Review Report

August 21, 2024
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Nuvaxovid Intramuscular Injection 1 mL
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	April 12, 2024
Dosage Form/Strength	Injection: Each vial contains 10 μg of SARS-CoV-2 rS.
Application Classification	Prescription drug; (4) Drug with new indications, (6) Drug with a new dosage, (8) Drug in an additional dosage form (during the re-examination period), (10-2) Other drugs (drugs including biological products which fall under the category [10] and whose manufacturing process is changed)
Items Warranting Special Mention	Applications and expedited review in accordance with "Handling of application for partial change approval of a drug and the review and investigation pertaining to the concerned application" (PSB/PED Notification No. 0318-1 dated March 18, 2024, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare). A prior assessment consultation was conducted on the product.
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of disease caused by Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) infection (COVID-19), and that the product has acceptable safety in view of its expected benefits (see Attachment).

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

Indication

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

(No change)

Dosage and Administration

Individuals aged ≥12 years

A single dose of 0.5 mL is injected intramuscularly.

Individuals aged ≥6 and <12 years

For the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 3 weeks apart.

(No change)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only limited information is available 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 plan, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product.
3. Results of clinical studies that are ongoing or planned in and outside of Japan should be submitted to PMDA promptly when they become available. At the same time, the applicant is required to take actions necessary to ensure that the updated efficacy and safety information on the product is easily accessible to healthcare professionals.
4. The efficacy and safety data of the product will be accrued 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.

Attachment

Review Report

August 21, 2024

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

Product Submitted for Approval

Brand Name	Nuvaxovid Intramuscular Injection 1 mL
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	April 12, 2024
Dosage Form/Strength	Injection: Each vial contains 10 μg of SARS-CoV-2 rS.

Proposed Indication

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

Applies to the following vaccine product:

- Vaccine product containing recombinant spike protein of SARS-CoV-2 (the Omicron variant)

(Underline denotes additions.)

Proposed Dosage and Administration

Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 3 weeks apart.

Booster dose: A single dose of 0.5 mL is injected intramuscularly.

Applies to the following vaccine product:

- Vaccine product containing recombinant spike protein of SARS-CoV-2 (the Omicron variant)

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

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

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

Nuvaxovid Intramuscular Injection is a vaccine containing SARS-CoV-2 recombinant spike protein (SARS-CoV-2 rS) produced using Sf9 cells as the active ingredient. It is supplemented with Matrix-M adjuvant, which is primarily composed of saponin. In Japan, a monovalent vaccine targeting the Wuhan-Hu-1 strain (original strain) (monovalent [Original] vaccine) was approved for marketing on April 19, 2022, with the indication for "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)," as a multidose vial vaccine product (10 doses per vial). The applicant has developed a monovalent vaccine targeting the SARS-CoV-2 Omicron JN.1 lineage (monovalent [Omicron JN.1] vaccine) as a multidose vial vaccine product (2 doses per vial) for supply during the fall-winter vaccination program in FY 2024. Based on the quality test results and non-clinical study data of the monovalent (Omicron JN.1) vaccine, as well as the quality test results, non-clinical study data, and clinical study data of vaccines targeting the SARS-CoV-2 Omicron BA.5 and XBB.1.5 lineages, the applicant submitted the application for marketing approval of the monovalent (Omicron JN.1) vaccine and the addition of the multidose vial vaccine product (2 doses per vial). Nuvaxovid has been developed with support from the "Vaccine development project" of the Japan Agency for Medical Research and Development and "Urgent improvement project for vaccine manufacturing systems" of the Ministry of Health, Labour and Welfare.

Outside of Japan, Nuvaxovid, as the monovalent (Original) vaccine, received conditional marketing authorization in Europe in December 2021 and Emergency Use Authorization in the United Stated (U.S.) in July 2022. The monovalent (Omicron XBB.1.5) vaccine was approved in both the U.S. and Europe in October 2023 and has been approved or authorized in over 40 countries or regions as of the end of July 2024. An application for the monovalent (Omicron JN.1) vaccine was submitted for

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

approval by Novavax in the U.S. and Europe in June 2024. However, as of the end of July 2024, no approval has been granted for it in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

The monovalent (Omicron JN.1) vaccine added by the present application contains SARS-CoV-2 rS of the SARS-CoV-2 Omicron JN.1 lineage as its active ingredient and is adjuvanted with Matrix-M, which is the same adjuvant as that of the monovalent (Original) vaccine. The monovalent (Original) vaccine is formulated with a labeled volume of 5 mL per vial, allowing for 10 doses per vial. In contrast, the monovalent (Omicron JN.1) vaccine is formulated with a labeled volume of 1 mL per vial, allowing for 2 doses per vial. Except for changes in the amino acid sequence of SARS-CoV-2 rS from the original SARS-CoV-2 strain to the Omicron JN.1 lineage, as well as changes in the vial size and the fill volume per vial, the active substance and vaccine product are manufactured using the same method as the monovalent (Original) vaccine. Prior to the development of the monovalent (Omicron JN.1) vaccine, the monovalent (Original) vaccine and monovalent (Omicron BA.5) vaccine formulated with a labeled volume of 1 mL were manufactured, and supporting data, including the comparability assessment of quality attributes, were submitted.

Based on the submitted data, PMDA conducted a review and confirmed that no particular issues were identified regarding the quality of the active substance and the vaccine product.

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

The applicant submitted data on primary pharmacodynamics of vaccines against the SARS-CoV-2 Omicron BA.5 lineage and the SARS-CoV-2 Omicron XBB.1.5 lineage, and the monovalent (Omicron JN.1) vaccine as non-clinical pharmacology data.

This section presents the study results on primary pharmacodynamics of the monovalent (Omicron JN.1) vaccine, which is the vaccine product submitted for approval.

3.1 Primary pharmacodynamics

3.1.1 Immunogenicity test in mice (CTD 4.2.1.1-1)

The immune response was evaluated in BALB/c mice (n = 20 females/group[2)]) following 2 doses of the monovalent (Omicron JN.1) vaccine[3)] administered at a 14-day interval as the primary series. One week after the second dose of the primary series, neutralizing antibody titers in serum were measured using a pseudovirus-based neutralization assay. The geometric mean titers (GMTs) of neutralizing antibodies against the original strain and Omicron sublineages (XBB.1.5 and HV.1) (50-56) were near the detection limit of the neutralization assay. In contrast, the GMTs of neutralizing antibodies against other Omicron sublineages (JN.1, JN.4, JN.1.11.1, JN.1.7, JN.1.13.1, JN.1.16, KP.2, KQ.1, KP.1.1, KP.3, and LA.2) (2,028-14,583) increased.

---

2) In the measurement of neutralizing antibody titers against each Omicron sublineages, specimens were obtained from 20 animals for Omicron sublineages XBB.1.5, HV.1, JN.1, JN.1.11.1, JN.1.7, and JN.1.13.1; 10 animals for Omicron sublineages JN.4, JN.1.16, KP.2, KQ.1, and KP.1.1; and 8 animals for Omicron sublineages KP.3 and LA.2.

3) On the day of vaccination, a formulation was prepared by mixing a solution containing SARS-CoV-2 rS with the Matrix-M adjuvant so that each 50 µL dose contained 1 µg of SARS-CoV-2 rS and 5 µg of the Matrix-M adjuvant, using 25 mM sodium phosphate (pH 7.2), 300 mM sodium chloride, and 0.01% polysorbate 80 as vehicle.

The immune response was evaluated in BALB/c mice (n = 20 female/group[4)]) following 2 doses of the monovalent (Omicron XBB.1.5) vaccine[3)] administered at a 14-day interval as the primary series, with a single booster dose of the monovalent (Omicron JN.1) vaccine given 2 months after the primary series. Two weeks after the booster dose, neutralizing antibody titers in serum were measured. The GMTs of neutralizing antibodies against all measured Omicron sublineages (XBB.1.5, HV.1, JN.1, JN.1.11.1, JN.1.7, JN.1.13.1, JN.1.16, KP.2, KQ.1, KP.1.1, KP.3, and LA.2) (928-46,668) increased.

3.1.2 Immunogenicity study in rhesus monkeys (CTD 4.2.1.1-2)

The immune response was evaluated in rhesus monkeys (5 animals/group, both male and female) following 2 doses of the monovalent (Omicron XBB.1.5) vaccine[5)] administered at a 21-day interval as the primary series. A single booster dose of the monovalent (Omicron XBB.1.5) vaccine was given 6 months after the primary series, followed by a single booster dose of the monovalent (Omicron JN.1) vaccine[5)] 11 months after the primary series. Two weeks after the second booster dose, neutralizing antibody titers in serum were measured using a pseudovirus-based neutralization assay. The GMTs of neutralizing antibodies against Omicron sublineages (XBB.1.5, HV.1, JN.1, JN.1.11.1, JN.1.7, JN.1.13.1, JN.1.16, KP.2, KQ.1, KP.1.1, KP.3, and LA.2) (1,841-13,394) increased.

3.R Outline of the review conducted by PMDA

The applicant explained that the results of immunogenicity studies in mice and rhesus monkeys demonstrate that administration of the monovalent (Omicron JN.1) vaccine induces neutralizing antibodies against the currently circulating Omicron sublineages and supports the use of the monovalent (Omicron JN.1) vaccine for the 2024/2025 season.

PMDA accepted the applicant’s explanation based on non-clinical pharmacology studies.

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

Although the present application relates to a new indication and the new dosage, the data related to non-clinical pharmacokinetics had been evaluated during the review process for the initial approval of Nuvaxovid Intramuscular Injection, and thus, no new data have been submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application relates to a new indication and a new dosage, and no data related to toxicity have been submitted.

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

No data related to biopharmaceutic studies and associated analytical methods and clinical pharmacology have been submitted in the present application. Regarding the immunogenicity assessment methods used in the submitted clinical studies in the present application, relevant details are provided in Section 7 as necessary.

---

4) In the measurement of neutralizing antibody titers against each Omicron sublineages, specimens were obtained from 20 animals for Omicron sublineages XBB.1.5, HV.1, JN.1, JN.1.11.1, JN.1.7, and JN.1.13.1; from 10 animals for Omicron sublineages JN.1.16, KP.2, KQ.1, and KP.1.1; and from 8 animals for Omicron sublineages KP.3 and LA.2.

5) Each 500 µL dose was formulated to contain 5 µg of SARS-CoV-2 rS and 50 µg of the Matrix-M adjuvant, using 25 mM sodium phosphate (pH 7.2), 300 mM sodium chloride, and 0.01% polysorbate 80 as vehicle.

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

The applicant submitted efficacy and safety evaluation data on the monovalent (Omicron JN.1) vaccine from 2 studies shown in Table 1. Study 2019nCoV-311 (Study 311) consisted of Part 1, which evaluated the immunogenicity and safety of a vaccine against the SARS-CoV-2 Omicron BA.1 lineage, and Part 2, which evaluated the immunogenicity and safety of a vaccine against the SARS-CoV-2 Omicron BA.5 lineage. For the present application, the study results related to Part 2 were submitted. Study 2019nCoV-313 (Study 313), which aimed to evaluate the immunogenicity and safety of a vaccine against the SARS-CoV-2 Omicron XBB.1.5 lineage, consisted of Part 1, targeting individuals previously vaccinated with a messenger RNA (mRNA) SARS-CoV-2 vaccine, and Part 2, targeting individuals with a history of SARS-CoV-2 infection who have not received a SARS-CoV-2 vaccine. For the present application, the study results related to Part 1 were submitted.

Table 1. Outline of clinical studies

Country	Study	Phase	Population	No. of subjects enrolled	Dosage regimen	Study objectives
Australia	Study 2019nCoV-311, Part 2	III	Individuals aged ≥18 years who had received at least 3 doses of mRNA vaccine[a)] who received their last vaccination at least 90 days ago	766	Intramuscular administration of the monovalent (Omicron BA.5) vaccine, the monovalent (Original) vaccine, or the bivalent (Original/Omicron BA.5) vaccine, 2 doses at a 90-day interval	Safety Immunogenicity
U.S.	Study 2019nCoV-313, Part 1	II/III	Individuals aged ≥18 years who had received at least 3 doses of mRNA vaccine[a)] who received their last vaccination at least 90 days ago	332	A single intramuscular dose of the monovalent (Omicron XBB.1.5) vaccine	Safety Immunogenicity

a) Mono- or bivalent Comirnaty or Spikevax vaccine

7.1 Foreign phase III study (CTD 5.3.5.1-1, Study 2019nCoV-311 Part 2; Study Period, ongoing since March 2023 [data cutoff date, May 31, 2023])

A randomized, observer-blinded,[6)] parallel-group study was conducted at 21 study sites in Australia to evaluate the immunogenicity and safety of the monovalent (Omicron BA.5) vaccine, the monovalent (Original) vaccine, and the bivalent (Original/Omicron BA.5) vaccine in individuals aged ≥18 years,[7)] who had received at least 3 doses of Comirnaty or Spikevax (either monovalent or bivalent vaccines) and who received their last vaccination at least 90 days ago (target sample size, approximately 750 subjects [about 250 per group])[8)].

