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	Comirnaty RTU Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: (a) Tozinameran [JAN*], (b) Tozinameran [JAN*] and Riltozinameran [JAN*])
Applicant	Pfizer Japan Inc.
Date of Application	August 8, 2022
Dosage Form/Strength	(a) Injection: Each vial contains 0.225 mg of Tozinameran. (b) Injection: Each vial contains a total of 0.225 mg of Tozinameran and Riltozinameran (at an RNA mass ratio of 1:1).
Application Classification	Prescription drug, (4) Drug with new indications, (6) Drug with a new dosage, (10-2) Other drugs (among other drugs classified in [10], those pertaining to change in 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 Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act ("Handling of Drugs Submitted for Special Approval for Emergency (Request)" [PSEHB/PED Notification 0906-1, dated 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 a booster dose with the vaccine product which contains messenger ribonucleic acid (mRNA) encoding spike proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Strain Wuhan-Hu-1 [original strain] and Omicron variant) has a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (Coronavirus

disease 2019 [COVID-19]), and that the product has acceptable safety without serious 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 spike protein of SARS-CoV-2 (original strain)

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

(Underline denotes additions.)

Dosage and Administration

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

For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.

For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

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

For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

(Strikethrough denotes deletions. Underline denotes additions.)

Approval Conditions and Other Requirements

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

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.

(2) 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 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	Comirnaty RTU Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: (a) Tozinameran, (b) Tozinameran and Riltozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	August 8, 2022
Dosage Form/Strength	(a) Injection: Each vial contains 0.225 mg of Tozinameran. (b) Injection: Each vial contains a total of 0.225 mg of Tozinameran and Riltozinameran (at an RNA mass ratio of 1:1).

Proposed Indication

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

The indication applies to the following vaccine products:

• Vaccine product containing 0.225 mg of Tozinameran (monovalent)

• Vaccine product containing 0.225 mg of tozinameran and riltozinameran (1:1) (bivalent)

(Underline denotes additions.)

Proposed Dosage and Administration

For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.

For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

The vaccine product containing 0.225 mg of tozinameran and riltozinameran (1:1) (bivalent) is used only for a booster dose.

(Strikethrough denotes deletions. Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Multiple therapeutic agents and preventive vaccines have been developed against the global pandemic of COVID-19 since January 2020, and various anti-infection measures including vaccination have been taken. However, because of mutations of SARS-CoV-2 genes resulting in emergence in succession of variants with altered infectivity, transmissibility, antigenicity, and pathogenicity, SARS-CoV-2 infection is repeating in ever increasing waves, showing no sign of the end of the pandemic. Omicron variant which is dominant as of August 2022 evades vaccine-induced immunity due to changes in the antigenicity from the original strain, resulting in decrease in the efficacy of vaccines (*N Engl J Med*. 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep*. 2022;71:255-63, etc.). In the face of these circumstances, necessity of novel vaccines against variants has been discussed globally (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)] etc.).

Comirnaty RTU Intramuscular Injection is a vaccine indicated for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as is the case with Comirnaty intramuscular injection used in Japan. It is approved as a monovalent vaccine with the active ingredient of tozinameran which is mRNA encoding S-protein of the original SARS-CoV-2 strain. Comirnaty RTU Intramuscular Injection is a "Ready To Use" vaccine product which can be used without dilution. As of the end of August 2022, Spikevax Intramuscular Injection (Moderna Japan Co., Ltd.[4)]), Vaxzevria Intramuscular Injection (AstraZeneca K.K.), etc., have been approved for marketing in Japan with the indication for "prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as is the case with Comirnaty RTU Intramuscular Injection. However, variant-adapted vaccines have not been developed or approved.

To meet the need for variant-adapted vaccines, the applicant developed a bivalent vaccine containing riltozinameran which is mRNA encoding spike protein (S-protein) of the Omicron BA.1 lineage, as an active ingredient in addition to tozinameran, and started to investigate the booster dose with the bivalent vaccine from February 2022, as a Substudy E added to the foreign phase III study (Study C4591031) which had been ongoing since July 2021. On the basis of data including the results from this study, a partial change of the conditional marketing approval was granted in the EU on September 1, 2022 and in the U.K. on September 3 of the same year.

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

---

1) https://icmra.info/drupal/en/covid-19/30june2022 (last accessed on September 2, 2022)
2) https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines (last assessed on September 2, 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 2, 2022)
4) The marketing authorization for Spikevax Intramuscular Injection was transferred from Takeda Pharmaceutical Company Limited to Moderna Japan Co., Ltd. in August 2022.

The review of the present application was conducted based on the data submitted by the applicant in accordance with the "Handling of Drugs Submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification 0906-1, dated September 6, 2022).

2. Quality and Outline of the Review Conducted by PMDA

The bivalent vaccine added in this application is a vaccine containing, encapsulated in lipid nanoparticles (LNP), tozinameran and riltozinameran which are mRNAs encoding S-protein of the original strain of SARS-CoV-2 and the Omicron BA.1 lineage, respectively.

2.1 Active substance

Two active substances, tozinameran and riltozinameran, are used in the manufacture of the bivalent vaccine. The active substance of tozinameran is identical with that of the monovalent vaccine containing tozinameran (parent vaccine), and its data on the quality has already been reviewed. In the following, descriptions on the active substance of riltozinameran are provided.

2.1.1 Preparation and control of cell substrate used for the preparation of a raw material

The deoxyribonucleic acid (DNA) template, a component of the source material, is prepared using a cell bank constructed by introducing riltozinameran-encoding plasmid DNA into *Escherichia coli*. The preparation process and control of the cell bank are identical to those for tozinameran, except the confirmatory test of DNA sequence unique to riltozinameran.

2.1.2 Manufacturing process and control for active substance

The method for the manufacture of the active substance of riltozinameran is identical to the method for the manufacture of the active substance of tozinameran, except that template DNA encoding riltozinameran is used in the *in vitro* transcription reaction.

The specifications for the active substance of riltozinameran are identical to those for the active substance of tozinameran, except the reagents and test solutions unique to riltozinameran that are used for identification (reverse transcription polymerase chain reaction [RT-PCR]) and purity test (template DNA [quantitative polymerase chain reaction (qPCR)]).

2.1.3 Stability of active substance

Table 1 shows the summary of the main stability study of the active substance of riltozinameran.

Table 1. Summary of main stability study of active substance

Study	Number of batches	Storage conditions	Test period	Storage package
Long-term	4	-20±5°C	1 month	Ethylene-vinyl acetate container

The long-term study is being continued up to 24 months.

The long-term testing showed no clear changes in quality attributes throughout the study period.

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is a six-dose vial formulation manufactured by mixing a 1:1 mixture of tozinameran and riltozinameran with lipid components of LNP (2-[(polyethylene glycol)-2000]-N,N-ditetradecyclacetamide [ALC-0159], [(4-hydroxybutyl) azanediyl]bis (hexane-6,1-diyl)bis(2-hexyldecanoate) [ALC-0315], 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC], and cholesterol) and filling the mixture in vials. Each vial (2.25 mL) contains 0.225 mg in total of tozinameran and riltozinameran (RNA mass ratio 1:1). The vaccine product contains excipients: purified sucrose, trometamol, trometamol hydrochloride, and water for injection.

2.2.2 Manufacturing process and control for vaccine product

The manufacturing process of the vaccine product is identical to that of the parent vaccine, except the process of mixing 2 types of the active substance in the dilution process of the active substance.

The specifications for the vaccine product are identical to those of the parent vaccine, except the following tests that were changed in order to test each of 2 types of the active substances: identification (RNA [droplet digital polymerase chain reaction (ddPCR)]), RNA ratio (ddPCR), and biological activity (confirmation of expression [flowcytometry]).

2.2.3 Stability of vaccine product

Table 2 shows the summary of the main stability tests for the vaccine product.

Table 2. Summary of the main stability tests for the vaccine product

Test	Number of batches	Storage condition	Test period	Storage package
Long-term	1	−90 to −60°C	1 month	Glass container with a butyl bromide rubber stopper
Accelerated	1	2 to 8°C	1 month	Glass container with a butyl bromide rubber stopper

The long-term test is being continued up to 24 months.
The accelerated test is being continued up to 6 months.

In the long-term testing, no clear changes were observed in the quality attributes throughout the test period.

2.R Outline of the review conducted by PMDA

As a result of the review based on the submitted data, no particular problem was identified in the quality of the bivalent vaccine.

2.R.1 Manufacture processes and control for active substance riltozinameran and bivalent vaccine

The applicant's explanation of the manufacturing processes and control for the active substance riltozinameran and the bivalent vaccine:

The mRNA sequence of riltozinameran is highly homologous to that of tozinameran with only a minor difference. Result of the specification tests confirmed that the quality attributes of the active substance riltozinameran manufactured by the process validated for the active substance tozinameran are the same as those of tozinameran, despite minor difference in the mRNA sequence. Accordingly, no additional

process validation was conducted on the active substance riltozinameran manufactured by the process validated for tozinameran. Instead, the quality of riltozinameran was controlled by the specifications established for the active substance tozinameran.

The manufacturing process of the bivalent vaccine is different from that of the parent vaccine in that the process of mixing the two types of the active substance is added to the dilution process of the active substance. However, the process parameters are the same as those of mixing the active substance of the parent vaccine with water for injection for adjusting the concentration in the dilution process. Characterization and specification analysis of the bivalent vaccine manufactured by the process validated with the parent vaccine confirmed that mRNAs of the two types of the active substances are mixed in 1:1 ratio and that the mixture of the two types of the active substance thus prepared has the same quality attributes as that of mRNA of the parent vaccine product. Considering the above findings, it was decided to control the quality of the bivalent vaccine (which is manufactured by the manufacturing process validated for the parent vaccine) according to the specifications established for the parent vaccine, instead of conducting an additional process validation.

