Review Report

September 6, 2024
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	Kostaive Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Meiji Seika Pharma Co., Ltd.
Date of Application	May 31, 2024
Dosage Form/Strength	Lyophilized powder for injection in a vial for reconstitution before use: Each vial contains 0.10 mg of mRNA encoding the spike protein of SARS-CoV-2.
Application Classification	Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage, and (10-2) Other drugs (drugs including biological products which fall under the category [10] and whose manufacturing process is changed)
Items Warranting Special Mention	Application and expedited review in accordance with "Handling of application for partial change approval of a drug and the review and inspection pertaining to the concerned application" (PSB/PED Notification No. 0521-7 dated May 21, 2024) and "Expedited reviews and inspections for drugs" (PSB/PED Notification No. 0822-1 dated August 22, 2024) A prior assessment consultation was conducted on the product.
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 Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) infection (COVID-19), and that the product has acceptable safety without 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 condition.

Indication

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

(No change)

Dosage and Administration

The product is reconstituted with 10 mL of physiological saline (Japanese Pharmacopoeia grade).
A single dose of 0.5 mL is injected intramuscularly.

(No change)

Approval Condition

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

Attachment

Review Report

September 6, 2024

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

Product Submitted for Approval

Brand Name	Kostaive Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Meiji Seika Pharma Co., Ltd.
Date of Application	May 31, 2024
Dosage Form/Strength	Lyophilized powder for injection in a vial for reconstitution before use: Each vial contains 0.10 mg of mRNA encoding the spike protein of SARS-CoV-2.

Proposed Indication

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

The indication applies to the following vaccine products:

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

(Underline denotes additions.)

Proposed Dosage and Administration

The product is reconstituted with 10 mL of physiological saline (Japanese Pharmacopoeia grade).
A single dose of 0.5 mL is injected intramuscularly.

The dosage and administration apply 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.)

Table of Contents

List of Abbreviations

See Appendix.

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

Since the outbreak of a pandemic of coronavirus disease 2019 (COVID-19) in January 2020, the pandemic was repeated across the world. However, on May 5, 2023, the World Health Organization (WHO) declared the end of the Public Health Emergency of International Concern (PHEIC) caused by COVID-19. In Japan, on May 8, 2023, the category of COVID-19 under the Infectious Diseases Control Act was reclassified from "pandemic influenza (novel influenza or re-emerging influenza)" (equivalent to Class II) to "Class V infectious diseases."[1)] The special temporary vaccination program for Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) vaccines was terminated on March 31, 2024.

However, SARS-CoV-2 variants with altered infectivity and transmissibility continue to emerge, leading to intermittent pandemics. Even among individuals previously infected with SARS-CoV-2, a considerable number experience SARS-CoV-2 reinfection and COVID-19 recurrence. Some patients have reported long-COVID (sequelae to the infection). From the fiscal year 2024 onward, SARS-CoV-2 vaccination is conducted as a routine vaccination (category B disease) for elderly individuals and other high-risk populations, with the aim of reducing severe COVID-19 cases by preventing exacerbation in individuals. From a public health perspective, the continued supply of effective SARS-CoV-2 vaccines against circulating variants remains essential.

Kostaive is a vaccine containing messenger ribonucleic acid (mRNA) encoding the replicase protein derived from Venezuelan equine encephalitis virus (VEEV) and the full-length S-protein of SARS-CoV-2 as the active ingredient. On November 28, 2023, Kostaive was granted marketing approval for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as a monovalent vaccine against Wuhan-Hu-1 variant (the original strain) (the monovalent [Original] vaccine). The applicant has developed a monovalent vaccine targeting the SARS-CoV-2 Omicron JN.1 lineage (monovalent [Omicron JN.1] vaccine) for supply during the fall and winter vaccination program in fiscal year 2024. The applicant submitted an application for partial change approval of Kostaive (the monovalent [Omicron JN.1] vaccine) based on the quality test results and non-clinical study data on the monovalent (Omicron JN.1) vaccine, as well as the non-clinical study data, clinical study data, and quality test results for the bivalent (Original/Omicron BA.4-5) vaccine targeting the SARS-CoV-2 Omicron BA.4-5 lineages. Kostaive has been developed with support from the "Urgent Improvement Project for Vaccine Manufacturing Systems" implemented by the Ministry of Health, Labour and Welfare.

An application for the Kostaive monovalent (Original) vaccine was submitted for emergency use authorization in Vietnam in December 2021 and for approval in Europe in May 2023. However, as of the end of August 2024, Kostaive has not been approved or granted authorization for use in any country or region outside Japan.

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1) "Ordinance to Partially Revise the Ordinance for Enforcement of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases" (Ministry of Health, Labour and Welfare Ordinance No. 74, dated April 28, 2023).

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

- Monovalent (Original) vaccine: Vaccine product containing mRNA encoding the full-length S protein of the original strain as the active substance.
- Bivalent (Original/Omicron BA.1) vaccine: Vaccine product containing mRNA encoding the full-length S proteins of the original strain and the Omicron BA.1 lineage as active substances.
- Bivalent (Original/Omicron BA.4-5) vaccine: Vaccine product containing mRNA encoding the full-length S proteins of the original strain and the Omicron BA.4/BA.5 lineages as active substances.
- Monovalent (Omicron XBB.1.5) vaccine: Vaccine product containing mRNA encoding the full-length S protein of the Omicron XBB.1.5 lineage as the active substance.
- Monovalent (Omicron JN.1) vaccine: Vaccine product containing mRNA encoding the full-length S protein of the Omicron JN.1 lineage as the active substance.

2. Quality and Outline of the Review Conducted by PMDA

The monovalent (Omicron JN.1) vaccine, for which the present application is submitted to propose its addition to the approved product information, is a freeze-dried vaccine encapsulating mRNA within lipid nanoparticles (LNP). This mRNA encodes the full-length spike protein subunits (S1 and S2) of the SARS-CoV-2 Omicron JN.1 lineage and the replicase proteins (nsP1, nsP2, nsP3, and nsP4) derived from VEEV. Except for changes to the RNA sequence (modification of S protein to that of the Omicron JN.1 lineage, [redacted]), change in [redacted], and change of the manufacturing site for some formulation steps, the active substance and vaccine product of the monovalent (Omicron JN.1) vaccine are manufactured using the same processes as those for the monovalent (Original) vaccine.

To confirm the functionality of the active substance (mRNA) within cells, a potency test for the active substance ([redacted] study) had been established. However, based on the following considerations, it was determined that the deletion of the potency test would not compromise the evaluation of the quality attributes of the active substance and the vaccine product. The potency test for the active substance was removed from the specifications in the present application. The potency test will, however, continue to be conducted as [redacted].

- The potency of the active substance correlates with [redacted], and [redacted] in the active substance potency has been confirmed to [redacted] with [redacted] ([redacted]).
- A potency test has been appropriately established for the vaccine product.

PMDA reviewed the quality test results for the monovalent (Omicron JN.1) vaccine submitted in the present application, as well as those for the monovalent (Original) vaccine, the bivalent (Original/Omicron BA.4-5) vaccine, and the monovalent (Omicron XBB.1.5) vaccine. The data submitted during the review process raised no particular concern about the quality of the active substance or the vaccine product. PMDA confirmed that the quality attributes of the monovalent (Omicron JN.1) vaccine are comparable to those of the monovalent (Original) vaccine and the bivalent (Original/Omicron BA.4-5) vaccine, except for changes in the RNA sequence of the region encoding the S protein. Effects of [redacted] on the immunogenicity and

safety profiles were evaluated in the non-clinical pharmacological studies [see Sections 3.1.2 and 3.1.3], among others.

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

The applicant submitted results of non-clinical pharmacological studies to support the efficacy of various vaccine products, including the monovalent (Omicron JN.1) vaccine as the proposed vaccine product, the monovalent (Original) vaccine, the monovalent (Omicron XBB.1.5) vaccine, and the bivalent (Original/Omicron BA.4-5) vaccine which was used in clinical studies.

This section presents the results of studies on the monovalent (Omicron JN.1) vaccine as the proposed vaccine product, the bivalent (Original/Omicron BA.4-5) vaccine, and the effects of [redacted]. All studies employed intramuscular administration.

