Report on Special Approval for Emergency

September 7, 2022
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Spikevax Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredients: (a) Elasomeran [JAN*], (b) Elasomeran [JAN*] and Imelasomeran [JAN*])
Applicant	Moderna Japan Co., Ltd.
Date of Application	August 10, 2022
Dosage Form/Strength	(a) Suspension for injection: Each vial contains 1.0 mg of Elasomeran. (b) Suspension for injection: Each vial contains 0.125 mg of Elasomeran and 0.125 mg of Imelasomeran.
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, (10-2) Other prescription drugs (Drugs falling under the category of [10] and involving changes in the manufacturing method of biological products, etc.)
Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as the "Pharmaceuticals and Medical Devices Act"), pursuant to the provisions of Article 14-3, Paragraph 1 of the Act ("Handling of Drugs Submitted for Special Approval for Emergency (Request)" [PSEHB/PED No. 0906-1, dated on September 6, 2022])
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the booster dose of the vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant) has a

certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety with no significant safety 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 the spike protein of SARS-CoV-2 (original strain)
- Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

(Underline denotes additions.)

Dosage and Administration

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

  For the primary series, ~~:~~ Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

  For a booster dose, ~~:~~ a single ~~booster~~ dose (0.25 mL) of Spikevax is administered intramuscularly.
- Vaccine product containing mRNA encoding the spike proteins of SARS-CoV-2 (original strain and Omicron variant)

  For a booster dose, a single dose (0.5 mL) of Spikevax is administered intramuscularly.

(Underline denotes additions and strikethrough denotes deletions.)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

(1) Matters related to Item 2

When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.

(2) Matters related to Item 3

The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(3) Matters related to Item 4

The applicant is required to report the quantity sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

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

(2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.

(3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

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

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

**Japanese Accepted Name (modified INN)*

Attachment

Report on Special Approval for Emergency

September 6, 2022

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

Product Submitted for Approval

Brand Name	Spikevax Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredients: (a) Elasomeran, (b) Elasomeran and Imelasomeran)
Applicant	Moderna Japan Co., Ltd.
Date of Application	August 10, 2022
Dosage Form/Strength	(a) Suspension for injection: Each vial contains 1.0 mg of Elasomeran (b) Suspension for injection: Each vial contains 0.125 mg of Elasomeran and 0.125 mg of Imelasomeran

Proposed Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19) (including infection with the original strain and Omicron variant)

(Underline denotes additions.)

Proposed Dosage and Administration

Spikevax Intramuscular Injection (monovalent)

Primary series: Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

Booster dose: A single booster dose (0.25 mL) of Spikevax is administered intramuscularly.

Spikevax Intramuscular Injection (bivalent)

A single dose (0.5 mL) of Spikevax is administered intramuscularly.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

Several therapeutic agents and vaccines have been developed to tackle the global pandemic of disease caused by SARS-CoV-2 infection (COVID-19) breaking out in January 2020, and various measures including vaccination roll-out programs have been implemented to control COVID-19. However, SARS-CoV-2 genetic mutations gave rise to variants with varying degrees of infectivity, transmissibility, antigenicity, and pathogenicity, resulting in repeated waves of SARS-CoV-2 infection; and the COVID-19 pandemic has yet to end. Recent literature reports that the Omicron variant, the currently dominant variant (as of August 2022), can evade pre-existing vaccine-induced immunity due to changes in the antigenicity of the original virus strain, and thus vaccine efficacy against the Omicron variant waned (e.g., *N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63). Under the circumstances, international regulatory authorities and the World Health Organization (WHO) have discussed the need for new vaccines that address emerging variants (e.g., *International Coalition of Medicines Regulatory Authorities SARS-CoV-2 Variant Workshop*. ICMRA. June 30, 2022,[1)] *Interim statement on the composition of current COVID-19 vaccines.* WHO. June 17, 2022,[2)] *Interim statement on decision making considerations for the use of variant updated COVID-19 vaccines.* WHO. June 17, 2022.[3)]).

Spikevax Intramuscular Injection (hereinafter also referred to as "Spikevax") is a vaccine indicated for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" and is approved as a monovalent vaccine containing the active ingredient elasomeran, a messenger ribonucleic acid (mRNA) encoding the spike protein (S protein) of the SARS-CoV-2 original strain. As of the end of August 2022, vaccines that have been approved for marketing in Japan with an indication for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" include not only Spikevax Intramuscular Injection but also Comirnaty Intramuscular Injection (Pfizer Japan Inc.) and Vaxzevria Intramuscular Injection (AstraZeneca K.K.); however, no vaccines have been developed or approved to address variants.

To meet the need for variant-adapted vaccines, the applicant developed the Spikevax bivalent (Original/Omicron) vaccine that contains a new active ingredient imelasomeran, an mRNA encoding the S protein of the SARS-CoV-2 Omicron BA.1 lineage (hereinafter also referred to as "Omicron BA.1"), in addition to elasomeran. The applicant amended the design of Study mRNA-1273-P205 (Study P205), which had been underway since May 2021, and initiated a study (Study P205 Part G) on the bivalent (Original/Omicron) vaccine as a booster dose in March 2022. On the basis of data including the results from this study, a conditional marketing authorization was granted in the UK on August 12, 2022 and in the EU on September 2, 2022.

Recently, a partial change application has been filed also in Japan to add the bivalent vaccine on the basis of the data including results from the above study.

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1) https://icmra.info/drupal/en/covid-19/30june2022 (last accessed on September 6, 2022)
2) https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines (last accessed on September 6, 2022)
3) https://www.who.int/news/item/17-06-2022-interim-statement-on-decision-making-considerations-for-the-use-of-variant-updated-covid-19-vaccines (last accessed on September 6, 2022)

The review of the present application was performed based on the data submitted by the applicant in accordance with the "Handling of Drugs Submitted for Special Approval for Emergency (Request)" (PSEHB/PED No. 0906-1, dated on September 6, 2022).

2. Quality and Outline of the Review Conducted by PMDA

The bivalent (Original/Omicron) vaccine, which is proposed in the present application, contains mRNA-1273 lipid nanoparticle (LNP) and mRNA-1273.529 LNP at a ratio of 1:1. The mRNA-1273 LNP contain elasomeran, an mRNA encoding the S protein of SARS-CoV-2 (Original strain), and mRNA-1273.529 LNP contain imelasomeran, an mRNA encoding the S protein of SARS-CoV-2 (Omicron BA.1), each embedded in lipid nanoparticles [redacted].

2.1 Active substance

Two active substances (mRNA), elasomeran and imelasomeran, are used in the manufacture of the Spikevax bivalent (Original/Omicron) vaccine. Elasomeran is identical to the one used in the active substance for Spikevax monovalent (Original) vaccine. The following subsections describe information on imelasomeran.

2.1.1 Characterization of active substance

Imelasomeran was subjected to characterization equivalent to that performed for elasomeran. However, no *in vitro* translation assays were performed because whether intended proteins are expressed from the mRNA can be confirmed by *in vitro* relative protein expression (IVRPE) assay, which was performed as part of characterization of the vaccine intermediate, mRNA-1273.529 LNP.

Product-related impurities and process-related impurities of imelasomeran are controlled in a manner equivalent to those of elasomeran.

2.1.2 Manufacturing process of active substance

The manufacturing process of imelasomeran is the same as that of elasomeran, and qualification of the process has been verified by process validation. The plasmid DNA templates encoding imelasomeran used for *in vitro* transcription are controlled in the cell bank system.

2.1.3 Control of active substance

The specifications of imelasomeran are identical to those of elasomeran. Testing methods for identification of imelasomeran are esteblished according to the difference in mRNA sequence between imelasomeran and elasomeran.

2.1.4 Stability of active substance

The storage temperature for elasomeran was changed from −20 ± 5°C to −75 ± 15°C in the present application. A storage temperature of −75 ± 15°C, the same as that of elasomeran, was specified for imelasomeran.

Table 1 and Table 2 summarize main stability studies, which form the basis for the shelf-life of elasomeran and imelasomeran.

Table 1. Summary of main stability studies for elasomeran

Study type	Manufacturing site	Number of batches	Storage condition	Study duration	Storage package
Long-term	ModernaTX	1[a)]	−20 ± 5°C	12 months	[redacted] bottle
			−75 ± 15°C	24 months	
		4[b)]	−20 ± 5°C	18 months[d)]	[redacted] bag
		3[c)]	−75 ± 15°C	0 months[d)]	
	Lonza Visp*	4[b)]	−20 ± 5°C	12 months[d)]	

* The manufacturing site for the active substance used for the production of the vaccine product supplied to the Japanese market
a) A batch for non-clinical testing
b) Process performance qualification (PPQ) batches
c) Commercial-scale batches
d) Testing will be continued for up to 48 months

Table 2. Summary of main stability studies for imelasomeran

Study type	Manufacturing site	Number of batches	Storage condition	Study duration	Storage package
Long-term	ModernaTX	1[a)]	−75 ± 15°C	0 months[b)]	[redacted] bag
	Lonza Visp*	1[a)]	−80 ± 10°C	0 months[c)]	

*, The manufacturing site for the active substance used for the production of the vaccine product supplied to the Japanese market
a) Commercial-scale batches
b) Testing will be continued for up to 60 months
c) Testing will be continued for up to 48 months

No clear changes were observed throughout the studies for elasomeran (PPQ and non-clinical testing batches) under the long-term storage conditions at −20 ± 5°C and elasomeran (non-clinical testing batch) under the long-term storage conditions at −75 ± 15°C. The stability studies for elasomeran and imelasomeran (commercial-scale batches for both) at −75 ± 15°C are currently underway.

Based on the stability studies, a shelf-life of 18 months has been proposed for elasomeran and imelasomeran when stored at −75 ± 15°C [see Section 2.R.2].

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

The Spikevax bivalent (Original/Omicron) vaccine is a suspension for injection, supplied in multiple-dose vials containing a nominal volume of 2.5 mL (0.5 mL per dose). Each vial contains 0.125 mg of elasomeran and 0.125 mg of imelasomeran. Excipients contained in the Spikevax bivalent (Original/Omicron) vaccine are the same as those contained in the Spikevax monovalent (Original) vaccine.

During the development of the bivalent vaccine, formulation changes were made (changes in mRNA concentration, lipid concentration, and volume filled). Quality attributes were assessed between the formulation used in the clinical studies or formulations under development (e.g., bivalent [Original/Beta] vaccine) and the marketed formulation, and the results demonstrated their comparability or similarity.

2.2.2 Manufacturing process for vaccine product

The bivalent (Original/Omicron) vaccine is manufactured by mixing the vaccine intermediates, elasomeran embedded in Lipid Mixture (mRNA-1273 LNP) and imelasomeran embedded in Lipid Mixture (mRNA-1273.529 LNP). The manufacturing process for the bivalent (Original/Omicron) vaccine is equivalent to that for the monovalent (Original) vaccine except that the mixing of vaccine intermediates is included in the manufacturing process for the bivalent vaccine. The qualification of the process has been verified by process validation.

2.2.3 Control of vaccine product

2.2.3.1 Control of vaccine intermediates

The control method for the vaccine intermediates, mRNA-1273 LNP and mRNA-1273.529 LNP, is similar to that for the intermediate of the monovalent (Original) vaccine. The test method for identification and the specification limit for lipid content are defined according to the composition of mRNA-1273 LNP and mRNA-1273.529 LNP.

2.2.3.2 Control of vaccine product

For the proposed specifications for the bivalent (Original/Omicron) vaccine product, mRNA content (Original/Omicron) ratio has been newly included, and liquid chromatography has been specified as identification testing. Except for the two changes, the proposed specifications are the same as those for the monovalent (Original) vaccine. The proposed specifications and specification limits for lipid content and extractable volume test are based on the composition of the bivalent (Original/Omicron) vaccine product, and its formulation and development. While IVRPE tests are performed as process control testing for the monovalent (Original) vaccine product, no IVRPE tests are specified as process control testing for the bivalent (Original/Omicron) vaccine product [see Section 2.R.1].

2.2.4 Stability of vaccine product

Table 3 shows the summary of planned main stability studies for the bivalent (Original/Omicron) vaccine product.

Table 3. Summary of planned main stability studies for bivalent (Original/Omicron) vaccine product

Study type	Manufacturing site	Number of batches	Storage condition	Planned study duration	Storage package
Long-term	Patheon Monza	3	−20 ± 5°C	12 months	Chlorobutyl rubber stopper and glass vial
	Rovi SSR*	1		12 months	

* The manufacturing site for the vaccine product supplied to the Japanese market.

Although results from the planned stability studies have not been received yet, a shelf life of 9 months has been proposed also for the bivalent (Original/Omicron) vaccine when stored at −20 ± 5°C. The shelf life was determined based on the proven data for the monovalent (Original) vaccine [see Section 2.R.2].

2.R Outline of the review conducted by PMDA

PMDA conducted its review on the issues addressed in the following sections based on the submitted data, and the review found no particular problems with the quality of the Spikevax bivalent vaccine.