The monovalent (Omicron BA.5) vaccine, the monovalent (Original) vaccine, or the bivalent (Original/Omicron BA.5) vaccine was administered intramuscularly twice at a 90-day interval.[9)]

Of 766 randomized subjects[10)] (255 in the monovalent [Omicron BA.5] vaccine group, 252 in the monovalent [Original] vaccine group, 259 in the bivalent [Original/Omicron BA.5] vaccine group), 764 subjects received the study vaccine. The remaining 1 subject each in the monovalent (Omicron BA.5) and monovalent (Original) vaccine groups was excluded. These 764 subjects were included in the safety analysis set and the full analysis set (FAS). Among the FAS, 694 subjects (236 in the monovalent [Omicron BA.5] vaccine group, 227 in the monovalent [Original] vaccine group, 231 in the bivalent [Original/Omicron BA.5] vaccine group) were included in the per-protocol analysis set (PPAS),[11)] and the following subjects were excluded from the analysis: 18 subjects in the monovalent (Omicron BA.5) vaccine group, 24 subjects in the monovalent (Original) vaccine group, and 28 subjects in the bivalent (Original/Omicron BA.5) vaccine group.[12)] The PPAS served as the primary population for the immunogenicity analysis.

---

6) The study vaccine preparers and administrators at the study sites, as well as the unblinded project team (project managers and clinical development monitors) and biostatisticians at the contract research organization (blinded until 28 days after administration of the study vaccine and unblinded at the time of statistical analysis), were unblinded. Other study site personnel (including evaluators [investigators] and study vaccine administrators) and personnel from the contract research organization, as well as the study sponsor, remained blinded.

7) Subjects were medically stable men and women aged ≥18 years (women had to be non-pregnant). Medical stability was assessed at screening by the investigator based on health status, vital signs, medical history, and physical examination.

8) The primary objectives of this study were to demonstrate the superiority of the bivalent (Original/Omicron BA.5) vaccine over the monovalent (Original) vaccine in terms of neutralizing antibody titers against SARS-CoV-2 Omicron BA.5 lineage and to confirm non-inferiority in terms of neutralizing antibody titers against SARS-CoV-2 original strain and antibody response rate for neutralizing antibodies against SARS-CoV-2 Omicron BA.5 lineage. The following verification hypotheses were established. Assuming a one-sided significance level of 2.5% for the entire study and a 10% proportion of unevaluable subjects, with 250 subjects per vaccination group, the overall study power was approximately 89%.
   - Superiority of GMT for neutralizing antibodies against SARS-CoV-2 Omicron BA.5 lineage: Assuming ratio of GMT (GMTR) of 1.5, log-transformed standard deviation of neutralizing antibody titers of 0.5, and a superiority margin of 1.0.
   - Non-inferiority of antibody response rate for neutralizing antibody against SARS-CoV-2 Omicron BA.5 lineage: Assuming an antibody response rate for neutralizing antibodies of 50% for the bivalent (Original/Omicron BA.5) vaccine group, 28% for the monovalent (Original) vaccine group, and a non-inferiority margin of 5%.
   - Non-inferiority of GMT for neutralizing antibodies against SARS-CoV-2 original strain: Assuming GMTR of 1.0, log-transformed standard deviation of neutralizing antibody titers of 0.5, and a non-inferiority margin of 0.67.

9) The study was designed to include 2 vaccinations at a 90-day interval. However, an interim analysis was planned once the necessary data were obtained for evaluating the primary endpoint at 28 days after the first dose of the study vaccine. The results of this interim analysis were submitted in the present application.

10) Subjects were randomized at each study site using stratification factors of 18-54 years and ≥55 years (≥55 years was 25% of the target sample size).

11) Among the FAS, most subjects reported no prior history of COVID-19. However, the proportion of subjects who tested positive for anti-N antibodies or SARS-CoV-2 polymerase chain reaction (PCR) at screening was 76.0% in the monovalent (Omicron BA.5) vaccine group, 73.3% in the monovalent (Original) vaccine group, and 79.5% in the bivalent (Original/Omicron BA.5) vaccine group. Subjects who were not classified as having a history of COVID-19 or who were not positive for SARS-CoV-2 PCR before administration of the study vaccine were included in the PPAS.

12) Subjects were excluded if they tested positive for SARS-CoV-2 by PCR at baseline (before administration of the study vaccine), had a prior history of COVID-19 before visiting the study site, had a significant protocol deviation, or had missing analysis results.

The primary immunogenicity endpoints were (1) the GMT of serum anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibodies (assessed using a pseudovirus neutralization assay); (2) the antibody response rate (defined as the proportion of subjects whose antibody titer at the assessment time point increased ≥4-fold from baseline [or from the lower limit of quantification (LLOQ) if the baseline value was below this threshold]); and (3) the GMT of serum anti-SARS-CoV-2 (original strain) neutralizing antibodies (assessed using a pseudovirus neutralization assay) on Day 28 after the first dose of the study vaccine. The primary analysis focused on the monovalent (Original) and bivalent (Original/Omicron BA.5) vaccine groups. The superiority and non-inferiority of the bivalent (Original/Omicron BA.5) vaccine compared to the monovalent (Original) vaccine were assessed based on the ratio of GMT (GMTR) (bivalent [Original/Omicron BA.5] vaccine/monovalent [Original] vaccine) and the difference in antibody response rates (bivalent [Original/Omicron BA.5] vaccine − monovalent [Original] vaccine). The criteria for superiority and non-inferiority were defined as shown below, and the study was considered successful if all 3 criteria were met (overall study significance level controlled at one-sided 2.5%):

- GMT of anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibodies: The lower bound of the 2-sided 95% confidence interval (CI) for GMTR exceeds the superiority threshold of 1.0.
- Antibody response rate for neutralizing antibodies against SARS-CoV-2 (Omicron BA.5 lineage): The lower bound of the 2-sided 95% CI for the difference in antibody response rates exceeds the non-inferiority threshold of −5%.
- GMT of anti-SARS-CoV-2 (original strain) neutralizing antibodies: The lower bound of the 2-sided 95% CI for GMTR exceeds the non-inferiority threshold of 0.67.

The primary immunogenicity analysis results are shown in Table 2. The lower bounds of the 2-sided 95% CI for GMTR exceeded the predefined thresholds, and the lower bound of the 2-sided 95% CI for the difference in antibody response rates exceeded the predefined threshold (−5%). The bivalent (Original/Omicron BA.5) vaccine was thus demonstrated to be superior to the monovalent (Original) vaccine in terms of the GMT of anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibodies, and its non-inferiority in terms of the antibody response rate as well as non-inferiority in terms of the GMT of anti-SARS-CoV-2 (original strain) neutralizing antibodies were shown.

Table 2. Neutralizing antibody titers and antibody response rates against SARS-CoV-2 (Omicron BA.5 lineage/original strain) in serum on Day 28 after the first dose of the study vaccine (Study 311 Part 2, PPAS)

	Omicron BA.5 lineage		Original strain	
	Bivalent (Original/Omicron BA.5) vaccine N = 231	Monovalent (Original) vaccine N = 227	Bivalent (Original/Omicron BA.5) vaccine N = 231	Monovalent (Original) vaccine N = 227
GMT				
n1	231	227	231	227
Adjusted GMT [2-sided 95% CI][a)]	1017.8 [891.0, 1162.6]	515.1 [450.4, 589.0]	2211.1 [1932.9, 2529.3]	2205.6 [1926.4, 2525.1]
GMTR [2-sided 95% CI][a)] Bivalent (Original/Omicron BA.5) vaccine/monovalent (Original) vaccine	2.0 [1.69, 2.33]		1.0 [0.84, 1.20]	
Antibody response rate				
n3/n2	92/231	28/227	54/230	52/227
Antibody response rate (%) [2-sided 95% CI][b)]	39.8 [33.5, 46.5]	12.3 [8.4, 17.3]	23.5 [18.2, 29.5]	22.9 [17.6, 28.9]
Difference in antibody response rate (%) [2-sided 95% CI][c)] Bivalent (Original/Omicron BA.5) vaccine − monovalent (Original) vaccine	27.5 [19.8, 35.0]		0.6 [−7.2, 8.3]	

N, Number of subjects analyzed; n1, Number of subjects with available immunogenicity data; n2, Number of subjects with available immunogenicity data both before and after the study vaccination; n3, Number of subjects who met the criteria for antibody response (≥4-fold increase from the baseline value [if the baseline value was below the LLOQ, the LLOQ was used as the baseline value]).
In the calculation of GMT and GMTR, when antibody titers were below the LLOQ, a value of 0.5 × LLOQ was used in the analysis; when actual measured values were not available due to antibody titers exceeding the upper limit of quantification (ULOQ), the ULOQ value was used in the analysis. (Quantification range [LLOQ-ULOQ]: 36-15,856 [Omicron BA.5 lineage], 42-14,863 [original strain])

a) Analysis of covariance (ANCOVA) was performed using neutralizing antibody titers after the study vaccination (log-transformed values) as the response variable, vaccination group and age group (18-54 years/≥55 years) as fixed effects, and baseline neutralizing antibody titers (log-transformed values) as a covariate.
b) Two-sided 95% CIs were calculated based on the Clopper-Pearson method.
c) Two-sided 95% CIs were calculated based on the Miettinen-Nurminen method.

The definition of safety observation periods was as follows[13)]:

- Solicited adverse events (local [pain, tenderness, redness, and swelling] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after each dose of the study vaccine (from the day of study vaccination to 6 days post-vaccination).[14)]
- Unsolicited adverse events were collected until Day 28 after each dose of the study vaccine.
- Adverse events requiring treatment were collected until Day 28 after each dose of the study vaccine (up to 270 days after the first dose [end of study] for events considered causally related to the study vaccine).
- Serious adverse events and adverse events of special interest (AESI) were collected for 270 days after the first dose of the study vaccine (end of study).

Table 3 shows the solicited adverse events observed within 7 days after the first dose of the study vaccine.

13) The severity of adverse events was assessed based on the Food and Drug Administration (FDA) guidance (Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007). Solicited adverse events were evaluated based on the criteria established with reference to the relevant guidance.
14) Events that persisted at Grade ≥1 beyond 7 days post-vaccination were collected as unsolicited adverse events starting from 7 days post-vaccination until resolution.

Table 3. Solicited adverse events observed within 7 days after the study vaccination (Study 311 Part 2, safety analysis population)

Event	Bivalent (Original/Omicron BA.5) vaccine N = 259		Monovalent (Original) vaccine N = 251		Monovalent (Omicron BA.5) vaccine N = 254	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local (all events)	169 (65.3)	2 (0.8)	168 (66.9)	2 (0.8)	153 (60.7)	4 (1.6)
Pain	98 (37.8)	2 (0.8)	98 (39.0)	0	83 (32.9)	3 (1.2)
Tenderness	153 (59.1)	1 (0.4)	149 (59.4)	2 (0.8)	140 (55.6)	1 (0.4)
Redness	6 (2.3)	0	8 (3.2)	0	5 (2.0)	0
Swelling	6 (2.3)	0	6 (2.4)	0	8 (3.2)	0
Systemic (all events)	155 (59.8)	10 (3.9)	139 (55.4)	10 (4.0)	142 (56.3)	5 (2.0)
Pyrexia[a)]	4 (1.5)	1 (0.4)	2 (0.8)	0	2 (0.8)	0
Fatigue	88 (34.0)	8 (3.1)	94 (37.5)	7 (2.8)	97 (38.5)	2 (0.8)
Malaise	36 (13.9)	4 (1.5)	42 (16.7)	3 (1.2)	48 (19.0)	3 (1.2)
Myalgia	67 (25.9)	2 (0.8)	71 (28.3)	2 (0.8)	59 (23.4)	1 (0.4)
Nausea/vomiting	19 (7.3)	0	18 (7.2)	0	19 (7.5)	1 (0.4)
Arthralgia	19 (7.3)	1 (0.4)	20 (8.0)	1 (0.4)	18 (7.1)	0
Headache	74 (28.6)	3 (1.2)	73 (29.1)	2 (0.8)	73 (29.0)	4 (1.6)

N, Number of subjects analyzed; n, Number of subjects with events; a) ≥38.0°C (Grade 3, 39.0°C to 40°C) (oral)

Table 4 shows the unsolicited adverse events observed in ≥1% of subjects in any group by Day 28 after the study vaccination, as well as those classified as adverse reactions. Severe unsolicited adverse events were observed in 3 of 259 subjects (1.2%) in the bivalent (Original/Omicron BA.5) vaccine group (limb injury, pelvic pain, and diarrhoea in 1 subject each) and in 1 of 254 subjects (0.4%) in the monovalent (Omicron BA.5) vaccine group (immune response). The event of diarrhoea in the bivalent (Original/Omicron BA.5) vaccine group was determined by the investigator to be related to the study vaccine.