3.1 Primary pharmacodynamics

3.1.1 Immunogenicity of the monovalent (Omicron JN.1) vaccine (CTD 4.2.1.1-06)

A single dose of the monovalent (Omicron JN.1) vaccine (2 μg RNA) was administered to BALB/c mice (n = 8 females/group). Serum neutralizing antibody titers were measured 28 days post-dose using a pseudovirus-based microneutralization assay. The results indicated that the geometric mean titers (GMTs) of the neutralizing antibodies against the Omicron BA.4-5 and XBB.1.5 lineages were near the detection limit of the neutralization assay. In contrast, the results demonstrated the induction of neutralizing antibodies (GMT, 785-3233) against other Omicron sublineages, including BA.2.86.1, JN.1, JN.4, XDQ.1, KP.2, KP.3, and LB.1.

BALB/c mice (n = 8 females/group) received a single dose of either the bivalent (Original/Omicron BA.4-5) vaccine or the monovalent (Omicron XBB.1.5) vaccine at an RNA level of 0.1 μg. On Day 69 after the initial dose, a single dose of the monovalent (Omicron JN.1) vaccine (2 μg RNA) was administered. Serum neutralizing antibody titers were measured at Day 28 after the second dose using a pseudovirus-based microneutralization assay. The results demonstrated the induction of neutralizing antibodies (GMT, 1598-4753) against all tested Omicron sublineages, including BA.4-5, XBB.1.5, BA.2.86.1, JN.1, JN.4, XDQ.1, KP.2, KP.3, and LB.1.

3.1.2 Study on the immunogenicity of the monovalent (Original) vaccine with or without [redacted] (CTD 4.2.1.1-01 [Reference data])

BALB/c mice (n = 5 females/group) received either the monovalent (Original) vaccine containing [redacted] in [redacted] (hereafter referred to as "with [redacted]"), the monovalent (Omicron BA.4-5) vaccine with [redacted], the monovalent (Original) vaccine [redacted] (hereafter referred to as "without [redacted]"), or the monovalent (Omicron BA.4-5) vaccine without [redacted]. Each vaccine was administered as a single dose (2 μg RNA). Serum anti-S protein antibody titers against the original strain or Omicron BA.5 lineage were measured at Days 14, 28, and 56. Immunogenic responses were observed in all groups. On Day 56, the anti-S protein antibody titer against the original strain was slightly higher in the monovalent (Original) vaccine without [redacted] group than in the monovalent (Original) vaccine with [redacted] group (GMT, 2092 vs. 3018). Other than that, however, no significant differences were observed regardless of [redacted].

3.1.3 Study on the immunogenicity of the bivalent (Original/Omicron BA.4-5) vaccine with or without [redacted] (CTD 4.2.1.1-03 [Reference data])

BALB/c mice (n = 5 females/group) received either the bivalent (Original/Omicron BA.4-5) vaccine with [redacted] or the bivalent (Original/Omicron BA.4-5) vaccine without [redacted] as a single dose (2 μg RNA). Serum anti-S protein antibody titers and neutralizing antibody titers against the original strain and Omicron BA.5 lineage were measured on Days 14, 27, 42, and 54.

Both vaccine groups exhibited the induction of anti-S protein antibodies and neutralizing antibodies. Anti-S protein antibody titers and neutralizing antibody titers were higher in the bivalent (Original/Omicron BA.4-5) vaccine without [redacted] group than in the bivalent (Original/Omicron BA.4-5) vaccine with [redacted] group.

BALB/c mice (n = 5 females/group) received a single dose of the monovalent (Original) vaccine with [redacted] that encoded only the S protein (no replicase protein encoded, 2 μg RNA). On Day 42 after the initial dose, a single dose of either the bivalent (Original/OmicronBA.4-5) vaccine with [redacted] or the bivalent (Original/Omicron BA.4-5) vaccine without [redacted] was administered (2 μg RNA). Serum anti-S protein antibody titers and neutralizing antibody titers against the original strain and Omicron BA.5 lineage were measured on Days 14, 27, and 42 after the second dose. At all sampling points, both vaccine groups demonstrated comparable levels of anti-S protein antibody and neutralizing antibody induction against the original strain and Omicron BA.5 lineage.

3.R Outline of the review conducted by PMDA

The applicant's explanation:

The results of primary pharmacodynamics studies of Kostaive demonstrated that the variant-adapted vaccines of Kostaive exhibited immunogenicity against their respective target variants. The Kostaive monovalent (Omicron JN.1) vaccine was shown to induce neutralizing antibodies against various Omicron sublineages, including the currently prevalent variants such as the KP.3 lineage, as well as the JN.1 lineage.

According to the studies on the immunogenicity of the vaccine [redacted], differences were observed at certain sampling points following the first dose of Kostaive [see Sections 3.1.2 and 3.1.3]. However, no consistent trends were identified at other sampling points, including those following the second dose. This result confirmed that [redacted] had no significant impact on the immunogenicity of Kostaive.

PMDA accepted the applicant's explanation based on the submitted non-clinical pharmacology study results.

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

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

5. Toxicology 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 toxicology have been submitted.

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

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

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

The applicant submitted the efficacy and safety evaluation data in the form of results from 2 clinical studies shown in Table 1. Results of Study ARCT-154-J01 were submitted for the initial application. In the present application, the applicant submitted a report including additional data up to 180 days after study vaccination as reference data.

Table 1. Outline of Clinical Studies

Study code (country)	Phase	Population	No. of subjects enrolled	Dosage regimen	Study objective
ARCT-2301-J01 (Japan)	III	Healthy adults aged ≥18 years who had received 2-4 doses of a SARS-CoV-2 RNA vaccine[a)] as a primary series and booster doses, followed by a Comirnaty bivalent vaccine[b)] as a booster dose at least 3 months before.	N = 930 Kostaive: 465 Comirnaty: 465	A single intramuscular dose of the Kostaive bivalent (Original/Omicron BA.4-5) vaccine[c)] at 5 μg or the Comirnaty bivalent (Original/Omicron BA.4-5) vaccine at 30 μg.	Immunogenicity Safety
ARCT-154-J01 (Japan)	III	Healthy adults aged ≥18 years who had received 2 doses of a SARS-CoV-2 original strain RNA vaccine as a primary series and the Comirnaty monovalent (Original) vaccine as a booster dose at least 3 months before.	N = 828 Kostaive: 420 Comirnaty: 408	A single intramuscular dose of the Kostaive monovalent (Original) vaccine at 5 μg or the Comirnaty monovalent (Original) vaccine at 30 μg.	Immunogenicity Safety

a) Comirnaty or Spikevax monovalent (Original) vaccine, bivalent (Original/Omicron BA.1) vaccine, or bivalent (Original/Omicron BA.4-5) vaccine.
b) Comirnaty bivalent (Original/Omicron BA.1) vaccine or bivalent (Original/Omicron BA.4-5) vaccine.
c) Vaccine product containing 2.5 μg of RNA encoding the S protein of the original strain, including mutations in the B.1 lineage (D614G), and 2.5 μg of RNA encoding the S protein of the Omicron BA.4-5 lineage.

The outline of Study ARCT-2301-J01 submitted as the evaluation data is described below.

7.1 Phase III study

7.1.1 Japanese phase III study (CTD 5.3.5.1-01, Study ARCT-2301-J01; Study period, ongoing since September 2023; data cutoff date, December 17, 2023)

A randomized, evaluator-blinded,[2)] active-control, parallel-group study was conducted at 9 study sites in Japan to evaluate the safety and immunogenicity of the Kostaive bivalent (Original/Omicron BA.4-5) vaccine in healthy adults aged ≥18 years. Subjects had to have previously received 2 to 4 doses of either Comirnaty or Spikevax vaccines, including monovalent (Original), bivalent (Original/Omicron BA.1), and bivalent (Original/Omicron BA.4-5) vaccines, followed by the last booster dose of the Comirnaty bivalent (Original/Omicron BA.1) or bivalent (Original/Omicron

2) The investigator, the personnel of the study sites, subjects, the staff of the organizations monitoring the conduct of the study, and the sponsor were blinded to the study vaccine.

BA.4-5) vaccine at least 3 months before. The target sample size was 850 subjects[3)] (425 in the Kostaive group, 425 in the Comirnaty group).