2.R.1 IVRPE assay

The IVRPE assay is not included in the in-process control of the bivalent (Original/Omicron) vaccine product.
The applicant's explanation:

- IVRPE assay for the components of the bivalent (Original/Omicron) vaccine, mRNA-1273 LNP and mRNA-1273.529 LNP, was performed as a characterization study. The results confirmed expression of proteins from both mRNA-1273 LNP and mRNA-1273.529 LNP.
- IVRPE assay was performed as a characterization study on bivalent vaccines including the bivalent (Original/Omicron) vaccine. The protein expression levels of bivalent vaccines were similar to those of the monovalent (Original) vaccine containing the same amount of mRNA, suggesting that 2 types of S proteins will be expressed according to the amount of mRNA contained in the bivalent (Original/Omicron) vaccine.
- The past manufacturing data for the monovalent (Original) vaccine indicate correlations between protein expression and RNA content or mRNA purity. The results of tests of these elements were consistent with those obtained by the IVRPE assay.

In light of the above findings, on the premise that the expression of the 2 types of proteins have been confirmed by characterization for the vaccine product and its intermediates, the applicant decided to implement the following quality control strategy: No IVRPE assay is included in the specifications for the bivalent (Original/Omicron) vaccine product, but the RNA content and mRNA purity of the vaccine product are controlled through quality control tests to ensure the expression levels of 2 types of proteins.

PMDA's view:
Based on the applicant's explanation, it is acceptable not to include IVRPE assay in the specifications for the bivalent (Original/Omicron) vaccine. However, while IVRPE is an important quality attribute to ensure the efficacy of the Spikevax bivalent vaccine, the currently available results of characterization for the vaccine intermediates are only based on a limited number of batches. Therefore, the applicant should verify the consistency of IVRPE based on the results of IVRPE assay performed as a characterization study on multiple batches of mRNA-1273 LNP and mRNA-1273.529 LNP.

2.R.2 Shelf life of active substance and vaccine product

The applicant's explanation about the shelf life of the active substance and vaccine product:
A shelf life of 18 months can be specified for the active substance when stored at −75 ± 15°C, based on the following reasons:

- Since the rate of RNA degradation is dependent on the length of RNA, the stability study results for elasomeran can demonstrate the stability of imelasomeran whose mRNA length is similar to that of elasomeran.

- The stability of elasomeran has been demonstrated on 1 batch stored at −75 ± 15°C for up to 24 months, and on 4 batches stored at −20 ± 5°C for up to 18 months.
- The results of the stability studies for elasomeran at −75 ± 15°C and −20 ± 5°C showed that the RNA degradation rate at −75 ± 15°C was lower than that at −20 ± 5°C.
- Although the filled volume of the active substance manufactured at the site for the Japanese market differs from that manufactured at ModernaTX, a comparison of the stability study data for the active substance between different filled volumes demonstrated that the difference in filled volume does not affect the stability (mRNA purity).
- Comparison of stability study data for the active substance manufactured at different sites demonstrated that the difference in the manufacturing site does not affect the stability (mRNA purity).

On the other hand, a shelf life of 9 months can be specified for the bivalent (Original/Omicron) vaccine, based on the following reasons:

- Since the rate of RNA degradation is dependent on the length of RNA, the stability study results for vaccines such as the monovalent (Original) and bivalent (Original/Beta) vaccines can demonstrate the stability of the bivalent (Original/Omicron) vaccine whose mRNA length is similar that of RNA contained in the above monovalent or bivalent vaccine.
- The results of the stability study for the monovalent (Original) vaccine support the shelf life of 9 months.
- The results of the stability study for vaccines including the monovalent (Original) and bivalent (Original/Beta) vaccines have demonstrated that differences in formulations (mRNA concentration, lipid concentration, and filled volume) between vaccines do not affect the stability (mRNA purity) of the vaccine product.
- Stability study data for vaccines, including the monovalent (Original) and bivalent (Original/Beta) vaccines, manufactured at different sites were compared with those for the bivalent (Original/Omicron) vaccine (development batches). Results shows that the differences in the manufacturing site and process are not expected to affect the stability (mRNA purity).

PMDA's view:

Based on the applicant's explanation, a shelf life of 18 months for the active substance when stored at −75 ± 15°C, and a shelf life of 9 months for the vaccine product when stored at −20 ± 5°C are acceptable. However, the applicant should verify the stability of commercial batches stored at −75 ± 15°C in the ongoing long-term study with elasomeran and imelasomeran. In the long-term study to be conducted with the bivalent (Original/Omicron) vaccine, the applicant should also verify that the stability profile of commercial batches is the same as that of the monovalent (Original) vaccine.

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

The applicant submitted only the results from primary pharmacodynamic studies as non-clinical pharmacology data on the bivalent (Original/Omicron) vaccine. The doses of the bivalent (Original/Omicron) vaccine are expressed as the amount of mRNA.

3.1 Primary pharmacodynamics

Table 4 summarizes the studies submitted (evaluation data).

Table 4. Summary of pharmacology studies

Animal species and sex	Number of animals	Dose and immunization schedule; method of virus challenge	Main endpoint (Section that outlines results)	Attached document CTD
BALB/c mice Females	N = 8/group	2 doses (21 days apart), intramuscular administration • Monovalent (Original) vaccine 1 μg • Bivalent (Original/Omicron) vaccine 1 μg • Monovalent (Omicron) vaccine 1 μg • PBS	Immunogenicity [e)] (3.1.1.1)	4.2.1.1.1
BALB/c mice Females	N = 8/group	3 or 4 doses, intramuscular administration (The second, third, and fourth doses administered at 21, 49, and 77 days post prime, respectively) • 2 doses of monovalent (Original) vaccine (0.25 μg) + 1 or 2 doses of monovalent (Original) vaccine (0.25 μg) • 2 doses of monovalent (Original) vaccine (0.25 μg) + 1 or 2 doses of monovalent (Omicron) vaccine (0.25 μg) • 2 doses of monovalent (Original) vaccine (0.25 μg) + 1 dose of bivalent (Original/Omicron) vaccine (0.25 μg) • 2 doses of monovalent (Original) vaccine (0.25 μg) + 1 dose of monovalent (Original) vaccine (0.25 μg) + 1 dose of monovalent (Omicron) vaccine (0.25 μg) • 3 or 4 doses of PBS	Immunogenicity [f)] and B cell responses[g)] (3.1.1.1)	4.2.1.1.2
129S2 mice Females	N = 8/group (N = 9 or 10 in the mRNA[a)] group)	3 doses, intramuscular administration (The second dose administered at 21 days post-prime, and the third dose administered at 98 or 99 days post-prime) • 2 doses of monovalent (Original) vaccine (0.25 or 5 μg) + 1 dose of monovalent (Original) vaccine (1 μg) • 2 doses of monovalent (Original) vaccine (0.25 or 5 μg) + 1 dose of monovalent (Omicron) vaccine (1 μg) • 2 doses of mRNA[a)] (0.25 or 5 μg) + 1 dose (1 μg) At 124 or 126 days post third-dose, D614G variant[b)] or Omicron BA.1[c)] (1×10^5 PFU/body) was inoculated intranasally	Protection from infection[h)] (3.1.2)	4.2.1.1.3
Rhesus monkeys Males/ females	N = 4/group (N = 8 in the mRNA[a)] group)	3 doses, intramuscular administration (The second and third doses administered at 4 and 41 weeks post-prime, respectively) • 2 doses of monovalent (Original) vaccine (100 μg) + 1 dose of monovalent (Original) vaccine (50 μg) • 2 doses of monovalent (Original) vaccine (100 μg) + 1 dose of monovalent (Omicron) vaccine (50 μg) • Untreated 2 times + 1 dose of mRNA[a)] (50 μg) At 4 weeks post-third dose, Omicron BA.1[d)] (1×10^6 PFU/body) was inoculated intranasally or intratracheally	Protection from infection[i)] (3.1.2)	4.2.1.1.4

a) UNFIX-01 (LNPs containing short chain mRNA)
b) WA1/2020 N501Y/D614G
c) hCoV-19/USA/WI-WSLH-221686/2021
d) Cell 2022; 185: 1556-71
e) Sampling date: 20 and 35 days post-prime
f) Sampling date: 20, 35, 48, and 92 days post-prime
g) Sampling date: 63 days post-prime
h) Sampling date: 97 or 98 days post-prime (before virus challenge), 121 or 122 days post-prime, 127 or 129 days post-prime
i) Sampling date: 6, 8, 39, 41, and 43 weeks post-prime, and 1, 2, 4, and 8 days post-virus challenge

3.1.1 Immunogenicity

3.1.1.1 Antibody production and B cell response (CTD 4.2.1.1.1, 4.2.1.1.2)

The S1 protein-specific antigen titers (enzyme-linked immunosorbent assay [ELISA]) and neutralizing antibody titers (luciferase reporter assay using a pseudovirus[4)]) were investigated using serum collected after administration of the bivalent (Original/Omicron) vaccine. B cells from iliac lymph nodes were studied for cross-reactivity between antigens (flow cytometry/surface antigen staining).

In mice immunized with 2 doses of the bivalent (Original/Omicron) vaccine or the monovalent (Omicron) vaccine, S1 protein-specific antibodies and neutralizing antibodies against variants (D614G variant, Omicron BA.1, and Omicron BA.2) were induced.

In mice immunized with the bivalent (Original/Omicron) vaccine or monovalent (Omicron) vaccine as the third dose following 2 doses of the monovalent (Original) vaccine, neutralizing antibodies against variants (D614G variant, Omicron BA.1, and Omicron BA.2) as well as BA.1 antigen-specific B cells were induced. In mice immunized with monovalent (Omicron) vaccine as the third and fourth doses following 2 doses of the monovalent (Original) vaccine, neutralizing antibodies against variants (D614G variant, Omicron BA.1, and Omicron BA.2) were induced. The neutralizing antibody titers against Omicron BA.1 and BA.2 were higher than those in mice immunized with 4 doses of the monovalent (Original) vaccine.

The applicant explained that the bivalent (Original/Omicron) vaccine is expected to produce neutralizing antibodies against Omicron variant.

3.1.2 Protection from infection (CTD 4.2.1.1.3, 4.2.1.1.4)

Protection against the Omicron variant was investigated in mice and monkeys boosted with the monovalent (Omicron) vaccine as the third dose following 2 doses of the monovalent (Original) vaccine. After virus challenge, virological and histopathological examinations were performed in the studies. In the virological examinations, virus genomic RNA and subgenomic RNA (sgRNA) were measured in mice and monkeys, respectively, by reverse transcription polymerase chain reaction (RT-PCR).

In the mouse study, the virus levels detected in nasal wash, nasal turbinate, and lung samples post-challenge were lower in the animals boosted with the monovalent (Omicron) vaccine as the third dose than in the negative control group, while the virus levels in the animals boosted with the monovalent (Omicron) were similar to or lower than those in the animals boosted with the monovalent (Original) vaccine.

In the monkey study, the virus levels detected in oral swab, bronchoalveolar lavage, and nasal swab samples post-challenge were lower in the animals boosted with the monovalent (Omicron) vaccine as the third dose than in the negative control group, while the virus levels in the animals boosted with the monovalent (Omicron) were similar to or lower than those in the animals boosted with the monovalent (Original) vaccine. The lung

4) Lentivirus harboring a luciferase reporter gene and pseudotyped with SARS-CoV-2 (Wuhan-1 strain) S protein bearing D614G mutation (aspartic acid at position 614 substituted by glycine), SARS-CoV-2 S protein of Omicron BA.1, or SARS-CoV-2 S protein of Omicron BA.2.

histopathology showed that while the negative control group presented with moderate to severe lesions, the animals boosted with the monovalent (Omicron) vaccine presented with mild to moderate lesions.

The applicant explained that the above findings suggest that the bivalent (Original/Omicron) vaccine is expected to provide protection against the Omicron variant.

3.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that there were no particular problems with the non-clinical pharmacology of the bivalent (Original/Omicron) vaccine.

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

Results from the studies of metabolism and excretion of heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102) [redacted] contained in the bivalent (Original/Omicron) vaccine were submitted (CTD 4.2.2.4).

The applicant's explanation:

In the studies of metabolism, the Lipid Mixture was added to rat, monkey, or human hepatocytes, and in the study of metabolism and excretion, a single intravenous dose of the Lipid Mixture was administered to rats. The results from these studies suggest that SM-102 is primarily metabolized to ester hydrolysis products and then to beta oxidation products, and excreted in urine and bile.

PMDA's view:

Based on the submitted data, there are no particular problems with the non-clinical pharmacokinetics of SM-102.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication and a new dosage, no new toxicity data were 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

Neutralizing antibodies against SARS-CoV-2 in serum were measured by pseudovirus neutralization assay, and SARS-CoV-2 S protein-specific binding antibodies were measured by electrochemiluminescence assay (ECL).

