Report on the Deliberation Results

November 10, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Comirnaty Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran [JAN])
Applicant	Pfizer Japan Inc.
Date of Application	September 28, 2021

Results of Deliberation

Under the current pandemic of disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on November 10, 2021, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below after changing the term *tsuika sesshu* to *tsuika meneki* (both words mean "booster dose," and therefore there is no change in the English translation) in "Dosage and Administration" and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

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

Report on Special Approval for Emergency

November 2, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Comirnaty Intramuscular Injection
Non-proprietary name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	September 28, 2021
Dosage Form/Strength	Injection: Each vial contains 0.225 mg of Tozinameran
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act. ("Handling of Drugs Submitted for Special Approval for Emergency (Request)" [PSEHB/PED Notification 1011-1, dated October 11, 2021]).
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the booster dose has efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19) and that the product has acceptable safety with no serious concerns about the safety profile.

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 approval conditions.

Indication

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

(No change)

Dosage and Administration

The product is diluted with 1.8 mL of physiological saline (Japanese Pharmacopoeia grade).
For the primary series, 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.
For a booster dose, a single dose of 0.3 mL is injected intramuscularly.

(Underlines donate additions)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (2) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (3) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.
   (4) The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of

the product in written form and have provided written informed consent through the vaccine screening questionnaire in advance.

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

Attachment

Report on Special Approval for Emergency (1)

October 20, 2021

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

Product Submitted for Approval

Brand Name	Comirnaty Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	September 28, 2021
Dosage Form/Strength	Injection: Each vial contains 0.225 mg of Tozinameran

Proposed Indication

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

(No change)

Proposed Dosage and Administration

The product is diluted with 1.8 mL of physiological saline (Japanese Pharmacopoeia grade).
Usually 2 doses (0.3 mL each) are injected intramuscularly, 3 weeks apart. <u>For a booster dose, a single dose of 0.3 mL is injected intramuscularly.</u>

(Underlines donate additions)

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List of Abbreviations

See Appendix.

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

Comirnaty is a vaccine containing messenger RNA (mRNA) encoding the spike protein of SARS-CoV-2 as the active ingredient. In February 2021, it was granted marketing approval for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)." In Japan, vaccination with Comirnaty in healthcare professionals was started in February 2021, followed by vaccination in elderly people and other populations. As of October 19, 2021, ≥60% of all Japanese population have received 2 doses of SARS-CoV-2 vaccine.
(https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html [last accessed on October 19, 2021])

While vaccination against SARS-CoV-2 was ongoing worldwide, SARS-CoV-2 infection started to resurge in many parts of the world around the summer of 2021.
(https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-october-2021 [last accessed on October 19, 2021]).
The resurgence was caused by the following factors:

(a) Relaxation of social activities such as lifting of coronavirus restrictions.
(b) Emergence of a highly infectious and transmissible Delta variant as the dominant strain (https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10623-covid19-57.html [last accessed on October 19, 2021]).
(c) Reduced preventive effect of SARS-CoV-2 vaccines, as suggested by breakthrough infection in some of the fully vaccinated people.
(https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html [last accessed on October 19, 2021]).

In response to these situations, some countries or regions in the world are giving a booster dose to individuals who have completed a primary series of a vaccine against SARS-CoV-2, as a hygienic measure against the resurgence. In Israel, for example, booster vaccination with Comirnaty was initiated at the end of July 2021 in elderly people who had completed the second dose of Comirnaty ≥5 months previously, and is being expanded to other age groups (*N Engl J Med.* 2021;385:1393-400).

The applicant amended the protocol of the then ongoing Study C4591001, which was initiated in April 2020 to investigate the efficacy and safety of the primary series of Comirnaty, and started a sub-study in February 2021 to investigate the immunogenicity and safety of a booster dose of Comirnaty in subjects who had completed the second dose of Comirnaty approximately 6 months previously. In September 22, 2021, based on the results of this study and other data, emergency use authorization was granted in the United States for a booster dose in populations at high risk of severe COVID-19. In EU, an extension of the conditional marketing authorization to introduce a booster dose was approved in October 5, 2021. In Japan, in addition to Comirnaty, COVID-19 Vaccine Moderna Intramuscular Injection (Takeda Pharmaceutical Co., Ltd.) and Vaxzevria Intramuscular Injection (AstraZeneca K.K.) are approved for marketing as vaccines against SARS-CoV-2; however, as of October 19, 2021, there is no SARS-CoV-2 vaccine approved for a booster dose.