Subjects received a single intramuscular dose of either Kostaive bivalent (Original/Omicron BA.4-5) vaccine (5 μg) or Comirnaty bivalent (Original/Omicron BA.4-5) vaccine (0.3 mL).[4)]

All of 930 randomized subjects[5)] (465 in the Kostaive group, 465 in the Comirnaty group) received at least 1 dose of the study vaccine. Of these, 927 subjects (463 in the Kostaive group, 464 in the Comirnaty group) were included in the safety analysis population. The remaining 1 subject with missing safety data and 2 subjects with duplicate vaccinations were excluded from the analysis. Among the subjects included in the safety analysis population, those without neutralizing antibody titer data for the original strain were excluded, resulting in 460 subjects in the Kostaive group and 462 subjects in the Comirnaty group for the full analysis set (FAS). From the FAS, subjects with SARS-CoV-2 nucleocapsid antibodies detected prior to study vaccination and those with major protocol deviations were excluded, yielding 398 subjects in the Kostaive group and 405 subjects in the Comirnaty group for the per protocol set 1 (PPS-1). Additionally, subjects with major protocol deviations were only excluded from the PPS-1, resulting in 455 subjects in the Kostaive group and 458 subjects in the Comirnaty group for the per protocol set 2 (PPS-2).

The primary endpoints for immunogenicity were defined as the GMT and seroresponse rate (SRR) against the Omicron BA.4-5 lineages at Day 28 after study vaccination in the PPS-1 population. SRR was calculated as the proportion of subjects whose neutralizing antibody titers increased ≥4-fold from the titer before the booster dose (with the titers below the lower limit of quantification [LLOQ] treated as half the LLOQ). Non-inferiority of Kostaive to Comirnaty could be demonstrated when both of the following criteria were met simultaneously:

- The lower limit of the two-sided 95% confidence interval (CI) for the ratio of geometric mean titers (GMR) of Kostaive to Comirnaty greater than 0.67.
- The lower limit of the two-sided 95% CI for the difference in SRR between Kostaive and Comirnaty (Kostaive– Comirnaty) greater than −10%.

Table 2 shows the results of the primary endpoints for immunogenicity at Day 28 after study vaccination. The lower limits of the two-sided 95% CIs for the GMR and the SRR difference against the Omicron BA.4-5 lineages greater than the non-inferiority thresholds of 0.67 and −10%, respectively. Thus, the pre-specified criteria for non-inferiority were met.

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3) Assuming a GMR of 1.0 for immunogenicity, a standard deviation of 0.62 for neutralizing antibody titers, and an SRR of 80% for each vaccine group, in order to demonstrate the non-inferiority of Kostaive to Comirnaty with 90% power (the non-inferiority margin for GMR is 0.67, the non-inferiority margin for SRR is 10%, and the one-sided significance level is 2.5%), a sample size of 340 subjects per group is required. Assuming that approximately 20% of the allocated subjects will be excluded from the primary analysis population due to pre-vaccination infection or protocol deviations, the total number of subjects to be allocated in this study was 850 (425 per group).

4) Comirnaty 0.3 mL contains 30 μg of RNA, comprising equal amounts of tozinameran and famtozinameran (based on RNA mass ratio).

5) Subjects were randomized by stratification factors, including sex, age (<65 years or ≥65 years), type of the most recent Comirnaty bivalent vaccine administered (bivalent [Original/Omicron BA.1] vaccine or bivalent [Original/Omicron BA.4-5] vaccine), and the time after the last dose of SARS-CoV-2 vaccine (<5 months or ≥5 months).

Table 2. Comparison of Neutralizing Antibody Titer Against Omicron BA.4-5 Lineages at Day 28 After Study Vaccination
(Study ARCT-2301-J01, PPS-1 population)

	Neutralizing antibody titer			Neutralizing antibody response rate			
	N	GMT[a)]	GMR[a)]	N	n	SRR (%)[b)]	Difference in SRR[c)]
Kostaive (bivalent, original/Omicron BA.4-5)	398	6489.4 [2787.9, 15105.5]	1.49 [1.26, 1.76]	398	250	62.8 [57.9, 67.6]	7.2 [0.6, 13.7]
Comirnaty (bivalent, original/Omicron BA.4-5)	405	4357.5 [1871.2, 10147.5]		405	225	55.6 [50.6, 60.5]	

The number in the brackets indicates the two-sided 95% CI, N = Number of subjects analyzed.
n = Number of subjects with antibody response. Antibody response is defined as a ≥4-fold increase in antibody titers from the titer before the booster dose (or half the LLOQ if below LLOQ). For antibody titers below the LLOQ, a value of 0.5 × LLOQ was used in the analysis. The quantification range (LLOQ - upper limit of quantification [ULOQ]) is 40-89947 (Omicron BA.4-5 lineages).

a) Neutralizing antibody titers were log-transformed and calculated based on analysis of covariance (ANCOVA), with vaccination group, sex, type of bivalent vaccine, and time since the last SARS-CoV-2 vaccination (<5 months or ≥5 months) as factors and age as a covariate.
b) Two-sided 95% CI was calculated using the Clopper-Pearson method.
c) Calculated using the Miettinen-Nurminen method, adjusting for sex, age (<65 years or ≥65 years), type of the last bivalent Comirnaty vaccine administered, and time after the last SARS-CoV-2 vaccination (<5 months or ≥5 months).

The safety observation period was as follows:

- Solicited adverse events[6)] (local [erythema, swelling, induration, tenderness, pain] and systemic [pyrexia, arthralgia, chills, diarrhoea, dizziness, headache, malaise, nausea, vomiting, myalgia]) were collected for 7 days after the study vaccination.
- Unsolicited adverse events (adverse events other than solicited adverse events observed within 7 days after the study vaccination) were collected for 28 days after the study vaccination.
- Serious adverse events and adverse events of special interest were collected for 180 days after the study vaccination.

Table 3 shows solicited adverse events.

6) The severity of adverse events was evaluated based on the US 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).

Table 3. Solicited Adverse Events (Study ARCT-2301-J01, safety analysis population)

MedDRA PT	Kostaive (bivalent, Original/Omicron BA.4-5) N = 463		Comirnaty (bivalent, Original/Omicron BA.4-5) N = 464	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	439 (94.8)	0	441 (95.0)	2 (0.4)
Erythema	47 (10.2)	0	52 (11.2)	0
Swelling	56 (12.1)	0	68 (14.7)	2 (0.4)
Induration	45 (9.7)	0	78 (16.8)	0
Tenderness	430 (92.9)	0	427 (92.0)	0
Pain	379 (81.9)	0	378 (81.5)	0
Systemic (all events)[a)]	264 (57.0)	5 (1.1)	244 (52.6)	6 (1.3)
Pyrexia[b)]	93 (20.1)	1 (0.2)	72 (15.5)	5 (1.1)
Arthralgia	82 (17.7)	0	72 (15.5)	0
Chills	69 (14.9)	0	59 (12.7)	0
Diarrhoea	18 (3.9)	0	15 (3.2)	0
Dizziness	9 (1.9)	0	8 (1.7)	1 (0.2)
Headache	118 (25.5)	3 (0.6)	110 (23.7)	1 (0.2)
Malaise	177 (38.2)	2 (0.4)	157 (33.8)	2 (0.4)
Nausea	14 (3.0)	1 (0.2)	9 (1.9)	0
Vomiting	2 (0.4)	0	3 (0.6)	0
Myalgia	89 (19.2)	0	97 (20.9)	1 (0.2)

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

a) Number of subjects with Grade ≥0 events. Grade 0 was used only for erythema, swelling, induration (<2.5 cm), and pyrexia (37.5°C-37.9°C).

b) ≥37.5°C (axillary)

Table 4 shows unsolicited adverse events and adverse reactions observed in ≥1% of subjects in either group.

Grade ≥3 unsolicited adverse events were observed in 5 subjects (1.1%) in the Kostaive group and 1 subject (0.2%) in the Comirnaty group. In the Kostaive group, pyrexia (2 subjects), influenza (1 subject), upper limb fracture (1 subject), and cough (1 subject) were reported, while in the Comirnaty group, only influenza (1 subject) was reported. All events were assessed as being unrelated to the study vaccination.