Table 4. Unsolicited adverse events and adverse reactions observed in ≥1% of subjects in any group by Day 28 after the study vaccination (Study 311 Part 2, safety analysis population)

	Adverse events			Adverse reactions		
	Bivalent (Original/ Omicron BA.5) vaccine N = 259	Monovalent (Original) vaccine N = 251	Monovalent (Omicron BA.5) vaccine N = 254	Bivalent (Original/ Omicron BA.5) vaccine N = 259	Monovalent (Original) vaccine N = 251	Monovalent (Omicron BA.5) vaccine N = 254
Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All events	58 (22.4)	64 (25.5)	54 (21.3)	8 (3.1)	5 (2.0)	3 (1.2)
Upper respiratory tract infection	14 (5.4)	11 (4.4)	8 (3.1)	1 (0.4)	0	0
COVID-19	6 (2.3)	6 (2.4)	4 (1.6)	0	0	0
Lymphadenopathy	3 (1.2)	2 (0.8)	0	3 (1.2)	2 (0.8)	0
Nasopharyngitis	3 (1.2)	1 (0.4)	0	0	0	0
Headache	2 (0.8)	4 (1.6)	5 (2.0)	0	0	1 (0.4)
Gastroenteritis	2 (0.8)	0	3 (1.2)	0	0	0
Oropharyngeal pain	1 (0.4)	4 (1.6)	1 (0.4)	0	0	0
Influenza like illness	1 (0.4)	2 (0.8)	4 (1.6)	0	0	0
Cough	1 (0.4)	1 (0.4)	4 (1.6)	0	0	0

N, Number of subjects analyzed; n, Number of subjects with events; Medical Dictionary for Regulatory Activities (MedDRA) version 25.0

As of the data cutoff date (May 31, 2023), serious adverse events were reported in 1 subject in the bivalent (Original/Omicron BA.5) vaccine group (limb injury), 1 subject in the monovalent (Original) vaccine group (overdose), and 4 subjects in the monovalent (Omicron BA.5) vaccine group (acute coronary syndrome, acute myocardial infarction, non-cardiac chest pain, and IVth nerve paralysis in 1

subject each). The event of IVth nerve paralysis in the monovalent (Omicron BA.5) vaccine group was determined by the physician to be related to the study vaccine.

No adverse events leading to death or study discontinuation were reported as of the data cutoff date.

7.2 Foreign Phase II/III Study (CTD 5.3.5.1-2, Study 2019nCoV-313, Part 1; Study period, ongoing since September 2023 [Data cutoff date, October 16, 2023])

An open-label study was conducted at 30 study sites in the U.S. to evaluate the immunogenicity and safety of the monovalent (Omicron XBB.1.5) vaccine in subjects aged ≥18 years who had received at least 3 doses of either the monovalent or bivalent Comirnaty or Spikevax vaccine and who received their last vaccine dose ≥90 days earlier[7)] (target sample size, approximately 330 subjects[15)])

The monovalent (Omicron XBB.1.5) vaccine was administered intramuscularly in a single dose.

All of 332 enrolled subjects received the study vaccine, and all 332 subjects who received the study vaccine were included in both the safety analysis set and the FAS. Of the FAS, 309 subjects were included in the PPAS, and the remaining 23 subjects were excluded from the analysis.[16)] The PPAS were the primary population for the immunogenicity analysis.

The primary immunogenicity endpoints were the GMT of serum anti-SARS-CoV-2 (Omicron XBB.1.5 lineage) neutralizing antibodies (assessed using a pseudovirus neutralization assay) and the antibody response rate (defined as the proportion of subjects whose antibody titer increased by ≥4-fold from baseline [LLOQ for those below the detection limit]) on Day 28 after the study vaccination. The primary analysis was designed to evaluate the superiority and non-inferiority of the monovalent (Omicron XBB.1.5) vaccine compared to the monovalent (Original) vaccine from Study 311 Part 2, based on the GMTR of neutralizing antibodies (monovalent [Omicron XBB.1.5] vaccine/monovalent [Original] vaccine) and the difference in antibody response rates (monovalent [Omicron XBB.1.5] vaccine – monovalent [Original] vaccine). The criteria for superiority and non-inferiority were as shown below, and the study was considered successful if both criteria were met (overall one-sided significance level controlled at 2.5%).

- For the GMT of anti-SARS-CoV-2 (Omicron XBB.1.5 lineage) neutralizing antibodies, the lower bound of the 2-sided 95% CI for GMTR must exceed the superiority margin of 1.0.
- For the antibody response rate for neutralizing antibodies against SARS-CoV-2 (Omicron XBB.1.5 lineage), the lower bound of the 2-sided 95% CI for the difference in antibody response rates must exceed the non-inferiority margin of −10%.

The results of the primary immunogenicity endpoints are shown in Table 5. As both the lower bounds of the 2-sided 95% CI for GMTR and the difference in antibody response rates exceeded the

15) The primary endpoints of this study were the superiority (neutralizing antibody titer against Omicron XBB.1.5) and non-inferiority (antibody response rate against Omicron XBB.1.5) of the monovalent (Omicron XBB.1.5) vaccine compared to the monovalent (Original) vaccine (monovalent [Original] vaccine group in Study 311 Part 2). The standard deviation of the log-transformed neutralizing antibody titer was assumed to be 0.6, with an overall one-sided significance level of 2.5% and an assumed proportion of subjects who were an unevaluable set at 25% of the total. With a target sample size of 330 subjects, the power to demonstrate both superiority for GMT (superiority margin of 1.0) and non-inferiority for the antibody response rate (non-inferiority margin of 10%) was at least 95%.

16) Subjects who had significant deviations from the clinical study protocol and those who tested positive for SARS-CoV-2 by PCR at baseline (before the study vaccination) were excluded.

predefined criteria, the superiority of the monovalent (Omicron XBB.1.5) vaccine over the monovalent (Original) vaccine in terms of GMT of anti-SARS-CoV-2 (Omicron BA.5 lineage) neutralizing antibodies and its non-inferiority in terms of antibody response rate were demonstrated.

Table 5. Neutralizing antibody titer and antibody response rate against SARS-CoV-2 (Omicron XBB.1.5 lineage) in serum on Day 28 after the study vaccination (Study 313 Part 1, PPAS).

	Study 313 Part 1	Study 311 Part 2
	Monovalent (Omicron XBB.1.5) vaccine N = 309	Monovalent (Original) vaccine N = 227
GMT		
n1	305	227
Adjusted GMT [2-sided 95% CI][a)]	905.9 [807.1, 1016.8]	156.6 [137.0, 179.0]
GMTR [2-sided 95% CI][a)] (monovalent [Omicron XBB.1.5] vaccine/monovalent [Original] vaccine)	5.8 [4.85, 6.91]	
Antibody response rate		
n2	196	16
Antibody response rate (%) [2-sided 95% CI][b)]	64.3 [58.6, 69.6]	7.0 [4.1, 11.2]
Difference in antibody response rates (%) [2-sided 95% CI][c)] (monovalent [Omicron XBB.1.5] vaccine − monovalent [Original] vaccine)	57.2 [50.5, 63.2]	

N, Number of subjects analyzed; n1, Number of subjects with immunogenicity data available both before and after the study vaccination; n2, Number of subjects who met the criteria for antibody response (≥4-fold increase from the baseline value [if the baseline value was below the LLOQ, the LLOQ was used as the baseline value]).
In the calculation of GMT and GMTR, when antibody titers were below the LLOQ, a value of 0.5 × LLOQ was used in the analysis; when actual measured values were not available due to antibody titers exceeding the ULOQ, the ULOQ value was used in the analysis. (Quantification range [LLOQ-ULOQ]: 37-7,561 [Omicron XBB.1.5 lineage])

a) ANCOVA was performed using post-vaccination neutralizing antibody titers (log-transformed values) as the response variable, vaccination group as a fixed effect, and baseline neutralizing antibody titers (log-transformed values) as a covariate.
b) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
c) Two-sided 95% CI was calculated based on the Miettinen-Nurminen method.

The definition of safety observation periods was as follows[13)]:

- Solicited adverse events (local [pain, tenderness, redness, and swelling] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after the study vaccination (from the day of study vaccination to 6 days post-vaccination).[14)]
- Unsolicited adverse events were collected until Day 28 after vaccination.
- Adverse events requiring treatment were collected until Day 28 after vaccination (up to 180 days after the study vaccination [end of study] for events considered causally related to the study vaccine).
- Serious adverse events and AESI were collected for 180 days after the vaccination (end of study).

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

Table 6. Solicited adverse events observed within 7 days after the study vaccination (Study 313 Part 1, safety analysis set).

Event	Monovalent (Omicron XBB.1.5) vaccine N = 332	
	All grades	Grade ≥3
	n (%)	n (%)
Local reactions (all events)	189 (56.9)	1 (0.3)
Pain	98 (29.5)	0
Tenderness	171 (51.5)	1 (0.3)
Redness	6 (1.8)	0
Swelling	4 (1.2)	0
Systemic (all events)	158 (47.6)	4 (1.2)
Pyrexia[a)]	2 (0.6)	0
Fatigue	97 (29.2)	1 (0.3)
Malaise	54 (16.3)	3 (0.9)
Myalgia	97 (29.2)	1 (0.3)
Nausea/vomiting	25 (7.5)	0
Arthralgia	39 (11.7)	0
Headache	74 (22.3)	2 (0.6)

N, Number of subjects analyzed; n, Number of subjects with events
a) ≥38.0°C (Grade 3, 39.0°C to 40°C) (oral)

Table 7 shows unsolicited adverse events that occurred in ≥2 subjects within 28 days after the study vaccination, and the subset classified as adverse reactions.

Table 7. Unsolicited adverse events and adverse reactions observed in multiple subjects within 28 days after the study vaccination (Study 313 Part 1, safety analysis set)

	Monovalent (Omicron XBB.1.5) vaccine N = 332	
	Adverse events	Adverse reactions
Adverse events/adverse reactions	n (%)	n (%)
All events (reactions)	29 (8.7)	5 (1.5)
COVID-19	5 (1.5)	0
Hypertension	2 (0.6)	1 (0.3)
Tooth abscess	2 (0.6)	0
Migraine	2 (0.6)	0
Cough	2 (0.6)	0

N, Number of subjects analyzed; n, Number of subjects with events; MedDRA Version 26.0

As of the data cut-off date (October 16, 2023), serious adverse events were reported in 2 subjects (gastrointestinal stromal tumor and appendiceal abscess in 1 subject each, both severe). Both events were assessed by the investigator as unrelated to the study vaccination.

No adverse events leading to death or study discontinuation were reported as of the data cut-off date.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and review policy

The applicant’s explanation about the clinical data package for primary series and booster dose with the Omicron variant-adapted vaccine:

Initially, SARS-CoV-2 was the original strain (Wuhan strain) at the beginning of the pandemic, but frequent mutations in the SARS-CoV-2 gene led to the emergence of the Omicron variant, which became globally dominant in 2022. The antigenic changes from the original strain have been reported to enable the Omicron variant to evade immunity induced by existing vaccines (*Nat Microbiol.* 2022;7:1161-79.). Even for the approved monovalent (Original) vaccines based on the original strain,

the third or fourth dose increases cross-reactivity against Omicron variants BA.1 and BA.4-5 (*N Engl J Med.* 2023;388:857-59.). While booster dose is expected to restore a certain level of efficacy, new variants may continue to emerge. Given the ongoing international discussion on the necessity of variant-adapted vaccines,[17)] ensuring sufficient immune protection requires the development of vaccines tailored to emerging variants. On October 3, 2023, Novavax was granted an Emergency Use Authorization in the U.S. for an Omicron XBB.1.5-adapted vaccine for individuals aged ≥12 years, allowing its use for both primary series and booster dose. Novavax and the applicant continue to monitor circulating strains and prepare pre-master seeds for potential vaccine production against variants of concern for epidemic. For the fall-winter vaccination campaign in FY 2024, the selected strain for vaccine manufacturing was determined to be the SARS-CoV-2 Omicron JN.1 lineage.

Regarding the regulatory approval process for strain changes in COVID-19 vaccines, the platform approach[17)] was proposed at the COVID-19 Omicron variant workshop held by the International Coalition of Medicines Regulatory Authorities (ICMRA) on May 8, 2023. The platform approach is shown as follows: If the efficacy, safety, and quality of the vaccine at the time of strain change is reasonably predictable the basic technology for the vaccine production is considered to be established; and in this case, the approval of an updated vaccine is allowed by confirming non-clinical and quality study data at the time of the strain change for currently approved vaccines. In Japan, the only approved formulation of Nuvaxovid is a monovalent (Original) vaccine. In the present application for the marketing of a monovalent (Omicron JN.1) vaccine adapted to the SARS-CoV-2 Omicron JN.1 lineage, the impacts of strain changes on the efficacy, safety, and quality of the vaccine were evaluated through non-clinical, clinical, and quality studies using monovalent (Omicron BA.5) and monovalent (Omicron XBB.1.5) vaccines. The applicant explained that the efficacy, safety, and quality of the monovalent (Omicron JN.1) vaccine would be predictable from the above results. In addition to the data, based on the non-clinical and quality data for the monovalent (Omicron JN.1) vaccine, the efficacy and safety of the vaccine was evaluated.

