 subject had more than 1 event])

Subjects with an interval ≥6 months

The Daichirona (bivalent, Original and Omicron BA.4-5) group: 2.6% (5 of 191) of subjects (injection site pain in 3 subjects; injection site swelling and injection site warmth in 1 subject each).

The Comirnaty (bivalent, Original and Omicron BA.4-5) group: 0.5% (1 of 191) of subjects (injection site warmth in 1 subject)

Severe solicited systemic adverse events were as follows:

Subjects with an interval <6 months

The Daichirona (bivalent, Original and Omicron BA.4-5) group: 2.5% (4 of 158) of subjects (fever in 3 subjects and myalgia in 1 subject)

The Comirnaty (bivalent, Original and Omicron BA.4-5) group: 1.9% (3 of 161) of subjects (malaise in 2 subjects; fever and myalgia in 1 subject each [1 subject had more than 1 event])

Subjects with an interval ≥6 months

The Daichirona (bivalent, Original and Omicron BA.4-5) group: 2.1% (4 of 191) of subjects (malaise in 3 subjects and fever in 2 subjects [1 subject had more than 1 event])

The Comirnaty (bivalent, Original and Omicron BA.4-5) group: 0 subjects

In the Daichirona (bivalent, Original and Omicron BA.4-5) group, the following solicited adverse events occurred more frequently (i.e., with a ≥5% higher incidence) in subjects with an interval <6 months than in those with an interval ≥6 months: injection site erythema, injection site swelling, injection site induration, injection site pruritus, malaise and myalgia. The incidences of severe solicited adverse events did not clearly differ between these sub-populations. Daichirona (bivalent, Original and Omicron BA.4-5) can be thus tolerated irrespective of the interval from the last SARS-CoV-2 vaccination.

Table 13. Solicited adverse events by interval from the last SARS-CoV-2 vaccination (safety analysis population, main part of Study 212)

Event	Daichirona (bivalent, Original and Omicron BA.4-5) N = 349		Comirnaty (bivalent, Original and Omicron BA.4-5) N = 352	
	<6 months N = 158	≥6 months N = 191	<6 months N = 161	≥6 months N = 191
	% (n)	% (n)	% (n)	% (n)
Adverse events at the injection site	89.9 (142)	89.0 (170)	83.9 (135)	89.5 (171)
Injection site erythema	11.4 (18)	5.2 (10)	4.3 (7)	6.3 (12)
Injection site swelling	22.8 (36)	11.0 (21)	9.3 (15)	11.0 (21)
Injection site induration	18.4 (29)	13.1 (25)	8.1 (13)	11.5 (22)
Injection site pain	85.4 (135)	86.4 (165)	81.4 (131)	88.5 (169)
Injection site warmth	39.9 (63)	36.6 (70)	31.7 (51)	40.3 (77)
Injection site pruritus	20.9 (33)	9.9 (19)	9.3 (15)	11.0 (21)
Systemic adverse events	47.5 (75)	39.3 (75)	50.9 (82)	46.1 (88)
Fever	15.2 (24)	11.5 (22)	14.3 (23)	11.0 (21)
Malaise	38.6 (61)	28.3 (54)	39.1 (63)	38.7 (74)
Headache	20.9 (33)	16.2 (31)	24.8 (40)	19.9 (38)
Rash	2.5 (4)	0.5 (1)	1.9 (3)	0
Myalgia	17.7 (28)	8.4 (16)	13.7 (22)	9.9 (19)

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver.26.0

The safety profile of Daichirona (monovalent, Omicron XBB.1.5) is unlikely to largely differ from that of Daichirona (monovalent, Original) or Daichirona (bivalent, Original and Omicron BA.4-5) [see Section 7.R.3]. In view of this and the above results from Study 212, there is no concern about the required interval from the last SARS-CoV-2 vaccination of "at least 3 months," which will be specified in the Precautions Concerning Dosage and Administration section of the package insert for Daichirona.

PMDA's view:

Study 212 included subjects with the interval from the last SARS-CoV-2 vaccination being ≥3 months, and immunogenicity results did not clearly differ irrespective of the interval. Analysis of solicited adverse events by the interval showed that, in the Daichirona (bivalent, Original and Omicron BA.4-5) group, some events occurred more frequently in subjects with an interval <6 months than in those with an interval ≥6 months, but incidences of severe events did not clearly differ between the populations.

Therefore the applicant's explanation that Daichirona (bivalent, Original and Omicron BA.4-5) can be tolerated irrespective of the interval is acceptable. Currently, the number of new patients with SARS-CoV-2 infection is not overwhelming, and therefore SARS-CoV-2 booster vaccination is not required every 3 months. However, the interval between the last SARS-CoV-2 vaccination and a Daichirona booster dose of "at least 3 months" is acceptable, because the same interval is required for receiving a booster dose of approved same-class vaccines (i.e., Comirnaty and Spikevax Intramuscular Injection).