Table 4. Unsolicited Adverse Events and Adverse Reactions Observed in ≥1% of Subjects in Either Group (Study ARCT-2301-J01, safety analysis population)

MedDRA PT	Adverse events		Adverse reactions	
	Kostaive (bivalent, Original/ Omicron BA.4-5) (N = 463)	Comirnaty (bivalent, Original/ Omicron BA.4-5) (N = 464)	Kostaive (bivalent, Original/ Omicron BA.4-5) (N = 463)	Comirnaty (bivalent, Original/ Omicron BA.4-5) (N = 464)
	n (%)	n (%)	n (%)	n (%)
All events	73 (15.8)	82 (17.7)	34 (7.3)	41 (8.8)
Nasopharyngitis	13 (2.8)	8 (1.7)	0	0
Influenza	6 (1.3)	5 (1.1)	0	0
Rhinorrhoea	5 (1.1)	3 (0.6)	3 (0.6)	1 (0.2)
Injection site pruritus	3 (0.6)	10 (2.2)	3 (0.6)	10 (2.2)
Oropharyngeal pain	1 (0.2)	5 (1.1)	1 (0.2)	1 (0.2)

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

No serious adverse events or adverse events resulting in death were reported.

7.R Outline of the review conducted by PMDA

7.R.1 Review policy

In general, when altering the antigen strain of a COVID-19 vaccine, it is necessary to analyze and evaluate the quality attributes of the vaccine before and after the antigen strain modification. Clinical study results should confirm that the vaccine exhibits immunogenicity against the newly targeted antigen strain and that its safety profile does not differ significantly from the vaccine product before modification (PSB/PED Notification No. 0523-1 and PSB/CND Notification No. 0523-3 “Handling of Changes to SARS CoV-2 Vaccine Strains” dated May 23, 2024).

The applicant’s explanation about its policy for development of the Kostaive monovalent (Omicron JN.1) vaccine:
Kostaive contains a shared mRNA encoding the replicase sequence, and its LNP composition remains identical, except for modifications made to the mRNA sequence encoding the S protein resulting from the antigen strain change. Since only the expressed SARS-CoV-2 S protein differs, the quality attributes, immunogenicity, safety, and tolerability profiles of the vaccine product with the altered antigen strain are anticipated to be similar, regardless of the antigen strain. The monovalent (Original) vaccine, which has already been approved, served as the parent vaccine for clinical development targeting newly emerging variants that may spread in the future.

Specifically, the Kostaive bivalent (Original/Omicron BA.4-5) vaccine was manufactured using the same process as the approved monovalent (Original) vaccine and targets the original strain and Omicron BA.4-5 lineages. The development methodology was designed to build the platform framework by demonstrating that the bivalent (Original/Omicron BA.4-5) vaccine does not differ in safety profile from the monovalent (Original) vaccine, and by confirming vaccine efficacy based on immunogenicity results from clinical studies using the bivalent (Original/Omicron BA.4-5) vaccine. Under this development policy, and based on non-clinical study results and quality testing data for the monovalent (Omicron JN.1) vaccine, the efficacy and safety of the monovalent (Omicron JN.1) vaccine were evaluated.

PMDA’s view on the review policy for the present application:
The quality-related data submitted in the present application confirm that the quality attributes of the monovalent (Omicron JN.1) vaccine are comparable to those of the monovalent (Original) vaccine and the bivalent (Original/Omicron BA.4-5) vaccine, except for changes to the mRNA sequence of the region encoding the S protein [see Section 2]. In non-clinical pharmacology studies, immune responses were observed in mice given either the monovalent (Omicron JN.1) vaccine or the bivalent (Original/Omicron BA.4-5) vaccine [see Section 3].

To evaluate the efficacy and safety of the monovalent (Omicron JN.1) vaccine, the following approach for the development of a SARS-CoV-2 variant vaccine is considered applicable to Kostaive:

(a) In the Japanese phase III study (Study ARCT-2301-J01), the efficacy (immunogenicity) and safety of the bivalent (Original/Omicron BA.4-5) vaccine were evaluated.

(b) In addition to the clinical study results of the approved monovalent (Original) vaccine, the submitted quality testing data and non-clinical study results for the monovalent (Omicron JN.1) vaccine were reviewed.

Based on the above, the submitted clinical and non-clinical study results were evaluated.

7.R.2 Efficacy

The applicant's explanation about the immunogenicity of the bivalent (Original/Omicron BA.4-5) vaccine used for booster dose in the Japanese phase III study (Study ARCT-2301-J01) submitted in the present application:

The "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 4), Immunogenicity-based evaluation of variant vaccines modified from parent vaccines and booster vaccines with new active ingredients" (Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency, dated July 15, 2022), which provides the method for evaluation of variant vaccines in Japan, state that: (1) 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; and (2) the primary endpoints of clinical studies of the new vaccine should employ the GMT and SRR of neutralizing antibody titers against the target SARS-CoV-2 strain, and the non-inferiority of the new vaccine to an appropriate control vaccine should be demonstrated using these primary endpoints. Based on the above, Study ARCT-2301-J01 for the bivalent (Original/Omicron BA.4-5) vaccine as a booster dose used the GMT and SRR of neutralizing antibody titers against the Omicron BA.4-5 lineages at Day 28 after study vaccination as primary endpoints. The control vaccine was the Comirnaty bivalent (Original/Omicron BA.4-5) vaccine, and the study aimed to verify the non-inferiority of the Kostaive bivalent (Original/Omicron BA.4-5) vaccine to the Comirnaty vaccine. The results of the study demonstrated the non-inferiority of Kostaive to Comirnaty [see Section 7.1.1]. Additionally, results satisfied the secondary endpoint, namely "the superiority criteria (a lower limit of the 95% CI of the GMR greater than 1 and a lower limit of the 95% CI of the SRR difference greater than 0)," pre-specified in case non-inferiority was demonstrated.

Beyond the immunogenicity against the Omicron BA.4-5 lineages, immunogenicity was evaluated for the original strain and the Omicron XBB.1 lineage. Table 5 shows the results of the immunogenicity against these strains before and after study vaccination in Study ARCT-2301-J01. For all strains and lineages tested, an increase in neutralizing antibody titers was observed following administration of the Kostaive bivalent (Original/Omicron BA.4-5) vaccine.

Based on the above, the applicant considered that the Kostaive monovalent (Omicron JN.1) vaccine exhibits immunogenicity comparable to that of the parent vaccine, even when the antigen strain is modified, and the vaccine is expected to have efficacy equivalent to or greater than that of currently approved vaccines.

Table 5. GMT, GMFR, and Seroresponse Rates of SARS-CoV-2 (Omicron BA.4-5 lineages, Original strain, and Omicron XBB.1.5 lineage) Neutralizing Antibody Titers in Blood (Study ARCT-2301-J01, PPS-1 population)

	Omicron BA.4-5 lineages		Original strain		Omicron XBB.1.5 lineage	
	Kostaive (bivalent, Original/Omicron BA.4-5) N = 398	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 405	Kostaive (bivalent, Original/Omicron BA.4-5) N = 398	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 405	Kostaive (bivalent, Original/Omicron BA.4-5) N = 398	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 405
Baseline						
GMT[a)]	879.1 [749.7, 1030.8]	812.6 [688.4, 959.1]	2131.8 [1908.7, 2381.0]	2025.7 [1804.6, 2274.0]	105.9 [91.7, 122.3]	98.5 [85.2, 113.9]
Day 28 after study vaccination						
GMT[b)]	6489.4 [2787.9, 15105.5]	4357.5 [1871.2, 10147.5]	9435.1 [5186.5, 17164.0]	6524.2 [3585.2, 11872.3]	1114.5 [455.3, 2727.9]	684.4 [279.5, 1675.9]
GMFR[a)]	6.91 [6.17, 7.75]	5.05 [4.59, 5.56]	4.11 [3.75, 4.50]	3.00 [2.80, 3.21]	7.45 [6.65, 8.33]	4.96 [4.49, 5.49]
GMR[b)]	1.49 [1.26, 1.76]		1.45 [1.28, 1.63]		1.63 [1.36, 1.94]	
Seroresponse rate						
No. of subjects (n)	250	225	177	130	278	214
SRR (%)[c)]	62.8 [57.9, 67.6]	55.6 [50.6, 60.5]	44.5 [39.5, 49.5]	32.1 [27.6, 36.9]	69.8 [65.1, 74.3]	52.8 [47.8, 57.8]
Difference in SRR[d)]	7.2 [0.6, 13.7]		12.5 [5.9, 19.0]		16.7 [10.1, 23.2]	

N = Number of subjects analyzed; The number in the brackets indicate the two-sided 95% CI; the PPS-1 population excludes subjects with a history of infection (anti-N antibody positive) [see Section 7.1.1].

n = Number of subjects with antibody response. The definition of subjects with antibody response and the quantification ranges (Omicron BA.4-5, original strain, and XBB.1.5) are as described in Table 2.

a) Two-sided 95% CIs were calculated assuming a t-distribution for the differences in the log-transformed values of antibody titers or the fold increase in antibody titers.

b) Neutralizing antibody titers were log-transformed and analyzed using ANCOVA, with vaccination group, type of bivalent vaccine, time since the last prior vaccine dose, and sex as factors, and age (continuous variable) as a covariate.

c) Two-sided 95% CIs were calculated using the Clopper-Pearson method.

d) Calculated using the Miettinen-Nurminen method, adjusting for type of bivalent vaccine, time after the last prior vaccine dose, sex, and age.