In Japan, the applicant has submitted a partial change application for introducing a dosage and administration of a booster dose of Comirnaty, based on the results of Study C4591001.

In this report, 2 doses of Comirnaty administered to SARS-CoV-2-unvaccinated individuals is referred to as “primary series,” and the third dose approximately 6 months after completing the primary series as “a booster dose.”

This report contains the results of review conducted based on the data submitted by the applicant, in accordance with the “Handling of Drugs Submitted for Special Approval for Emergency (Request)” (PSEHB/PED Notification 1011-1, dated October 11, 2021).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application relates to a new dosage, “Data Relating to Quality” were not submitted.

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

Although the present application relates to a new dosage, no new data were submitted under this section, because the non-clinical pharmacology data had been evaluated during the review process for the initial approval.

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

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

5. Toxicity and Outline of the Review Conducted by PMDA

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

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

6.1 Biopharmaceutic Studies and Associated Analytical Methods

Neutralizing antibody in serum was measured by a neutralization using SARS-CoV-2 (reference strain) transfected with fluorescent protein reporter gene (phase II/III part of Study C4591001).

6.2 Clinical pharmacology

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

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

The applicant submitted the results of a clinical study (Table 1) as the efficacy and safety evaluation data. Study C4591001 data related to the 2 dose-primary series of Comirnaty had been evaluated during the review process for the initial approval. For the present application, the applicant submitted results of the sub-study related to the booster dose after the primary series.

Table 1. Summary of clinical study

Country	Phase	Population	No. of subjects enrolled	Dosage regimen	Main evaluation items
USA	C4591001 sub-study (phase I/II/III parts)	Phase I part: Healthy adults 18-55 and 65-85 years of age who had completed a 2-dose primary series of Comirnaty or BNT162b1 [a)] Phase II/III part: Healthy subjects 18 to 55 years of age who had completed a 2-dose primary series of Comirnaty	Phase I part: 23 subjects who had received Comirnaty 30 μg in the primary series Phase II/III part: 312 subjects (Comirnaty group)	Phase I part: A single dose of Comirnaty 30 μg was administered intramuscularly 6 to 12 months after the primary series. Phase II/III part: A single dose of Comirnaty 30 μg or BNT162b2$_{SA}$ [b)] 30 μg was administered intramuscularly 5 to 7 months after the primary series.	Immunogenicity Safety Tolerability

a) BNT162b1: A vaccine candidate containing mRNA that encodes RBD of SARS-CoV-2 spike protein
b) BNT162b2$_{SA}$: A vaccine candidate targeted at Beta variant

7.1 Foreign Phase I/II/III Study (CTD 5.3.5.1.1: Study C4591001; study period - Phase I Part, ongoing since April 2020 [data cutoff date, May 13, 2021]); Phase II/III Part, ongoing since July 2020 [data cutoff date, June 17, 2021])

Study C4591001 was initiated as a randomized, observer-blind, placebo-controlled, parallel-group study to investigate the efficacy, safety, etc., of the primary series of Comirnaty. Table 2 shows the outline of the study plan for the primary series. Data on the efficacy, safety, etc., of the primary series (data cut-off date: November 14, 2021) were evaluated during the review process for the initial approval of Comirnaty (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021]).

Table 2. Study C4591001: Outline of study plan for primary series (previously evaluated)

Country	Part	Population	Target sample size	Dosage regimen	Objectives
United States	I	Healthy subjects 18-55 and 65-85 years of age	Combination of each dose of Comirnaty or BNT162b1 [a)] and age ranges (18-55, 65-85): 12 in each group [b)] Placebo: 3 in each group [b)]	Comirnaty (10, 20, 30 μg), BNT162b1 (10, 20, 30, 100 μg), or placebo was administered intramuscularly twice, 21 days apart.	Safety Tolerability
Six foreign counties including US	II/III	Healthy subjects ≥12 years of age	Comirnaty: 21,999 Placebo: 21,999	Two doses of Comirnaty 30 μg or placebo were administered intramuscularly, 21 days apart.	Efficacy Safety

a) BNT162b1: A vaccine candidate containing mRNA that encodes RBD of SARS-CoV-2 spike protein
b) Treatment groups consisted of subjects 18 to 55 years of age receiving Comirnaty or BNT162b1 at 10, 20, or 30 μg; subjects 65 to 85 years of age receiving Comirnaty or BNT162b1 at 10, 20, or 30 μg; and subjects 18 to 55 years of age receiving BNT162b1 100 μg.