6.2 Clinical pharmacology

No clinical pharmacology data were submitted in the present application.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 study (Table 5). The evaluation data consisted of results from Part G of Study P205, which evaluated the bivalent (Original/Omicron) vaccine as a booster dose, and results from the monovalent (Original) vaccine group in Cohort 2 of Part F,[5)] the control of Part G.

Table 5. Overview of clinical studies

Data category	Country	Study ID	Phase	Study population	Number of participants	Dosing regimen	Study objective
Evaluation	US	mRNA-1273-P205 Part G Part F [a)]	II/III	Adults aged ≥18 years who received 2 doses of the monovalent (Original) vaccine 100 µg as primary series and 1 booster dose of the monovalent (Original) vaccine 50 µg	Part G: 440 Part F[a)]: 379	Part G: 1 dose (IM) of bivalent (Original/Omicron) 50 µg Part F [a)]: 1 dose (IM) of monovalent (Original) vaccine 50 µg	Safety Immunogenicity

a) Only information on the monovalent (Original) vaccine group in Cohort 2 of Part F is shown.

7.1 Foreign phase II/III study (CTD 5.3.5.1-1, Study mRNA-1273-P205, ongoing since May 2021 [data cut-off date of April [redacted], 2022 for interim analysis])

Study P205 was an open-label, phase II/III study consisting of 7 parts (Parts A through G), which was conducted to investigate the safety and immunogenicity of mRNA vaccines[6)] as a booster dose against SARS-CoV-2 variants. The study was initiated to investigate the first booster dose; however, the study design was changed during the study period so as to evaluate the second booster dose (Protocol amendment: addition of Part F Cohort 2[7)] and study design change on January [redacted], 2022, February [redacted], 2022; addition of Part G and study design change on February [redacted], 2022, March [redacted], 2022).

7.1.1 Part G of Study P205

In Part G, the safety and immunogenicity of the bivalent (Original/Omicron) vaccine was evaluated using data from the monovalent (Original) vaccine group in Part F Cohort 2 (hereinafter referred to as “Part F”) serving as a comparator. Parts G and F of the study were conducted at 23 study centers in the US to evaluate the safety and immunogenicity of the bivalent (Original/Omicron) vaccine (Part G) or the monovalent (Original) vaccine (Part F) in participants aged ≥18 years who had received 2 doses of the monovalent (Original) vaccine 100 µg as the primary series, and 1 booster dose of the monovalent (Original) vaccine 50 µg (target sample size, 375

5) Part F was originally intended to evaluate the efficacy of the monovalent (Omicron) vaccine, which contains the mRNA encoding the Omicron BA.1 S protein as the active substance. The first and second booster doses were studied in Cohorts 1 and 2, respectively.

6) The mRNA vaccines used were not only the bivalent (Original/Omicron) vaccine but also the bivalent (Original/Beta) vaccine against the Beta variant (B.1.351), the monovalent and bivalent vaccines against the Delta variant (B.1.617.2), and the monovalent (Omicron) vaccine.

7) While the study with Cohort 2 of Part F included investigation of the monovalent (Omicron) vaccine as the second booster dose, the study results for the monovalent (Omicron) vaccine were not included in the data submitted in support of the present application.

participants in Part G; 375 participants in Part F[8]). The bivalent (Original/Omicron) vaccine (Part G) or the monovalent (Original) vaccine (Part F) was given as the second booster dose at ≥3 months after the first booster dose.

Participants were to receive 1 dose of the bivalent (Original/Omicron) vaccine 50 μg (Part G) or 1 dose of the monovalent (Original) vaccine 50 μg (Part F) intramuscularly.

Of the enrolled participants[9] (440 in Part G and 379 in Part F), those who received the study vaccine (437 in Part G and 377 in Part F) were included in the full analysis set (FAS) and safety analysis set. Of the participants included in the safety analysis set, those who had had solicited adverse event data from their participant diary (437 in Part G and 351 in Part F) were included in the solicited adverse event analysis set. The Per-protocol set for immunogenicity - SARS-CoV-2 negative at baseline (PPSI-Neg) consisted of 334 participants (Part G) and 260 participants (Part F) from the FAS, while 103 participants (Part G) and 117 participants (Part F) included in the FAS were excluded from the PPSI-Neg for the following reasons: "no data on neutralizing antibody titer against the Omicron variant before or 28 days after vaccination with the study vaccine" (7 in Part G and 4 in Part F), "major protocol deviation" (0 in Part G and 1 in Part F), "human immunodeficiency virus (HIV) infection" (0 in Part G and 1 in Part F), "positive for SARS-CoV-2 before the second booster dose or unknown" (96 in Part G and 110 in Part F), and "blood sample for 28 days post study-vaccine collected out-of-window" (0 in Part G and 1 in Part F). The PPSI-Neg was the primary immunogenicity analysis set. The Per-protocol set for immunogenicity (PPSI) consisted of 428 participants (Part G) and 367 participants (Part F) included in the FAS, while the remaining 9 participants (Part G) and 10 participants (Part F) included the FAS were excluded from the PPSI for the following reasons: "no data on neutralizing antibody titer against the Omicron variant before or 28 days after vaccination with the study vaccine" (9 in Part G and 5 in Part F), "major protocol deviation" (0 in Part G and 2 in Part F), "HIV infection" (0 in Part G and 1 in Part F), and "blood sample for 28 days post study-vaccine collected out-of-window" (0 in Part G and 2 in Part F). The PPSI was used for the analysis of immunogenicity regardless of SARS-CoV-2 testing status before the second booster dose. In the SARS-CoV-2 test prior to the second booster dose, RT-PCR and antibody testing based on binding antibodies specific to SARS-CoV-2 nucleocapsid were used. Participants who tested positive by RT-PCR, or those who tested positive by antibody testing and who had virological or immunological evidence of prior SARS-CoV-2

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8) Both at 28 days and 90 days after vaccination with study vaccine, when the results shown below were assumed for primary endpoint evaluation of neutralizing antibodies, and if the results demonstrate the non-inferiority or superiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine at two-sided α of 0.025, approximately 300 participants per group would provide approximately 71% of power for detection in the overall study. Assuming that approximately 20% of participants were to be excluded from the per-protocol set for immunogenicity (PPSI), a target sample size of 375 participants each for Part G and Part F was specified.
- Assuming that the ratio of geometric mean titers (GMR) (ratio of the bivalent [Original/Omicron] to the monovalent [Original]) for neutralizing antibodies against Omicron BA.1 after the second booster dose (primary endpoint) is 1.5, and that the standard deviation for the log-transformed value is 1.5, the result is assessed for non-inferiority with a margin of 0.67. On the same assumption, the result is assessed for superiority with a margin of 1.
- Assuming that the seroresponse rates following the second booster dose against the original strain (primary endpoint) are 90% for both those receiving the bivalent (Original/Omicron) vaccine and those receiving the monovalent (Original) vaccine, the difference in the seroresponse rates (i.e., the bivalent [Original/Omicron]) vaccine minus the monovalent [Original) vaccine]) is assessed for non-inferiority with a margin of −10%.
- Assuming that the neutralizing antibody GMRs against the original strain (ratio of bivalent [Original/Omicron] to monovalent [Original]) after the second booster dose (primary endpoint) is 1, and that the standard deviation for the log-transformed value is 1.5, the result is assessed for non-inferiority with a margin of 0.67.

9) The enrolled participants include participants who received the primary series and the first booster dose in Study P301 conducted to evaluate the efficacy of the monovalent (Original) vaccine, and participants who received the primary series and the first booster dose under an emergency use authorization (EUA) in the US.

infection were considered SARS-CoV-2 positive. Participants who tested negative for SARS-CoV-2 by RT-PCR and tested negative for antibody testing were considered SARS-CoV-2 negative.

The median interval between the first booster and second booster was as follows: (1) in the safety analysis set, 136.0 days (range, 88-408 days) in Part G and 134.0 days (range, 90-310 days) in Part F; (2) in the PPSI-Neg, 136.0 days (range, 88-408 days) in Part G and 133.0 days (range, 90-310 days) in Part F.

The primary immunogenicity endpoints were as follows: the neutralizing antibody GMR (bivalent [Original/Omicron] vaccine to monovalent [Original] vaccine) against Omicron BA.1; the difference in the seroresponse rates (proportion of participants achieving a ≥4-fold rise in neutralizing antibody titers from pre-primary series [or if the baseline is below the lower limit of quantification (LLOQ), a change to ≥4 × LLOQ]), i.e., the bivalent (Original/Omicron) vaccine minus the monovalent (Original) vaccine; and the neutralizing antibody GMR (bivalent [Original/Omicron] vaccine to monovalent [Original] vaccine) against the original strain. Seroresponse was defined as achieving a ≥4-fold rise in neutralizing antibody titers from pre-primary series (if the neutralizing antibody titers at baseline are below the LLOQ, a change to ≥4 × LLOQ). For participants who did not have pre-primary series antibody titer data, if the participant tested negative for SARS-CoV-2 before primary series, a titer of <LLOQ was imputed; if the participant had tested positive for SARS-CoV-2 before primary series, the data were handled as missing pre-primary series antibody data, which were not evaluated for seroresponse. For participants who had neither pre-primary series neutralizing antibody data nor pre-primary series SARS-CoV-2 status information, the SARS-CoV-2 status reported pre-second booster was imputed as the pre-primary series SARS-CoV-2 test result.

For the primary endpoints, the 4 main hypotheses (1 through 4) were specified as shown below. The hypotheses were to be evaluated at the time point of the interim analysis (28 days after study vaccination) and at the time point of the final analysis (90 days after study vaccination). A two-sided α of 0.025 was used for both the interim and final analyses (however, if all the hypotheses (1 through 4) were tested at the time point of the interim analysis, a two-sided α of 0.05 was to be used at the time point of the final analysis. The superiority of the bivalent vaccine (Hypothesis 4) was to be assessed only if the non-inferiority of the bivalent vaccine (Hypotheses 1 to 3) was demonstrated at each time point. When non-inferiority was demonstrated for the three hypotheses (1 to 3) for at least one of the time points for interim and final analyses, the results of this study were considered to demonstrate efficacy.

1. Non-inferiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the neutralizing antibody GMR against Omicron BA.1.
2. Non-inferiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the difference in neutralizing antibody seroresponse rate against Omicron BA.1.
3. Non-inferiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the neutralizing antibody GMR against the original strain.
4. Superiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the neutralizing antibody GMR against Omicron BA.1.

Table 6 shows the results of primary immunogenicity endpoints at 28 days after study vaccination. The lower bound of the 2-sided 97.5% confidence interval (CI) of the neutralizing antibody GMR against Omicron BA.1 and that against the original strain, and the lower bound of the 2-sided 97.5% CI of difference in the neutralizing antibody seroresponse rate against Omicron BA.1 were all greater than the non-inferiority margins (0.67 and −10%, respectively), indicating that the results met the prespecified success criteria for non-inferiority. The lower bound of the 2-sided 97.5% CI of the neutralizing antibody GMR against the Omicron variant was greater than the superiority margin, 1, indicating that the results met the prespecified success criterion for superiority.