7.R.2.1 Antibody titers by age and infection history

Table 6 shows the results of the immunogenicity analysis for efficacy by age group. While the number of subjects aged ≥65 years was limited, and thus there are limitations to the interpretation, no significant differences were observed between age groups.

Table 6. GMT, GMFR, and Seroresponse Rates of SARS-CoV-2 Neutralizing Antibody Titers Against Omicron BA.4-5 by Age Ggroup (Study ARCT-2301-J01, PPS-1 population)

	All subjects		Subjects aged ≥18 and <65 years		Subjects aged ≥65 years	
	Kostaive (bivalent, Original/Omicron BA.4-5) N = 398	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 405	Kostaive (bivalent, Original/Omicron BA.4-5) N = 369	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 374	Kostaive (bivalent, Original/Omicron BA.4-5) N = 29	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 31
Baseline						
GMT[a)]	879.1 [749.7, 1030.8]	812.6 [688.4, 959.1]	927.9 [785.8, 1095.7]	825.6 [695.9, 979.4]	442.0 [264.1, 739.8]	671.1 [332.9, 1352.7]
Day 28 after study vaccination						
GMT[b)]	6489.4 [2787.9, 15105.5]	4357.5 [1871.2, 10147.5]	6749.3 [2907.6, 15666.9]	4514.6 [1943.5, 10487.3]	4465.0 [1857.0, 10735.7]	3156.7 [1397.3, 7131.5]
GMFR[a)]	6.91 [6.17, 7.75]	5.05 [4.59, 5.56]	6.73 [5.98, 7.57]	5.10 [4.62, 5.63]	9.79 [6.33, 15.13]	4.53 [3.12, 6.59]
GMR[b)]	1.49 [1.26, 1.76]		1.49 [1.26, 1.78]		1.41 [0.72, 2.77]	
Seroresponse rate						
No. of subjects (n)	250	225	226	209	24	16
SRR (%)[c)]	62.8 [57.9, 67.6]	55.6 [50.6, 60.5]	61.2 [56.1, 66.2]	55.9[50.7, 61.0]	82.8 [64.2, 94.2]	51.6 [33.1, 69.8]
Difference in SRR[d)]	7.2 [0.6, 13.7]		5.4 [-1.7, 12.4]		31.1 [7.3, 51.8]	

N = Number of subjects analyzed; The number in the brackets indicates the two-sided 95% CI; the PPS-1 population excludes subjects with a history of infection (anti-N antibody positive) [see Section 7.1.1].
n = Number of subjects with antibody response. The definition of subjects with antibody response and the quantification ranges (Omicron BA.4-5) are as described in Table 2.
a) to d) are the same as in Table 5. Age was excluded as a factor in the calculation of GMR and SRR.

Table 7 shows the immunogenicity analysis for efficacy, classified by the presence or absence of infection history. Although the number of subjects with a prior infection history was limited, making stringent comparisons challenging, the group with a prior infection exhibited higher baseline antibody titers. However, an increase in antibody titers was observed after the study vaccination, and this was consistent with the response seen in the overall population.

Table 7. GMT, GMFR, and Seroresponse Rates of SARS-CoV-2 Neutralizing Antibody Titers Against Omicron BA.4-5 by Infection History (Study ARCT-2301-J01, PPS-2 population)

	All subjects		Without history of infection		With history of infection	
	Kostaive (bivalent, Original/Omicron BA.4-5) N = 455	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 458	Kostaive (bivalent, Original/Omicron BA.4-5) N = 398	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 405	Kostaive (bivalent, Original/Omicron BA.4-5) N = 57	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 53
Baseline						
GMT[a)]	1053.3 [907.1, 1223.0]	963.4 [821.6, 1129.7]	879.1 [749.7, 1030.8]	812.6 [688.4, 959.1]	3721.1 [2871.3, 4822.5]	3539.5 [2381.6, 5260.4]
Day 28 after study vaccination						
GMT[b)]	7526.2 [3784.3, 14968.1]	5140.9 [2592.4, 10194.8]	6489.4 [2787.9, 15105.5]	4357.5 [1871.2, 10147.5]	10749.9 [4019.8, 28748.0]	7613.6 [2944.4, 19687.3]
GMFR[a)]	6.23 [5.61, 6.92]	4.66 [4.26, 5.10]	6.91 [6.17, 7.75]	5.05 [4.59, 5.56]	3.02 [2.52, 3.60]	2.51 [2.03, 3.11]
GMR[b)]	1.46 [1.25, 1.71]		1.49 [1.26, 1.76]		1.41 [0.98, 2.04]	
Seroresponse rate						
No. of subjects (n)	269	236	250	225	19	11
SRR (%)[c)]	59.1 [54.4, 63.7]	51.5 [46.8, 56.2]	62.8 [57.9, 67.6]	55.6 [50.6, 60.5]	33.3 [21.4, 47.1]	20.8 [10.8, 34.1]
Difference in SRR [d)]	7.0 [0.8, 13.2]		7.3 [0.5, 14.0]		12.2 [-4.2, 28.7]	

N = Number of subjects analyzed; The number in the brackets indicates the two-sided 95% CI; n = Number of subjects with antibody response. The definition of antibody response and the quantification ranges are as described in Table 2.
a) to c) are the same as in Table 5.
d) Two-sided 95% CI was calculated using the Miettinen-Nurminen method.

7.R.2.2 Persistence of antibody titers

In Study ARCT-154-J01, the neutralizing antibody titers were evaluated on Days 28, 90, and 180 after a single dose of the monovalent (Original) vaccine as a booster dose. Table 8 shows the results for immunogenicity (GMT and SRR).

In the Comirnaty group, GMT and SRR peaked on Day 28 after study vaccination and declined over time. In contrast, in the Kostaive group, no decrease in GMT or SRR was observed on Day 90 after study vaccination, and these values remained higher than those in the Comirnaty group even at 180 days post-dose. The neutralizing antibody titers on Days 90 and 180 after administration of the bivalent (Original/Omicron BA.4-5) vaccine in Study ARCT-2301-J01 are planned to be evaluated in the future.