Both Study 311 Part 2 and Study 313 Part 1 were conducted in subjects aged ≥18 years. However, according to the “Principles for the Evaluation of Vaccines Against Novel Coronavirus SARS-CoV-2 (Appendix 1): Evaluation of vaccines against variants)” (Office of Vaccines and Blood Products, PMDA, dated April 5, 2021) (hereinafter referred to as “Appendix 1”), the results of clinical study evaluating the efficacy of a variant-adapted vaccine in a single age group can generally be extrapolated into other age groups in which the parent vaccine is approved. Furthermore, in previous clinical studies of monovalent (Original) vaccines, similar immunogenicity was observed between primary series and booster dose, with no significant differences in the safety profile. It was thus deemed that the efficacy and safety of variant-adapted vaccines could be explained for primary series in individuals aged ≥6 years and for booster dose in individuals aged ≥12 years.

In light of these considerations, the present application was submitted using the clinical data package, including data from Study 311 Part 2, a foreign phase III clinical study evaluating the immunogenicity and safety of the monovalent (Omicron BA.5) and bivalent (Original/Omicron BA.5) vaccines, and

17) https://icmra.info/drupal/en/covid-19/8may2023 (last accessed on August 21, 2024)

Study 313 Part 1, a foreign phase II/III clinical study evaluating the immunogenicity and safety of the monovalent (Omicron XBB.1.5) vaccine.

PMDA's view on the review policy for the present application:
Since January 2020, multiple therapeutic drugs and vaccines for COVID-19 have been developed, and various infection control measures, including vaccination, have been implemented. However, due to mutations in the SARS-CoV-2 gene, variants with altered infectivity, transmissibility, antigenicity, and pathogenicity have continuously emerged, leading to recurrent waves of SARS-CoV-2 outbreaks. On May 5, 2023, the WHO declared the end of the Public Health Emergency of International Concern caused by COVID-19.[18)] In Japan, on May 8, 2023, the category of COVID-19 under the Infectious Diseases Control Act was reclassified from "pandemic influenza (novel influenza or re-emerging influenza)" (equivalent to Class II) to "Class V infectious disease."[19)] Nevertheless, SARS-CoV-2 variants with altered infectivity and transmissibility continue to emerge, causing intermittent pandemics. From FY 2024 onward, SARS-CoV-2 vaccination is to be conducted as a routine vaccination (for category B diseases) for elderly individuals and other high-risk populations.[20)] From a public health perspective, the continued supply of effective SARS-CoV-2 vaccines against circulating variants remains necessary.

At the COVID-19 Omicron variant workshop[17)] held by ICMRA on May 8, 2023, a consensus was reached among regulatory authorities on the utilization of the platform approach. The applicant's policy of obtaining approval for SARS-CoV-2 vaccines adapted to emerging variants using the platform approach is acceptable. Thus, although no clinical study has been conducted using the monovalent (Omicron JN.1) vaccine, the efficacy, safety, and quality of the vaccine with strain change are predictable from clinical study results, non-clinical study results, and quality testing results for vaccines adapted to the Omicron BA.5 and Omicron XBB.1.5 lineages. The feasibility of the platform approach was confirmed, and the quality testing results and non-clinical study results of the monovalent (Omicron JN.1) vaccine were reviewed to evaluate its efficacy and safety.

The present application aims to enable primary series with the monovalent (Omicron JN.1) vaccine for individuals aged ≥6 years and booster dose for individuals aged ≥12 years. The submitted clinical studies were all booster dose studies conducted in subjects aged ≥18 years, and there were no study results available for primary series using a variant-adapted vaccine or for variant-adapted vaccines in subjects aged <18 years. However, given high SARS-CoV-2 vaccination coverage and the substantial increase in the number of individuals with prior infection due to repeated COVID-19 outbreaks, the number of SARS-CoV-2 vaccine-naïve individuals and SARS-CoV-2 infection-naïve individuals has become limited (Number of COVID-19 Vaccine Doses Administered [Published on April 1, 2024],[21)] Survey on the Proportion of Individuals with COVID-19 Antibodies[22)]). Under the current

18) https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic (last accessed on August 21, 2024)
19) Ministerial Ordinance to Partially Revise the Ordinance for Enforcement of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Ministry of Health, Labour and Welfare Ordinance No. 74, dated April 28, 2023)
20) Notice on COVID-19 Vaccination from FY 2024 Onward (in Japanese) (Administrative Notice, dated November 22, 2023, by the Vaccination Division, Department of Infectious Disease Prevention and Control, Public Health Bureau, Ministry of Health, Labour and Welfare)
21) https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/yobou-sesshu/syukeihou_00002.html (last accessed on August 21, 2024)
22) https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00132.html (last accessed on August 21, 2024)

circumstances, conducting studies on primary series with SARS-CoV-2 vaccines is challenging. Given these factors and Appendix 1, the approach proposed by the applicant is understandable. Given that variant-adapted vaccines have been available for primary series in Japan since FY 2023, allowing primary series with the variant-adapted Nuvaxovid is reasonable and clinically meaningful. The present application was reviewed based on the submitted 2 clinical studies and non-clinical study results.

7.R.2 Efficacy

The applicant's explanation about the efficacy of the monovalent (Omicron JN.1) vaccine:
In Japan, the methodology for evaluating vaccines against SARS-CoV-2 variants is outlined in the document titled "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 4): Immunogenicity-based evaluation of variant-adapted vaccines modified from parent vaccines and booster vaccines with new active ingredients" (Office of Vaccines and Blood Products, PMDA, dated July 15, 2022) (hereinafter referred to as "Appendix 4"). According to Appendix 4, the efficacy of a variant-adapted vaccine administered as a booster dose should be evaluated based on the GMT of neutralizing antibodies and the antibody response rate against the variant strain, which serve as co-primary endpoints. The superiority or non-inferiority of the variant-adapted vaccine to the parent vaccine should be demonstrated for each endpoint. In Study 311 Part 2 and Study 313 Part 1, the immunogenicity of vaccines against variant strains was evaluated in accordance with Appendix 4. The efficacy of each variant-adapted vaccine was assessed based on the results of these studies.

Study 311 Part 2

Study 311 Part 2 included subjects aged ≥18 years who had received at least 3 doses (primary series + at least 1 booster dose) of an approved mRNA SARS-CoV-2 vaccine (Comirnaty or Spikevax) and who received their last vaccination ≥3 months ago. The study compared the immune responses to either the bivalent (Original/Omicron BA.5) or the monovalent (Original) vaccine administered. The results demonstrated that the GMTR and the difference in antibody response rate against SARS-CoV-2 Omicron BA.5 lineage or the original strain at Day 28 after the study vaccination met the predefined criteria for superiority and non-inferiority [see Section 7.1].

Table 8 shows the results of neutralizing antibody titers before and after the study vaccination in Study 311 Part 2, including the immunogenicity evaluation of the monovalent (Omicron BA.5) vaccine, which was selected as an exploratory endpoint. A greater increase in neutralizing antibodies against the Omicron BA.5 lineage was observed in subjects who had received the bivalent (Original/Omicron BA.5) vaccine or the monovalent (Omicron BA.5) vaccine than in subjects who had received the monovalent (Original) vaccine.

Table 8. Neutralizing antibody titers and antibody response rates against SARS-CoV-2 (Omicron BA.5 lineage/original strain) in serum (Study 311 Part 2, PPAS)

	Omicron BA.5 lineage			Original strain		
	Bivalent (Original/Omicron BA.5) vaccine N = 231	Monovalent (Original) vaccine N = 227	Monovalent (Omicron BA.5) vaccine N = 236	Bivalent (Original/Omicron BA.5) vaccine N = 231	Monovalent (Original) vaccine N = 227	Monovalent Omicron (BA.5) vaccine N = 236
GMT						
Baseline (before study vaccination)						
n1	231	227	236	230	227	236
GMT [2-sided 95% CI][a)]	293.3 [237.3, 362.6]	326.6 [260.0, 410.4]	348.4 [283.9, 427.6]	1222.1 [1024.5, 1457.9]	1259.7 [1044.1, 1519.8]	1355.4 [1141.7, 1609.2]
Day 28 post-vaccination						
n1	231	227	235	231	227	236
GMT [2-sided 95% CI][a)]	1068.1 [886.3, 1287.2]	582.0 [476.3, 711.1]	1507.3 [1259.0, 1804.5]	2310.1 [1985.1, 2688.3]	2337.7 [2007.5, 2722.2]	2220.0 [1940.1, 2540.3]
n2	231	227	235	230	227	236
GMFR [2-sided 95% CI][a)]	3.6 [3.2, 4.2]	1.8 [1.6, 2.0]	4.4 [3.8, 5.1]	1.9 [1.6, 2.2]	1.9 [1.6, 2.1]	1.6 [1.4, 1.9]
Antibody response rate						
n3/n2	92/231	28/227	107/235	54/230	52/227	53/236
Antibody response rate (%) [2-sided 95% CI][b)]	39.8 [33.5, 46.5]	12.3 [8.4, 17.3]	45.5 [39.0, 52.1]	23.5 [18.2, 29.5]	22.9 [17.6, 28.9]	22.5 [17.3, 28.3]

N, Number of subjects analyzed; n1, Number of subjects with available immunogenicity data; n2, Number of subjects with immunogenicity data available both before and after the study vaccination; n3, Number of subjects who met the criteria for antibody response (≥4-fold increase from the baseline value [if the baseline value was below the LLOQ, the LLOQ was used as the baseline value]).
In the calculation of GMT and geometric mean fold rise (GMFR), when antibody titers were below the LLOQ, a value of 0.5 × LLOQ was used in the analysis; when actual measured values were not available due to antibody titers exceeding the ULOQ, the ULOQ value was used in the analysis. (Quantification range [LLOQ-ULOQ]: 36-15,856 [Omicron BA.5 lineage], 42-14,863 [original strain])
a) Two-sided 95% CI was calculated by assuming a t-distribution for the log-transformed values.
b) Two-sided 95% CI was calculated based on the Clopper-Pearson method.

As an additional post-hoc analysis, a comparison between the monovalent (Omicron BA.5) vaccine group and the monovalent (Original) vaccine group was conducted. The adjusted GMT [2-sided 95% CI] of neutralizing antibodies against the Omicron BA.5 lineage was 1279.1 [1119.7, 1461.1] in the monovalent (Omicron BA.5) vaccine group and 515.1 [450.4, 589.0] in the monovalent (Original) vaccine group. The GMTR [2-sided 95% CI] (monovalent [Omicron BA.5] vaccine/monovalent [Original] vaccine) was 2.5 [2.10, 2.94]. The difference in antibody response rates [2-sided 95% CI] (monovalent [Omicron BA.5] vaccine – monovalent [Original] vaccine) was 33.2% [25.4%, 40.7%]. Both results met the predefined criteria for super superiority described in Appendix 4.

Table 9 and Table 10 show the results of neutralizing antibody titers before and after the study vaccination, stratified by age group and SARS-CoV-2 infection history (positive or negative for baseline anti-N antibodies), respectively.