Table 6. Comparison of serum neutralizing antibody titers against Omicron BA.1 and original strain (50% inhibitory dilution) (PPSI-Neg)

	Omicron BA.1		Original strain	
	Part G	Part F	Part G	Part F
	Bivalent (Original/Omicron) 50 μg N = 334	Monovalent (Original) 50 μg N = 260	Bivalent (Original/Omicron) 50 μg N = 334	Monovalent (Original) 50 μg N = 260
Pre-second booster dose				
n	334	260	334	260
GMT [2-sided 95% CI][a)]	298.127 [258.753, 343.492]	332.023 [282.047, 390.854]	1,266.743 [1,120.190, 1,432.469]	1,520.998 [1,352.766, 1,710.151]
28 days after the second booster dose				
n	334	260	334	260
GMT [2-sided 95% CI][a)]	2,372.424 [2,070.634, 2718.200]	1,473.462 [1,270.849, 1,708.379]	5,977.257 [5,321.897, 6,713.320]	5,649.331 [5,056.848, 6,311.231]
GMFR [2-sided 95% CI][a)]	7.958 [7.181, 8.819]	4.438 [3.971, 4.960]	4.719 [4.358, 5.109]	3.714 [3.420, 4.034]
GLSM [2-sided 95% CI][b)]	2,479.890 [2,264.472, 2,715.801]	1,421.243 [1,282.975, 1,574.412]	6,422.323 [5,990.117, 6,885.714]	5,286.626 [4,887.065, 5,718.855]
GMR [2-sided 97.5% CI][b)] Bivalent (Original/Omicron) to monovalent (Original)	1.745 [1.493, 2.040]		1.215 [1.078, 1.370]	
Seroresponse rate				
N1	333	258	334	260
n[c)]	333	256	334	260
Seroresponse rate (%) [2-sided 95% CI][d)]	100 [98.9, 100]	99.2 [97.2, 99.9]	100 [98.9, 100]	100 [98.6, 100]
Difference in seroresponse rate [2-sided 97.5% CI][e)] Bivalent (Original/Omicron) minus monovalent (Original)	1.5 [−1.1, 4.0]		0	

N = number of participants evaluated
N1 = number of participants with non-missing data before the primary series and after the second booster dose
n = number of participants with non-missing data at the time point of evaluation
Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the upper limit of quantification (ULOQ) were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 19.85-15,502.7 (Omicron); 18.5-45,118 (Original strain)

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT or GMFR, respectively.
b) An analysis of covariance model, with adjustment for age group (<65 years vs. ≥65 years) and pre-second booster titer, with the post-second booster titer as the dependent variable and the study vaccine group (bivalent [Original/Omicron] vs. monovalent [Original]) as a fixed effect.
c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ). For participants who did not have pre-primary series antibody titer data, if the participant tested negative for SARS-CoV-2 before primary series, a titer of <LLOQ was imputed; if the participant had tested positive for SARS-CoV-2 before primary series, the data were to be handled as missing pre-primary series antibody data, which were not evaluable for seroresponse. If the participant did not have pre-primary series SARS-CoV-2 status information, the SARS-CoV-2 status reported pre-second booster was imputed as the pre-primary series SARS-CoV-2 test result.
d) Two-sided 95% CI was calculated using the Clopper-Pearson method.
e) Two-sided 97.5% CI was calculated using the stratified Miettinen-Nurminen method, with adjustment for age group

The safety follow-up period is as follows:

- Solicited adverse events [10]; local adverse events (pain, erythema [redness], swelling/induration, lymphadenopathy [11]) and systemic adverse events (headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, fever): Reported through 7 days after study vaccination
- Unsolicited adverse events (excluding solicited adverse events reported through 7 days after study vaccination): Reported through 28 days of the dose of study vaccine
- Serious adverse events: Reported through 12 months after study vaccination

Table 7 shows the solicited adverse events reported through 7 days after study vaccination.

Table 7. Solicited adverse events reported through 7 days after study vaccination (Solicited adverse event analysis set)

	Part G Bivalent (Original/Omicron) 50 μg N = 437			Part F Monovalent (Original) 50 μg N = 351		
		All Grades	Grade ≥3		All Grades	Grade ≥3
	N1	n (%)	n (%)	N1	n (%)	n (%)
Local adverse event (total)	437	347 (79.4)	15 (3.4)	351	279 (79.5)	12 (3.4)
Pain	437	338 (77.3)	4 (0.9)	351	269 (76.6)	4 (1.1)
Erythema (redness)	437	30 (6.9)	9 (2.1)	351	13 (3.7)	2 (0.6)
Swelling/induration	437	30 (6.9)	5 (1.1)	351	23 (6.6)	5 (1.4)
Lymphadenopathy[a)]	437	76 (17.4)	1 (0.2)	351	54 (15.4)	4 (1.1)
Systemic adverse event (total)	437	307 (70.3)	24 (5.5)	351	232 (66.1)	16 (4.6)
Headache	437	192 (43.9)	5 (1.1)	350	144 (41.1)	2 (0.6)
Fatigue	437	240 (54.9)	15 (3.4)	350	180 (51.4)	11 (3.1)
Myalgia	437	173 (39.6)	10 (2.3)	350	135 (38.6)	13 (3.7)
Arthralgia	437	136 (31.1)	4 (0.9)	350	111 (31.7)	3 (0.9)
Nausea/vomiting	437	45 (10.3)	1 (0.2)	350	35 (10.0)	0
Chills	437	104 (23.8)	1 (0.2)	350	74 (21.1)	1 (0.3)
Fever[b)]	436	19 (4.4)	1 (0.2)	351	12 (3.4)	0

N = number of participants evaluated
N1 = number of participants who provided adverse event data
n = number of participants who experienced the event
a) Axillary swelling or tenderness ipsilateral to the injection site
b) ≥38°C (oral temperature)

The incidence of unsolicited adverse events reported through 28 days after study vaccination was 18.5% (81 of 437 participants) in Part G and 20.7% (78 of 377 participants) in Part F, while the incidence of adverse reactions (adverse events for which a causal relationship to the study vaccine could not be ruled out) was 5.7% (25 of 437 participants) in Part G and 5.8% (22 of 377 participants) in Part F.

Up to the data cut-off date (April [redacted], 2022), serious adverse events occurred in 3 participants in Part G (prostate cancer, traumatic fracture, nephrolithiasis in 1 participant each) and 1 participant in Part F (spinal osteoarthritis). A causal relationship to the study vaccine was ruled out for all these events, and the outcome was reported as "resolved" or "ongoing" at the data cut-off date. No adverse events resulted in death, and no adverse events led to study discontinuation.

[10] The severity of adverse events was evaluated according to the Food and Drug Administration (FDA) Guidance (*Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.* September 2007).
[11] This was reported as axillary swelling or tenderness ipsilateral to the injection site in the participant diary.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical significance of bivalent (Original/Omicron) vaccine as a booster dose

The applicant's explanation about the clinical significance of the bivalent (Original/Omicron) vaccine as a booster dose:

Record-high new SARS-CoV-2 infection cases were reported worldwide after the emergence of Omicron BA.1 in November 2021, independent of the vaccination rate of the country. In 2022, Omicron became the epidemiologically dominant variant in many countries. In addition to the BA.1 lineage, new lineages and sub-lineages bearing additional S protein mutations (e.g., BA.2, BA.2.12.1, BA.4, and BA.5) emerged one after another. The COVID-19 pandemic is not yet over. While the primary series and booster doses of the monovalent (Original) vaccine have been demonstrated to contribute to the reduced incidence of COVID-19 caused by the SARS-CoV-2 variant and a reduction in the number of people hospitalized due to COVID-19, the vaccine has limited efficacy to prevent COVID-19 caused by the Omicron variant compared to that by other variants such as the Delta variant (*Nat Med.* 2022;28:1063-71).

It has been reported that robust immune response was not induced in Omicron-infected patients by existing vaccines that had been developed based on the S protein genes of the SARS-CoV-2 original strain (*Science.* 2022;376:1-8), and the effectiveness of existing mRNA vaccines used as a booster dose for the prevention of COVID-19 may wane over time (*Lancet Infect Dis.* 2022;22:1313-20). Based on these and other findings, it is important for a booster vaccine to provide not only protection against future variants of concern but also maintenance of protection against the original strain; therefore, the development of an updated vaccine to address both the original strain and Omicron variant is desired.

Under the circumstances, the applicant developed a bivalent vaccine that contains elasomeran, an mRNA encoding the S protein of the original strain, and imelasomeran, an mRNA encoding the S protein of the Omicron BA.1 lineage. In Study P205 Part G, the levels of neutralizing activity against Omicron BA.1 induced by vaccination with the bivalent (Original/Omicron) vaccine in participants who had 3 doses of the monovalent (original) vaccine were higher than those after the fourth dose of the monovalent (Original) vaccine [see Section 7.1.1]. The results of a study, albeit exploratory, also showed a similar trend in neutralizing activity against the Omicron BA.4 and BA.5 lineages and an increase in binding antibody titers against circulating variants [see Section 7.R.3]. The safety profiles of vaccination with the bivalent (Original/Omicron) vaccine were demonstrated to be similar to those of vaccination with the monovalent (Original) vaccine.

Based on the above, vaccination with the bivalent (Original/Omicron) vaccine as a booster dose is clinically significant to boost immunity against COVID-19 caused by currently circulating Omicron variants.

PMDA's view:

Several vaccines have become commercially available and the number of vaccinated people is increasing across the world, but studies have suggested the waning efficacy of existing vaccines over time; therefore, booster vaccination is needed to maintain high vaccine efficacy in the prevention of COVID-19. In addition, the currently dominant variant Omicron is highly infectious, and the variant is able to evade immunity induced

by pre-existing vaccines because of its change in virus antigenicity from that of the original strain. Although booster vaccination with existing vaccines offered a certain level of protection (efficacy) against the Omicron variant, vaccine efficacy waned in a short time (e.g., *N Engl J Med.* 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep*. 2022;71:255-63).

Under the circumstances, international regulatory authorities and the WHO have discussed the need for new vaccines against new variants (e.g., *International Coalition of Medicines Regulatory Authorities SARS-CoV-2 Variant Workshop*. ICMRA. June 30, 2022,[1)] *Interim statement on the composition of current COVID-19 vaccines.* WHO. June 17, 2022,[2)] *Interim statement on decision making considerations for the use of variant updated COVID-19 vaccines*. WHO. June 17, 2022[3)]). PMDA issued "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" on July 15, 2022. At the 34th meeting of the Sub-committee on Immunization and Vaccines of the Health Sciences Council (held on August 8, 2022), the result of discussion in the review meeting on SARS-CoV-2 vaccine strains was reported as follows: "it is reasonable to switch to vaccination with Omicron-adapted vaccines available as soon as possible, and therefore, 'Omicron BA.1-adapted vaccine,' which would become available soon, should be selected first," and "since the viruses will continue to mutate, the availability of vaccines targeting new variants should further be investigated. Based on the report, it was decided to introduce 'Omicron BA.1-adapted vaccine' first in Japan (Materials 1 and 2[12)] for the 34th meeting of the Sub-committee on Immunization and Vaccines of the Health Sciences Council).

The data from Study P205 Part G submitted for the present application demonstrate the immunogenicity of the bivalent (Original/Omicron) vaccine, a bivalent vaccine containing mRNA encoding the S protein of the original strain and mRNA encoding the S protein of Omicron BA.1, suggesting that the bivalent vaccine has a certain level of efficacy in the prevention of COVID-19 and prevention of severe COVID-19 and that the safety profiles are similar to those of the approved monovalent (Original) vaccine [see Sections 7.R.3 and 7.R.4]. In the current surge of Omicron cases, it is clinically significant to make the bivalent (Original/Omicron) vaccine available for use in clinical practice. The WHO stated that it is important to elicit immunity against a broad range of mutating SARS-CoV-2 variants and that the use of an updated vaccine targeting Omicron as a booster dose in individuals who previously received COVID-19 vaccination primary series would be beneficial for those individuals (Interim statement on the composition of current COVID-19 vaccines. WHO. June 17, 2022[2)]). Booster vaccination with the bivalent (Original/Omicron) vaccine, which is expected to elicit broader immunity, in individuals who previously received the monovalent (Original) vaccine may be a useful vaccination strategy in future.

New variants are likely to emerge and the benefit of a vaccine may be changed depending on variants; therefore, the vaccination strategy should be updated according to the changing situation.

12) https://www.mhlw.go.jp/stf/newpage_27303.html (last accessed on September 6, 2022)

7.R.2 Review strategy

The applicant submitted the data from Study P205 Part G.

The applicant's explanation about the control used for evaluation of immunogenicity in Study P205 Part G:
Enrollment of participants in Study P205 Part G was performed between February and March 2022, at which time booster COVID-19 vaccination had already been approved in the US. For this reason, it was decided to evaluate the immunogenicity of the bivalent (Original/Omicron) vaccine in individuals who had received 2 doses of the monovalent (Original) vaccine 100 μg as the primary series and 1 dose of the monovalent (Original) vaccine 50 μg. In Part F, which served as the control of Part G, the monovalent (Original) vaccine 50 μg was given as the second booster dose to participants who had received the monovalent (Original) vaccine doses, as with those in Part G. Enrollment in Study P205 Part G and Part F started on March 8, 2022 and February 18, 2022, respectively. There were no differences in variants circulating during the enrollment period (Omicron BA.1 and BA.2 lineages) between the 2 parts and the characteristics of participants in Part G were similar to those in Part F; therefore, the use of data from Part F as the control is justifiable.

PMDA's view:
Although a concurrent control group should have been established in the same part (Part G), the applicant used the data from a different part (Part F) as the control. However, immunogenicity data from Part G can be compared with those from Part F, for the following reasons: (i) the interval between the first and second booster doses in Part G was similar to that in Part F [see Section 7.1], (ii) the characteristics of participants in Part G were similar to those in Part F, and (iii) antibody titers were determined by the same method in both parts. PMDA, therefore, decided to evaluate the immunogenicity and safety of the bivalent (Original/Omicron) vaccine as a booster dose on the basis of the results of Study P205 Part G. Although the PPSI-Neg was to be used as the primary analysis set of Study P205 Part G for immunogenicity evaluation, it was decided to assess also the results of the PPSI, i.e., the analysis set for immunogenicity regardless of the SARS-CoV-2 status reported before the second booster dose, because (1) the number of individuals with evidence of prior SARS-CoV-2 infection is increasing also in Japan, and (2) those with evidence of prior SARS-CoV-2 infection are likely to be eligible for vaccination with the bivalent (Original/Omicron) vaccine.