Table 8. GMT and Seroresponse Rate of SARS-CoV-2 (original strain, Omicron BA.4-5 lineages, and Omicron XBB.1.5 lineage) Neutralizing Antibody Titers in Blood (Study ARCT-154-J01, PPS-1 population)

	Original strain		Omicron BA.4-5 lineages		Omicron XBB.1.5 lineage	
	Kostaive (monovalent, Original) N = 385	Comirnaty (monovalent, Original) N = 374	Kostaive (monovalent, Original) N = 385	Comirnaty (monovalent, Original) N = 374	Kostaive (monovalent, Original) N = 359	Comirnaty (monovalent, Original) N = 349
Baseline						
GMT[a)]	813.1 [715.6, 924.0]	865.6 [754.8, 992.7]	275.4 [226.7, 334.5]	291.7 [236.1 360.3]	30.2 [26.4 34.5]	34.7 [30.2 40.0]
Day 28 after study vaccination						
N1	378	367	378	367	352	343
GMT[a)]	5390.4 [4899.3, 5930.6]	3738.3 [3442.1, 4059.9]	2124.9 [1840.9, 2452.8]	1623.5 [1418.2 1858.4]	142.6 [125.1, 162.6]	121.1 [105.6, 138.7]
GMR[a)]	1.44 [1.27 1.64]		1.31 [1.07, 1.59]		1.18 [0.98, 1.42]	
SRR[b)] (n/N1[%])	250/378 (66.1) [66.1, 70.9]	188/367 (51.2) [46.0, 56.4]	268/378 (70.9) [66.0, 75.4]	213/367 (58.0) [52.8 63.1]	210/352 (59.7) [54.3, 64.8]	171/343 (49.9) [44.4, 55.3]
Difference in SRR[c)]	14.9 [7.9, 21.8]		12.9 [6.0, 19.6]		9.8 [2.4 17.1]	
Day 90 after study vaccination						
N1	369	356	369	356	-	-
GMT[a)]	5927.9 [5413.8, 6490.9]	2899.4 [2647.6, 3175.1]	1891.7 [1645.5, 2174.8]	887.6 [764.1, 1031.1]	-	-
GM [a)]	2.04 [1.80, 2.32]		2.13 [1.74, 2.61]			-
SRR[b)] (n/N1[%])	246/369 (66.7) [61.6, 71.5]	147/356 (41.3) [36.1, 46.6]	240/369 (65.0) [59.9, 69.9]	141/356 (39.6) [34.5, 44.9]	-	-
Difference in SRR[c)]	25.4 [18.2, 32.3]		25.4 [18.3 32.3]		-	-
Day 180 after study vaccination						
N1	332	313	332	313	-	-
GMT[a)]	4118.7 [3722.7, 4556.8]	1860.9 [1666.5, 2078.0]	1119.1 [959.9 1304.6]	495.4 [412.6 595.0]	-	-
GMR[a)]	2.21 [1.91, 2.57]		2.26 [1.78, 2.86]			-
SRR[b)] (n/N1[%])	182/332 (54.8) [49.3, 60.3]	62/313 (19.8) [15.5, 24.7]	155/332 (46.7) [41.2, 52.2]	59/313 (18.8) [14.7 23.6]	-	-
Difference in SRR[c)]	35.0 [27.9, 41.8]		27.8 [20.8, 34.6]			-

N = Number of subjects analyzed; N1 = Number of subjects with available immunogenicity data; The value in the brackets indicates the two-sided 95% CI.
The PPS-1 population excludes subjects with a history of infection (anti-N antibody positive) [see Section 7.1.1]. Data obtained after interim events that could affect immunogenicity (SARS-CoV-2 infection, administration of other coronavirus vaccines, or anti-N antibody positivity) at each measurement point were excluded.
n = Number of subjects with antibody response. The definition of subjects with antibody response and the quantification ranges (Omicron BA.4-5 lineage, original strain, and XBB.1.5 lineage) are as described in Table 2.
a) Two-sided 95% CIs were calculated assuming a t-distribution for the log-transformed antibody titers or the log-transformed fold increase in antibody titers.
b) Two-sided 95% CIs were calculated using the Clopper-Pearson method.
c) Two-sided 95% CIs were calculated using the Miettinen-Nurminen method.

The applicant's explanation about the efficacy of the monovalent (Omicron JN.1) vaccine:

In Study ARCT-2301-J01, the non-inferiority of Kostaive bivalent (Original/Omicron BA.4-5) vaccine to Comirnaty bivalent (Original/Omicron BA.4-5) vaccine was demonstrated in terms of GMT and SRR for neutralizing antibodies against the Omicron BA.4-5 lineages at Day 28 after study vaccination, the primary endpoint. In Study ARCT-154-J01 submitted at the time of the initial approval, the non-inferiority of the Kostaive monovalent (Original) vaccine to the Comirnaty monovalent (Original) vaccine was confirmed in terms of GMT and SRR for neutralizing antibodies against the original strain. In mouse immunogenicity studies evaluated for the initial approval, the Kostaive monovalent (Original) vaccine and bivalent (Original/Omicron BA.4-5) vaccine both demonstrated increased neutralizing antibody titers against the corresponding antigen strains.[7)] The

[7)] Review Report of Kostaive Intramuscular Injection, dated November 9, 2023.

above study results suggest that Kostaive maintains immunogenicity comparable to the parental vaccine, even with modifications to the antigen strains.

The quality attributes of the newly proposed Kostaive monovalent (Omicron JN.1) vaccine have been confirmed to be comparable to those of the monovalent (Original) vaccine and the bivalent (Original/Omicron BA.4-5) vaccine, except for differences in the RNA sequence of the region encoding the S protein [see Section 2]. An increase in neutralizing antibody titers against Omicron sublineages, including the KP.3 lineage, was observed in mice after primary and booster doses [see Section 3.1.1]. These findings suggest that administration of the monovalent (Omicron JN.1) vaccine will lead to increased neutralizing antibody titers in the blood against currently circulating Omicron sublineages; therefore, the vaccine could have efficacy against Omicron variants.

PMDA's view:
Based on the review policy outlined in Section 7.R.1 and the data submitted in the present application, the following findings were confirmed. It is reasonable to expect that the monovalent (Omicron JN.1) vaccine will have efficacy in the prevention of SARS-CoV-2 infection.

- The monovalent (Omicron JN.1) vaccine is a variant-adapted vaccine derived from the antigen strain of the monovalent (Original) vaccine, which has been approved for marketing in Japan.
- The quality attributes of the monovalent (Omicron JN.1) vaccine, excluding differences in the gene sequence resulting from strain (lineage) variation, have been confirmed to be comparable to those of the monovalent (Original) vaccine [see Section 2].
- In non-clinical pharmacological studies, mice given the monovalent (Omicron JN.1) vaccine showed immune responses against various Omicron sublineages, including the JN.1 and KP.3 lineages [see Section 3.1.1].
- In clinical studies evaluating booster dose with the bivalent (Original/Omicron BA.4-5) vaccine, the non-inferiority of the Kostaive bivalent (Original/Omicron BA.4-5) vaccine to the Comirnaty bivalent (Original/Omicron BA.4-5) vaccine was demonstrated in terms of GMT and SRR for neutralizing antibodies against the Omicron BA.4-5 lineages.

However, regarding the superiority assessment with immunogenicity [see Section 7.R.2], thresholds for neutralizing antibody titers required for infection prevention remain undefined. As such, it is difficult to estimate the degree of improvement in vaccine efficacy (VE) compared to approved vaccines based on differences in antibody titers. Additionally, given that the primary objective and success criteria of Study ARCT-2301-J01 were to demonstrate non-inferiority, the results of superiority assessments in this study do not provide sufficient evidence to conclude that the vaccine offers greater efficacy than that of approved vaccines. Similarly, while the persistence of antibody titers [see Section 7.R.2.2] suggests that Kostaive's antibody titers tended to be maintained for a longer duration than those of approved vaccines, the clinical significance of this observation remains unclear at present. Caution should be exercised in interpreting intergroup differences in antibody titers.

Considering that circulating SARS-CoV-2 variants continue to evolve and that other Omicron sublineages or new variants are likely to emerge, it is essential to continue gathering epidemiological information on variant prevalence and vaccine efficacy. This information should be collected both

domestically and internationally, and appropriate measures should be considered based on the accrued data and research findings.

7.R.3 Safety

7.R.3.1 Safety in clinical study

Table 9 summarizes the incidences of adverse events in the Japanese phase III study (Study ARCT-2301-J01) using the bivalent (Original/Omicron BA.4-5) vaccine. No significant differences were observed between the Kostaive group and the Comirnaty group.

Table 9. Summary of Incidences of Adverse Events in Study ARCT-2301-J01 (safety analysis population)

	Kostaive (bivalent, Original/Omicron BA.4-5) N = 463	Comirnaty (bivalent, Original/Omicron BA.4-5) N = 464
	n (%)	n (%)
Solicited local adverse events[a)]	439 (98.4)	441 (95.0)
Grade ≥3	0	2 (0.4)
Solicited systemic adverse events[b)]	264 (57.0)	244 (52.6)
Grade ≥3	5 (1.1)	6 (1.3)
Unsolicited adverse events	73 (15.8)	82 (17.7)
Grade ≥3	5 (1.1)	1 (0.2)
Adverse events leading to death	0	0
Serious adverse events	0	0

N = Number of subjects analyzed, n = Number of subjects with events
a) Number of subjects with Grade ≥0 events. Grade 0 was used only for erythema, swelling, and induration (<2.5 cm).
b) Body temperature of ≥37.5°C (axillary) was handled as pyrexia.