The study protocol included a 24-month observation period after a 2-dose primary series of the study vaccine. During the observation period, the protocol was amended to add a sub-study to evaluate a booster dose administered approximately 6 months after completion of the primary series (protocol amendment date: phase I part on [redacted], 20[redacted]; phase II/III part on [redacted], 20[redacted]).[1)]

[1)] In addition to the sub-study of a booster dose of Comirnaty 30 μg, the following plans were added to Phase II/III part: (a) 2 booster doses of BNT162b2$_{SA}$ and a 2-dose primary series of BNT162b2$_{SA}$ (protocol amendment date: [redacted], 20[redacted]) and (b) a single booster dose of Comirnaty at a low dose (5 or 10 μg) (protocol amendment date: [redacted], 20[redacted]). Results of (a) and (b) were not submitted in the present application.

7.1.1 Sub-study in phase I part

In the phase I part of Study C4591001, the safety of Comirnaty administered 6 to 12 months after the primary series was investigated in an exploratory manner in subjects 18 to 55 years and 65 to 85 years of age who had received a 2-dose primary series of Comirnaty or BNT162b1. The investigation was conducted at 2 study sites in the United States.

A single dose of Comirnaty 30 μg was administered intramuscularly.

For the present application, the applicant submitted data regarding a booster dose of Comirnaty in subjects who had been assigned to receive a primary series of Comirnaty 30 μg.

Of the 24 subjects assigned to the Comirnaty 30 μg group who received a 2-dose primary series of Comirnaty, 23 (11 subjects 18 to 55 years old and 12 subjects 65 to 85 years old) received a booster dose of Comirnaty, and the remaining 1 subject did not consent to receive a booster dose. All of the 23 subjects were included in the safety analysis population.

The severity of adverse events were evaluated according to the Food and Drug Administration (FDA) Guidance "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).[2)]

The definition of observation periods:

- Reactogenicity events (local reactions [injection site pain, redness, and swelling] and systemic events [pyrexia (≥38°C), fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia]) were collected by the subject diary for 7 days after the booster dose.
- Adverse events (excluding reactogenicity events collected by the subject diary for 7 days after the booster dose) and serious adverse events were collected for 1 month after the booster dose.

Table 3 shows reactogenicity events that occurred within 7 days after the booster dose of Comirnaty.

Table 3. Reactogenicity events occurring within 7 days after booster dose (safety analysis population)

Event terms	18-55 years of age (N = 11) n (%)	65-85 years of age (N = 12) n (%)
Local reactions (total)	9 (81.8)	8 (66.7)
Injection site pain	9 (81.8)	8 (66.7)
Swelling	0	0
Redness	0	0
Systemic events (total)	10 (90.9)	8 (66.7)
Fatigue	7 (63.6)	5 (41.7)
Myalgia	7 (63.6)	4 (33.3)
Chills	7 (63.6)	2 (16.7)
Headache	6 (54.5)	5 (41.7)
Pyrexia	3 (27.3)	0
Arthralgia	2 (18.2)	2 (16.7)
Diarrhoea	1 (9.1)	0
Vomiting	0	0

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

2) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (last accessed on October 19, 2021)

No adverse events were reported up to 1 month after the booster dose of Comirnaty.

7.1.2 Sub-study in phase II/III part

In phase II/III part of Study C4591001, the safety and immunogenicity of a booster dose of Comirnaty or BNT162b2$_{SA}$ administered 5 to 7 months after the second dose of the primary series were investigated in part of 18- to 55-year-old subjects[3)] (approximately 600 subjects)[4)] who had completed a 2-dose primary series of Comirnaty 30 μg and consented to receive a booster dose. The investigation was conducted at 24 study sites in the United States. For the study of the booster dose, subjects were randomized to the Comirnaty group and the BNT162b2$_{SA}$ group at a 1:1 ratio (300 subjects each). The subjects, the investigators, and other study staff (except for study vaccine storage manager, and those who prepared or injected the study vaccine) and the sponsor (except for prespecified staff members independent of the study) were blinded to the study.

A single dose of Comirnaty 30 μg or BNT162b2$_{SA}$ 30 μg was administered intramuscularly.