PMDA's view:
The quality attributes of the active substance riltozinameran and the bivalent vaccine are similar to those of the active substance tozinameran and the parent vaccine, as demonstrated with the currently available data of the commercial scale production. Therefore, the following policy of the applicant is acceptable: To manufacture the active substance riltozinameran and the bivalent vaccine and control their quality attributes by the manufacturing process and the specifications validated for the active substance tozinameran and the parent vaccine.

2.R.2 Shelf-life of active substance riltozinameran and bivalent vaccine

The applicant determined the shelf-life of the active substance riltozinameran and the bivalent vaccine to be 6 months and 12 months, respectively, but results of the long-term storage study at 6- and 12-month time point are unavailable either for the active substance riltozinameran or for the bivalent vaccine at present.

The applicant's explanation about the shelf-life of the active substance riltozinameran and the bivalent vaccine:
It is appropriate to propose the shelf-life of the active substance riltozinameran and the bivalent vaccine to be 6 months and 12 months, respectively, the same shelf-life with established stability for the active substance tozinameran and the parent vaccine, for the following reasons: (a) According to the currently available data of the stability studies on the active substance riltozinameran and the bivalent vaccine, their stability profiles do not tend to differ from those of the active substance tozinameran and the parent vaccine, and (b) the quality attributes of the active substance riltozinameran and the bivalent vaccine manufactured by the process validated for the active substance tozinameran and the parent vaccine are similar to those of the active substance tozinameran and the parent vaccine. In the ongoing long-term storage test on the active substance riltozinameran and the bivalent vaccine, the stability of ≥6 months and ≥12 months, respectively, will be confirmed.

PMDA's view:

The quality attributes of the active substance riltozinameran and the bivalent vaccine manufactured by the process validated for the active substance tozinameran and the parent vaccine are similar to those of the active substance tozinameran and the parent vaccine. Also, the currently available stability profiles of the active substance riltozinameran and the bivalent vaccine do not tend to differ from those of the active substance tozinameran and the parent vaccine. Accordingly, it is acceptable to determine the shelf-life of the active substance riltozinameran to be 6 months when stored at −20 ± 5℃ as is the case with the active substance tozinameran, and the shelf-life of the bivalent vaccine to be 12 months when stored at −75 ± 15℃ as is the case with the parent vaccine. It should be confirmed, in the ongoing long-term storage test on the active substance riltozinameran and the bivalent vaccine, that they show stability profiles identical to those of the active substance tozinameran and the parent vaccine.

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

Although the present application relates to a new indication and a new dosage, no new data were submitted under this section, because the non-clinical pharmacology data had been evaluated during the review process for the initial approval for Comirnaty Intramuscular Injection.[5)]

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

Although the present application relates to a new indication and a new dosage, no new data were submitted under this section, because the non-clinical pharmacokinetic data had been evaluated during the review process for the initial approval.[5)]

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application relates to a new indication and a new dosage, no data relating to toxicity were submitted.

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

No data relating to biopharmaceutic studies and associated analytical methods and clinical pharmacology 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 results from 2 substudies of a foreign phase III study (Study C4591031[6)]) shown in Table 3. In these substudies, the following study vaccines were used: (a) Monovalent vaccine containing tozinameran (parent vaccine), (b) monovalent vaccine containing riltozinameran (OMI monovalent vaccine), and (c) bivalent vaccine containing tozinameran and riltozinameran (at an RNA mass ratio of 1:1) (bivalent vaccine).

5) Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021]
6) Study C4591031 is a foreign phase III study consisting of multiple substudies to evaluate the safety, tolerability, and immunogenicity of the parent vaccine given as the booster dose or the variant vaccine given as the primary series or as a booster dose.

Table 3. Outline of clinical studies

Data category	Country	Study ID	Phase	Population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	U.S.	Study C4591031 Substudy E	III	Healthy subjects >55 years of age who received 3 doses of parent vaccine 30 µg (2 doses as the primary series, 1 dose as a booster) with the third dose being 5-12 months earlier	120[a)] 1,846[b)]	Parent vaccine (30 or 60 µg), OMI monovalent vaccine (30 or 60 µg), or bivalent vaccine (30 or 60 µg) administered intramuscularly as a fourth dose.	Safety Immunogenicity
Evaluation	U.S.	Study C4591031 Substudy D Cohort 2	III	Healthy subjects ≥18-≤55 years of age who received 3 doses of parent vaccine 30 µg (2 doses as the primary series, 1 dose as a booster) with the third dose being 3-6 months earlier	640	Parent vaccine (30 µg) or OMI monovalent vaccine (30 µg) administered intramuscularly as a fourth dose.	Safety Immunogenicity

a) Sentinel cohort
b) Expanded cohort

The following describes the outline of Study C4591031 Substudy E which evaluated the bivalent vaccine of the present application.

7.1 Foreign phase III study (CTD 5.3.5.1.1: Study C4591031 Substudy E; ongoing since February 2022 [data cut-off on April 5, 2022 in the sentinel cohort and May 16, 2022 in the expanded cohort])

This is a randomized, observer-blind, parallel-group substudy to evaluate the safety and immunogenicity of the parent vaccine (30 or 60 µg), OMI monovalent vaccine (30 or 60 µg), or the bivalent vaccine (30 or 60 µg) in healthy subjects >55 years of age who completed 3 prior doses of the parent vaccine 30 µg (2 doses as the primary series, 1 dose as a booster) with the third dose being 5 to 12 months[7)] earlier (target sample size: 1,920 subjects [20 in each group of sentinel cohort, 300 in each group of the expanded cohort][8)]). This substudy was conducted in 35 study sites in the U.S.

A single dose of the parent vaccine, OMI monovalent vaccine, or bivalent vaccine was administered intramuscularly at the dose of 30 or 60 µg.

A total of 120 subjects (20 per group) were randomized in the sentinel cohort, and all of them received the study vaccine and were included in the safety analysis set.

A total of 1,846 subjects (306 in parent vaccine 30 µg group, 302 in parent vaccine 60 µg group, 308 in OMI monovalent vaccine 30 µg group, 308 in OMI monovalent vaccine 60 µg group, 306 in bivalent vaccine 30 µg group, 316 in bivalent vaccine 60 µg group) were randomized in the expanded cohort. Among them, 1,842 subjects received the study vaccine and 1,841 subjects (305 in parent vaccine 30 µg

7) The period was "6 to 12 months" in the initial plan but was changed to "5 to 12 months" before the enrollment of the first subject in order to increase the number of subject candidates who meet the inclusion criteria (protocol amendment 6 [revised on February 8, 2022]).

8) The target sample size in each vaccine group was determined to allow the construction of the safety database. For the evaluation of the immunogenicity, the immunogenicity subset is required to include 150 subjects of each vaccination group in order to meet the following 2 criteria. Accordingly, 230 subjects in each vaccination group were randomly extracted from the entire population to allow 35% of subjects excluded from the evaluation:
- By assuming GMR ("OMI monovalent vaccine or bivalent vaccine"/"parent vaccine 30 µg") to be 1.5 and the standard deviation of the log-transformed value to be 1.05, the statistical power of 91.5% for demonstrating the superiority in GMR is achieved if each vaccination group contains 150 evaluable subjects.
- By assuming the seroresponse rate of 70% with OMI mono- or bivalent vaccine and 55% with the parent vaccine 30 µg, the non-inferiority (non-inferiority margin: −5%) of OMI mono- or bi-valent vaccine against the parent vaccine 30 µg is demonstrated with the statistical power of 94.9%, if 150 subjects are ensured for each vaccination group.

group, 302 in parent vaccine 60 μg group, 307 in OMI monovalent vaccine 30 μg group, 306 in OMI monovalent vaccine 60 μg group, 305 in bivalent vaccine 30 μg group, and 316 in bivalent vaccine 60 μg group) were included in the safety analysis set after excluding 1 subject (OMI monovalent vaccine 60 μg group) who did not submit the informed consent form. As the immunogenicity subset, 230 subjects were randomly extracted from each group (1,380 subjects in total), and 1,316 subjects (221 in parent vaccine 30 μg group, 220 in parent vaccine 60 μg group, 223 in OMI monovalent vaccine 30 μg group, 219 in OMI monovalent vaccine 60 μg group, 216 in bivalent vaccine 30 μg group, 217 in bivalent vaccine 60 μg group) were included in the evaluable immunogenicity population after excluding 64 subjects (7 with serious protocol deviation within 1 month after the study vaccine administration, 54 without valid immunogenicity data at least once during the specified period [28 to 42 days] after the study vaccine administration, 6 who did not fulfill the criteria for study participation or randomization, 1 who did not submit the informed consent form [some subjects met more than 1 condition above]). Of the subjects in the evaluable immunogenicity population, 1,112 subjects without history of SARS-CoV-2 infection within 1 month after the study vaccine administration (182 in parent vaccine 30 μg group, 198 in parent vaccine 60 μg group, 180 in OMI monovalent vaccine 30 μg group, 185 in OMI monovalent vaccine 60 μg group, 186 in bivalent vaccine 30 μg group, 181 in bivalent vaccine 60 μg group) were included in the primary immunogenicity population.