1) Solicited adverse events

Table 3 shows the incidence of solicited adverse events (observed within 7 days after vaccination) [see Section 7.1]. Most of them were mild or moderate in severity. The most common solicited local adverse events were injection site tenderness (92.9% in the Kostaive group and 92.0% in the Comirnaty group) and injection site pain (81.9% and 81.5%). The most common solicited systemic adverse event was malaise (38.2% and 33.8%).

The median time-to-onset (range) of solicited local adverse events was 1 day (1-7 days) in the Kostaive group and 1 day (1-4 days) in the Comirnaty group. The duration of these events was 4 days (2-9 days) in the Kostaive group and 4 days (2-14 days) in the Comirnaty group. The median time-to-onset of solicited systemic adverse events was 2 days (1-7 days) in both the Kostaive and Comirnaty groups. The duration was 2 days (1-15 days) in the Kostaive group and 2 days (1-10 days) in the Comirnaty group.

2) Unsolicited adverse events and serious adverse events

Table 4 shows the incidence of unsolicited adverse events [see Section 7.1]. Most of these events were mild or moderate in severity. No serious adverse events were observed.

3) Adverse events by age group

Table 10 shows solicited adverse events (all and Grade ≥3 events) by age group. Although comparisons are challenging due to the very limited number of elderly subjects, no clear differences were observed between the subgroups.

Table 10. Solicited Adverse Events by Age Group (Study ARCT-2301-J01, safety analysis population)

MedDRA PT	All Grades				Grade ≥3			
	Kostaive (bivalent, Original/ Omicron BA.4-5)		Comirnaty (bivalent, Original/ Omicron BA.4-5)		Kostaive (bivalent, Original/ Omicron BA.4-5)		Comirnaty (bivalent, Original/ Omicron BA.4-5)	
	<65 years N = 429	≥65 years N = 34	<65 years N = 430	≥65 years N = 34	<65 years N = 429	≥65 years N = 34	<65 years N = 430	≥65 years N = 34
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	410 (95.6)	29 (85.3)	410 (95.3)	31 (91.2)	0	0	2 (0.5)	0
Erythema	41 (9.6)	6 (17.6)	47 (10.9)	5 (14.7)	0	0	0	0
Swelling	52 (12.1)	4 (11.8)	59 (13.7)	9 (26.5)	0	0	2 (0.5)	0
Induration	39 (9.1)	6 (17.6)	70 (16.3)	8 (23.5)	0	0	0	0
Tenderness	401 (93.5)	29 (85.3)	396 (92.1)	31 (91.2)	0	0	0	0
Pain	356 (83.0)	23 (67.6)	354 (82.3)	24 (70.6)	0	0	0	0
Systemic (all events)[a)]	250 (58.3)	14 (41.2)	232 (54.0)	12 (35.3)	5 (1.2)	0	6 (1.4)	0
Pyrexia[b)]	89 (20.7)	4 (11.8)	68 (15.8)	4 (11.8)	1 (0.2)	0	5 (1.2)	0
Arthralgia	79 (18.4)	3 (8.8)	69 (16.0)	3 (8.8)	0	0	0	0
Chills	66 (15.4)	3 (8.8)	57 (13.3)	2 (5.9)	0	0	0	0
Diarrhoea	18 (4.2)	0	13 (3.0)	2 (5.9)	0	0	0	0
Dizziness	9 (2.1)	0	8 (1.9)	0	0	0	1 (0.2)	0
Headache	116 (27.0)	2 (5.9)	110 (25.6)	0	3 (0.7)	0	1 (0.2)	0
Malaise	166 (38.7)	11 (32.4)	151 (35.1)	6 (17.6)	2 (0.5)	0	2 (0.5)	0
Nausea	14 (3.3)	0	8 (1.9)	1 (2.9)	1 (0.2)	0	0	0
Vomiting	2 (0.5)	0	3 (0.7)	0	0	0	0	0
Myalgia	83 (19.3)	6 (17.6)	93 (21.6)	4 (11.8)	0	0	1 (0.2)	0

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

a) Number of subjects with Grade ≥0 events. Grade 0 was used only for erythema, swelling, induration (<2.5 cm), and pyrexia (37.5°C-37.9°C).

b) ≥37.5°C (axillary)

7.R.3.2 Long-term safety

The long-term safety of vaccine was evaluated in the Japanese phase III study (Study ARCT-154-J01) using the monovalent (Original) vaccine. The serious adverse events reported within 180 days after study vaccination were as follows: 5 events (haemorrhoids, osteoarthritis, myelopathy, rhegmatogenous retinal detachment, and enterocolitis) in the Kostaive group; and 5 events (foot deformity, cataract, retinal detachment, severe invasive streptococcal infection, and meniscus injury) in the Comirnaty group. All events were reported as resolved, and their relationships to the study vaccine were ruled out.

The applicant's explanation about the safety of the Kostaive monovalent (Omicron JN.1) vaccine:
In Study ARCT-2301-J01, the incidence of adverse events was similar between the Kostaive bivalent (Original/Omicron BA.4-5) vaccine group and the Comirnaty bivalent (Original/Omicron BA.4-5) vaccine group. The safety outcomes obtained in Study ARCT-2301-J01 were comparable to those observed in the Japanese phase III study (Study ARCT-154-J01)[8)] submitted for the initial application, which evaluated the booster dose of the monovalent (Original) vaccine. The results suggest that modifying the antigen component of Kostaive does not alter its safety profile. Myocarditis and pericarditis, which have been observed in association with other SARS-CoV-2 RNA vaccines, were not reported in Study ARCT-2301-J01, as with the case of the clinical study results submitted for the initial application. The safety profile of the Kostaive monovalent (Omicron JN.1) vaccine is thus considered comparable to that of the Kostaive monovalent (Original) and bivalent (Original/Omicron BA.4-5) vaccines, and its safety is deemed acceptable.

PMDA's view on the safety of Kostaive:
Study ARCT-2301-J01 identified no significant differences between the safety of the Kostaive bivalent (Original/ Omicron BA.4-5) vaccine for booster dose and that of the Comirnaty bivalent (Original/Omicron BA.4-5) vaccine. The safety profile was largely consistent with that observed in the clinical studies reviewed for the initial application for the Kostaive monovalent (Original) vaccine. The safety of the Kostaive bivalent (Original/Omicron BA.4-5) vaccine in individuals aged ≥18 years is acceptable.

The Kostaive monovalent (Omicron JN.1) vaccine is a modified version of the monovalent (Original) vaccine. In view of the safety profiles observed in clinical studies of the monovalent (Original) vaccine and the bivalent (Original/Omicron BA.4-5) vaccine, the safety of the monovalent (Omicron JN.1) vaccine for booster dose, as explained by the applicant, is acceptable. The applicant should collect further information on the safety of the Kostaive monovalent (Omicron JN.1) vaccine during clinical use through the planned clinical studies of the monovalent (Omicron JN.1) vaccine and post-marketing surveillance. The information obtained should be disseminated to healthcare professionals, and the necessity of issuing additional safety alerts should be evaluated as needed.

7.R.4 Clinical positioning and indication

PMDA's view on the clinical positioning and indication of the Kostaive monovalent (Omicron JN.1) vaccine:
The efficacy and safety of the monovalent (Original) vaccine have already been reviewed.[7)] According to the applicant, results from non-clinical studies on the monovalent (Omicron JN.1) vaccine, in addition to the findings of Study ARCT-2301-J01 of the bivalent (Original/Omicron BA.4-5) vaccine, have demonstrated that the monovalent (Omicron JN.1) vaccine induces neutralizing antibodies against various Omicron sublineages, including currently circulating strains (such as KP.3 lineage) [see Section 3.R]. The efficacy and safety evaluation in Study ARCT-2301-J01 suggest that the efficacy of the bivalent (Original/Omicron BA.4-5) vaccine for booster dose is promising [see Section 7.R.2], and that its safety is acceptable [see Section 7.R.3]. Thus, the monovalent (Omicron JN.1) vaccine is expected to serve as one of SARS-CoV-2 vaccines targeting Omicron variants.