Table 9. Neutralizing antibody titers and antibody response rates against SARS-CoV-2 (Omicron BA.5 lineage/original strain) in serum by age group (Study 311 Part 2, PPAS)

	Omicron BA.5 lineage			Original strain		
18-54 years of age						
	Bivalent (Original/Omicron BA.5) vaccine N = 190	Monovalent (Original) vaccine N= 188	Monovalent (Omicron BA.5) vaccine N = 198	Bivalent (Original/Omicron BA.5) vaccine N = 190	Monovalent (Original) vaccine N = 188	Monovalent (Omicron BA.5) vaccine N = 198
Baseline (before study vaccination)						
n1	190	188	198	190	188	198
GMT [2-sided 95% CI][a)]	314.8 [250.6, 395.4]	344.7 [270.9, 438.6]	392.5 [317.0, 485.9]	1260.3 [1040.5, 1526.6]	1226.0 [1007.7, 1491.6]	1421.0 [1187.6, 1700.4]
28 days after study vaccination						
n1	190	188	197	190	188	198
GMT [2-sided 95% CI][a)]	1275.0 [1048.2, 1550.8]	616.9 [501.6, 758.8]	1667.9 [1380.7, 2014.8]	2485.3 [2103.0, 2937.1]	2358.0 [2019.3, 2753.5]	2316.6 [2001.7, 2681.0]
n2	190	188	197	190	188	198
GMFR [2-sided 95% CI][a)]	4.1 [3.5, 4.7]	1.8 [1.6, 2.1]	4.3 [3.6, 5.0]	2.0 [1.6, 2.4]	1.9 [1.7, 2.2]	1.6 [1.4, 1.9]
n3/n2	85/190	25/188	89/197	48/190	44/188	44/198
Antibody response rate (%) [2-sided 95% CI][c)]	44.7 [37.5, 52.1]	13.3 [8.8, 19.0]	45.2 [38.1, 52.4]	25.3 [19.3, 32.1]	23.4 [17.6, 30.1]	22.2 [16.6, 28.7]
Between-group comparison	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)
GMTR [2-sided 95% CI][b)]	2.2 [1.84, 2.62]	2.5 [2.08, 2.99]	1.1 [0.95, 1.39]	1.0 [0.86, 1.25]	0.9 [0.77, 1.07]	0.9 [0.73, 1.06]
Difference in antibody response rates (%) [2-sided 95% CI][d)]	31.4 [22.7, 39.8]	31.9 [23.2, 40.2]	0.4 [−9.4, 10.3]	1.9 [−6.8, 10.5]	−1.2 [−9.6, 7.2]	−3.0 [−11.6, 5.4]
≥55 years of age						
	Bivalent (Original/Omicron BA.5) vaccine N = 41	Monovalent (Original) vaccine N = 39	Monovalent (Omicron BA.5) vaccine N = 38	Bivalent (Original/Omicron BA.5) vaccine N = 41	Monovalent (Original) vaccine N = 39	Monovalent (Omicron BA.5) vaccine N = 38
Baseline (before study vaccination)						
n1	41	39	38	40	39	38
GMT [2-sided 95% CI][a)]	211.4 [119.6, 373.6]	251.8 [129.1, 490.9]	187.3 [102.6, 342.0]	1056.0 [663.7, 1680.2]	1435.9 [812.5, 2537.6]	1059.6 [625.5, 1794.9]
28 days after study vaccination						
n1	41	39	38	41	39	38
GMT [2-sided 95% CI][a)]	470.1 [293.6, 753.0]	439.2 [235.7, 818.3]	891.8 [531.2, 1497.4]	1646.4 [1151.2, 2354.5]	2242.1 [1365.0, 3682.9]	1778.3 [1246.7, 2536.5]
n2	41	39	38	40	39	38
GMFR [2-sided 95% CI][a)]	2.2 [1.6, 3.0]	1.7 [1.3, 2.3]	4.8 [3.1, 7.2]	1.5 [1.1, 2.3]	1.6 [1.0, 2.5]	1.7 [1.0, 2.8]
n3/n2	7/41	3/39	18/38	6/40	8/39	9/38
Antibody response rate (%) [2-sided 95% CI][c)]	17.1 [7.2, 32.1]	7.7 [1.6, 20.9]	47.4 [31.0, 64.2]	15.0 [5.7, 29.8]	20.5 [9.3, 36.5]	23.7 [11.4, 40.2]
Between-group comparison	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)
GMTR [2-sided 95% CI][b)]	1.2 [0.86, 1.75]	2.5 [1.64, 3.93]	2.1 [1.34, 3.15]	0.8 [0.52, 1.39]	0.9 [0.53, 1.52]	1.1 [0.70, 1.70]
Difference in antibody response rates (%) [2-sided 95% CI][d)]	9.4 [−5.9, 25.0]	39.7 [20.9, 56.7]	30.3 [9.8, 48.8]	−5.5 [−23.1, 11.9]	3.2 [−15.7, 22.1]	8.7 [−9.2, 26.8]

N, Number of subjects analyzed; n1, Number of subjects with available immunogenicity data; n2, Number of subjects with immunogenicity data available both before and after study vaccination; n3, Number of subjects who met the criteria for antibody response (≥4-fold increase from the baseline value [if the baseline value was below the LLOQ, the LLOQ was used as the baseline value]).

In the calculation of GMT, GMFR, and GMTR, when antibody titers were below the LLOQ, a value of 0.5 × LLOQ was used in the analysis; when actual measured values were not available due to antibody titers exceeding the ULOQ, the ULOQ value was used in the analysis. (Quantification range [LLOQ-ULOQ]: 36-15,856 [Omicron BA.5 lineage], 42-14,863 [original strain])

a) Two-sided 95% CI was calculated by assuming a t-distribution for the log-transformed values.

b) ANCOVA was performed using post-vaccination neutralizing antibody titers (log-transformed values) as the response variable, vaccination group as a fixed effect, and baseline neutralizing antibody titers (log-transformed values) as a covariate.

c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.

d) Two-sided 95% CI was calculated based on the Miettinen-Nurminen method.

Table 10. Neutralizing antibody titers and antibody response rates against SARS-CoV-2 (Omicron BA.5 lineage/original strain) in serum by SARS-CoV-2 infection history (Study 311 Part 2, PPAS)

	Omicron BA.5 lineage			Original strain		
Anti-N protein negative						
	Bivalent (Original/Omicron BA.5) vaccine N = 49	Monovalent (Original) vaccine N = 62	Monovalent (Omicron BA.5) vaccine N = 53	Bivalent (Original/Omicron BA.5) vaccine N = 49	Monovalent (Original) vaccine N = 62	Monovalent (Omicron BA.5) vaccine N = 53
Baseline (before study vaccine administration)						
n1	49	62	53	48	62	53
GMT [2-sided 95% CI][a)]	41.6 [31.9, 54.2]	64.9 [42.7, 98.8]	70.9 [47.8, 105.1]	358.6 [247.7, 519.2]	451.4 [300.4, 678.3]	541.3 [363.1, 806.9]
28 days after study vaccination						
n1	49	62	53	49	62	53
GMT [2-sided 95% CI][a)]	242.2 [163.1, 359.7]	148.3 [100.4, 219.1]	439.4 [275.2, 701.5]	1243.1 [854.2, 1809.0]	1204.5 [862.6, 1681.8]	1223.5 [911.1, 1643.2]
n2	49	62	53	48	62	53
GMFR [2-sided 95% CI][a)]	5.8 [4.3, 7.9]	2.3 [1.6, 3.2]	6.2 [4.1, 9.3]	3.4 [2.2, 5.3]	2.7 [2.0, 3.6]	2.3 [1.5, 3.4]
n3/n2	23/49	13/62	25/53	21/48	22/62	21/53
Antibody response rate (%) [2-sided 95% CI][c)]	46.9 [32.5, 61.7]	21.0 [11.7, 33.2]	47.2 [33.3, 61.4]	43.8 [29.5, 58.8]	35.5 [23.7, 48.7]	39.6 [26.5, 54.0]
Between-group comparison	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)
GMTR [2-sided 95% CI][b)]	2.2 [1.40, 3.37]	2.8 [1.73, 4.51]	1.2 [0.75, 2.05]	1.1 [0.74, 1.73]	0.9 [0.64, 1.38]	0.9 [0.57, 1.41]
Difference in antibody response rates (%) [2-sided 95% CI][d)]	26.0 [8.4, 42.6]	26.2 [8.9, 42.4]	0.2 [−18.9, 19.3]	8.3 [−10.0, 26.4]	4.1 [−13.5, 21.7]	−4.1 [−23.0, 15.0]
Anti-N antibody positive						
	Bivalent (Original/Omicron BA.5) vaccine N = 181	Monovalent (Original) vaccine N = 164	Monovalent (Omicron BA.5) vaccine N = 181	Bivalent (Original/Omicron BA.5) vaccine N = 181	Monovalent (Original) vaccine N = 164	Monovalent (Omicron BA.5) vaccine N = 181
Baseline (before study vaccination)						
n1	181	164	181	181	164	181
GMT [2-sided 95% CI][a)]	492.8 [403.4, 602.0]	608.8 [495.1, 748.6]	561.0 [462.0, 681.2]	1696.5 [1425.1, 2019.4]	1861.5 [1557.4, 2225.0]	1769.9 [1489.1, 2103.6]
28 days after study vaccination						
n1	181	164	180	181	164	181
GMT [2-sided 95% CI][a)]	1591.6 [1339.5, 1891.0]	987.8 [825.5, 1181.9]	2167.4 [1852.8, 2535.3]	2733.1 [2333.7, 3200.8]	3000.7 [2571.4, 3501.7]	2635.1 [2280.1, 3045.3]
n2	181	164	180	181	164	181
GMFR [2-sided 95% CI][a)]	3.2 [2.8, 3.8]	1.6 [1.5, 1.8]	3.9 [3.3, 4.5]	1.6 [1.4, 1.9]	1.6 [1.4, 1.9]	1.5 [1.3, 1.7]
n3/n2	69/181	15/164	80/180	33/181	30/164	31/181
Antibody response rate (%) [2-sided 95% CI][c)]	38.1 [31.0, 45.6]	9.1 [5.2, 14.6]	44.4 [37.1, 52.0]	18.2 [12.9, 24.6]	18.3 [12.7, 25.1]	17.1 [11.9, 23.4]
Between-group comparison	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)	Bivalent (Original/Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Monovalent (Original)	Monovalent (Omicron BA.5) vs. Bivalent (Original/Omicron BA.5)
GMTR [2-sided 95% CI][b)]	1.9 [1.59, 2.20]	2.3 [1.98, 2.71]	1.3 [1.06, 1.50]	1.0 [0.79, 1.16]	0.9 [0.76, 1.07]	0.9 [0.78, 1.13]
Difference in antibody response rates (%) [2-sided 95% CI][d)]	29.0 [20.5, 37.2]	35.3 [26.6, 43.6]	6.3 [−3.8, 16.4]	−0.1 [−8.4, 8.1]	−1.2 [−9.4, 6.9]	−1.1 [−9.1, 6.8]

N, Number of subjects analyzed; n1, Number of subjects with available immunogenicity data; n2, Number of subjects with immunogenicity data available both before and after study vaccination; n3, Number of subjects who met the criteria for antibody response (≥4-fold increase from the baseline value [if the baseline value was below the LLOQ, the LLOQ was used as the baseline value]).

In the calculation of GMT, GMFR, and GMTR, when antibody titers were below the LLOQ, a value of 0.5 × LLOQ was used in the analysis; when actual measured values were not available due to antibody titers exceeding the ULOQ, the ULOQ value was used in the analysis. (Quantification range [LLOQ-ULOQ]: 36-15,856 [Omicron BA.5 lineage], 42-14,863 [original strain])

a) Two-sided 95% CI was calculated by assuming a t-distribution for the log-transformed values.

b) ANCOVA was performed using post-vaccination neutralizing antibody titers (log-transformed values) as the response variable, vaccination group and age group (18-54/≥55) as fixed effects, and baseline neutralizing antibody titers (log-transformed values) as a covariate.

c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.

d) Two-sided 95% CI was calculated based on the Miettinen-Nurminen method.

Study 313 Part 1

Study 313 Part 1 included individuals aged ≥18 years who had received at least 3 doses (primary series + at least one booster dose) of an approved mRNA SARS-CoV-2 vaccine (Comirnaty or Spikevax) and who received their last vaccination ≥3 months ago. The study aimed to compare the immune response to SARS-CoV-2 Omicron XBB.1.5 lineage at Day 28 post-vaccination with the monovalent (Omicron XBB.1.5) vaccine to that of the monovalent (Original) vaccine group in Study 311 Part 2. The results showed that both the GMTR and the difference in antibody response rate for neutralizing antibodies against SARS-CoV-2 Omicron XBB.1.5 lineage at Day 28 post-vaccination met the predefined criteria for superiority and non-inferiority [see Section 7.2].

Regarding subject characteristics in Study 313 Part 1 and Study 311 Part 2, factors such as sex, race, weight, and SARS-CoV-2 vaccination history were similar, except for age distribution and baseline neutralizing antibody titers against Omicron XBB.1.5 lineage. Regarding age distribution, the proportion of subjects aged 18 to 54 years and ≥55 years was 52.8% (163 of 309 subjects) and 47.2% (146 of 309 subjects), respectively, in the monovalent (Omicron XBB.1.5) vaccine group, whereas it was 82.8% (188 of 227 subjects) and 17.2% (39 of 227 subjects), respectively, in the monovalent (Original) vaccine group, indicating a difference in age distribution between studies. However, considering that the GMFR at Day 28 post-vaccination in the monovalent (Original) vaccine group was 1.5 in subjects aged 18 to 54 years and 1.3 in those aged ≥55 years (Table 11) showing no significant difference between age groups, the differences in age distribution was considered to have had no significant impact on the immunogenicity assessment in terms of the comparability between studies. While there were minor differences in baseline neutralizing antibody titers against Omicron XBB.1.5 lineage between studies, adjusted GMT and GMTR at Day 28 post-vaccination were calculated using analysis of covariance (ANCOVA) with baseline neutralizing antibody titers as a covariate, ensuring that the baseline antibody titers were appropriately accounted for in the analysis.