For immunogenicity, the following primary endpoints were defined based on the serum neutralizing antibody titer (50% neutralizing antibody titer) against SARS-CoV-2 (Omicron BA.1 lineage) in subjects without history of SARS-CoV-2 infection within 1 month after the study vaccine administration: (a) "geometric mean ratio (GMR) of neutralizing antibody titer 1 month after the study vaccine administration (OMI mono- or bi-valent vaccine/parent vaccine 30 μg)" and (b) "difference in seroresponse rate 1 month after study vaccine administration [percentage of subjects showing ≥4-fold increase in neutralizing antibody titer from before the study vaccine administration (titer below the lower quantitation limit was imputed by lower quantitation limit)"] (OMI mono- or bi-valent vaccine – parent vaccine 30 μg). The study was planned to confirm the superiority in GMR, and non-inferiority in antibody response rate, of OMI mono- or bi-valent vaccine to parent vaccine 30 μg.[9)]

Table 4 shows serum neutralizing antibody titer against Omicron BA.1 lineage and against Strain USA-WA1/2020 (the reference strain). In the OMI monovalent vaccine 60 μg group as well as in the bivalent vaccine 30 μg and 60 μg groups, the lower limit of the 2-sided 95% confidence interval (CI) of GMR of the serum neutralizing antibody titer against Omicron BA.1 lineage exceeded 1.0, the pre-defined superiority limit, compared to the titer in the parent vaccine 30 μg group, demonstrating the superiority

9) In order to adjust for the multiplicity of testing, multiple primary endpoints and secondary endpoints on immunogenicity were subjected to between-group comparison with the parent vaccine 30 μg in a stepwise manner according to the following order under the 1-sided significance level of 0.025. Since no significant superiority was observed in (7), results of between-group comparison in (8) and later steps were not handled as statistically valid results.
- Superiority in GMR of immune response against Omicron BA.1 lineage (superiority threshold 1.0) and non-inferiority in antibody response rate (non-inferiority threshold −5%): (1) Monovalent vaccine 60 μg group → (2) bivalent vaccine 60 μg group → (3) bivalent vaccine 30 μg group →
- Non-inferiority in GMR of immune response to the reference strain (non-inferiority threshold 0.67 and GMR point estimate ≥0.8): (4) Bivalent vaccine 60 μg group → (5) bivalent vaccine 30 μg group →
- Significant superiority in GMR of immune response to Omicron BA.1 lineage (significant superiority threshold 1.5): (6) Monovalent vaccine 60 μg group → (7) bivalent vaccine 60 μg group → (8) bivalent vaccine 30 μg group →
- Superiority in GMR of immune response to Omicron BA.1 lineage (superiority threshold 1.0) and non-inferiority in antibody response rate (non-inferiority threshold −5%): (9) Monovalent vaccine 30 μg group → (10) significant superiority in GMP of monovalent vaccine 30 μg group (significant superiority threshold 1.5)

of OMI monovalent vaccine 60 μg, the bivalent vaccine 30 μg and 60 μg to the parent vaccine 30 μg. Due to the problem in the multiplicity of testing, results of the primary endpoint in OMI monovalent vaccine 30 μg group were not handled as statistically valid data.

Table 4. Serum neutralizing antibody titer against SARS-CoV-2 in subjects without history of SARS-CoV-2 infection within 1 month after the study vaccine administration (expanded cohort, evaluable immunogenicity population)

Treatment group	Before fourth dose		1 month after fourth dose		GMR [2-sided 95% CI][b] (variant vaccine/parent vaccine 30 μg)
	No. of subjects	GMT [2-sided 95% CI][a]	No. of subjects	GMT [2-sided 95% CI][a]	
Immune response to Omicron BA.1 lineage					
Parent vaccine 30 μg	167	67.5 [52.9, 86.3]	163	455.8 [365.9, 567.6]	—
OMI monovalent vaccine 30 μg	174	70.8 [57.4, 87.4]	169	1014.5 [825.6, 1246.7]	2.23 [1.65, 3.00]
OMI monovalent vaccine 60 μg	176	68.6 [54.3, 86.8]	174	1435.2 [1208.1, 1794.8]	3.15 [2.38, 4.16]
Bivalent vaccine 30 μg	177	76.7 [61.1, 96.1]	178	711.0 [588.3, 859.2]	1.56 [1.17, 2.08]
Bivalent vaccine 60 μg	168	81.9 [63.9, 104.9]	175	900.1 [726.3, 1115.6]	1.97 [1.45, 2.68]
Immune response to the reference strain					
Parent vaccine 30 μg	179	1389.1 [1142.1, 1689.5]	182	5998.1 [5223.6, 6887.4]	—
Bivalent vaccine 30 μg	186	1387.1 [1158.9, 1660.2]	186	5933.2 [5188.2, 6785.2]	0.99 [0.82, 1.02]
Bivalent vaccine 60 μg	179	1396.7 [1149.9, 1696.3]	180	7816.9 [6820.7, 8958.6]	1.30 [1.07, 1.58]

a) The 2-sided 95% CI was calculated by assuming t-distribution of log-transformed antibody titer. Values below LLOQ were imputed by LLOQ×0.5 for analysis.
b) The 2-sided 95% CI was calculated by assuming t-distribution of the difference of the mean log-transformed antibody titer.

Table 5 shows the serum neutralizing antibody response rate 1 month after the study vaccine administration. In the OMI monovalent vaccine 60 μg group as well as in the bivalent vaccine 30 μg and 60 μg groups, the lower limit of the 2-sided 95% CI of the difference in the antibody response rate against Omicron BA.1 lineage, compared with that in the parent vaccine 30 μg group, exceeded the pre-defined non-inferiority threshold of −5%, demonstrating the non-inferiority to the parent vaccine 30 μg.

Table 5. Response rate of serum anti-SARS-CoV-2 neutralizing antibody in subjects without history of SARS-CoV-2 infection within 1 month after the study vaccine administration (expanded cohort, evaluable immunogenicity population)

Treatment group	Antibody response rate (No. of subjects)	Difference in antibody response rate [2-sided 95% CI][a] (variant vaccine – parent vaccine 30 μg)
Immune response to Omicron BA.1 lineage		
Parent vaccine 30 μg	57.0% (85/149)	—
OMI monovalent vaccine 30 μg	76.7% (125/163)	19.6% [9.3, 29.7]
OMI monovalent vaccine 60 μg	86.1% (143/166)	29.1% [19.4, 38.5]
Bivalent vaccine 30 μg	71.6% (121/169)	14.6% [4.0, 24.9]
Bivalent vaccine 60 μg	67.9% (110/162)	10.9% [0.1, 21.4]
Immune response to reference strain		
Parent vaccine 30 μg	49.2% (88/179)	—
OMI monovalent vaccine 30 μg	55.7% (98/176)	—
OMI monovalent vaccine 60 μg	57.5% (104/181)	—
Bivalent vaccine 30 μg	50.0% (93/186)	—
Bivalent vaccine 60 μg	61.8% (110/178)	—

a) Calculated by Miettinen and Nurminen's method.

As for safety, severity of adverse events was assessed according to the guidance of the Food and Drug Administration (FDA) "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).[10)]

10) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (last accessed on September 2, 2022)

- Reactogenicity events (local reactions [injection site pain, redness, and swelling] and systemic events [pyrexia (≥38℃), fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia]) are collected by the subject diary within 7 days after study vaccine administration.
- Adverse events (excluding reactogenicity events within 7 days after study vaccine administration) are collected during 28 days after study vaccine administration.
- Serious adverse events are collected during 6 months after study vaccine administration.

Tables 6 and 7 show reactogenicity events observed within 7 days after the study vaccine administration in the sentinel cohort and the expanded cohort.

Table 6. Reactogenicity events observed within 7 days after the study vaccine administration (sentinel cohort, safety analysis set)

	Event	Parent vaccine		OMI monovalent vaccine		Bivalent vaccine	
		30 μg (N=20)	60 μg (N=20)	30 μg (N=20)	60 μg (N=20)	30 μg (N=20)	60 μg (N=20)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reaction	All events	14 (70.0)	14 (70.0)	15 (75.0)	20 (100.0)	13 (65.0)	17 (85.0)
	Injection site pain	14 (70.0)	14 (70.0)	13 (65.0)	20 (100.0)	13 (65.0)	17 (85.0)
	Redness	0	3 (15.0)	4 (20.0)	2 (10.0)	0	2 (10.0)
	Swelling	0	2 (10.0)	3 (15.0)	1 (5.0)	1 (5.0)	2 (10.0)
Systemic reaction	All events	10 (50.0)	13 (65.0)	12 (60.0)	15 (75.0)	13 (65.0)	15 (75.0)
	Fatigue	9 (45.0)	11 (55.0)	9 (45.0)	13 (65.0)	8 (40.0)	14 (70.0)
	Headache	4 (20.0)	6 (30.0)	7 (35.0)	3 (15.0)	6 (30.0)	10 (50.0)
	Chills	1 (5.0)	4 (20.0)	3 (15.0)	7 (35.0)	5 (25.0)	6 (30.0)
	Vomiting	1 (5.0)	0	0	1 (5.0)	0	1 (5.0)
	Diarrhoea	3 (15.0)	3 (15.0)	3 (15.0)	0	1 (5.0)	1 (5.0)
	Myalgia	5 (25.0)	4 (20.0)	5 (25.0)	7 (35.0)	4 (20.0)	7 (35.0)
	Arthralgia	4 (20.0)	5 (25.0)	3 (15.0)	4 (20.0)	3 (15.0)	7 (35.0)
	Pyrexia[a)]	1 (5.0)	2 (10.0)	2 (10.0)	1 (5.0)	4 (20.0)	4 (20.0)

N = Number of subjects analyzed, n = number of subjects with events
a) ≥38°C

Table 7. Reactogenicity events observed within 7 days after the study vaccine administration (expanded cohort, safety analysis set)