Various SARS-CoV-2 variants have emerged so far. If a novel variant spreads in the future, prompt development of new variant-specific vaccines may be required. Compared to conventional vaccines, mRNA vaccines allow for more rapid development and production. Given that Kostaive is being manufactured domestically, establishing a production and supply system for Kostaive variant-adapted vaccines in Japan is significant for enabling swift responses to COVID-19 outbreaks.

In light of the above, the indication of the monovalent (Omicron JN.1) vaccine can be specified as "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as with that of the initial approval of the monovalent (Original) vaccine. In the present application, the applicant included a statement specifying the applicable formulation in the indication, based on the results of the clinical study evaluating the immunogenicity and safety of the variant-specific vaccine. However, the evaluation of data submitted in the present application indicates that the quality and safety of Kostaive are unlikely to be affected by antigen strain changes. The immunogenicity of vaccines with altered

antigen strains is predictable from non-clinical studies. Thus, for the next and subsequent regulatory submissions involving antigen strain changes for Kostaive, applications will be reviewed through an expedited review procedure without modifications to the indication or dosage and administration under the "Handling of Changes to COVID-19 Vaccine Strains (notification)" (PSB/PED Notification No. 0523-1 and PSB/CND Notification No. 3, dated May 23, 2024). The description specifying the applicable formulation specified by the applicant is deemed unnecessary.

7.R.5. Dosage and administration

The approved dosage and administration for the Kostaive monovalent (Original) vaccine was "As the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 4 weeks apart. As the booster dose, a single dose of 0.5 mL is injected intramuscularly." Subsequently, in accordance with the notification "Modification of Dosage and Administration of COVID-19 Vaccines (in Japanese)" (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1, dated March 6, 2024), the "Dosage and Administration" for COVID-19 vaccines in individuals other than infants (aged ≥5 years) were revised to reflect the current booster dose as the primary description for "Dosage and Administration." The description was updated to the dosage regimen for booster dose, "A single dose of 0.5 mL is injected intramuscularly," at the time of the initial approval.[8)] The dosage regimen for the proposed monovalent (Omicron JN.1) vaccine was established in accordance with this revision.

7.R.5.1 Dose setting

The applicant's explanation about the rationale for determining the dosage of the monovalent (Omicron JN.1) vaccine:

Both the monovalent (Original) vaccine and the bivalent (Original/Omicron BA.4-5) vaccine contain 5 μg of RNA per 0.5 mL dose as the active substance. In the bivalent (Original/Omicron BA.4-5) vaccine, the RNA content of sequence of each strain or variant is 2.5 μg. Study ARCT-2301-J01 demonstrated that a single dose of the vaccine provided a booster effect equal to or greater than that of approved vaccines for each antigen component. On the basis of these findings, the applicant considers it appropriate to administer the monovalent vaccine with 5 μg of RNA (0.5 mL) intramuscularly and the bivalent vaccine with 2.5 μg of RNA per component (5.0 μg total in 0.5 mL) intramuscularly.

PMDA's view:

Based on the review on the efficacy and safety of the bivalent (Original/Omicron BA.4-5) vaccine [see Sections 7.R.2 and 7.R.3] and on the applicant's explanation, it is reasonable to administer the monovalent (Omicron JN.1) vaccine as a single dose of 0.5 mL intramuscular injection, like the monovalent (Original) vaccine.

As mentioned in Section 7.R.4 regarding the description of indications, the applicable formulations specified by the applicant were deemed unnecessary for the Dosage and Administration section as well.

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

The applicant's explanation about the post-marketing surveillance, etc. for Kostaive:

8) Changed by minor change notification submitted on March 29, 2024

The results of Study ARCT-2301-J01 and safety information on the monovalent (Original) vaccine show that the safety profile of Kostaive is consistent, regardless of the SARS-CoV-2 strain/variant used as the antigen or its valency. The safety of the monovalent (Omicron JN.1) vaccine is considered acceptable [see Section 7.R.3]. No additional safety specifications need to be established for the present application. As outlined for the initial approval of the monovalent (Original) vaccine,[7)] the applicant will conduct a general use-results survey to confirm the safety of Kostaive in clinical practice (planned sample size of 1500; observation period of up to 12 weeks after the final dose), as a part of additional pharmacovigilance activities. In order to detect at least 1 case of adverse events with the lowest incidence (0.2%, 1 of 463 subjects) reported from previous Japanese clinical studies with over 95% probability, 1497 subjects were required; therefore, the planned sample size of 1500 is determined sufficient for safety analysis. The survey will also collect information on the safety of Kostaive in clinical practice, including safety data in populations from which only limited information was obtained during development (e.g., individuals with underlying diseases), or no information was obtained during development (e.g., pregnant women). If new safety concerns or need for enhancements to risk minimization measures is identified through periodic safety update reports or the general use-results survey, this information should be promptly provided to healthcare professionals involved in SARS-CoV-2 vaccination and vaccine recipients.

PMDA's view:

Following the market launch of the Kostaive monovalent (Omicron JN.1) vaccine, the applicant should collect and evaluate information on the safety of Kostaive in clinical practice, taking into account the information planned to be gathered in the post-marketing setting as described during the approval process for the monovalent (Original) vaccine. The applicant's policy of promptly providing evaluation results based on the collected information is appropriate. Based on the above, the current risk management plan (draft) for Kostaive should include the safety specifications presented in Table 11, and the applicant should conduct the additional pharmacovigilance activities and additional risk minimization activities described in Tables 12 and 13.

Table 11. Safety and efficacy specifications in the risk management plan (draft)

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

No change from the initial approval

Table 12. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey • Post-marketing clinical study (Study ARCT-154-J01)	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for vaccine recipients • Periodical publication of the occurrence of adverse reactions

No change from the initial approval

Table 13. Outline of general use-results survey (draft)

Objective	To evaluate the safety of Kostaive administered in post-marketing clinical practice
Survey method	Central registry system
Population	Individuals aged ≥18 years who receive Kostaive
Observation period	12 weeks
Planned sample size	1500 (safety analysis population)
Main survey items	Characteristics of vaccine recipients, status of vaccination with Kostaive, concomitant drugs, incidence of adverse events and adverse reactions, development of COVID-19

Underlined part: Changes pursuant to the present application

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 5.3.5.1-01) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation

On the basis of the data submitted, PMDA has concluded that the monovalent (Omicron JN.1) vaccine is expected to have a certain level of efficacy in the prevention of COVID-19, and that the monovalent (Omicron JN.1) vaccine is unlikely to raise serious safety concerns and thus has acceptable safety. Based on an assessment of the benefit-risk balance in view of the prevalence of SARS-CoV-2 and characteristics of individuals, PMDA considers that there is clinical significance in making the proposed vaccine adapted to variant strains available for use in clinical practice.

As per the PMDA's assessment in Sections "7.R.4 Clinical positioning and indications" and "7.R.5 Dosage and administration," it was determined that the descriptions specifying applicable formulations added at the time of submission of the application are unnecessary for the approved indications and dosage regimen.

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and the dosage and administration, with approval condition shown below. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until November 27, 2031).

Indication

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

Dosage and Administration

The product is reconstituted with 10 mL of physiological saline (Japanese Pharmacopoeia grade).
A single dose of 0.5 mL is injected intramuscularly.

Approval Condition

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

Appendix

List of Abbreviations

CI	Confidence interval
Comirnaty	Comirnaty Intramuscular Injection, etc. (non-proprietary name, coronavirus [SARS-CoV-2] RNA vaccine), Pfizer Japan Inc.
COVID-19	Coronavirus disease 2019
CTD	Common technical document
FAS	Full analysis set
GMFR	Geometric mean fold rise
GMR	Ratio of Geometric mean titers
GMT	Geometric mean titer
Kostaive	Kostaive Intramuscular Injection
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
Original strain	Strain Wuhan-Hu-1
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
PT	Preferred term
RNA	Ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus-2
Spikevax	Spikevax Intramuscular Injection, etc. (non-proprietary name, coronavirus [SARS-CoV-2] RNA vaccine), Moderna Japan Co., Ltd.
SRR	Seroresponse rate
ULOQ	Upper limit of quantification
VEEV	Venezuelan equine encephalitis virus