7.R.3 Efficacy

The applicant's explanation about the efficacy of the bivalent (Original/Omicron) vaccine as a booster dose:
Eligible participants in both Study P205 Part G and Part F were individuals aged ≥18 years who had previously received 2 doses of the monovalent (Original) vaccine 100 μg as the primary series and the first booster dose of the monovalent (Original) vaccine 50 μg at least 6 months after the completion of the primary series.[9)]

To compare data from P205 Part G with those from Part F, the following 4 main hypotheses were tested [see Section 7.1]:

1. Non-inferiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the neutralizing antibody GMR against Omicron BA.1.

2. Non-inferiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the difference in neutralizing antibody seroresponse rate against Omicron BA.1.
3. Non-inferiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the neutralizing antibody GMR against the original strain.
4. Superiority of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine based on the neutralizing antibody GMR against Omicron BA.1.

Success criteria were specified at the time of planning Study P205 Part G. The pre-specified success criteria were to demonstrate the non-inferiority of the bivalent vaccine (Hypotheses 1, 2, and 3), and the demonstration of superiority of the bivalent vaccine (Hypothesis 4) was not pre-specified as a success criterion in the protocol to mitigate the risk of study failure. However, the testing of superiority (Hypothesis 4) had been taken into consideration, in addition to testing of non-inferiority (Hypotheses 1, 2, and 3), when the sample size was determined at the time of planning of Study P205 Part G. Assuming that the neutralizing antibody titer GMR of the bivalent (Original/Omicron) vaccine to the monovalent (Original) vaccine against Omicron BA.1 is 1.5 and that the standard deviation for the log-transformed value is 1.5, approximately 300 participants per group would provide approximately 86% of power to demonstrate the superiority of the bivalent vaccine (Hypothesis 4), indicating a sufficiently high power. The resulting neutralizing antibody GMR against Omicron BA.1 was 1.745, a value higher than the expected value; and the superiority of the bivalent vaccine (Hypothesis 4), one of the main hypotheses, was also demonstrated. Therefore, the applicant considered that the results demonstrated the bivalent (Original/Omicron) vaccine can induce higher seroresponse than the monovalent (Original) vaccine.

Table 8 shows the results for neutralizing antibody titers in the PPSI, the analysis set for immunogenicity regardless of SARS-CoV-2 status reported before the second booster dose. The results are similar to those for the PPSI-Neg, the primary analysis set (Table 6).

Table 8. Neutralizing antibody titers against Omicron variant BA.1 and the original strain (50% inhibitory dilution) (PPSI)

	Omicron BA.1		Original strain	
	Part G	Part F	Part G	Part F
	Bivalent (Original/Omicron) 50 μg N = 428	Monovalent (Original) 50 μg N = 367	Bivalent (Original/Omicron) 50 μg N = 428	Monovalent (Original) 50 μg N = 367
Pre-second booster dose				
n	428	367	428	367
GMT [2-sided 95% CI][a)]	432.051 [372.466, 501.168]	511.984 [433.386, 604.836]	1,603.353 [1,420.264, 1810.045]	1,944.781 [1,725.353, 2,192.116]
28 days after the second booster dose				
n	428	367	428	367
GMT [2-sided 95% CI][a)]	3,070.379 [2,685.375, 3,510.581]	1,932.785 [1,681.186, 2,222.037]	6,619.010 [5,941.728, 7,373.494]	6,047.489 [5,465.873, 6,690.994]
GMFR [2-sided 95% CI][a)]	7.107 [6.484, 7.789]	3.775 [3.422, 4.165]	4.128 [3.840, 4.438]	3.110 [2.877, 3.361]
GLSM [2-sided 95% CI][b)]	3,232.516 [2,951.832, 3,539.890]	1,815.135 [1,650.045, 1,996.743]	6,555.689 [6,122.337, 7,019.715]	5,301.367 [4,931.769, 5,698.663]
GMR [2-sided 97.5% CI][b)] Bivalent (Original/Omicron) to monovalent (Original)	1.781 [1.557, 2.037]		1.237 [1.117, 1.369]	
Seroresponse rate				
N1	380	342	383	347
n[c)]	380	340	383	347
Seroresponse rate (%) [2-sided 95% CI][d)]	100 [99.0, 100]	99.4 [97.9, 99.9]	100 [99.0, 100]	100 [98.9, 100]
Difference in seroresponse rate [2-sided 97.5% CI][e)] Bivalent (Original/Omicron) minus monovalent (Original)	1.2 [−1.3, 3.7]		0	

N = number of participants evaluated
N1 = number of participants with non-missing data before the primary series and after the second booster dose
n = number of participants with non-missing data at the time point of evaluation
Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the ULOQ were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 19.85-15,502.7 (Omicron); 18.5-45,118 (Original).

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT or GMFR, respectively.
b) An analysis of covariance model, with adjustment for age group (<65 years vs. ≥65 years), pre-second booster SARS-CoV-2 status (positive vs. negative), and pre-second booster titer, with the post-second booster titer as the dependent variable, and the study vaccine group (bivalent [Original/Omicron] vs. monovalent [Original]) as a fixed effect.
c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ). For participants who did not have pre-primary series antibody titer data, if the participant tested negative for SARS-CoV-2 before primary series, a titer of <LLOQ was imputed; if the participant tested positive for SARS-CoV-2 before primary series, the data were to be handled as missing pre-primary series antibody data, which were not evaluable for seroresponse. If the participant did not have pre-primary series SARS-CoV-2 status information, the SARS-CoV-2 status reported pre-second booster was imputed as the pre-primary series SARS-CoV-2 test result.
d) Two-sided 95% CI was calculated using the Clopper-Pearson method
e) Two-sided 97.5% CI was calculated using the stratified Miettinen-Nurminen method, with adjustment for age group and pre-second booster SARS-CoV-2 status

Table 9 summarizes the demographics and baseline characteristics of participants included in the PPSI of Study P205 Part G and Part F. There were no clear differences in participant characteristics between the parts. The participant characteristics in PPSI-Neg, the primary analysis set, were similar to those of the PPSI.

Table 9. Demographics and baseline characteristics of participants included in P205 Part G versus Part F (PPSI)

	Part G	Part F
	Bivalent (Original/Omicron) 50 μg N = 428	Monovalent (Original) 50 μg N = 367
Age		
Mean ± SD	57.6 ± 14.44	57.5 ± 15.32
Median (Min, Max)	61.0 (20, 88)	60.0 (20, 96)
Age group, n (%)		
≥18 years and <65 years	255 (59.6)	221 (60.2)
≥65 years	173 (40.4)	146 (39.8)
Sex, n (%)		
Male	176 (41.1)	179 (48.8)
Female	252 (58.9)	188 (51.2)
Race, n (%)		
White	376 (87.9)	316 (86.1)
Black or African American	30 (7.0)	26 (7.1)
Asian	12 (2.8)	15 (4.1)
Other[a)] or unknown	10 (2.3)	10 (2.7)
Ethnicity, n (%)		
Hispanic or Latino	46 (10.7)	36 (9.8)
Not Hispanic or Latino	381 (89.0)	331 (90.2)
Not reported	1 (0.2)	0
BMI (kg/m^2)		
Mean ± SD	30.29 ± 7.117	30.78 ± 7.549
Median (Min, Max)	29.02 (17.8, 71.8)	29.33 (18.4, 61.8)
Pre-second booster SARS-CoV-2 status[b)]		
Positive	94 (22.0)	98 (26.7)
Negative	334 (78.0)	260 (70.8)
Unknown	0	9 (2.5)
Time interval from the second dose of the primary series to the first booster dose (days)		
Median (Min, Max)[c)]	245.0 (143, 457)	242.0 (170, 438)
Time interval from the first booster dose to second booster dose (days)		
Median (Min, Max)[c)]	136.0 (88, 408)	133.5 (90, 310)

N = number of participants evaluated
n = number of participants applicable
a) Races that are not White, Black or African American, or Asian; or not reported
b) SARS-CoV-2 status was determined to be positive if there was virologic or immunologic evidence of prior SARS-CoV-2 infection (positive RT-PCR test or positive antibody test result) before the second booster dose (Day 1), and negative when both RT-PCR and antibody test results were negative.
c) Bivalent (Original/Omicron) vaccine group: n = 426; monovalent (Original) vaccine group: n = 366

The results of analyses for neutralizing antibody titers against the Omicron variant and the original strain by age group and by pre-second booster SARS-CoV-2 status are presented in Table 10 and Table 11, respectively. The results of analysis by age group show similarity between the age groups. The results of analysis by pre-second booster SARS-CoV-2 status show that overall, GMT tends to be higher in the SARS-CoV-2 positive group, while GMR and seroresponse rate are similar to those of SARS-CoV-2 negative group (PPSI-Neg) (Table 6), with higher neutralizing antibody titers in the bivalent (Original/Omicron) vaccine group than in the monovalent (Original) vaccine group.

Table 10. Neutralizing antibody titers by age group (50% inhibitory dilution) (PPSI)

	18-64 years				≥65 years			
	Omicron BA.1		Original strain		Omicron BA.1		Original strain	
	Part G	Part F	Part G	Part F	Part G	Part F	Part G	Part F
	Bivalent (Original/Omicron) 50 μg N = 255	Monovalent (Original) 50 μg N = 221	Bivalent (Original/Omicron) 50 μg N = 255	Monovalent (Original) 50 μg N = 221	Bivalent (Original/Omicron) 50 μg N = 173	Monovalent (Original) 50 μg N = 146	Bivalent (Original/Omicron) 50 μg N = 173	Monovalent (Original) 50 μg N = 146
Pre-second booster dose								
n	255	221	255	221	173	146	173	146
GMT [2-sided 95% CI][a)]	405.507 [336.528, 488.625]	544.543 [433.642, 683.805]	1,419.711 [1,223.570, 1,647.294]	1,838.544 [1,576.098, 2,144.693]	474.377 [371.281, 606.101]	466.365 [366.655, 593.189]	1,918.222 [1,564.659, 2,351.680]	2,117.386 [1,748.035, 2,564.778]
28 days after the second booster dose								
N	255	221	255	221	173	146	173	146
GMT [2-sided 95% CI][a)]	2,864.576 [2,418.193, 3,393.358]	1,829.062 [1,519.079, 2,202.301]	5,631.746 [4,932.104, 6,430.635]	5,084.458 [4,503.820, 5,739.952]	3,400.992 [2,731.607, 4,234.411]	2,101.088 [1,700.688, 2,595.756]	8,398.339 [7,031.789, 10,030.461]	7,863.259 [6,642.005, 9,309.063]
GMFR [2-sided 95%CI][a)]	7.064 [6.283, 7.942]	3.359 [2.978, 3.788]	3.967 [3.612, 4.357]	2.765 [2.506, 3.051]	7.169 [6.179, 8.318]	4.505 [3.822, 5.310]	4.378 [3.904, 4.910]	3.714 [3.284, 4.199]
GLSM [2-sided 95% CI][b)]	3,122.563 [2,802.509, 3,479.168]	1,636.508 [1,465.216, 1,827.825]	5,571.388 [5,128.643, 6,052.355]	4,381.281 [4,024.276, 4,769.957]	3,319.014 [2,832.848, 3,888.614]	2,060.001 [1,723.236, 2,462.578]	8,078.738 [7,195.509, 9,070.381]	6,921.400 [6,066.923, 7,896.224]
GMR [2-sided 97.5% CI][b)]	1.908 [1.614, 2.256]		1.272 [1.118, 1.447]		1.611 [1.285, 2.020]		1.167 [0.986, 1.382]	
Seroresponse rate								
N1	230	205	233	209	150	137	150	138
n[c)]	230	204	233	209	150	136	150	138
Seroresponse rate (%) [2-sided 95% CI][d)]	100 [98.4, 100]	99.5 [97.3, 100]	100 [98.4, 100]	100 [98.3, 100]	100 [97.6, 100]	99.3 [96.0, 100]	100 [97.6, 100]	100 [97.4, 100]
Difference in seroresponse rate [2-sided 97.5% CI][e)]	1.1 [−2.1, 4.2]		0		1.4 [−2.7, 5.5]		0	

N = number of participants evaluated
N1 = number of participants with non-missing data before the primary series and after the second booster dose
n = number of participants with non-missing data at the time point of evaluation
Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the ULOQ were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 19.85-15,502.7 (Omicron); 18.5-45,118 (Original).