Table 11 and Table 12 show the neutralizing antibody titers before and after study vaccination in Study 313 Part 1, stratified by age group and SARS-CoV-2 infection history (positive/negative for baseline anti-N antibodies), respectively.

Table 11. Neutralizing antibody titers and antibody response rates against SARS-CoV-2 (Omicron XBB.1.5 lineage) in serum by age group (Study 313 Part 1, PPAS)

	All age groups		18-54 years		≥55 years	
	Study 313 Part 1	Study 311 Part 2	Study 313 Part 1	Study 311 Part 2	Study 313 Part 1	Study 311 Part 2
	Monovalent (Omicron XBB.1.5) vaccine	Monovalent (Original) vaccine	Monovalent (Omicron XBB.1.5) vaccine	Monovalent (Original) vaccine	Monovalent (Omicron XBB.1.5) vaccine	Monovalent (Original) vaccine
	N = 309	N = 227	N = 163	N = 188	N = 146	N = 39
Baseline (before study vaccination)						
n1	305	227	161	188	144	39
GMT [2-sided 95% CI][a)]	120.8 [101.5, 143.8]	100.0 [80.8, 123.8]	122.8 [98.0, 153.9]	102.0 [81.5, 127.7]	118.5 [90.3, 155.6]	90.9 [48.3, 171.0]
28 days after study vaccination						
GMT [2-sided 95% CI][a)]	955.5 [814.0, 1121.4]	145.8 [119.4, 177.9]	1027.9 [829.5, 1273.9]	152.8 [124.0, 188.4]	880.5 [691.2, 1121.5]	116.1 [64.3, 209.8]
GMFR [2-sided 95% CI][a)]	7.9 [6.8, 9.2]	1.5 [1.3, 1.6]	8.4 [6.8, 10.3]	1.5 [1.3, 1.7]	7.4 [5.9, 9.3]	1.3 [1.0, 1.6]
Adjusted GMT [2-sided 95% CI][b)]	905.9 [807.1, 1016.8]	156.6 [137.0, 179.0]	960.4 [825.0, 1118.0]	162.0 [140.7, 186.4]	849.5 [707.7, 1019.7]	132.5 [93.3, 188.3]
GMTR [2-sided 95% CI][b)]	5.8 [4.85, 6.91]		5.9 [4.82, 7.29]		6.4 [4.31, 9.53]	
n2	196	16	112	15	84	1
Antibody response rate (%) [2-sided 95% CI][c)]	64.3 [58.6, 69.6]	7.0 [4.1, 11.2]	69.6 [61.8, 76.6]	8.0 [4.5, 12.8]	58.3 [49.8, 66.5]	2.6 [0.1, 13.5]
Difference in antibody response rates (%) [2-sided 95% CI][d)]	57.2 [50.5, 63.2]		61.6 [53.0, 69.1]		55.8 [43.5, 64.3]	

N, Number of subjects analyzed; n1, Number of subjects with available immunogenicity data both before and after study vaccination; n2, Number of subjects who met the criteria for antibody response (≥4-fold increase from the baseline value [if the baseline value was below the LLOQ, the LLOQ was used as the baseline value]); GMTR, Monovalent (Omicron XBB.1.5) vaccine/monovalent (Original) vaccine; Difference in antibody response rate, monovalent (Omicron XBB.1.5) vaccine − monovalent (Original) vaccine

In the calculation of GMT, GMFR, and GMTR, when antibody titers were below the LLOQ, a value of 0.5 × LLOQ was used in the analysis; when actual measured values were not available due to antibody titers exceeding the ULOQ, the ULOQ value was used in the analysis. (Quantification range [LLOQ-ULOQ]: 37-7,561 [Omicron XBB.1.5 lineage])

a) Two-sided 95% CI was calculated by assuming a t-distribution for the log-transformed values.

b) ANCOVA was performed using post-vaccination neutralizing antibody titers (log-transformed values) as the response variable, vaccination group as a fixed effect, and baseline neutralizing antibody titers as a covariate.

c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.

d) Two-sided 95% CI was calculated based on the Miettinen-Nurminen method.

Table 12. Neutralizing antibody titers and antibody response rates against SARS-CoV-2 (Omicron XBB.1.5 lineage) in serum by SARS-CoV-2 infection history (Study 313 Part 1, PPAS)

	Anti-N protein negative		Anti-N protein positive	
	Study 313 Part 1	Study 311 Part 2	Study 313 Part 1	Study 311 Part 2
	Monovalent (Omicron XBB.1.5) vaccine	Monovalent (Original) vaccine	Monovalent (Omicron XBB.1.5) vaccine	Monovalent (Original) vaccine
	N = 94	N = 62	N = 215	N = 164
Baseline (before study vaccination)				
n1	91	62	214	164
GMT [2-sided 95% CI][a)]	44.9 [35.0, 57.8]	35.0 [24.6, 49.7]	183.9 [150.5, 224.6]	150.3 [118.6, 190.5]
28 days after study vaccination				
GMT [2-sided 95% CI][a)]	404.8 [296.6, 552.4]	43.5 [32.1, 59.0]	1376.7 [1167.7, 1623.0]	233.1 [188.8, 287.9]
GMFR [2-sided 95% CI][a)]	9.0 [6.7, 12.0]	1.2 [0.9, 1.6]	7.5 [6.3, 8.9]	1.6 [1.4, 1.7]
Adjusted GMT [2-sided 95% CI][b)]	381.7 [299.4, 486.8]	47.4 [35.3, 63.7]	1306.4 [1154.4, 1478.4]	249.6 [216.7, 287.5]
GMTR [2-sided 95% CI][b)]	8.0 [5.49, 11.80]		5.2 [4.34, 6.32]	
n2	51	1	145	15
Antibody response rate (%) [2-sided 95% CI][c)]	56.0 [45.2, 66.4]	1.6 [0.0, 8.7]	67.8 [61.0, 74.0]	9.1 [5.2, 14.6]
Difference in antibody response rates (%) [2-sided 95% CI][d)]	54.4 [43.2, 64.5]		58.6 [50.4, 65.8]	

N, Number of subjects analyzed; n1, Number of subjects with immunogenicity data available both before and after study vaccination; n2, Number of subjects who met the criteria for antibody response (≥4-fold increase from the baseline value [if the baseline value was below the LLOQ, the LLOQ was used as the baseline value]); GMTR, Monovalent (Omicron XBB.1.5) vaccine/monovalent (Original) vaccine; Difference in antibody response rate, monovalent (Omicron XBB.1.5) vaccine − monovalent (Original) vaccine

In the calculation of GMT, GMFR, and GMTR, when antibody titers were below the LLOQ, a value of 0.5 × LLOQ was used in the analysis; when actual measured values were not available due to antibody titers exceeding the ULOQ, the ULOQ value was used in the analysis. (Quantification range [LLOQ-ULOQ]: 37-7,561 [Omicron XBB.1.5 lineage])

a) Two-sided 95% CI was calculated by assuming a t-distribution for the log-transformed values.
b) ANCOVA was performed using post-vaccination neutralizing antibody titers (log-transformed values) as the response variable, vaccination group as a fixed effect, and baseline neutralizing antibody titers as a covariate.
c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
d) Two-sided 95% CI was calculated based on the Miettinen-Nurminen method.

Based on the above results, the bivalent (Original/Omicron BA.5) vaccine, the monovalent (Omicron XBB.1.5) vaccine, and the monovalent (Omicron BA.5) vaccine, which was exploratorily evaluated in Study 311 Part 2, all demonstrated higher immune responses to their corresponding variant strains than the approved monovalent (Original) vaccine. These results could support the efficacy of booster dose with any of these vaccines.

According to Appendix 1, clinical studies evaluating the efficacy of variant-adapted vaccines in a single age group generally support the extrapolation of findings to other age groups for which the parent vaccine has been approved. Based on this, the efficacy data for booster dose obtained in Study 311 Part 2 and Study 313 Part 1 in subjects aged ≥18 years are considered extrapolatable to the age group of 12 to 17 years, where booster dose with the monovalent (Original) vaccine has been approved.

Although there are no clinical studies evaluating primary series with variant-adapted vaccines, results from clinical studies investigating primary series and booster dose with the approved monovalent (Original) vaccine (Studies 2019nCoV-301 and TAK-019-3001) have confirmed that, in individuals aged ≥18 years, the immunogenicity of primary series with the monovalent (Original) vaccine was comparable to that of booster dose (Review Report on Nuvaxovid Intramuscular Injection dated April 11, 2022; *Vaccine*. 2023;41:3763-71). It is thus expected that primary series with the monovalent (Omicron BA.5) vaccine and monovalent (Omicron XBB.1.5) vaccine in individuals aged ≥18 years

would yield efficacy results (immunogenicity) similar to those observed for booster dose in this age group. Clinical studies evaluating the immunogenicity and safety of the monovalent (Original) vaccine (Studies 2019nCoV-301 and 2019nCoV-503) demonstrated that the immunogenicity of the monovalent (Original) vaccine was comparable across age groups (6-11 years, 12-17 years, and ≥18 years).[23)] This result shows that primary series with the monovalent (Omicron BA.5) vaccine and monovalent (Omicron XBB.1.5) vaccine exhibit comparable immunogenicity across the above age groups, suggesting vaccine efficacy.

In conclusion, results from previously conducted clinical studies support the expected efficacy of variant-adapted vaccines, and the immunogenicity of the monovalent (Omicron JN.1) vaccine has been confirmed in non-clinical studies [see Section 3.1], indicating that the monovalent (Omicron JN.1) vaccine has efficacy.

PMDA's view:
In Study 311 Part 2 and Study 313 Part 1, which evaluated booster dose with the bivalent (Original/Omicron BA.5) vaccine and the monovalent (Omicron XBB.1.5) vaccine, the GMT of neutralizing antibodies and the antibody response rate against each variant met the success criteria of the study. Therefore, the efficacy of booster dose with the bivalent (Original/Omicron BA.5) vaccine and the monovalent (Omicron XBB.1.5) vaccine can be expected. Results of the exploratory immunogenicity assessment of the monovalent (Omicron BA.5) vaccine in Study 311 Part 2 suggest that booster dose with the monovalent (Omicron BA.5) vaccine is also expected to have efficacy against the Omicron BA.5 lineage.

Study 311 Part 2 and Study 313 Part 1 were conducted as booster dose studies in subjects aged ≥18 years. From the results of these studies, the following applicant's explanation is acceptable: The monovalent (Omicron XBB.1.5) vaccine and the monovalent (Omicron BA.5) vaccine are expected to have efficacy for primary series in subjects aged ≥6 years and for booster dose in subjects aged ≥12 years. Upon reviewing the quality test results of these variant-adapted vaccines, the efficacy, safety, and quality of the vaccines after changes in the antigenic strain are reasonably predictable. Thus, the use of the platform approach for the present application is considered feasible.

Based on the above and the review policy outlined in Section 7.R.1, the following findings were confirmed from the submitted data on the monovalent (Omicron JN.1) vaccine in the present application. It is therefore possible to conclude that the monovalent (Omicron JN.1) vaccine is expected to have efficacy in subjects aged ≥6 years for the primary series and in subjects aged ≥12 years for booster dose.

- The monovalent (Omicron JN.1) vaccine is a variant-adapted vaccine derived from the monovalent (Original) vaccine of Nuvaxovid, which has been approved for marketing in Japan.

[23)] Based on the study results of the cohort involving subjects aged ≥12 and <18 years in Study 2019nCoV-301 and the cohort involving subjects aged ≥6 and <12 years in Study 2019nCoV-503, the package insert was revised on July 21, 2022, and March 21, 2024, respectively. The revision changed the "vaccination target population" in the "Precautions concerning dosage and administration" for primary series from "subjects aged ≥18 years" to "subjects aged ≥12 years" and from "subjects aged ≥12 years" to "subjects aged ≥6 years." For details on the study results, refer to the "17. Clinical Studies" section in the package insert of "Nuvaxovid Intramuscular Injection."

- The quality attributes of the monovalent (Omicron JN.1) vaccine were confirmed to be generally similar to those of the monovalent (Original) vaccine, except for the modification of the amino acid sequence of SARS-CoV-2 rS [see Section 2].
- In non-clinical pharmacology studies, administration of the monovalent (Omicron N.1) vaccine to mice or rhesus monkeys demonstrated the induction of an immune response to the SARS-CoV-2 Omicron JN.1 lineage and other Omicron sublineages [see Section 3.1].

As SARS-CoV-2 continues to evolve, with the potential emergence of new Omicron sublineages or other novel variants, the applicant should continue collecting information and research reports on the emergence and prevalence of variant strains, as well as epidemiological data on vaccine efficacy, both in and outside of Japan, and should consider appropriate measures based on the information obtained.

7.R.3 Safety

The applicant's explanation about the safety of the monovalent (Omicron JN.1) vaccine is provided in the following subsections.