	Event	Parent vaccine		OMI monovalent vaccine		Bivalent vaccine	
		30 μg (N=298)	60 μg (N=298)	30 μg (N=301)	60 μg (N=301)	30 μg (N=301)	60 μg (N=312)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reaction	All events	182 (61.1)	214 (71.8)	205 (68.1)	217 (72.1)	179 (59.5)	216 (69.2)
	Injection site pain	179 (60.1)	212 (71.1)	199 (66.1)	213 (70.8)	175 (58.1)	212 (67.9)
	Redness	19 (6.4)	31 (10.4)	19 (6.3)	32 (10.6)	21 (7.0)	23 (7.4)
	Swelling	18 (6.0)	39 (13.1)	25 (8.3)	30 (10.0)	20 (6.6)	17 (5.4)
Systemic reaction	All events	167 (56.0)	195 (65.4)	192 (63.8)	204 (67.8)	182 (60.5)	211 (67.6)
	Fatigue	135 (45.3)	156 (52.3)	158 (52.5)	177 (58.8)	148 (49.2)	179 (57.4)
	Headache	79 (26.5)	116 (38.9)	110 (36.5)	110 (36.5)	101 (33.6)	114 (36.5)
	Chills	49 (16.4)	72 (24.2)	77 (25.6)	77 (25.6)	39 (13.0)	74 (23.7)
	Vomiting	4 (1.3)	5 (1.7)	9 (3.0)	8 (2.7)	5 (1.7)	4 (1.3)
	Diarrhoea	13 (4.4)	17 (5.7)	24 (8.0)	31 (10.3)	27 (9.0)	20 (6.4)
	Myalgia	59 (19.8)	76 (25.5)	72 (23.9)	92 (30.6)	67 (22.3)	85 (27.2)
	Arthralgia	27 (9.1)	48 (16.1)	50 (16.6)	59 (19.6)	34 (11.3)	58 (18.6)
	Pyrexia[a)]	11 (3.7)	22 (7.4)	25 (8.3)	27 (9.0)	15 (5.0)	24 (7.7)

N = Number of subjects analyzed, n = number of subjects with events
a) ≥38°C

The incidence of adverse events in the sentinel cohort within 1 month after the study vaccine administration was 10% (2 of 20) of subjects in the parent vaccine 30 μg group, 0% (0 of 20) of subjects in the parent vaccine 60 μg group, 15% (3 of 20) of subjects in the OMI monovalent vaccine 30 μg

group, 5% (1 of 20) of subjects in the OMI monovalent vaccine 60 μg group, 5% (1 of 20) of subjects in the bivalent vaccine 30 μg group, and 5% (1 of 20) of subjects in the bivalent vaccine 60 μg group. There were no events observed in ≥2 subjects. Among these adverse events, adverse reactions were skin infection and rash observed in 1 subject in the OMI monovalent vaccine 30 μg group and feeling abnormal in the OMI monovalent 60 μg group. The "feeling abnormal" was recovered, whereas skin infection and rash were not recovered as of the data cut-off date (April 5, 2022). In the sentinel cohort, there were no adverse events that were serious, resulted in death or study discontinuation on or before the data cut-off date.

Table 8 shows the incidence of adverse events and adverse reactions within 1 month after the study vaccine administration and adverse events with a ≥1% incidence in any group. Except lymphadenopathy and dizziness, all adverse events were those defined as reactogenicity events.

Table 8. Incidence of adverse events and adverse reactions within 1 month after the study vaccine administration and adverse events with a ≥1% incidence in any group (expanded cohort, safety analysis set)

	Parent vaccine				OMI monovalent vaccine				Bivalent vaccine			
	30 μg (N=305)		60 μg (N=302)		30 μg (N=307)		60 μg (N=306)		30 μg (N=305)		60 μg (N=316)	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions	Adverse events	Adverse reactions	Adverse events	Adverse reactions	Adverse events	Adverse reactions	Adverse events	Adverse reactions
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All events	18 (5.9)	4 (1.3)	20 (6.6)	13 (4.3)	26 (8.5)	10 (3.3)	11 (3.6)	5 (1.6)	19 (6.2)	7 (2.3)	33 (10.4)	16 (5.1)
Injection site pain	0	0	4 (1.3)	4 (1.3)	3 (1.0)	3 (1.0)	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)	2 (0.6)	2 (0.6)
Headache	0	0	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	1 (0.3)	0	4 (1.3)	3 (1.0)	2 (0.6)	1 (0.3)
Fatigue	0	0	4 (1.3)	4 (1.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.6)	1 (0.3)
Lymphadenopathy	1 (0.3)	1 (0.3)	3 (1.0)	3 (1.0)	1 (0.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Myalgia	0	0	0	0	1 (0.3)	1 (0.3)	0	0	3 (1.0)	2 (0.7)	2 (0.6)	2 (0.6)
Dizziness	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)	3 (1.0)	1 (0.3)	0	0
Diarrhoea	0	0	0	0	3 (1.0)	3 (1.0)	0	0	0	0	0	0

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

In the expanded cohort, serious adverse events were observed in 8 subjects on or before the data cut-off date (May 16, 2022) (pneumonia and ischaemic stroke in 1 subject each in parent vaccine 30 μg group, dehydration, prostate cancer, and nephrolithiasis in 1 subject each in OMI monovalent vaccine 30 μg group, gastroesophageal reflux disease in 1 subject in bivalent vaccine 30 μg group, atrial fibrillation in 2 subjects in bivalent vaccine 60 μg group). The outcome of these events was "recovered" except in 3 subjects in whom the events persisted on the data cut-off date (pneumonia, prostate cancer, and nephrolithiasis in 1 subject each). Causal relationship to the study vaccine was not ruled out for dehydration observed in 1 subject in the OMI monovalent vaccine 30 μg group. There were no adverse events that resulted in death or study discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical significance of booster dose of bivalent vaccine (original strain/Omicron variant [BA.1 lineage])

The applicant's explanation about the clinical significance of the booster dose of the bivalent vaccine:
Despite the progress of SARS-CoV-2 vaccine administration as the primary series and the booster dose in the world, COVID-19 pandemic has not yet been controlled because of mutations of viral genes resulting in the emergence of mutants with altered infectivity, transmissibility, antigenicity, etc. Omicron variant, which is designated as a variant of concern (VOC) by WHO as of August 2022, has high

infectivity and transmissibility and is reported to evade immunity. Although a booster dose with existing vaccines has a certain efficacy against symptomatic diseases caused by Omicron variant, it is suggested to be less effective than against Delta variant and is short-lasting (*N Engl J Med.* 2022;386:1532-46). The booster dose of existing vaccines is also effective in preventing severe disease caused by Omicron variant (ACIP [Apr/20/2022] COVID-19 Vaccine Effectiveness during Omicron[11)]), but there are reports suggesting the waned efficacy over time (*Morb Mortal Wkly Rep.* 2022;71:255-63, *Lancet Respir Med*. 2022;10:689-99). BA.4/BA.5 lineages have higher infectivity and immune evasion than other Omicron lineages (*Nature*. 2022;doi:10.1038/s41586-022-05053-w). In vaccinated people and in those infected with BA.1 or BA.2 lineage, serum neutralizing antibody titer against BA.4/BA.5 lineages is lower than against BA.1 and BA.2 lineages (*N Engl J Med.* 2022;387:86-8).

It is difficult to predict the future trend of COVID-19 epidemic, and whether Omicron variant prevails for some time or a new variant emerges is unclear. However, given the situation where variants emerge that evade the immunity gained by existing vaccines that are designed based on the gene of S-protein of the original strain, resulting in the spread of infection, modified vaccines adapted to mutant strains are essential for ensuring sufficient immune protection.

For this purpose, we developed a bivalent vaccine containing mRNA encoding S-protein of Omicron BA.1 lineage (riltozinameran) in addition to mRNA encoding S-protein of the original strain (tozinameran). In the Study C4591031 Substudy E, the fourth dose with the bivalent vaccine elicited neutralizing activity against BA.1 lineage and demonstrated a certain level of immune response against BA.4/BA.5 lineages as well, albeit in an exploratory analysis [see Section 7.R.3], with a similar safety profile as that of the parent vaccine [see Section 7.R.4]. Thus, the bivalent vaccine is expected to contribute to prevention against currently dominant Omicron variant.

PMDA's view:
Because the efficacy of SARS-CoV-2 vaccine wanes over time, it is necessary to give a booster dose in order to maintain a sufficiently high preventive effect. The currently dominant Omicron variant has a high infectivity, and possibility of immune evasion is pointed out. Although a booster dose of existing vaccines provides a certain level of efficacy against Omicron variant, the efficacy declines within a short period (*N Engl J Med*. 2022;386:1532-46, *MMWR Morb Mortal Wkly Rep.* 2022;71:255-63, etc.). In these circumstances, necessity of modified vaccines adapted to variants was discussed internationally (International Coalition of Medicines Regulatory Authorities SARS-CoV-2 Variant Workshop. ICMRA. June 30, 2022[12)], Interim statement on the composition of current COVID-19 vaccines. WHO. June 17, 2022[13)], Interim statement on decision making considerations for the use of variant updated COVID-19 vaccines. WHO. June 17, 2022[14)], etc.). On July 15, 2022, PMDA issued a notification "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

11) https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-04-20/02-COVID-Link-Gelles-508.pdf (last accessed on September 2, 2022)
12) https://icmra.info/drupal/en/covid-19/30june2022 (last accessed on September 2, 2022)
13) https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines (last accessed on September 2, 2022)
14) 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 2, 2022)

vaccines with new active ingredients." At the 34th meeting of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (held on August 8, 2022), the following reports were made as a result of the discussion on SARS-CoV-2 vaccine strains: (a) It is appropriate to switch to available anti-Omicron vaccines as soon as possible. For this purpose, the promptly available BA.1-adapted vaccine should be selected. (b) Viral evolution of SARS-CoV-2 is expected to continue in the future. Therefore, the availability of new variant-updated vaccines should be investigated. On the basis of these reports, the policy of introducing "BA.1-adapted vaccine" was laid out as the first step in Japan (Materials 1 and 2 [in Japanese][15] for the 34th meeting of the Subcommittee on Immunization and Vaccines of the Health Sciences Council).