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT or GMFR, respectively.
b) An analysis of covariance model, with adjustment for pre-second booster SARS-CoV-2 status (positive vs negative) and pre-second booster titer, with the post-second booster titer as the dependent variable and the study vaccine group (bivalent [Original/Omicron] vs monovalent [Original]) as a fixed effect
c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ). For participants who did not have pre-primary series antibody titer data, if the participant tested negative for SARS-CoV-2 before primary series, a titer of <LLOQ was imputed; if the participant tested positive for SARS-CoV-2 before primary series, the data were to be handled as missing pre-primary series antibody data, which were not evaluable for seroresponse. If the participant did not have pre-primary series SARS-CoV-2 status information, the SARS-CoV-2 status reported pre-second booster was imputed as the pre-primary series SARS-CoV-2 test result.
d) Two-sided 95% CI was calculated using the Clopper-Pearson method
e) Two-sided 97.5% CI was calculated using the stratified Miettinen-Nurminen method, with adjustment for pre-second booster SARS-CoV-2 status

Table 11. Neutralizing antibody titers (50% inhibitory dilution) by pre-second booster SARS-CoV-2 status (PPSI)

	SARS-CoV-2 positive				SARS-CoV-2 negative			
	Omicron BA.1		Original strain		Omicron BA.1		Original strain	
	Part G	Part F	Part G	Part F	Part G	Part F	Part G	Part F
	Bivalent (Original/Omicron) 50 µg N = 94	Monovalent (Original) 50 µg N = 98	Bivalent (Original/Omicron) 50 µg N = 94	Monovalent (Original) 50 µg N = 98	Bivalent (Original/Omicron) 50 µg N = 334	Monovalent (Original) 50 µg N = 260	Bivalent (Original/Omicron) 50 µg N = 334	Monovalent (Original) 50 µg N = 260
Pre-second booster dose								
n	94	98	94	98	334	260	334	260
GMT [2-sided 95% CI][a)]	1,614.640 [1,149.671, 2,267.658]	1,558.360 [1,088.941, 2,230.136]	3,703.953 [2,793.198, 4,911.670]	3,637.972 [2,742.046, 4,826.629]	298.127 [258.753, 343.492]	332.023 [282.047, 390.854]	1,266.743 [1,120.190, 1,432.469]	1,520.998 [1,352.766, 1,710.151]
28 days after the second booster dose								
n	94	98	94	98	334	260	334	260
GMT [2-sided 95% CI][a)]	7,676.226 [5,618.245, 10,488.050]	3,885.596 [2,877.774, 5,246.367]	9,509.727 [7,345.948, 12,310.856]	7,003.503 [5,592.574, 8,770.390]	2,372.424 [2,070.634, 2,718.200]	1,473.462 [1,270.849, 1,708.379]	5,977.257 [5,321.897, 6,713.320]	5,649.331 [5,056.848, 6,311.231]
GMFR [2-sided 95% CI][a)]	4.754 [3.954, 5.716]	2.493 [2.058, 3.021]	2.567 [2.245, 2.936]	1.925 [1.649, 2.247]	7.958 [7.181, 8.819]	4.438 [3.971, 4.960]	4.719 [4.358, 5.109]	3.714 [3.420, 4.034]
GLSM [2-sided 95% CI][b)]	7,669.159 [6,470.661, 9,089.642]	4,041.480 [3,375.056, 4,839.493]	9,891.516 [8,732.181, 11,204.771]	7,776.531 [6,813.034, 8,876.285]	2,479.890 [2,264.472, 2,715.801]	1,421.243 [1,282.975, 1,574.412]	6,422.323 [5,990.117, 6,885.714]	5,286.626 [4,887.065, 5,718.855]
GMR [2-sided 97.5% CI][b)]	1.898 [1.499, 2.403]		1.272 [1.070, 1.512]		1.745 [1.493, 2.040]		1.215 [1.078, 1.370]	
Seroresponse rate								
N1	47	76	49	79	333	258	334	260
n[c)]	47	76	49	79	333	256	334	260
Seroresponse rate (%) [2-sided 95% CI][d)]	100 [92.5, 100]	100 [95.3, 100]	100 [92.7, 100]	100 [95.4, 100]	100 [98.9, 100]	99.2 [97.2, 99.9]	100 [98.9, 100]	100 [98.6, 100]
Difference in seroresponse rate [2-sided 97.5% CI][e)]	0		0		1.5 [−1.1, 4.0]		0	

N = number of participants evaluated
N1 = number of participants with non-missing data before the primary series and after the second booster dose
n = number of participants with non-missing data at the time point of evaluation

- Pre-second booster SARS-CoV-2 testing consisted of RT-PCR and antibody tests. SARS-CoV-2 status was determined to be positive if there was virologic or immunologic evidence of prior SARS-CoV-2 infection (positive RT-PCR test or positive antibody test result) before the second booster dose (Day 1), and negative when both RT-PCR and antibody test results were negative.
- Antibody titer values below the LLOQ were replaced by 0.5 × LLOQ for analysis. Antibody titer values greater than the ULOQ were replaced by the ULOQ for analysis if actual values were not available. Quantification range (LLOQ-ULOQ): 19.85-15,502.7 (Omicron); 18.5-45,118 (Original).

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT or GMFR, respectively.
b) An analysis of covariance model, with adjustment for age group (<65 years vs. ≥65 years) and pre-second booster titer, with the post-second booster titer as the dependent variable and the study vaccine group (bivalent [Original/Omicron] vs monovalent [Original]) as a fixed effect.
c) Number of participants who met the definition of seroresponse, i.e., a ≥4-fold rise in antibody titers from pre-primary series (if below the LLOQ, a ≥4-fold rise from LLOQ). For participants who did not have pre-primary series antibody titer data, if the participant tested negative for SARS-CoV-2 before pre-primary series, a titer of <LLOQ was imputed; if the participant tested positive for SARS-CoV-2 before pre-primary series, the data were to be handled as missing pre-primary series antibody data, which were not evaluable for seroresponse. If the participant did not have pre-primary series SARS-CoV-2 status information, the SARS-CoV-2 status reported pre-second booster was imputed as the pre-primary series SARS-CoV-2 test result.
d) Two-sided 95% CI was calculated using the Clopper-Pearson method
e) Two-sided 97.5% CI was calculated using the stratified Miettinen-Nurminen method, with adjustment for age group

In the per protocol set for efficacy, [13)] the number of participants who had COVID-19[14)] starting 14 days after study vaccination through data cut-off were 5 participants (1.5%) in the bivalent (Original/Omicron) group (a

13) All participants in the FAS who were negative for SARS-CoV-2 prior to the second booster dose and had no major protocol deviations.
14) Case definition: Having a positive RT-PCR test result, together with at least one of the following systemic or respiratory symptoms: fever (≥38°C), chills, cough, shortness of breath or difficulty breathing, fatigue, muscle ache (non-exercise induced) or body aches, headache, new loss of taste or smell, sore throat, nasal congestion, runny nose, nausea, vomiting, and diarrhea.

median follow-up of 43 days) and 1 participant (0.4%) in the monovalent (Original) vaccine group (a median follow-up of 57 days).

Table 12 shows the results of an exploratory analysis,[15)] which evaluated neutralizing antibody titers against Omicron BA.4/BA.5. Regardless of pre-second booster SARS-CoV-2 status, neutralizing antibody GMT against Omicron BA.4/BA.5 was higher in participants vaccinated with the bivalent (Original/Omicron) vaccine than in those vaccinated with the monovalent (Original) vaccine, and the lower bound of the 2-sided 95% CI for GMR was greater than 1.

Table 12. Neutralizing antibody titers against Omicron BA.4/5 (50% inhibitory dilution) (PPSI)

Analysis population	Overall population (PPSI)		SARS-CoV-2 positive		SARS-CoV-2 negative	
	Part G Bivalent (Original/ Omicron) 50 µg N = 428	Part F Monovalent (Original) 50 µg N = 367	Part G Bivalent (Original/ Omicron) 50 µg N = 94	Part F Monovalent (Original) 50 µg N = 98	Part G Bivalent (Original/ Omicron) 50 µg N = 334	Part F Monovalent (Original) 50 µg N = 260
Pre-second booster dose, n	428	367	94	98	334	260
GMT [2-sided 95% CI][a)]	172.716 [147.449, 202.313]	209.307 [179.475, 244.097]	719.542 [531.639, 973.857]	609.123 [448.078, 828.051]	115.590 [98.507, 135.635]	139.683 [119.510, 163.260]
28 days after the second booster dose, n	427	367	94	98	333	260
GMT [2-sided 95% CI][a)]	940.567 [826.319, 1,070.611]	645.365 [570.113, 730.551]	2,337.435 [1,825.510, 2,992.918]	1,270.823 [987.277, 1,635.804]	727.427 [632.846, 836.143]	492.126 [431.053, 561.853]
GMFR [2-sided 95% CI][a)]	5.444 [5.005, 5.922]	3.083 [2.842, 3.345]	3.249 [2.780 3.795]	2.086 [1.795, 2.425]	6.299 [5.739, 6.913]	3.523 [3.212, 3.864]
GLSM [2-sided 95% CI][b)]	985.376 [914.769, 1,061.434]	588.359 [544.078, 636.244]	2,246.251 [1,975.519, 2,554.085]	1,406.894 [1,227.880, 1,612.006]	776.447 [719.488, 837.915]	458.282 [420.621, 499.316]
GMR [2-sided 95% CI][b)]	1.675 [1.521, 1.844]		1.597 [1.336, 1.909]		1.694 [1.511, 1.900]	

N = number of participants evaluated
n = number of participants with measured data
Antibody titer values reported as below the LLOQ were replaced by 0.5 × LLOQ
a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT or GMFR, respectively
b) An analysis of covariance model, with adjustment for age group (<65 years vs. ≥65 years), pre-second booster SARS-CoV-2 status (positive vs. negative; only for the overall population), and pre-second booster titer, with the post-second booster titer as the dependent variable, and the study vaccine group (bivalent [Original/Omicron] vs. monovalent [Original]) as a fixed effect

Based on the above results, the bivalent (Original/Omicron) vaccine as a booster dose is expected to be effective.

PMDA's view on the efficacy of the bivalent (Original/Omicron) vaccine:
The pre-specified success criteria in Study P205 Part G were demonstration of the 3 hypotheses for non-inferiority. However, to explain the clinical significance of the bivalent (Original/Omicron) vaccine that was developed to address variants in the situation where the monovalent (Original) vaccine is available in clinical settings, the study design should incorporate testing for the superiority of the bivalent (Original/Omicron) vaccine over the monovalent (Original) vaccine for neutralizing antibody titers against Omicron BA.1. The

15) While the assay method used was the same as that used to determine neutralizing antibody titers against Omicron BA.1, the quantification range, dilution linearity, precision, and limit of quantification have not been defined.

demonstration of the superiority should also have been included in the success criteria of Study P205 Part G. On the other hand, according to the applicant's explanation, the sample size for Study P205 was determined assuming that the sample size would provide a sufficient power to demonstrate the superiority of the bivalent vaccine compared to the monovalent vaccine based on GMR against Omicron BA.1. Furthermore, the situation required the urgent development of variant-adapted vaccines, and in fact, the status of the COVID-19 pandemic and policies on the development of variant-adapted vaccines were constantly changing globally. For the primary endpoints in Study P205 Part G, all pre-specified requirements for non-inferiority were met and the requirement for superiority of the bivalent (Original/Omicron) vaccine compared to the monovalent (Original) vaccine against Omicron BA.1 was met based on GMR. Taken together, it is possible to conclude that the study demonstrated the superiority of the bivalent (Original/Omicron) vaccine over the monovalent (Original) vaccine against Omicron BA.1 based on seroresponse, as well as its non-inferiority against the original strain based on seroresponse. In addition, the results of neutralizing antibodies against Omicron BA.4/BA.5, albeit exploratory, also showed that higher seroresponse was achieved in bivalent (Original/Omicron) vaccine recipients than in monovalent (Original) vaccine recipients. A publication reports that the neutralizing antibody titers following SARS-CoV-2 vaccination are correlated with the vaccine efficacy for the prevention of COVID-19 (*Nat Med.* 2021;27:1205-11), and another publication reports the vaccine efficacy in the prevention of symptomatic COVID-19 and severe COVID-19 caused by the Omicron variant following vaccination with the monovalent (Original) vaccine (ACIP [Apr/20/2022] COVID-19 Vaccine Effectiveness during Omicron[16)]). Given these, the bivalent (Original/Omicron) vaccine as a booster dose, which has been demonstrated to elicit higher immune response against the Omicron variant, is expected to be effective in the prevention of COVID-19 and severe COVID-19. Furthermore, the bivalent (Original/Omicron) vaccine as a booster dose is likely to enhance vaccine efficacy in the prevention of COVID-19 caused by the Omicron variant.

However, only immunogenicity data for a short period of time following the booster dose of the bivalent (Original/Omicron) vaccine are currently available; so far, no information is available on the change over time or persistence of neutralizing antibody titers after booster vaccination. Information on the efficacy of variant-adapted vaccines should be gathered from study reports and data to be accumulated in other countries and regions, future actions should be considered based on the obtained information and the epidemic of SARS-CoV-2.

7.R.4 Safety

7.R.4.1 Safety profile

The applicant's explanation about the safety of the (Original/Omicron) vaccine as a booster dose:

The incidence of solicited adverse events in the recipients of the bivalent (Original/Omicron) 50 μg as the second booster dose in Study P205 Part G was similar to that in the recipients of the monovalent (Original) vaccine 50 μg as the second booster dose. There were no Grade ≥3 events that were more common in the recipients of the bivalent (Original/Omicron) vaccine in Part G than in the recipients of the monovalent

16) https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-04-20/02-COVID-Link-Gelles-508.pdf (last accessed on September 6, 2022)

(Original) vaccine as the second booster dose (Table 7). The median duration was 2.0 days (range, 1-10 days) for solicited local adverse events and 2.0 days (1-21 days) for solicited systemic adverse events.