(1) Incidence of adverse events in clinical studies

Table 13 shows the summary of safety for Study 311 Part 2 and Study 313 Part 1.

Table 13. Summary of safety (safety analysis set)

	Study 311 Part 2			**Study 313 Part 1**
	Bivalent (Original/Omicron BA.5) vaccine N = 259	Monovalent (Original) vaccine N = 251	Monovalent (Omicron BA.5) vaccine N = 254	Monovalent (Omicron XBB.1.5) vaccine N = 332
	n (%)	n (%)	n (%)	n (%)
Local solicited adverse events[a)]	169 (65.3)	168 (66.9)	153 (60.7)	189 (56.9)
Grade ≥3	2 (0.8)	2 (0.8)	4 (1.6)	1 (0.3)
Systemic solicited adverse events[a)]	155 (59.8)	139 (55.4)	142 (56.3)	158 (47.6)
Grade ≥3	10 (3.9)	10 (4.0)	5 (2.0)	4 (1.2)
Unsolicited adverse events[b)]	58 (22.4)	64 (25.5)	54 (21.3)	29 (8.7)
Severe	3 (1.2)	0	1 (0.4)	2 (0.6)
Unsolicited adverse reactions[b)]	8 (3.1)	5 (2.0)	3 (1.2)	5 (1.5)
Severe	1 (0.4)	0	0	0
Death [c)]	0	0	0	0
Serious adverse events[c)]	1 (0.4)	1 (0.4)	4 (1.6)	2 (0.6)

N, Number of subjects analyzed, n, Number of subjects with events
a) Adverse events observed within 7 days after study vaccination
b) Adverse events observed within 28 days after study vaccination
c) Adverse events observed up to the data cut-off time point

(a) Solicited adverse events

In Study 311 Part 2, the incidence of local solicited adverse events was 65.3% in the bivalent (Original/Omicron BA.5) vaccine group, 66.9% in the monovalent (Original) vaccine group, and 60.7% in the monovalent (Omicron BA.5) vaccine group, showing similar rates across the 3 groups. Most events were Grade 1 or 2, and the incidence of Grade 3 events was 0.8%, 0.8%, and 1.6%, respectively. No Grade 4 events were observed. The main local solicited adverse event was pain/tenderness. The median time to onset of each event ranged from 1.0 to 2.0 days, and the median duration ranged from 1.5 to 2.5 days. The incidence of systemic solicited adverse events was 59.8%, 55.4%, and 56.3%, respectively, showing similar rates across the 3 groups. Most events were Grade 1 or 2, and the incidence of Grade 3 events was 2.0%, 4.0%, and 3.9%, respectively. No Grade 4 events

were observed. The main systemic solicited adverse events were fatigue/malaise, headache, and myalgia. The median time to onset of each systemic solicited adverse event ranged from 1.0 to 4.0 days, and the median duration was 1 to 2 days, except for pyrexia in the monovalent (Original) vaccine group, which had a median duration of 3.5 days.

In Study 313 Part 1, the incidence of local solicited adverse events was 56.9%. Most events were Grade 1 or 2, and the incidence of Grade 3 events was 0.3% (only tenderness in 1 subject). No Grade 4 events were observed. The main local solicited adverse event was pain/tenderness. The median time to onset of local solicited adverse events ranged from 1.0 to 3.0 days, and the median duration ranged from 1.0 to 2.0 days. The incidence of systemic solicited adverse events was 47.6%. Most events were Grade 1 or 2, and the incidence of Grade 3 events was 1.2%. No Grade 4 events were observed. The main systemic solicited adverse events were fatigue/malaise, headache, and myalgia. The median time to onset of systemic solicited adverse events ranged from 2.0 to 4.0 days, and the median duration ranged from 1.0 to 3.5 days.

Table 14 shows the age-specific solicited adverse events.

Table 14. Age-specific solicited adverse events (safety analysis set)

Event	Study 311 Part 2						Study 313 Part 1	
	18-54 years of age			≥55 years of age			18-54 years of age	≥55 years of age
	Bivalent (Original/ Omicron BA.5) vaccine N = 212	Monovalent (Original) vaccine N = 209	Monovalent (Omicron BA.5) vaccine N = 211	Bivalent (Original/Omicron BA.5) vaccine N = 47	Monovalent (Original) vaccine N = 42	Monovalent (Omicron BA.5) vaccine N = 43	Monovalent (Omicron XBB.1.5) vaccine N = 176	Monovalent (Omicron XBB.1.5) vaccine N = 156
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reactions (all events)	143 (67.5)	146 (69.9)	136 (65.1)	26 (55.3)	22 (52.4)	17 (39.5)	113 (64.2)	76 (48.7)
Grade ≥3	2 (0.9)	2 (1.0)	4 (1.9)	0	0	0	1 (0.6)	0
Pain	86 (40.6)	88 (42.1)	78 (37.3)	12 (25.5)	10 (23.8)	5 (11.6)	60 (34.1)	38 (24.4)
Grade ≥3	2 (0.9)	0	3 (1.4)	0	0	0	0	0
Tenderness	129 (60.8)	132 (63.2)	124 (59.3)	24 (51.1)	17 (40.5)	16 (37.2)	102 (58.0)	69 (44.2)
Grade ≥3	1 (0.5)	2 (1.0)	1 (0.5)	0	0	0	1 (0.6)	0
Redness	5 (2.4)	6 (2.9)	5 (2.4)	1 (2.1)	2 (4.8)	0	2 (1.1)	4 (2.6)
Grade ≥3	0	0	0	0	0	0	0	0
Swelling	5 (2.4)	5 (2.4)	7 (3.3)	1 (2.1)	1 (2.4)	1 (2.3)	2 (1.1)	2 (1.3)
Grade ≥3	0	0	0	0	0	0	0	0
Systemic (all events)	137 (64.6)	120 (57.4)	127 (60.8)	18 (38.3)	19 (45.2)	15 (34.9)	91 (51.7)	67 (42.9)
Grade ≥3	8 (3.8)	9 (4.3)	5 (2.4)	2 (4.3)	1 (2.4)	0	3 (1.7)	1 (0.6)
Pyrexia	4 (1.9)	2 (1.0)	2 (1.0)	0	0	0	0	2 (1.3)
Grade ≥3	1 (0.5)	0	0	0	0	0	0	0
Fatigue	78 (36.8)	84 (40.2)	89 (42.6)	10 (21.3)	10 (23.8)	8 (18.6)	58 (33.0)	39 (25.0)
Grade ≥3	6 (2.8)	6 (2.9)	2 (1.0)	2 (4.3)	1 (2.4)	0	0	1 (0.6)
Malaise	34 (16.0)	39 (18.7)	44 (21.1)	2 (4.3)	3 (7.1)	4 (9.3)	34 (19.3)	20 (12.8)
Grade ≥3	3 (1.4)	2 (1.0)	3 (1.4)	1 (2.1)	1 (2.4)	0	2 (1.1)	1 (0.6)
Myalgia	61 (28.8)	63 (30.1)	55 (26.3)	6 (12.8)	8 (19.0)	4 (9.3)	58 (33.0)	39 (25.0)
Grade ≥3	2 (0.9)	2 (1.0)	1 (0.5)	0	0	0	0	1 (0.6)
Nausea/Vomiting	17 (8.0)	15 (7.2)	18 (8.6)	2 (4.3)	3 (7.1)	1 (2.3)	19 (10.8)	6 (3.8)
Grade ≥3	0	0	1 (0.5)	0	0	0	0	0
Arthralgia	17 (8.0)	16 (7.7)	16 (7.7)	2 (4.3)	4 (9.5)	2 (4.7)	20 (11.4)	19 (12.2)
Grade ≥3	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Headache	65 (30.7)	59 (28.2)	64 (30.6)	9 (19.1)	14 (33.3)	9 (20.9)	51 (29.0)	23 (14.7)
Grade ≥3	3 (1.4)	2 (1.0)	4 (1.9)	0	0	0	1 (0.6)	1 (0.6)

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

(b) Unsolicited adverse events

In Study 311 Part 2, the incidence of unsolicited adverse events up to 28 days after the study vaccination was 22.4% in the bivalent (Original/Omicron BA.5) vaccine, 25.5%, in the monovalent (Original) vaccine group, and 21.3% in the monovalent (Omicron BA.5) vaccine groups. Most unsolicited adverse events were mild or moderate in severity. The incidence of unsolicited adverse events assessed as related to the study vaccine was 3.1%, 2.0%, and 1.2%, respectively [see Section 7.1].

In Study 313 Part 1, the incidence of unsolicited adverse events up to 28 days after the study vaccination was 8.7%, with the most frequently observed adverse event being COVID-19 (1.5%). Adverse reactions were observed in 5 subjects (1.5%, diarrhoea, axillary pain, presyncope, asthma, and hypertension in 1 subject each). Severe adverse events were reported in 2 subjects (0.6%, gastrointestinal stromal tumor and appendiceal abscess in 1 subject each), both of which were assessed as unrelated to the study vaccine.

(c) Serious adverse events

In Study 311 Part 2, as of the data cutoff date (May 31, 2023), 6 serious adverse events were reported in 6 subjects (limb injury, overdose, acute coronary syndrome, acute myocardial infarction, non-cardiac chest pain, and IVth nerve paralysis in 1 subject each). The event of IVth nerve paralysis (monovalent [Omicron BA.5] vaccine group) was assessed as related to the study vaccine, and the subject's second dose of the study vaccine was discontinued.

In Study 313 Part 1, as of the data cutoff date (October 16, 2023), serious adverse events were reported in 2 subjects (gastrointestinal stromal tumor and appendiceal abscess in 1 subject each), both of which were assessed as unrelated to the study vaccine.

No deaths were reported in either study.

(2) Post-marketing safety information

According to the latest Summary Safety Report (30th report; survey period from June 1, 2024 to June 30, 2024), the cumulative number of vaccinations with Nuvaxovid from its international birthdate (December 20, 2021) to June 30, 2024, in countries or regions where vaccination data is available,[24)] was 2,989,177 doses for the monovalent (Original) vaccine and 1,203,001 doses for the monovalent (Omicron XBB.1.5) vaccine. Post-marketing adverse event reports related to the monovalent (Original) vaccine[25)] amounted to 18,394 events in 5,159 individuals, including 2,846 serious adverse events in 1,009 subjects. Among them, 34 cases resulted in death. For the monovalent (Omicron XBB.1.5) vaccine, there were 2,056 adverse events in 526 individuals, including 177 serious adverse events in 67 individuals. Of these, 8 cases resulted in death. The most commonly reported serious adverse events (top 3 by number of events) were chest pain (91 events), headache (84 events), and fatigue (80 events) for the monovalent (Original) vaccine, and pyrexia (7 events), asthenia (6 events),

24) Countries and regions where vaccination data were available:
Monovalent (Original) vaccine: Australia, Canada, the EU, Israel, India, New Zealand, Singapore, South Korea, Switzerland, Taiwan, the U.K., the U.S., and Japan.
Monovalent (Omicron XBB.1.5) vaccine: Canada, the EU, South Korea, Taiwan, and the U.S.

25) Regarding all spontaneously reported adverse events, the causal relationship to Nuvaxovid was assessed as related.

and vaccination failure (6 events) for the monovalent (Omicron XBB.1.5) vaccine. The most commonly reported adverse events leading to death (top 3 by number of events) were death (14 events), dyspnoea (4 events), and pyrexia (3 events) for the monovalent (Original) vaccine, and death (5 events), asthenia (2 events), and pyrexia (2 events) for the monovalent (Omicron XBB.1.5) vaccine. A comparison between the monovalent (Original) vaccine and the monovalent (Omicron XBB.1.5) vaccine in Novavax's global safety database has so far revealed no new safety signals for the monovalent (Omicron XBB.1.5) vaccine. The safety profile is consistent between the monovalent (Original) vaccine and the monovalent (Omicron XBB.1.5) vaccine.

The accrued global safety information indicates that the benefit-risk balance of both the monovalent (Original) vaccine and the monovalent (Omicron XBB.1.5) vaccine remains favorable.

Based on the results of Study 311 Part 2 and Study 313 Part 1, the tolerability of booster dose with the Omicron BA.5-adapted vaccine and the monovalent (Omicron XBB.1.5) vaccine in individuals aged ≥18 years was favorable, the safety profile was acceptable, and no safety concerns were identified from post-marketing safety information. The safety profile of booster dose with the Omicron BA.5-adapted vaccine or the monovalent (Omicron XBB.1.5) vaccine was similar to that of the previously approved monovalent (Original) vaccine. Although the safety of the Omicron BA.5-adapted vaccine and the monovalent (Omicron XBB.1.5) vaccine for primary series and booster dose in individuals aged ≥12 and <18 years has not been evaluated in clinical studies, clinical studies of the monovalent (Original) vaccine have shown no differences in the safety profile across age groups or between primary series and booster dose (Review Report on Nuvaxovid Intramuscular Injection dated April 11, 2022, etc.[23)]). Given the above findings, it is inferred that the safety profile of primary series in individuals aged ≥6 years and booster dose in individuals aged ≥12 and <18 years with the Omicron BA.5-adapted vaccine and the monovalent (Omicron XBB.1.5) vaccine would be similar to that of booster dose in individuals aged ≥18 years and is considered acceptable.