In the present application, the applicant submitted only data from the Comirnaty group and did not submitted data from the BNT162b2$_{SA}$ group.

Of 312 subjects randomized to the Comirnaty group, 306 who received the booster dose of Comirnaty were included in the safety analysis population. A total of 306 subjects with at least 1 valid immunogenicity result after the booster dose of Comirnaty were included in the all-available immunogenicity population. Of the above 312 subjects, 268 were included in the evaluable immunogenicity population, and the remaining 44 were excluded (30 with serious protocol deviation within 1 month after the booster dose, 15 without a valid immunogenicity result within the specified period after the booster dose, 6 not receiving the booster dose of Comirnaty, 1 not complying with the specified interval between the first and second doses of the primary series [some had more than 1 deviation]). Both the all-available immunogenicity population and the evaluable immunogenicity population were included in the primary immunogenicity analysis set.

The following 2 primary endpoints were used to evaluate immunogenicity, based on the 50% neutralizing antibody titer in serum against SARS-CoV-2 (reference strain) in subjects without serological or virological evidence of SARS-CoV-2 infection up to 1 month after the booster dose:

(a) Geometric mean ratio (GMR) of the neutralizing antibody titer at 1 month after the booster dose to the titer at 1 month after the second dose

(b) Difference in the neutralizing antibody response rate between 1 month after the booster dose and 1 month after the second dose. (The neutralizing antibody response rate means “the percentage of subjects who showed a ≥4-fold increase in the neutralizing antibody titer from

3) Subjects at some of the study sites in the United States who met the criterion “serum sample at 1 month after the second dose is available” in addition to the same inclusion/exclusion criteria used for the primary series.

4) By assuming that GMR of the neutralizing antibody titer after the booster dose of Comirnaty to that after the second dose to be 1 and the logarithmically transformed standard deviation to be 0.7.4, the statistical power with 240 subjects in each group is >99.9%, with 1-sided significance level of 0.0125 and the non-inferiority margin of 0.67. By assuming the antibody response rate after the second dose and after the booster dose to be 90% and the percentage of different antibody response at the 2 time points to be 10%, the statistical power is 99% with 240 subjects in each group, with 1-sided significance level of 0.0125 and non-inferiority margin of −10%. The target sample size was set at 300 subjects in each group by assuming the percentage of unevaluable subjects to be 20%.

the titer before the first dose" [the titer below the lower quantitation limit was regarded as the lower limit of quantitation.])

The non-inferiority of the booster dose to the second dose was evaluated based on these endpoints.

Different regulatory agencies required, as a prerequisite condition for approval, that the test be confirmed either by (a) the non-inferiority test of GMR alone or (b) the non-inferiority test of both GMR and the difference in the neutralizing antibody response rate. Therefore the one-sided significance level of 0.0125 was used for each endpoint to evaluate the endpoints separately.

Table 4 shows neutralizing antibody titer in serum at 1 month after the booster dose and at 1 month after the second dose of Comirnaty. The lower limit of the 2-sided 97.5% confidence interval (CI) of GMR exceeded the lower non-inferiority margin of 0.67, with the point estimate of ≥0.8. Thus the prespecified non-inferiority criterion was met.

Table 4. Serum anti-SARS-CoV-2 neutralizing antibody titer

Analysis set	Number of subjects analyzed	GMT [2-sided 95%CI]		GMR [2-sided 97.5%CI] (after booster dose/ after second dose)
		After booster dose	After second dose	
All-available immunogenicity population	236[a)]	2382.4 [2140.8, 2651.3]	764.9 [670.4, 872.6]	3.11 [2.63, 3.68]
Evaluable immunogenicity population	210[a)]	2476.4 [2210.1, 2774.9]	753.7 [658.2, 863.1]	3.29 [2.76, 3.91]

a) Subjects who had no serological or virological evidence of SARS-CoV-2 infection within 1 month after a booster dose, and were tested for neutralizing antibody at 1 month after the second dose and at 1 month after the booster dose.

Table 5 shows the serum neutralizing antibody response rate at 1 month after the booster dose and at 1 month after the second dose.

The lower limit of the 2-sided 97.5% CI of the difference in the antibody response rate exceeded the non-inferiority margin of -10%, meeting the prespecified non-inferiority criterion.