As shown in Table 13, the incidence of solicited adverse events in the recipients of the bivalent (Original/Omicron) vaccine as the second booster dose in Study P205 Part G was comparable to or less than that in the recipients of the monovalent (Original) vaccine 50 μg as the first booster dose in Study P201 Part B or that in the recipients of the monovalent (Original) vaccine 100 μg as the second dose of the primary series in Study P301.

Table 13. Incidence of solicited adverse events occurring within 7 days of vaccination with the bivalent (Original/Omicron) vaccine or the monovalent (Original) vaccine by dose number (Solicited adverse event analysis set, aged ≥18 years)

Study	P205 Part G		P201 Part B		P301	
Dose number	Bivalent (Original/Omicron) Second booster 50 μg N = 437		Monovalent (Original) First booster 50 μg N = 167		Monovalent (Original) Primary series (Dose 2) 100 μg N = 14,691	
Event	All grades n (%)	Gr ≥3[a)] n (%)	All grades n (%)	Gr ≥3[a)] n (%)	All grades n (%)	Gr ≥3[a)] n (%)
Local (total)	347 (79.4)	15 (3.4)	143 (85.6)	8 (4.8)	13,029 (88.7)[e)]	1,023 (7.0)[e)]
Pain	338 (77.3)	4 (0.9)	140 (83.8)	6 (3.6)	12,964 (88.3)[e)]	606 (4.1)[e)]
Erythema/ redness	30 (6.9)	9 (2.1)	8 (4.8)	1 (0.6)	1,274 (8.7)[f)]	287 (2.0)[f)]
Swelling/ induration	30 (6.9)	5 (1.1)	9 (5.4)	1 (0.6)	1,807 (12.3)[f)]	255 (1.7)[f)]
Lymphadenopathy	76 (17.4)	1 (0.2)	34 (20.4)	1 (0.6)	2,092 (14.2)[f)]	68 (0.5)[f)]
Systemic (total)	307 (70.3)	24 (5.5)	126 (75.4)	12 (7.2)	11,678 (79.5)[g)]	2,350 (16.0)[g)]
Headache	192 (43.9)	5 (1.1)	92 (55.1)	2 (1.2)	8,637 (58.8)[f)]	666 (4.5)[f)]
Fatigue	240 (54.9)	15 (3.4)	98 (58.7)	7 (4.2)	9,607 (65.4)[f)]	1,433 (9.8)[f)]
Myalgia	173 (39.6)	10 (2.3)	82 (49.1)	5 (3.0)	8,529 (58.1)[f)]	1,321 (9.0)[f)]
Arthralgia	136 (31.1)	4 (0.9)	69 (41.3)	5 (3.0)	6,303 (42.9)[f)]	775 (5.3)[f)]
Nausea/ vomiting	45 (10.3)	1 (0.2)	19 (11.4)	0	2,794 (19.0)[f)]	22 (0.1)[f)]
Chills	104 (23.8)	1 (0.2)	59 (35.3)	0	6,500 (44.3)[f)]	191 (1.3)[f)]
Fever[b)]	19 (4.4)[c)]	1 (0.2)	11 (6.6)[d)]	2 (1.2)[d)]	2,276 (15.5)[h)]	216 (1.5)[h)]

N = number of participants evaluated; n = number of participants who experienced the event
a) Gr ≥3 = Grade ≥3
b) Grade 3, 39°C to 40°C; Grade 4, >40°C
c) N = 436; d) N = 166; e) N = 14,688; f) N = 14,687; g) N = 14,690; h) N = 14,682

In Study P205 Part G, the incidence of unsolicited adverse events (excluding solicited adverse events reported through 7 days after study vaccination) and the incidence of adverse reactions reported through 28 days after the second booster dose of the bivalent (Original/Omicron) vaccine 50 μg were 18.5% (81 of 437 participants) and 5.7% (25 of 437 participants), respectively, which are similar to the incidences of unsolicited adverse events and adverse reaction reported through 28 days after the second booster dose of the monovalent (Original) vaccine 50 μg in Study P205 Part F (unsolicited adverse events: 20.7%, 78 of 377 participants; adverse reactions: 5.8%, 22 of 377 participants). In Study P205 Part G, unsolicited adverse events occurring in ≥1% of participants (≥5 participants) through 28 days after the second booster dose of the bivalent (Original/Omicron) vaccine 50 μg were fatigue (2.5%, 11 of 437 participants); headache (1.6%, 7 of 437 participants), arthralgia (1.6%, 7 of 437 participants), myalgia (1.1%, 5 of 437 participants), COVID-19 (1.1%, 5 of 437 participants), and upper respiratory tract infection (1.1%, 5 of 437 participants).

By the data cut-off date (April [redacted], 2022), no deaths occurred, nor were there any serious adverse events or adverse events leading to study discontinuation for which a causal relationship to the bivalent (Original/Omicron) vaccine could not be ruled out.

As described above, the majority of adverse events occurring in the recipients of the bivalent (Original/Omicron) vaccine 50 μg were consistent with the known safety profiles of the monovalent (Original) vaccine, and the incidence of adverse events were also consistent with that in the recipients of the monovalent (Original) vaccine regardless of pre-second booster SARS-CoV-2 status. There have been no identified safety concerns about the bivalent (Original/Omicron) vaccine.

7.R.4.2 Myocarditis/pericarditis

As of August 1, 2022, in Study P205 Part G and ongoing Study P305, a phase I/II study evaluating the immune response elicited by booster vaccination with the monovalent (Omicron) vaccine or bivalent (Original/Omicron) vaccine in comparison with that elicited by the monovalent (Original) vaccine, there were no reports of myocarditis/pericarditis following vaccination with the bivalent vaccine. In Study P205 Part G, events coded to the Standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) "cardiomyopathy," "arrhythmia," "hypersensitivity," and other events were tabulated as myocarditis/pericarditis and evaluated to identify adverse events of special interest (AESI). No cases were classified as myocarditis or pericarditis according to the US Centers for Disease Control and Prevention (CDC) case definition.

The risk of myocarditis/pericarditis associated with vaccination with the monovalent (Original) vaccine is evaluated on a regular basis at the Working Group on Adverse Events of the Subcommittee on the Immunization and Vaccines of the Health Sciences Council and the Subcommittee on Drug Safety of the Committee on Drug Safety of the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council. The results of the evaluation indicated that none of the identified risks were higher than the benefits.

PMDA's view on the safety of the bivalent (Original/Omicron) vaccine:

The safety of the bivalent (Original/Omicron) vaccine as the second booster dose was evaluated based on the analysis of safety data from Study P205 Part G versus those from Part F [see Section 7.1], and in comparison with the safety data of the monovalent (Original) vaccine as the primary series and as the first booster dose (Table 13). There are no clear differences in safety profiles, nor have any significant concerns been identified so far. In addition, no currently available data suggest unacceptable risks of myocarditis/pericarditis. However, due to the limited number of evaluable participants receiving the bivalent (Original/Omicron) vaccine, the applicant should provide precautionary statements regarding the risk of myocarditis/pericarditis associated with the use of the bivalent (Original/Omicron) vaccine as in the case of the monovalent (Original) vaccine. The applicant also should continue to gather data on the safety of the bivalent (Original/Omicron) vaccine, including myocarditis/pericarditis, and should consider taking appropriate actions based on the obtained information.

7.R.5 Indication

The proposed indication was “prevention of disease caused by SARS-CoV-2 infection (COVID-19) (including infection with the original strain and Omicron variant).”

PMDA’s view:

The results from Study P205 Part G suggest that the bivalent (Original/Omicron) vaccine is effective [see Section 7.R.3] and that the vaccine has acceptable safety [see Section 7.R.4]; therefore, the proposed indication, “prevention of disease caused by SARS-CoV-2 infection (COVID-19),” which is the same as that for the monovalent (Original) vaccine, can be selected for the bivalent (Original/Omicron) vaccine.

7.R.6 Dosage and administration

The proposed dosage regimen for the bivalent (Original/Omicron) vaccine was “A single dose (0.5 mL) of Spikevax is administered intramuscularly.” The following statements regarding the eligible individuals and dosing interval were included in the proposed Precautions Concerning Dosage and Administration section of the package insert of the bivalent (Original/Omicron) vaccine:

- Individuals eligible to receive the bivalent (Original/Omicron) vaccine must be 18 years of age or older.
- The bivalent (Original/Omicron) vaccine can be administered at least 3 months after the previous dose of the monovalent (Original) vaccine or other approved SARS-CoV-2 vaccines.

PMDA’s view:

Based on the reviews in Sections “7.R.1 Clinical significance of the booster dose of bivalent (Original/Omicron) vaccine,” “7.R.3 Efficacy,” and “7.R.4 Safety,” and Sections 7.R.6.1 to 7.R.6.3, an intramuscular dose of 0.5 mL (containing 50 μg of mRNA) can be selected as the dosage regimen for the bivalent (Original/Omicron) vaccine as a booster dose, and the Precautions Concerning Dosage and Administration section of the package insert should include statements to the effect that individuals eligible to receive the bivalent (Original/Omicron) vaccine must be 18 years of age or older, and that the dosing interval should be at least 5 months after the previous dose of a SARS-CoV-2 vaccine.

7.R.6.1 Dosage

The applicant’s explanation about the proposed dosage of the bivalent (Original/Omicron) vaccine:

The approved dosage of the monovalent (Original) vaccine as a booster dose is 50 μg, which was selected based on the results from Study P201 Part B. In the development of the bivalent (Original/Beta) vaccine (for booster vaccination) which contains mRNA encoding the S protein from the original strain and mRNA encoding the S protein of the Beta variant at a ratio of 1:1, a booster dose of 50 μg was selected and was evaluated. The selected dosage was the same as that for the monovalent (Original) vaccine as a booster dose. The results of the evaluation demonstrated that the safety profile for the bivalent (Original/Beta) vaccine when administered as a booster dose was similar to that for the monovalent (Original) vaccine when administered as a booster dose, and that the bivalent (Original/Beta) vaccine as a booster dose showed higher immunogenicity compared to the monovalent (Original) vaccine as a booster dose. Accordingly, a dose of 50 μg was selected

for the bivalent (Original/Omicron) vaccine in Study P205 Part G. The Spikevax monovalent (Original) vaccine approved in Japan is a dispersion containing the active substance at 200 μg/mL, and each booster dose of 0.25 mL contains 50 μg of the active substance. The Spikevax bivalent (Original/Omicron) vaccine is a dispersion containing the active substance at 100 μg/mL (50 μg of each mRNA), and each booster dose of 0.5 mL contains 50 μg of the active substance.

PMDA's view:
Based on the reviews presented in Sections 7.R.1, 7.R.3, and 7.R.4, in addition to the applicant's explanation above, a dose of 50 μg (injectable volume of 0.5 mL) can be selected for the bivalent (Original/Omicron) vaccine as a booster dose.

7.R.6.2 Timing of booster dose (interval between the previous dose and the booster dose)

The applicant's explanation about the interval between the previous dose and the dose of the bivalent (Original/Omicron):
When the study started, some data suggested that vaccine efficacy declined over time in individuals receiving a booster dose in addition to the primary series. A significant decline in vaccine efficacy was reported particularly during the Delta-predominant and Omicron-predominant periods (e.g., *Nat Med.* 2022;28:1063-71, *Clin Infect Dis.* 2022;75:e361-7); therefore, it was desired to start booster vaccination as early as possible with a vaccine containing an mRNA sequence encoding the S protein from variants of concern (VOC). The shortest interval evaluated previously was 3 months between the completion of the primary series and the first booster dose (medRxiv[17] preprint, doi: https://doi.org/10.1101/2021.10.10.21264827). Based on this report and other factors, eligible participants for Study P205 Parts F and G were defined as individuals who received the first booster dose at least 3 months prior to enrollment.

Table 14 shows neutralizing antibody titers in Study P205 Part G by interval between the first booster dose and study vaccination (divided by the first and third quartiles).