From the data of Study C4591031 Substudy E submitted in the present application, the bivalent vaccine containing mRNAs encoding S-protein of the original strain and Omicron BA.1 lineage is expected to demonstrate a certain level of prevention of COVID-19 and severe disease, determined from its immunogenicity data [see Section 7.R.3] with a similar safety profile as that of the parent vaccine [see Section 7.R.4]. Given the current prevalence of Omicron variant, it is of clinical significance to make the bivalent vaccine available for use. Also, WHO states that it is important to achieve broad immunity against continuously mutating SARS-CoV-2 variants, and that a modified vaccine that targets at Omicron variant may be useful if administered as a booster dose to those who have already received the primary series of existing vaccines (Interim statement on the composition of current COVID-19 vaccines. WHO. June 17, 2022[13]). It may be a useful preventive strategy that people who have received the parent vaccine are administered with a booster dose of the bivalent vaccine which is expected to provide broader immunity.

Novel variants may emerge in the future, possibly resulting in change in the usefulness of the vaccine depending on the property of the variants. Appropriate measures should be taken depending on situations.

7.R.2 Data for review

Data of Study C4591031 Substudy E and Substudy D Cohort 2 were submitted in the present application. Substudy E is a randomized, observer-blind, parallel-group study in healthy subjects >55 years of age who completed 3 doses of the parent vaccine 5 to 12 months earlier. The subjects were randomly assigned to receive OMI monovalent vaccine, bivalent vaccine, or parent vaccine. Substudy D Cohort 2 is a randomized, observer-blind, parallel-group study in healthy subjects 18 to 55 years of age who received 3 doses of the parent vaccine 3 to 6 months earlier. The subjects were randomly assigned to receive OMI monovalent vaccine or the parent vaccine.

PMDA's view:

The notification "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 4): Immunogenicity-based evaluation of variant vaccines modified from parent vaccines and booster vaccines with new active ingredients." (Office of Vaccines and Blood Products, PMDA, July 15, 2022) states that, in order to evaluate the efficacy of a booster dose with a variant-targeted vaccine modified from the parent vaccine, a randomized study should be conducted where subjects are randomly assigned to receive the variant vaccine or the parent vaccine (limited to a vaccine with its

[15] https://www.mhlw.go.jp/stf/newpage_27303.html (last accessed on September 2, 2022)

dosage regimen approved for booster dose in Japan) and the efficacy of the booster dose with the variant vaccine should be evaluated. Study C4591031 Substudy E was planned and conducted as a randomized study in which subjects who had completed 3 doses of the parent vaccine were randomly assigned to receive OMI monovalent vaccine, bivalent vaccine, or the parent vaccine. PMDA concluded that it is acceptable to evaluate the efficacy of the booster dose with the bivalent vaccine based on the results of the above study.

PMDA decided to evaluate the immunogenicity based on the results of Study C4591031 Substudy E, and to confirm the safety based on the results of Study C4591031 Substudy D Cohort 2 in addition to the result of Study C4591031 Substudy E.

7.R.3 Efficacy

The applicant's explanation about the efficacy of the booster dose with the bivalent vaccine:
Study C4591031 Substudy E investigated the immunogenicity of a booster dose of variant vaccines (OMI monovalent vaccine 30 and 60 μg, bivalent vaccine 30 and 60 μg). In subjects without history of SARS-CoV-2 infection within 1 month after vaccination with the study vaccine, the following results were obtained in OMI monovalent vaccine 60 μg group, bivalent vaccine 30 and 60 μg groups: (a) GMR of the neutralizing antibody titer against Omicron BA.1 lineage 1 month after study vaccine administration was higher than in the parent vaccine 30 μg group, and (b) the antibody response rate to Omicron BA.1 lineage at 1 month after the study vaccine administration was not lower than that in the parent vaccine 30 μg group [see Section 7.1]. Tables 9 and 10 show results in subjects regardless of history of SARS-CoV-2 infection. The results were similar to those observed in subjects without history of SARS-CoV-2 infection within 1 month after the study vaccine administration, the primary analysis population (see Tables 4 and 5).

Table 9. Serum neutralizing antibody titer against SARS-CoV-2 in subjects regardless of history of SARS-CoV-2 infection (expanded cohort, evaluable immunogenicity population)

Treatment group	Before fourth dose		1 month after fourth dose		GMR [2-sided 95% CI][b] (variant vaccine/parent vaccine)
	No. of subjects	GMT [2-sided 95% CI] [a]	No. of subjects	GMT [2-sided 95% CI] [a]	
Immune response to Omicron BA.1 lineage					
Parent vaccine 30 μg	205	106.4 [81.5, 138.9]	201	663.1 [530.6, 829.0]	—
OMI monovalent vaccine 30 μg	212	113.3 [88.6, 145.0]	211	1346.3 [1109.9, 1633.0]	2.03 [1.51, 2.72]
OMI monovalent vaccine 60 μg	205	100.9 [78.1, 130.4]	208	1835.9 [1544.8, 2181.8]	2.77 [2.09, 3.67]
Bivalent vaccine 30 μg	205	107.4 [83.8, 137.7]	207	883.8 [733.8, 1064.5]	1.33 [1.00, 1.78]
Bivalent vaccine 60 μg	201	119.7 [91.8, 156.1]	208	1140.1 [930.6, 1396.7]	1.72 [1.27, 2.32]
Immune response to reference strain					
Parent vaccine 30 μg	218	1776.0 [1465.6, 2152.2]	221	7376.6 [6427.1, 8466.3]	—
Bivalent vaccine 30 μg	216	1751.4 [1461.0, 2099.6]	216	6944.9 [6067.3, 7949.4]	0.94 [0.78, 1.14]
Bivalent vaccine 60 μg	215	1780.4 [1460.6, 2170.3]	216	9354.7 [8150.9, 10736.4]	1.27 [1.04, 1.54]

a) The 2-sided 95% CI was calculated by assuming t-distribution of log-transformed antibody titer. Values below LLOQ were imputed by LLOQ×0.5 for analysis.
b) The 2-sided 95% CI was calculated by assuming t-distribution of the difference of the mean log-transformed antibody titer.

Table 10. Response rate of serum anti-SARS-CoV-2 neutralizing antibody in subjects regardless of history of SARS-CoV-2 infection (expanded cohort, evaluable immunogenicity population)

Treatment group	Antibody response rate (number of subjects)	Difference in antibody response rate [2-sided 95% CI][a] (variant vaccine – parent vaccine 30μg)
Immune response to Omicron BA.1 lineage		
Parent vaccine 30 μg	52.2% (97/186)	—
OMI monovalent vaccine 30 μg	71.5% (143/200)	19.3% [9.7, 28.7]
OMI monovalent vaccine 60 μg	82.1% (160/195)	29.9% [20.7, 38.7]
Bivalent vaccine 30 μg	66.8% (131/196)	14.7% [4.8, 24.3]
Bivalent vaccine 60 μg	63.5% (122/192)	11.4% [1.4, 21.1]
Immune response to reference strain		
Parent vaccine 30 μg	46.8% (102/218)	—
OMI monovalent vaccine 30 μg	50.5% (110/218)	—
OMI monovalent vaccine 60 μg	56.3% (121/215)	—
Bivalent vaccine 30 μg	47.2% (102/216)	—
Bivalent vaccine 60 μg	57.5% (123/214)	—

a) Calculated by Miettinen and Nurminen's method.

Serious protocol deviations were confirmed in 4 subjects after data release. They should have been excluded from the evaluable immunogenicity population but were not excluded at the time of the interim report because of delay in receiving the reports of the protocol deviations. Another 4 subjects who should not have been excluded[16] were excluded from the evaluable immunogenicity population. However, the above mishandling events were considered to have a small impact on the immunogenicity assessment, because the results in the all-available immunogenicity population (the population consisting of subjects with at least one valid immunogenicity result among immunogenicity subsets) (Tables 11 and 12) were similar to those observed in the evaluable immunogenicity population.

Table 11. Serum neutralizing antibody titer against SARS-CoV-2 (expanded cohort, all-available immunogenicity population)

Treatment group	Before fourth dose		1 month after fourth dose		GMR [2-sided 95% CI][b] (variant vaccine/parent vaccine 30 μg)
	No. of subjects	GMT [2-sided 95% CI] [a]	No. of subjects	GMT [2-sided 95% CI] [a]	
Immune response to Omicron BA.1 lineage					
Parent vaccine 30 μg	209	106.6 [81.9, 138.7]	205	670.6 [538.7, 835.0]	—
OMI monovalent vaccine 30 μg	217	113.9 [89.4, 145.1]	216	1373.3 [1135.8, 1660.6]	2.05 [1.53, 2.73]
OMI monovalent vaccine 60 μg	210	98.5 [76.6, 126.6]	213	1811.8 [1529.8, 2145.8]	2.70 [2.05, 3.56]
Bivalent vaccine 30 μg	214	106.4 [83.5, 135.5]	215	895.0 [744.8, 1075.6]	1.33 [1.00, 1.78]
Bivalent vaccine 60 μg	205	123.1 [94.6, 160.3]	214	1179.1 [963.9, 1442.3]	1.76 [1.31, 2.36]
Immune response to reference strain					
Parent vaccine 30 μg	222	1779.8 [1472.7, 2150.8]	225	7451.6 [6504.6, 8536.4]	—
Bivalent vaccine 30 μg	225	1702.7 [1419.0, 2043.1]	225	6875.7 [6019.5, 7853.8]	0.92 [0.76, 1.12]
Bivalent vaccine 60 μg	221	1792.2 [1475.0, 2177.7]	222	9439.5 [8239.2, 10814.7]	1.27 [1.05, 1.53]

a) The 2-sided 95% CI was calculated by assuming t-distribution of log-transformed antibody titer. Values below LLOQ were imputed by LLOQ × 0.5 for analysis.
b) The 2-sided 95% CI was calculated by assuming t-distribution of the difference of the mean log-transformed antibody titer.