Based on the quality test results and non-clinical study results of the monovalent (Omicron JN.1) vaccine, the use of the platform approach for the present application indicates that the safety profile of the monovalent (Omicron JN.1) vaccine is also acceptable.

PMDA's view:
In Study 311 Part 2 and Study 313 Part 1, the safety of booster dose with the bivalent (Original/Omicron BA.5) vaccine, monovalent (Omicron BA.5) vaccine, and monovalent (Omicron XBB.1.5) vaccine showed no significant differences compared to the monovalent (Original) vaccine. The safety profiles were generally consistent with those observed in clinical studies reviewed at the time of the initial approval of the monovalent (Original) vaccine. The safety of the bivalent (Original/Omicron BA.5) vaccine, monovalent (Omicron BA.5) vaccine, and monovalent (Omicron XBB.1.5) vaccine is considered acceptable. Study 311 Part 2 and Study 313 Part 1, as submitted, were conducted for booster dose in individuals aged ≥18 years. Considering the clinical study results obtained so far for the monovalent (Original) vaccine, the applicant's assumption that the safety of primary series with the Omicron BA.5-adapted vaccine or monovalent (Omicron XBB.1.5) vaccine and the safety of booster dose in individuals aged <18 years are acceptable is understandable.

Although no clinical study data are available for the monovalent (Omicron JN.1) vaccine, it is a modified version of the monovalent (Original) vaccine. Taking into account the quality attributes of the monovalent (Omicron JN.1) vaccine, the safety profiles observed in clinical studies for the monovalent (Original) vaccine, bivalent (Original/Omicron BA.5) vaccine, monovalent (Omicron BA.5) vaccine, and monovalent (Omicron XBB.1.5) vaccine, as well as post-marketing safety information on the monovalent (Original) vaccine and monovalent (Omicron XBB.1.5) vaccine, the applicant's explanation that the safety of the monovalent (Omicron JN.1) vaccine is acceptable based on the platform approach is understandable.

7.R.4 Clinical positioning and indication

PMDA's view on the clinical positioning of Nuvaxovid:

Based on the evaluation of efficacy and safety, the efficacy of the monovalent (Omicron JN.1) vaccine is expected [see Section 7.R.2], and its safety is considered acceptable [see Section 7.R.3]. As of the end of July 2024 in Japan, only mRNA vaccines have been approved as vaccines adapted to SARS-CoV-2 variants. The availability of Nuvaxovid, a recombinant protein vaccine using a modality different from mRNA vaccines, in clinical practice is of significance because the vaccine product will provide a new option for SARS-CoV-2 vaccination targeting variants.

The monovalent (Omicron JN.1) vaccine may be indicated for the "prevention of disease caused by SARS-CoV-2 infection," consistent with the indication of the already approved monovalent (Original) vaccine. In the present application, the immunogenicity and safety of the variant-specific vaccine were evaluated based on the clinical study results, and the proposed indication included a specification of the applicable formulation. However, the submitted data suggest that the quality and safety of Nuvaxovid are highly unlikely to be affected by changes in the antigen strain, and the immunogenicity of the variant-adapted vaccine is considered predictable from the non-clinical studies. Next and subsequent applications involving changes in the antigen strain of Nuvaxovid will be subject to expedited review, without changes to the Indication or Dosage and Administration statement based on clinical study results, in accordance with the "Handling of Changes to COVID-19 Vaccine Strains (notification)" (PSB/PED Notification No. 0523-1 and PSB/CND Notification No. 0523-3, dated May 23, 2024). Therefore, the specification of the applicable formulation as set by the applicant is unnecessary.

7.R.5 Dosage and administration

After the filing of the present application, the applicant revised the Dosage and Administration statement for the already approved formulation of "Nuvaxovid Intramuscular Injection" in accordance with the "Modification of Dosage and Administration of COVID-19 Vaccines (in Japanese)" (PSB/PED Notification No. 0306-4 and PSB/PSD Notification No. 0306-1, dated March 6, 2024). Consequently, the applicant explained that the dosage regimen of the proposed product Nuvaxovid Intramuscular Injection 1 mL would be aligned with that of the approved formulation and that the dosage regimen would also be set for the monovalent (Omicron JN.1) vaccine. The proposed Dosage and Administration presented during the review are as follows:

Individuals aged ≥12 years
A single dose of 0.5 mL is injected intramuscularly.

Individuals aged ≥6 and <12 years
As the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 3 weeks apart.
Applies to the following vaccine product:
• Vaccine product containing recombinant spike protein of SARS-CoV-2 (the Omicron variant)

(Underline denotes additions.)

The applicant's explanation about the dosage regimen setting:
For the approved formulation of the monovalent (Original) vaccine, the dosage regimen was approved for primary series and booster doses before the revision of the Dosage and Administration statement. The approved primary series targeted individuals aged ≥6 years, while the approved booster dose targeted individuals aged ≥12 years.

As explained in Sections 7.R.2 and 7.R.3, the monovalent (Omicron JN.1) vaccine is expected to exhibit adequate efficacy with acceptable safety when administered to individuals aged ≥6 years for primary series and in individuals aged ≥12 years for booster dose. The dosage regimen of the monovalent (Omicron JN.1) vaccine should align with that of the approved monovalent (Original) vaccine, as well as with the dosages regimens for the vaccines used in Study 311 Part 2 and Study 313 Part 1, and the following dosage regimen is selected: 0.5 mL (5 μg of SARS-CoV-2 rS) per dose administered intramuscularly, as the primary series in individuals aged ≥6 years and booster dose in individuals aged ≥12 years. Since the Dosage and Administration for the already approved vaccine product have been revised in accordance with the notification, the applicant has reflected this revision in the proposed Dosage and Administration for the proposed product. For individuals aged ≥12 years, the Dosage and Administration of the monovalent (Omicron JN.1) vaccine are "A single dose of 0.5 mL is injected intramuscularly," and for individuals aged ≥6 and <12 years, the dosage regimen are "For the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 3 weeks apart." Currently, clinical studies are being conducted to allow primary series for children aged <6 years and booster dose for individuals aged <12 years, with plans to expand the target age for vaccination in the future.

PMDA's view:
Based on the review results in Sections "7.R.2 Efficacy" and "7.R.3 Safety," it is acceptable to select the dosage of the monovalent (Omicron JN.1) vaccine at 0.5 mL per dose (5 μg of SARS-CoV-2 rS) to match that of the approved monovalent (Original) vaccine, and to specify the dosage regimen for each age group as proposed by the applicant. The specification of the applicable formulation, as proposed by the applicant, is unnecessary in the Dosage and Administration statement, as addressed in Section 7.R.4 regarding the description of indication.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance for Nuvaxovid:

The clinical study results submitted for the present application, results of clinical studies on both the monovalent (Original) vaccine and variant-adapted vaccines conducted in and outside of Japan, and safety information obtained from post-marketing surveillance data, suggest that the safety profile of Nuvaxovid is consistent, regardless of the target SARS-CoV-2 strain or the valency of the vaccine. The safety of the monovalent (Omicron JN.1) vaccine is also considered acceptable [see Section 7.R.3]. No new safety specifications have been identified for the present application. Accordingly, the applicant should conduct routine pharmacovigilance activities, including the collection, evaluation, and analysis of various information, such as spontaneous reports, published literature, and conference presentation in and outside of Japan, as well as regulatory actions in foreign countries. Then, safety measures should be determined and implemented based on the results of these activities.

PMDA's view:

Although no specific data are currently available regarding the vaccination with the monovalent (Omicron JN.1) vaccine, the accrued safety data on Nuvaxovid have identified no new safety concerns. At this stage, no additional post-marketing surveillance is necessary for the collection of safety data on the monovalent (Omicron JN.1) vaccine. Instead, routine pharmacovigilance activities are sufficient for monitoring its safety profile. If the results of pharmacovigilance activities reveal new safety concerns about Nuvaxovid, appropriate measures should be taken as necessary. Accordingly, PMDA concluded that the risk management plan (draft) for Nuvaxovid should include the safety specifications presented in Table 15, and the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 16.

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

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis	• Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) • Myocarditis, pericarditis	• Safety in pregnant and lactating women receiving the vaccination • Safety of booster dose of <u>Nuvaxovid Intramuscular Injection (monovalent, original strain)</u> after the primary series of another COVID-19 vaccine
Efficacy specification		
None		

Underline denotes additions arising from the present application.

Table 16. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Cohort survey (Research Program on Emerging and Re-emerging Infectious Diseases and Immunization) [Nuvaxovid Intramuscular Injection (monovalent, original strain)] • Post-marketing clinical study as an extension of Japanese booster dose clinical study (Study TAK-019-3001) [Nuvaxovid Intramuscular Injection (monovalent, original strain)] • Foreign phase III study (Study 2019nCoV-301) [Nuvaxovid Intramuscular Injection (monovalent, original strain) • Foreign phase I/II study (Study 2019nCoV-101) [Nuvaxovid Intramuscular Injection (monovalent, original strain)	• Organize and disseminate information for healthcare professionals (a proper use guide for Nuvaxovid) • Organize and disseminate information for vaccine recipients (for those who receive Nuvaxovid Intramuscular Injection)

Underline denotes additions arising from the present application.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) 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 monovalent (Omicron JN.1) vaccine has a certain level of efficacy in the prevention of COVID-19 and acceptable safety with no significant safety concerns. Taking into account the benefit-risk assessment based on the spread of SARS-CoV-2, individual characteristics, and other factors, the clinical significance of enabling the use of this variant-adapted vaccine is acknowledged.

As stated in the PMDA's conclusion in Sections "7.R.4 Clinical positioning and indication" and "7.R.5 Dosage and administration," the specification of the applicable formulation, which was included in the proposed Indication and Dosage and Administration, is unnecessary.

As a result of the above review, PMDA has concluded that Nuvaxovid may be approved for the indication and dosage and administration as shown below, with the following approval conditions. The re-examination period for the present application is the remainder of the re-examination period for the

initial approval of the product (until April 18, 2030). The product is classified as a biological product. The vaccine product is classified as a powerful drug.

Indication

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

Dosage and Administration

Individuals aged ≥12 years

A single dose of 0.5 mL is injected intramuscularly.

Individuals aged ≥6 and <12 years

For the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 3 weeks apart.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only limited information is available 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 plan, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product.
3. Results of the clinical studies that are ongoing or planned in and outside of Japan should be submitted to PMDA promptly when they become available. At the same time, the applicant is required to take actions necessary to ensure that the updated efficacy and safety information on the product is easily accessible to healthcare professionals
4. The efficacy and safety data of the product will be accrued 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.

Appendix

List of Abbreviations

AESI	Adverse events of special interest
Bivalent (Original/Omicron BA.5) vaccine	Product containing SARS-CoV-2 rS (SARS-CoV-2 Omicron BA.5 lineage) 2.5 µg and SARS-CoV-2 rS (SARS-CoV-2 original strain) 2.5 µg, together with Matrix-M (adjuvant) 50 µg
CI	Confidence interval
COVID-19	Coronavirus disease
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GMTR	Ratio of GMT
ICMRA	International Coalition of Medicines Regulatory Authorities
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
Monovalent (Omicron BA.5) vaccine	Vaccine product containing SARS-CoV-2 rS (SARS-CoV-2 Omicron BA.5 lineage) 5 µg and Matrix-M (adjuvant) 50 µg
Monovalent (Omicron JN.1) vaccine	Vaccine product containing SARS-CoV-2 rS (SARS-CoV-2 Omicron JN.1 lineage) 5 µg and Matrix-M (adjuvant) 50 µg
Monovalent (Original) vaccine	Vaccine product containing SARS-CoV-2 rS (original SARS-CoV-2 strain) 5 µg and Matrix-M (adjuvant) 50 µg
Monovalent (Omicron XBB.1.5) vaccine	Vaccine product containing SARS-CoV-2 rS (SARS-CoV-2 Omicron XBB.1.5 lineage) 5 µg and Matrix-M (adjuvant) 50 µg
mRNA	Messenger RNA
Original strain	Wuhan-Hu-1 strain
PCR	Polymerase chain reaction
PMDA	Pharmaceuticals and Medical Devices Agency
PPAS	Per-Protocol Analysis Set
RNA	Ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
SARS-CoV-2 rS	SARS-CoV-2 recombinant spike protein
Study 311	Study 2019nCoV-311
Study 313	Study 2019nCoV-313
Nuvaxovid	Nuvaxovid Intramuscular Injection
ULOQ	Upper limit of quantification
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
WHO	World Health Organization