Table 14. Neutralizing antibody titers by interval between the first booster dose and study vaccination (50% inhibitory dilution) (PPSI-Neg)

	≥88 days and <118 days		≥118 days and <150 days		≥150 days	
	Omicron	Original strain	Omicron	Original strain	Omicron	Original strain
Pre-second booster dose, n	76	76	172	172	84	84
GMT [2-sided 95% CI][a)]	381.55 [286.35, 508.41]	1,577.87 [1,215.14, 2,048.88]	323.8 [266.95, 392.74]	1,390.22 [1,178.82, 1,639.55]	209.02 [156.28, 279.55]	891.95 [701.43, 1134.23]
28 days after the second booster dose, n	76	76	172	172	84	84
GMT [2-sided 95% CI][a)]	2,209.72 [1,680.21, 2,906.1]	5,696.05 [4,519.19, 7,179.38]	2,516.23 [2,077.82, 3,047.16]	6,425.73 [5,406.01, 7,637.79]	2,330.49 [1,759.86, 3,086.15]	5,572.75 [4,531.35, 6,853.47]
GMFR [2-sided 95% CI][a)]	5.791 [4.657, 7.203]	3.61 [3.064, 4.253]	7.771 [6.856, 8.808]	4.622 [4.177, 5.115]	11.15 [8.807, 14.116]	6.248 [5.26, 7.421]

a) Two-sided 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT or GMFR, respectively.

17) medRxiv (The Preprint Server For Health Sciences): https://www.medrxiv.org/ (last accessed on September 6, 2022)

Neutralizing antibody titers against Omicron BA.1 and the original strain at pre-second booster dose were both lower in the groups with longer interval between the first booster dose and study vaccination than in the groups with shorter interval. In contrast, GMT at 28 days after the second booster dose were similar across the interval groups, suggesting that interval between the previous dose and the second booster dose is unlikely to affect the seroresponse after booster vaccination.

While Study P205 Part G was designed to include individuals who were to receive the study vaccine as the second booster dose, a previous study of the bivalent (Original/Beta) vaccine was conducted to evaluate its immunogenicity and safety in individuals vaccinated with the bivalent vaccine as the first booster dose. The bivalent (Original/Beta) vaccine elicited higher seroresponse against multiple variants and the original strain, compared to the monovalent (Original) vaccine. This result was similar to that of the evaluation in Part G, and the safety profile was similar to that for the monovalent (Original) vaccine 50 μg as a booster dose. Based on the above findings, the bivalent (Original/Omicron) vaccine when administered as the first booster dose is also expected to elicit similar immune response. In addition, there would be no significant safety concerns about the bivalent (Original/Omicron) vaccine as the first booster dose; therefore, the bivalent (Original/Omicron) vaccine can be administered regardless of the number of prior booster doses.

PMDA's view:
Study P205 Part G was conducted in participants who had received the first booster dose at least 3 months before. Taking into consideration the results of analyses by interval between the previous dose and the second booster dose, the applicant's explanation about the rationale for an interval of ≥3 months between the first and second booster doses is reasonable. In Japan, on the other hand, the monovalent (Original) vaccine as a booster dose (i.e., third or fourth dose) can be administered to individuals at least 5 months after receipt of their previous vaccination. Because of this and other factors, the use of the bivalent (Original/Omicron) vaccine as a booster dose at least 5 months after the previous vaccination is beneficial to the public from the perspective of avoidance of confusion in clinical practice.

No clinical study data are available on the immunogenicity and safety of the bivalent (Original/Omicron) vaccine as the first or third booster dose (i.e., third or fifth dose) or subsequent booster doses. Not just the applicant's justification above, but for the purpose of public health, it is important to allow people to receive vaccination with a SARS-CoV-2 vaccine at a certain interval in order to boost antibody titers which waned over time. Therefore, there is little need to define the number of booster doses for the bivalent (Original/Omicron) vaccine, and the package insert should state that the vaccine as a booster dose can be administered to individuals at least 5 months after receipt of their previous dose.

7.R.6.3 Age indication

While individuals aged ≥12 years are eligible for the primary series of the monovalent (Original) vaccine, "individuals aged ≥18 years" was selected as the eligible population for the use of the bivalent

(Original/Omicron) vaccine as a booster dose. PMDA asked the applicant to explain the rationale for the proposed age indication.

The applicant's explanation:
In Japan, individuals aged ≥18 years are eligible for the use of the monovalent (Original) vaccine as a booster dose, and in Study P205 Parts F and G, individuals aged ≥18 years were eligible for the use of the bivalent (Original/Omicron) vaccine as a booster dose. Based on these and other factors, "individuals aged ≥18 years" was selected as the eligible population for the booster dose of the bivalent (Original/Omicron) vaccine.

On the basis of the results from Study P203 Part C, which evaluated the safety and efficacy of the monovalent (Original) vaccine 50 μg as a booster dose in individuals aged 12 to 17 years who had completed the primary series of the monovalent (original) vaccine 100 μg, the applicant plans to extend the age indication for the use of the bivalent (Original/Omicron) vaccine as a booster dose down to 12 years.

PMDA's view
Because of the age of participants (≥18 years) eligible for Study P205 Part G and other reasons, the age indication proposed by the applicant for the use of the bivalent (Original/Omicron) as a booster dose (≥18 years) is appropriate at this point.

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

7.R.7.1 Measures to prevent vaccine administration errors resulting from differences between bivalent (Original/Omicron) and approved vaccines

There are differences in injectable volume, eligible population, and other aspects between the bivalent (Original/Omicron) vaccine and the approved monovalent (Original) vaccine. The applicant provided the following explanation about measures to prevent vaccine administration errors:
Vaccine administration errors that may be caused by the differences between the bivalent (Original/Omicron) vaccine and monovalent (Original) vaccine include administration errors involving product mix-up and dosage mix-up. The applicant plans to implement the following precautionary measures:

- To prevent product mix-up, different vial cap colors and label colors are used to help differentiating the product from others; in addition, identification labels that can be affixed to a syringe after withdrawing the vaccine into the syringe are prepared and distributed.
- To ensure the proper use of the vaccine (e.g., correct injectable volume), a two-dimensional barcode is printed on the label to allow users to access the latest product information. Further, information materials containing a list that outlines the dosage regimen, eligible population, difference in vial packaging between vaccines are provided to alert healthcare professionals.

PMDA's view:
Errors involving vaccine preparation, storage management, wrong vaccine administration have been reported for the use of approved SARS-CoV-2 vaccines including the Spikevax monovalent (Original) vaccine. Several administrative notices regarding the proper use of vaccines were issued (e.g., "Information on SARS-CoV-2

vaccine administration errors: No.1 and No.2" [Administrative Notice dated August 3, 2021, issued by the Immunization Office, Health Service Division, Health Service Bureau, Ministry of Health, Labour and Welfare], "Information on SARS-CoV-2 vaccine administration errors: No.3" [Administrative Notice dated November 10, 2021, issued by the Immunization Office, Health Service Division, Health Service Bureau, Ministry of Health, Labour and Welfare]). Although the Spikevax bivalent (Original/Omicron) vaccine and the Spikevax monovalent (Original) vaccine have the same brand name, there is a difference in the injectable volume for the booster dose between the bivalent and monovalent vaccines, which have different compositions. Besides product mix-up, there are other cases requiring precautions. Therefore, the applicant must plan measures to prevent vaccine administration errors. To appropriately implement the planned measures, the applicant should ensure that all institutions to which the vaccines are supplied are informed of the planned measures and that their healthcare professionals become fully familiar with such measures. The applicant should also continue to gather information on the proper use of the vaccine, and should consider further safety measures as necessary.

7.R.7.2 Post-marketing surveillance

The applicant's explanation:

As with the monovalent (Original) vaccine, the bivalent (Original/Omicron) vaccine has acceptable safety, and safety concerns specific to the bivalent (Original/Omicron) vaccine is unlikely to arise [see Section 7.R.4]. Because of these and other reasons, there is no newly identified safety specification for the present application, and there is little need to conduct new post-marketing surveillance on the bivalent (Original/Omicron) vaccine immediately. Therefore, the applicant plans to gather safety data through routine pharmacovigilance activities.

PMDA's view:

The applicant's explanation was accepted. In light of the above discussion, the risk management plan (draft) for Spikevax should include the safety specifications presented in Table 15, and the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 16.

Currently, no post-marketing surveillance has been planned. When a government-initiated survey is conducted in the future to investigate issues such as whether there is any new risk regardless of the valency of the vaccine, and whether the safety profile of the bivalent (Original/Omicron) vaccine is inconsistent with that of the monovalent (Original) vaccine in clinical settings, the applicant should assess the risk-benefit balance of the vaccine in an appropriate manner, based on safety information obtained in and outside of Japan, including information that will become available from the government-initiated survey.

Table 15. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Myocarditis, pericarditis	• Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) • Guillain-Barre syndrome	• Safety of Spikevax in pregnant and breastfeeding women
Efficacy specification		
None		

No change to the present application.

Table 16. 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 (bivalent [Original/Omicron] vaccine) • General use-results survey (a follow-up of participants in the Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan) (monovalent [Original] vaccine) • Post-marketing database survey: shock, anaphylaxis (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) (monovalent [Original] vaccine) • Post-marketing database survey: acute phase solicited adverse events (primary series) (monovalent [Original] vaccine) • Post-marketing database survey: non-acute phase hospitalization events (persons with underlying medical conditions who are at increased risk of severe COVID-19) (primary series) (monovalent [Original] vaccine) • Post-marketing clinical study (TAK-919-1501) (primary series) (monovalent [Original] vaccine) • Foreign phase III study (mRNA-1273-301) (primary series) (monovalent [Original] vaccine)	• Disseminate data gathered during early post-marketing phase vigilance (bivalent [Original/Omicron] vaccine) • Develop and distribute information materials for healthcare professionals • Develop and distribute information materials for vaccine recipients • Publish information on reported adverse reactions periodically (bivalent [Original/Omicron] vaccine)

Underline denotes additions made 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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

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

9. Overall Evaluation

On the basis of the data submitted, PMDA has concluded that the bivalent (Original/Omicron) vaccine as a booster dose has a certain level of efficacy in the prevention of the disease caused by SARS-CoV-2 infection (COVID-19), and that the vaccine has acceptable safety with no significant safety concerns. It is clinically significant to make the variant-adapted bivalent (Original/Omicron) vaccine available for use in clinical settings, based on its benefit-risk balance assessed taking into account the status of COVID-19 outbreaks and the presence of risk factors in individuals.

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The re-examination period for the present application should be the remainder of the ongoing re-examination period (until May 20, 2029).

Indication

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

This indication applies to the following vaccine products:

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

(Underline denotes additions.)

Dosage and Administration

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

For the primary series, ~~:~~Spikevax is administered intramuscularly as a series of 2 doses (0.5 mL each) at a recommended interval of 4 weeks.

For a booster dose, ~~:~~a single ~~booster~~ dose (0.25 mL) of Spikevax is administered intramuscularly.

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

For a booster dose, a single dose (0.5 mL) of Spikevax is administered intramuscularly.

(Underline denotes additions and strikethrough denotes deletions.)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

(1) Matters related to Item 2

When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.

(2) Matters related to Item 3

The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable

representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(3) Matters related to Item 4

The applicant is required to report the quantity sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

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

(2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.

(3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

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

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

Appendix

List of Abbreviations

AESI	Adverse events of special interest
Bivalent (Original/Beta) vaccine	Bivalent vaccine containing mRNA encoding the S protein of the original strain and mRNA encoding the S protein of the Beta variant at a ratio of 1:1
Bivalent (Original/Omicron) vaccine	Bivalent vaccine containing elasomeran and imelasomeran at a mass ratio of 1:1
BMI	Body mass index
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of 1961)
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
D614G	Aspartic acid-to-glycine substitution at position 614
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECL	Electrochemiluminescence assay
ELISA	Enzyme-linked immunosorbent assay
FAS	Full Analysis Set
FDA	Food and Drug Administration (United States)
GLSM	Geometric least squares mean
GMFR	Geometric mean fold rise
GMR	Ratio of Geometric mean titers
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
ICMRA	International Coalition of Medicines Regulatory Authorities
IVRPE	*in vitro* Relative Protein Expression
Lipid Mixture	A lipid mixture prepared using the following raw materials: SM-102, cholesterol, DSPC, and PEG2000-DMG
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
Monovalent (Omicron) vaccine	Monovalent vaccine containing imelasomeran
Monovalent (Original) vaccine	Monovalent vaccine containing elasomeran
mRNA	Messenger RNA
Original strain	Wuhan-Hu-1 strain (D614G)
PBS	Phosphate-buffered saline
PEG2000-DMG	1,2-Dimyristoyl-*rac*-glycero-3-methylpolyoxyethylene
PFU	Plaque-forming units
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
PPQ	Process Performance Qualification
PPSI	Per-protocol set for immunogenicity
PPSI-Neg	Per-protocol set for immunogenicity - SARS-CoV-2 negative at baseline
RBD	Receptor binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction

S protein	Spike protein
S1	Amino-terminal region of the S protein containing the receptor binding domain (RBD)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard Deviation
sgRNA	subgenomic RNA
SM-102	Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SMQ	Standardised MedDRA queries
Spikevax	Spikevax Intramuscular Injection
Study P201	Study mRNA-1273-P201
Study P203	Study mRNA-1273-P203
Study P205	Study mRNA-1273-P205
Study P301	Study mRNA-1273-P301
ULOQ	Upper limit of quantification
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VOC	Variants of concern
WHO	World Health Organization