16) Study subjects were assigned to 2 types of IDs: ID unique to each subject and ID for each enrollment. Subject-unique ID had been used to identify subjects who did not meet the exclusion criteria. As it occurred, some screen failures after the initial screening, but were subsequently enrolled in the study after being rescreened, were mistakenly excluded from the evaluable immunogenicity population.

Table 12. Response rate of serum anti-SARS-CoV-2 neutralizing antibody (expanded cohort, all-available immunogenicity population)

Treatment group	Antibody response rate (number of subjects)	Difference in antibody response rate [2-sided 95% CI][a] (variant vaccine – parent vaccine 30μg)
Immune response to Omicron BA.1 lineage		
Parent vaccine 30 μg	52.6% (100/190)	—
OMI monovalent vaccine 30 μg	72.2% (148/205)	19.6% [10.1, 28.8]
OMI monovalent vaccine 60 μg	82.5% (165/200)	29.9% [20.8, 38.5]
Bivalent vaccine 30 μg	67.2% (137/204)	14.5% [4.8, 24.0]
Bivalent vaccine 60 μg	62.8% (123/196)	10.1% [0.3, 19.8]
Immune response to reference strain		
Parent vaccine 30 μg	47.3% (105/222)	—
OMI monovalent vaccine 30 μg	50.2% (112/223)	—
OMI monovalent vaccine 60 μg	56.4% (124/220)	—
Bivalent vaccine 30 μg	47.6% (107/225)	—
Bivalent vaccine 60 μg	57.3% (126/220)	—

a) Calculated by Miettinen and Nurminen's method.

As of the data cut-off date (May 16, 2022), 30 subjects developed COVID-19 after the study vaccine administration (7 in parent vaccine 30 μg group, 6 in parent vaccine 60 μg group, 7 in OMI monovalent vaccine 30 μg group, 3 in OMI monovalent vaccine 60 μg group, 1 in bivalent vaccine 30 μg group, 6 in bivalent vaccine 60 μg group). No severe COVID-19 was observed.

Neutralizing antibody titer against Omicron BA.4/BA.5 lineages at 1 month after the study vaccine administration was investigated in an exploratory manner in the sentinel cohort. Table 13 shows the results.

Table 13. Serum neutralizing antibody titer against Omicron variant (sentinel cohort, evaluable immunogenicity population)

	No. of subjects	GMT [2-sided 95% CI][a]	
		BA.1 lineage	BA.4/BA.5 lineages
Subjects without history of SARS-CoV-2 infection			
Parent vaccine 30 μg	17	425.7 [226.6, 799.9]	110.9 [67.9, 180.9]
OMI monovalent vaccine 30 μg	17	501.1 [231.8, 1083.4]	78.4 [42.8, 143.7]
OMI monovalent vaccine 60 μg	18	822.0 [403.6, 1674.3]	145.3 [74.7, 282.8]
Bivalent vaccine 30 μg	13	771.3 [387.9, 1533.6]	226.3 [120.7, 424.1]
Bivalent vaccine 60 μg	18	678.1 [394.1, 1166.6]	137.2 [77.3, 243.5]
Subjects regardless of history of SARS-CoV-2 infection			
Parent vaccine 30 μg	19	533.3 [279.0, 1019.3]	135.8 [80.4, 229.2]
OMI monovalent vaccine 30 μg	20	629.0 [311.4, 1270.5]	105.6 [56.8, 196.1]
OMI monovalent vaccine 60 μg	20	920.9 [463.2, 1830.7]	162.8 [86.3, 307.1]
Bivalent vaccine 30 μg	17	1132.6 [585.1, 2192.7]	294.9 [163.0, 533.5]
Bivalent vaccine 60 μg	19	782.2 [432.4, 1414.9]	160.0 [85.2, 300.4]

a) The 2-sided 95% CI was calculated by assuming t-distribution of log-transformed antibody titer. Values below LLOQ were imputed by LLOQ × 0.5 for analysis.

The above results suggest the efficacy of a booster dose with bivalent vaccine.

PMDA's view:
Study C4591031 Substudy E demonstrated the following for both bivalent vaccine 30 μg and 60 μg:
(a) GMR and antibody response rate to Omicron BA.1 lineage was superior and non-inferior, respectively, to the parent vaccine.
(b) A certain level of immune response against Omicron BA.4/BA.5 lineages was achieved, albeit in an exploratory assessment.

It is reported that the neutralizing antibody titer after SARS-CoV-2 vaccine administration is correlated with COVID-19-preventive effect (*Nat Med*. 2021;27:1205-11). Given the report on the effectiveness of the booster dose of the parent vaccine on symptomatic COVID-19 and severe COVID-19 caused by Omicron variant (ACIP [Apr/20/2022] COVID-19 Vaccine Effectiveness during Omicron[11]), the booster dose with the bivalent vaccine, which is demonstrated to induce more potent immune response against Omicron variant than the parent vaccine, is expected to effectively prevent the onset and exacerbation of COVID-19 to a certain level and, furthermore, may provide enhanced preventive effect against COVID-19 caused by Omicron variant.

The currently available data on the bivalent vaccine are those of immunogenicity only in an early stage after administration; it is unknown how long the immunogenicity lasts. Moreover, prevalent strain of SARS-CoV-2 evolves rapidly, and different Omicron lineages and novel variants are likely to emerge in the future. Information on the efficacy (including immunogenicity) of the bivalent vaccine should be collected from data accumulated in each country and from study reports, and appropriate measures should be taken based on the information thus obtained.

7.R.4 Safety

7.R.4.1 Safety profile

The applicant's explanation about safety of the bivalent vaccine containing the mRNA encoding S-protein of Omicron BA.1 lineage:

(a) Reactogenicity events

In the Study C4591031 Substudy E expanded cohort, reactogenicity events such as injection site pain, fatigue, and headache were frequently observed within 7 days after the study vaccine administration (Table 7), but most of them were Grade 1 or 2, with only a low incidence of Grade ≥3 events (Table 14). No Grade 4 reactogenicity events were observed in any group.

In all groups, the median time to onset was 2 to 3 days after vaccination both for local reactions and for systemic reactions. Reactogenicity events lasted for ≥1 month in some subjects, but the median duration was 1 to 2 days for local reactions as well as for systemic reactions.

Table 14. Incidence of Grade ≥3 reactogenicity events
(Substudy E expanded cohort, safety analysis set)

		Parent vaccine		OMI monovalent vaccine		Bivalent vaccine	
		30 µg (N=298)	60 µg (N=298)	30 µg (N=301)	60 µg (N=301)	30 µg (N=301)	60 µg (N=312)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reaction	Injection site pain	1 (0.3)	1 (0.3)	0	2 (0.7)	1 (0.3)	1 (0.3)
	Redness	1 (0.3)	1 (0.3)	1 (0.3)	0	0	2 (0.6)
	Swelling	0	0	0	2 (0.7)	0	1 (0.3)
Systemic reaction	Fatigue	1 (0.3)	9 (3.0)	8 (2.7)	11 (3.7)	5 (1.7)	6 (1.9)
	Headache	1 (0.3)	3 (1.0)	3 (1.0)	4 (1.3)	1 (0.3)	4 (1.3)
	Chills	0	2 (0.7)	2 (0.7)	7 (2.3)	0	0
	Vomiting	0	0	0	0	0	0
	Diarrhoea	0	0	2 (0.7)	0	4 (1.3)	0
	Myalgia	0	3 (1.0)	1 (0.3)	6 (2.0)	0	1 (0.3)
	Arthralgia	0	1 (0.3)	0	1 (0.3)	0	1 (0.3)
	Pyrexia [a)]	0	0	3 (1.0)	5 (1.7)	4 (1.3)	2 (0.6)

N = Number of subjects analyzed, n = number of subjects with events
a) Pyrexia is not classified by Grade but handled as Grade ≥3 if >38.9°C in this table.

Table 15 shows the reactogenicity events observed within 7 days after the study vaccine administration in Study C4591031 Substudy D Cohort 2 in which healthy subjects ≥18 to ≤55 years of age received the fourth dose with the parent vaccine or OMI monovalent vaccine 30 µg (study period, ongoing since January 2022; data cut-off date, March 11, 2022; participating country, the U.S.).

Table 15. Incidence of reactogenicity events (Substudy D Cohort 2, safety analysis set)

		All events		Grade ≥3	
		Parent vaccine 30 µg (N = 306)	OMI monovalent vaccine 30 µg (N = 294)	Parent vaccine 30 µg (N = 306)	OMI monovalent vaccine 30 µg (N = 294)
		n (%)	n (%)	n (%)	n (%)
Local reaction	All events	243 (79.4)	231 (78.6)	—	—
	Injection site pain	240 (78.4)	229 (77.9)	3 (1.0)	2 (0.7)
	Redness	13 (4.2)	21 (7.1)	0	0
	Swelling	27 (8.8)	25 (8.5)	0	0
Systemic reaction	All events	223 (72.9)	228 (77.6)	—	—
	Fatigue	185 (60.5)	189 (64.3)	8 (2.6)	10 (3.4)
	Headache	138 (45.1)	140 (47.6)	6 (2.0)	6 (2.0)
	Chills	80 (26.1)	93 (31.6)	3 (1.0)	4 (1.4)
	Vomiting	5 (1.6)	8 (2.7)	0	0
	Diarrhoea	36 (11.8)	25 (8.5)	2 (0.7)	0
	Myalgia	87 (28.4)	99 (33.7)	3 (1.0)	2 (0.7)
	Arthralgia	46 (15.0)	69 (23.5)	0	3 (1.0)
	Pyrexia[a)]	22 (7.2)	25 (8.5)	1 (0.3)	1 (0.3)

N = Number of subjects analyzed, n = number of subjects with events
a) Pyrexia is not classified by Grade but handled as Grade ≥3 if >38.9°C in this table.