7.R.6 Post-marketing investigations and risk management plan (draft)

The applicant's explanation about post-marketing surveillance, etc. of Daichirona:

The results from Study 212 submitted for the present application and safety information on Daichirona (monovalent, Original) showed that the safety of Daichirona was consistent irrespective of the target SARS-CoV-2 strain/variant and valency (monovalent or bivalent), and the safety profile of a booster dose of Daichirona (monovalent, Omicron XBB.1.5) is considered to be tolerable in individuals aged ≥12 years [see Section 7.R.3]. No additional safety specification is therefore required for the present application. In view of the already established safety specification, the applicant will conduct a general use-results survey (planned sample size of 3,000 individuals) as a part of additional pharmacovigilance activities, as explained for the review for approval of Daichirona (monovalent, Original) (Review Report on Daichirona for Intramuscular Injection dated July 19, 2023). The survey will collect the safety information on Daichirona in clinical use including safety data in populations from which only limited or no information was obtained during development (e.g., individuals with underlying diseases, ones aged 12 to 17 years, pregnant women). The applicant will promptly provide the obtained information to people involved in SARS-CoV-2 vaccination such as healthcare professionals and vaccine recipients.

PMDA's view:

Currently, no clinical data on Daichirona (monovalent, Omicron XBB.1.5) are available, and Study 212 yielded only limited data in subjects aged 12 to 17 years. Therefore, after the market launch of Daichirona (monovalent, Omicron XBB.1.5), the applicant is required to collect and evaluate the safety information on Daichirona (monovalent, Omicron XBB.1.5) in the entire eligible population including individuals aged 12 to 17 years, in addition to the plan to collect information after the market launch of Daichirona (monovalent, Original) proposed by the applicant during review for the approval of Daichirona (monovalent, Original). The applicant's plan to promptly disseminate evaluation results based on the obtained information is appropriate. Accordingly, the current risk management plan (draft) for Daichirona should include the safety specification presented in Table 14, and the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 15 and 16. The planned general use-results survey alone is insufficient to fully evaluate adverse events that occur infrequently, such as myocarditis and pericarditis, which have been reported from recipients of approved SARS-CoV-2 RNA vaccines and thus are classified as important potential risks of Daichirona. The applicant therefore should evaluate such events based on extensively collected information including spontaneous reports and take safety measures without delay as necessary.

Table 14. 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		

Table 15. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	• Disseminate data collected from early post-marketing phase vigilance • Organize and disseminate information material for healthcare professionals • Organize and disseminate information material for vaccine recipients • Periodical publication of the occurrence of adverse reactions

Table 16. Outline of general use-results survey (draft)

Objective	To survey the safety of Daichirona in clinical use and incidence of COVID-19
Survey method	Central registry system
Population	Individuals aged ≥12 years who received the primary series or a booster dose(s) of other approved SARS-CoV-2 vaccines and receive Daichirona for the first time at least 3 months after the last vaccination
Observation period	90 days after Daichirona vaccination
Planned sample size	3,000 (safety analysis population)
Main survey items	Characteristics of vaccine recipients, use status of Daichirona, concomitant medication, adverse events, SARS-CoV-2 infection (yes/no), COVID-19 (yes/no), etc.

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

On the basis of the data submitted, PMDA has concluded that a booster dose of Daichirona is expected to have efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) to a certain extent, and that Daichirona is unlikely to raise critical safety concerns and therefore has

acceptable safety. Based on assessment of benefit/risk balance in view of prevalence of SARS-CoV-2 and characteristics of individual recipients, PMDA considers that it is clinically meaningful to make the proposed vaccine adapted to Omicron XBB.1.5 available for use.

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

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)

(Underline denotes additions.)

Dosage and Administration

A single dose of 0.6 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.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information on the product at the current moment, the applicant is required to (a) promptly collect the safety data of the product, such as information on adverse reactions after the market launch based on the pre-designed schedule, (b) submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and (c) take necessary actions to ensure the proper use of the product.
3. The applicant is required to submit results of the ongoing or planned Japanese clinical studies of the product to PMDA as soon as they become available and take necessary actions to make the latest efficacy and safety data of the product easily accessible to healthcare professionals and vaccine recipients.
4. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the latest efficacy and safety data of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

Appendix

List of Abbreviations

CI	Confidence interval
Comirnaty	Comirnaty Intramuscular Injection or Comirnaty RTU Intramuscular Injection
Comirnaty (bivalent, Original and Omicron BA.1)	Comirnaty RTU Intramuscular Injection (bivalent, Original and Omicron BA.1)
Comirnaty (bivalent, Original and Omicron BA.4-5)	Comirnaty RTU 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 RBD of the S protein of the original strain) as the active substance (Daichirona for Intramuscular Injection)
Daichirona (monovalent, Omicron XBB.1.5)	Vaccine containing MAFB-7256a (mRNA encoding RBD analog of the S protein of Omicron XBB.1.5 lineage) as the active substance
Daichirona (monovalent, Omicron BA.4-5)	Vaccine containing MAFB-6282a (mRNA encoding RBD analog of the S protein of Omicron BA.4/BA.5 lineages) as the active substance
Daichirona (bivalent, Original and Omicron BA.4-5)	Vaccine containing ufrenmeran and MAFB-6282a (mRNA encoding RBD analog of the S protein of Omicron BA.4/BA.5 lineages) as the active substances
DNA	Deoxyribonucleic acid
[redacted]	[redacted]
FAS	Full analysis set
FDA	U.S. 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
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RNA	Ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
S protein	Spike protein
Study 212	Study DS5670-212
WHO	World Health Organization