Table 16 shows the reactogenicity events observed after the primary series and the third dose with the parent vaccine (submitted in the past application) for reference purpose.

Table 16. Incidence of reactogenicity events after administration of the parent vaccine 30 μg (phase II/III part of Study C4591001, safety analysis set)

Dose #		Primary series (First or Second)[a]		Third[b]	
Subjects		≥16 years of age (N = 4,108)		18 to 55 years of age (N = 289)	
Event terms		All events	Grade ≥3	All events	Grade ≥3
		n (%)	n (%)	n (%)	n (%)
Local reaction	All events	3,481 (84.7)	—	240 (83.0)	—
	Injection site pain	3,455 (84.1)	59 (1.4)	240 (83.0)	1 (0.3)
	Redness	389 (9.5)	27 (0.7)	17 (5.9)	0
	Swelling	430 (10.5)	17 (0.4)	23 (8.0)	1 (0.3)
Systemic reaction	All events	3,181 (77.4)	—	223 (77.2)	—
	Fatigue	2,585 (62.9)	172 (4.2)	184 (63.7)	13 (4.5)
	Headache	2,265 (55.1)	98 (2.4)	140 (48.4)	3 (1.0)
	Chills	1,312 (31.9)	71 (1.7)	84 (29.1)	3 (1.0)
	Vomiting	84 (2.0)	5 (0.1)	5 (1.7)	0
	Diarrhoea	644 (15.7)	12 (0.3)	25 (8.7)	0
	Myalgia	1,573 (38.3)	74 (1.8)	113 (39.1)	4 (1.4)
	Arthralgia	968 (23.6)	34 (0.8)	73 (25.3)	1 (0.3)
	Pyrexia	582 (14.2)	—[c]	25 (8.7)	—[c]

N = Number of subjects analyzed, n = number of subjects with events
a) Comirnaty Intramuscular Injection: Report on Special Approval for Emergency (February 8, 2021), Table 22 (partially modified)
b) Comirnaty Intramuscular Injection: Report on Special Approval for Emergency (November 2, 2021), Table 9 (partially modified)
c) Not classified by Grade. The incidence of >38.9°C was 0.9% (37 of 4,108) of subjects after the primary series and 0.3% (1 of 289) of subjects after the third dose.

(b) Adverse events

Table 8 shows the incidence of adverse events and adverse reactions observed within 1 month after the study vaccine administration in Study C4591031 Substudy E expanded cohort. Adverse events observed in ≥2 subjects in any group were lymphadenopathy, dizziness, rash, and those defined as reactogenicity events. Most of them were considered to have a causal relationship with the study vaccine. The incidence of adverse events and adverse reactions observed within 1 month after the study vaccine administration in Study C4591031 Substudy D Cohort 2 was 3.7% (12 of 325) of subjects and 1.5% (5 of 325) of subjects, respectively, in the parent vaccine 30 μg group, and 5.7% (18 of 315) of subjects and 3.2% (10 of 315) of subjects, respectively, in the OMI monovalent vaccine 30 μg group. The incidence of adverse events observed in ≥2 subjects in any group was lymphadenopathy (0.9% [3 of 305] of subjects in the parent vaccine group, 0.3% [1 of 302] of subjects in the OMI monovalent vaccine group), chest pain (0% [0 of 305] of subjects in the parent vaccine group, 0.6% [2 of 302] of subjects in the OMI monovalent vaccine group), and those defined as reactogenicity events. Most of them were considered to have a causal relationship to the study vaccine.

Serious adverse events were observed in 8 subjects in the Study C4591031 Substudy E expanded cohort on or before the data cut-off date (May 16, 2022). The causal relationship to the study vaccine was denied for all of them except dehydration in 1 subject (OMI monovalent vaccine 30 μg group). No serious adverse events were observed in the sentinel cohort up to the cut-off date (April 5, 2022). In Study C4591031 Substudy D Cohort 2, serious adverse events were observed in 2 subjects (fluid retention in 1 subject in the parent vaccine 30 μg group, migraine in 1 subject in the OMI monovalent vaccine 30 μg group) on or before the data cut-off date (March 11, 2022), but causal relationship to the study vaccine was denied for both.

No death nor adverse events leading to study vaccine discontinuation were observed in either of the Substudies up to the data cut-off date.

From the data cut-off date through August 4, 2022, death occurred in 3 subjects (cardiopulmonary failure, gangrene, septic shock, and overdose in 1 subject each [1 subject had more than 1 event]; treatment group unknown due to the ongoing blinded study), and serious adverse events occurred in 21 subjects in Study C4591031 Substudy E and Substudy D Cohort 2, but causal relationship to the study vaccine was denied for all of them.

Thus, reactogenicity events were observed in many subjects in the Study C4591031 Substudies, and lymphadenopathy was observed as non-reactogenicity events; most of them were mild to moderate in severity and disappeared within a short period after the vaccination. The safety profile of the booster dose with the bivalent vaccine containing Omicron BA.1 lineage is similar to that confirmed with the parent vaccine, posing no serious concern.

PMDA's view:
On the basis of the currently available results of the Study C4591031Substudies, PMDA confirmed that the safety profile of the booster dose with the bivalent vaccine containing Omicron BA.1 lineage is generally similar to that of the booster dose with the parent vaccine, and that there are no serious safety concerns at present. However, because the number of subjects evaluated after booster vaccination with variant vaccine was limited, both domestic and foreign information should be collected continuously, and appropriate measures should be taken based on the information thus obtained.

7.R.4.2 Myocarditis/pericarditis

No myocarditis/pericarditis was reported in Study C4591031 Substudy E or Substudy D Cohort 2 up to the data cut-off date.

The risk of myocarditis/pericarditis associated with vaccination with the parent vaccine is assessed on a regular basis at the Working Group on Adverse Reactions of the Subcommittee on 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. There are no serious concerns affecting the vaccination system.

PMDA considers that the currently available findings on the parent vaccine do not suggest unacceptable risk of myocarditis/pericarditis. Caution should be exercised against myocarditis/pericarditis after the bivalent vaccine administration as after the parent vaccine administration, and appropriate measures should be taken based on the information thus obtained.

7.R.5 Indication

The proposed indication was as follows:

Proposed Indication

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

The indication applies to the following vaccine products:

- Vaccine product containing 0.225 mg of Tozinameran (monovalent)
- Vaccine product containing 0.225 mg of tozinameran and riltozinameran (1:1) (bivalent)

PMDA's view:

The efficacy of the bivalent vaccine is expected from the results of Study C4591031 Substudy E [see Section 7.R.3] with acceptable safety [see Section 7.R.4]. It is acceptable to indicate the bivalent vaccine for "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as is the case with the parent vaccine.

7.R.6 Dosage and administration

7.R.6.1 Dose setting

The applicant's explanation about dose-setting:

The dosage regimen for the booster dose of the parent vaccine is "a single dose of 0.3 mL is injected intramuscularly," with the single dose of 0.3 mL containing 30 μg of tozinameran.

In Study C4591031 Substudy E, the booster dose with 30 μg of the bivalent vaccine (15 μg each of tozinameran and riltozinameran) was shown to be effective against Omicron BA.1 lineage and induced a certain level of immune response to Omicron BA.4/BA.5 lineages, with the similar safety profile as that of the parent vaccine. A single dose of the bivalent vaccine was set at 0.3 mL (15 μg each of tozinameran and riltozinameran) as is the case with the single dose of the parent vaccine, taking account of the following findings: (a) The neutralizing antibody titer against Omicron BA.1 lineage was not significantly different between 30 μg and 60 μg of the bivalent vaccine, and (b) the incidence of reactogenicity events tended to be higher after 60 μg administration than after 30 μg administration.

PMDA's view:

It is acceptable to determine the booster dose of the bivalent vaccine as 0.3 mL (15 μg each of tozinameran and riltozinameran) as is the case with the booster dose of the parent vaccine.

7.R.6.2 Timing of administration

The applicant's explanation about the timing of administration:

In Study C4591031 Substudy E, eligible subjects were those who had received 3 prior doses of the parent vaccine with the third dose being 5 to 12 months earlier. In Study C4591031 Substudy D, eligible subjects were those who had received 3 prior doses of the parent vaccine with the third dose being 3 to 6 months earlier, although the bivalent vaccine was not evaluated in this substudy. From the results of these substudies, efficacy was expected regardless of the interval between the third and the fourth dose. Since the proposed timing of the fourth dose in foreign countries was ≥4 months after the third dose, the timing of the booster dose of bivalent vaccine was defined in the "PRECAUTIONS CONCERNING

DOSAGE AND ADMINISTRATION" of the package insert as follows: "Usually, the third dose (the first booster dose) may be given ≥5 months after the primary series. The fourth dose (the second booster dose) may be given ≥4 months after the third dose."

PMDA's view:
The bivalent vaccine should be given "≥5 months after the previous dose" as is the case with the parent vaccine, given the following:
(a) Study C4591031 Substudy E included subjects who had received 3 prior doses of the parent vaccine with the third dose being 5 to 12 months earlier, and (b) in Japan, the timing of the booster dose with the parent vaccine is defined as "≥5 months after the previous dose," and this system has been applied so far. From public health point of view, it is important to make a booster dose with bivalent vaccine available for anyone after a certain period has elapsed since the previous dose, taking account of the following:
(a) Study C4591031 Substudy E showed that there is no clinically significant difference in the safety of the fourth dose between the parent vaccine and the bivalent vaccine and that the safety profile of the fourth dose is similar to those observed in the primary series and the third dose of the parent vaccine, and (b) although the neutralizing antibody titer decreases over time after vaccine administration, the booster dose can increase the titer again, resulting in the recovery of the SARS-CoV-2-preventive effect. It is acceptable to provide information in the package insert of the bivalent vaccine that "usually, the booster dose may be administered ≥5 months after the previous dose" without specifying the number of booster doses.

7.R.6.3 Age indication

The applicant's explanation about the age indication for vaccination:
Individuals aged ≥12 years are eligible for receiving the parent vaccine, both for the primary series and for the booster dose.

Study C4591031 Substudy E demonstrated the efficacy of the bivalent vaccine 30 μg in subjects >55 years of age. Although no clinical data are currently available on the bivalent vaccine given to healthy people ≤55 years of age, it is expected that the bivalent vaccine provides at least similar extent of immunogenicity to those 12 to 55 years as that achieved in those >55 years, given the following observations: In clinical studies on the primary series with the parent vaccine, the neutralizing antibody titer after the second dose of the parent vaccine 30 μg was higher in the younger age group (20 to 64 years of age) than in the older age group (65 to 85 years of age) (Japanese phase I/II study [Study C4591015]) and in the age group of 12 to 15 years than in the age group of 16 to 25 (foreign phase III study [Study C4591001]).

Also, the safety profile of the bivalent vaccine in those 12 to 55 years of age is expected to be similar to that of the parent vaccine, given the following:
(a) In Study C4591031 Substudy E, the bivalent vaccine in subjects >55 years of age showed acceptable safety similar to that of the parent vaccine, and (b) the profiles of the local and systemic reactions after administration of 30 μg of modified vaccines to other variants (e.g., Beta variant) so far tested by the applicant were similar to those of the parent vaccine (CTD 5.3.5.1.3).

On the basis of the above, the age indication for the bivalent vaccine was set at ≥12 years as is the case with the booster dose of the parent vaccine.

PMDA's view:
According to the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1) Evaluation of vaccines against variants (April 5, 2021: Reviewing Office of Vaccines and Blood Products, PMDA," results of clinical studies on variant vaccines conducted in a single age group can be generally extrapolated into other age groups that are approved for parent vaccine. Taking account of this notification in addition to the explanation of the applicant, it is acceptable to set the age indication for the bivalent vaccine as ≥12 years as is the case with the booster dose of the parent vaccine.

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 and approved vaccines

The bivalent vaccine is different from the parent vaccine and other approved vaccines in the dilution of vaccine preparation, vaccination dose, intended population, and other aspects.

The applicant's explanation about the measures to prevent vaccine administration errors:
In order to prevent vaccine administration errors caused by the differences between the bivalent and the approved vaccines, the following preventive measures will be continued, as employed currently.

- To prevent product mix-up, color-coded vial caps and labels are used to help differentiate products, and identification stickers that can be attached to a syringe after withdrawing the vaccine dose are prepared and distributed.
- To ensure the proper preparation method and administration volume of the vaccine, information will be prepared and provided appropriately to healthcare professionals. For this purpose, (a) information material on the appearance of each vaccine, filling volume, preparation method (handling procedure from thawing to administration), dosage regimen, and their differences will be prepared, and (b) briefing sessions will be held for healthcare professionals.

In order to further ensure the above measures, the applicant plans to prepare and distribute information material containing examples of vaccination errors and their preventive measures.

PMDA's view:
Errors related to preparation of vaccine, storage management, and wrong vaccination have been reported with approved SARS-CoV-2 vaccines, and several administrative notices on the proper use of vaccines have been issued ("Information on SARS-CoV-2 vaccine administration error: 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], "Request on the proper use of Comirnaty Intramuscular Injection [Pfizer Japan Inc., dated May 2021],[17] "Request to prevent vaccine administration errors with Comirnaty Intramuscular Injection for 5 to 11 years old and

[17] https://www.pmda.go.jp/files/000240928.pdf (last accessed on September 2, 2022)

Comirnaty Intramuscular Injection [Pfizer Japan Inc., dated April 2022][18]). There may be cases where the bivalent vaccine, which contains different active ingredients, and the parent vaccine (Comirnaty Intramuscular Injection) are used in the same vaccination venue/medical institution. In order to facilitate the preventive measures proposed by the applicant, it is mandatory to make sure that all facilities delivered with the bivalent vaccine and the parent vaccine are informed of the preventive measures and to facilitate the understanding of healthcare professionals on the measures. In the present application, enhanced measures for preventing vaccination errors are discussed. Since the bivalent vaccine is different from existing vaccine products in that no dilution is required, careful attention is required more than ever. In addition to the activities planned by the applicant, it is required to collect information on proper use continuously and to consider further safety measures as necessary.

7.R.7.2 Post-marketing investigations

The applicant's explanation about the post-marketing investigations:

Results of Study C4591031 Substudy E showed that the bivalent vaccine has acceptable safety similar to that of the parent vaccine, suggesting that the bivalent vaccine is unlikely to pose any safety problem unique to the bivalent vaccine [see Section 7.R.4]. Also, the specified use-results survey on the parent vaccine conducted in Japan (C4591019) did not reveal any new safety concerns. Therefore, the applicant considers that new safety issues have not been specified, and that there is little need to immediately conduct a new post-marketing investigation on the bivalent vaccine at present. Instead, safety information will be collected in early post-marketing phase vigilance and routine pharmacovigilance activities. A system will be developed that allows prompt planning and conduct of a post-marketing surveillance, etc., in case if issues of particular concerns with the bivalent vaccines are raised in the information collected from the early post-marketing phase vigilance and routine pharmacovigilance activities in Japan and foreign countries.

PMDA's view:

The applicant's explanation is acceptable. PMDA has concluded that the risk management plan (draft) should include the safety specifications presented in Table 16, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 17.

Table 16. Safety and efficacy specifications in the risk management plan (draft)

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

No change pursuant to the present application

[18]) https://www.pmda.go.jp/files/000246187.pdf (last accessed on September 2, 2022)

Table 17. 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 (child vaccine recipients 5 to 11 years of age) • Early post-marketing phase vigilance (vaccine recipients ≥12 years of age: RTU Intramuscular Injection [bivalent: original strain/Omicron BA.1 lineage]) • Post-marketing clinical study (C4591005) (Comirnaty Intravenous Injection [monovalent: original strain]) • Use-results survey in post-approval early vaccine recipients (healthcare professionals) (follow-up study) (C4591006) (Comirnaty Intravenous Injection [monovalent: original strain]) • Specified use-results survey in individuals with underlying diseases who are at high risk of severe COVID19 (C4591019) (Comirnaty Intravenous Injection [monovalent: original strain]) • Foreign phase II/III study (C4591001) (Comirnaty Intravenous Injection [monovalent: original strain]) • Foreign phase II/III study in pregnant women (C4591015) (Comirnaty Intravenous Injection [monovalent: original strain])	• Disseminate data gathered during early post-marketing phase vigilance (child vaccine recipients 5 to 11 years of age) • Disseminate data gathered during early post-marketing phase vigilance (vaccine recipients ≥12 years of age: RTU Intramuscular Injection [bivalent: original strain/Omicron BA.1 lineage]) • Organize and disseminate information for healthcare professionals • Organize and disseminate information (a brochure) for vaccine recipients • Organize and disseminate information (a brochure) for child vaccine recipients • Periodical publication of the occurrence of adverse reactions (child vaccine recipients 5 to 11 years of age) • Periodical publication of the occurrence of adverse reactions (vaccine recipients ≥12 years of age: RTU Intramuscular Injection [bivalent: original strain/Omicron BA.1 lineage])

Underlined parts: additions pursuant to the present application

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

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

The new drug application data were subjected to a document-based 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 booster dose with the bivalent vaccine has a certain level of efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19), and its safety is acceptable with no significant safety concerns. In view of its benefit/risk balance by considering the status of COVID-19 outbreaks and the risk factors in individuals, PMDA considers that it is clinically significant to make the booster dose with the variant-adapted bivalent vaccine available.

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 approval conditions. The re-

examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until February 13, 2029).

Indication

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

The indication applies to the following vaccine products:

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

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

(Underline denotes additions.)

Dosage and Administration

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

For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.

For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

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

For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

(Strikethrough denotes deletions. Underline denotes additions.)

Approval Conditions and Other Requirements

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

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) 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 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

Adverse reaction	Adverse event for which causal relation to the study vaccine cannot be ruled out
ALC-0159	2-[(polyethylene glycol)-2000]-N,N-ditetradecyclacetamide
ALC-0315	[(4-hydroxybutyl)azanediyl]bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
Bivalent vaccine	Bivalent vaccine containing tozinameran and riltozinameran (at an RNA mass ratio of 1:1)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CTD	Common technical document
ddPCR	Droplet digital polymerase chain reaction
DNA	Deoxyribonucleic acid
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
FDA	Food and Drug Administration
GCP	Good clinical practice
GMR	Geometric mean ratio
GMT	Geometric mean titer
ICMRA	International Coalition of Medicines Regulatory Authorities
LLOQ	Lower limit of quantitation
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
OMI monovalent vaccine	Monovalent vaccine containing riltozinameran
Original strain	Strain Wuhan-Hu-1
Parent vaccine	Monovalent vaccine containing tozinameran
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
qPCR	Quantitative polymerase chain reaction
Reference strain	Strain USA-WA1/2020
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S-protein	Spike protein
The vaccine product	Comirnaty RTU Intramuscular Injection
VOC	Variant of Concern
WHO	World Health Organization