Table 5. Serum anti-SARS-CoV-2 neutralizing antibody response rate

Analysis set	Number of subjects analyzed	Antibody response rate (number of subjects)		Difference in antibody response rate [2-sided 97.5% CI] [b)] (after booster dose/ after second dose)
		After booster dose	After second dose	
All-available immunogenicity population	224[a)]	99.6% (223 of 224)	98.2% (220 of 224)	1.3% [-0.6, 3.3]
Evaluable immunogenicity population	198[a)]	99.5% (197 of 198)	98.0% (194 of 198)	1.5% [-0.7, 3.7]

a) Subjects who had no serological or virological evidence of SARS-CoV-2 infection within 1 month after a booster dose, and were tested for neutralizing antibody before the first dose, at 1 month after the second dose, and at 1 month after the booster dose.
b) Adjusted Wald test (*Stat Med.* 2005;24:729-40)

The severity of adverse events was graded based on the same grading scale used in phase I part [see Section 7.1.1].

The definition of observation periods:

- Reactogenicity events (local reactions [injection site pain, redness, and swelling] and systemic events [pyrexia (≥38°C), fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia]) were collected by the subject diary for 7 days after the booster dose.
- Adverse events (excluding reactogenicity events collected by the subject diary for 7 days after the booster dose) were collected for 1 month after the booster dose.
- Serious adverse events were collected for 6 months after the booster dose.

In the safety analysis population, the median follow-up period between the booster dose and the data cut-off date (June 17, 2021) was 2.6 months (range, 1.1 to 2.8 months; <2 months in 1 subject and ≥2 months in 305 subjects).

Table 6 shows reactogenicity events occurring within 7 days after the booster dose of Comirnaty in 289 subjects who provided the subject diary.

Table 6. Reactogenicity events occurring within 7 days after booster dose (safety analysis population)

Event terms	Comirnaty (N=289) n (%)
Local reactions (total)	240 (83.0)
Injection site pain	240 (83.0)
Swelling	23 (8.0)
Redness	17 (5.9)
Systemic reaction (total)	223 (77.2)
Fatigue	184 (63.7)
Headache	140 (48.4)
Myalgia	113 (39.1)
Chills	84 (29.1)
Arthralgia	73 (25.3)
Diarrhoea	25 (8.7)
Pyrexia	25 (8.7)
Vomiting	5 (1.7)

N = number of subjects analyzed, n = number of subjects with events (%)

The incidences of adverse events and adverse reactions (adverse events for which causal relationship to the study vaccine could not be ruled out) within 1 month after the booster dose were 14.4% (44 of 306 subjects) and 7.8% (24 of 306 subjects), respectively. Table 7 shows adverse events and adverse reactions observed in ≥2 subjects.

Table 7. Adverse events and adverse reactions observed in ≥2 subjects within 1 month after booster dose

Event terms (preferred term: MedDRA ver.24.0)	Comirnaty (N=306)	
	Adverse events n (%)	Adverse reactions n (%)
All events	44 (14.4)	24 (7.8)
Lymphadenopathy	16 (5.2)	16 (5.2)
Nausea	2 (0.7)	2 (0.7)
Injection site pain	2 (0.7)	2 (0.7)
Pain	2 (0.7)	2 (0.7)
Back pain	2 (0.7)	0
Neck pain	2 (0.7)	1 (0.3)
Headache	2 (0.7)	1 (0.3)
Anxiety	2 (0.7)	0
Dermatitis contact	2 (0.7)	0

N = number of subjects analyzed, n = number of subjects with events (%)

A serious adverse event (acute myocardial infarction) was observed in 1 subject on or before the data cut-off date (June 17, 2021). The outcome was reported as recovered/resolved with sequelae, and its causal relationship to Comirnaty was ruled out.

There were no death or adverse events leading to study discontinuation on or before the data cut-off date (June 17, 2021).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical significance of booster dose

The applicant's explanation about the clinical significance of the booster dose of Comirnaty:
After the initial approval of Comirnaty, the following information on the efficacy of the primary series of Comirnaty was obtained from clinical studies and reports from foreign countries.

(a) Results of Study C4591001

Efficacy and immunogenicity data approximately 6 months after the primary series became available (data cut-off date: March 13, 2021, CTD 5.3.5.1.2).

Efficacy results:

The results of analysis at approximately 6 months (median) after the second dose of the study vaccine in the evaluable efficacy population (the primary efficacy population for the primary series in phase II/III part)[5], showed that vaccine efficacy (VE) [2-sided 95% CI] against COVID-19[6] was 91.3% [89.0, 93.2] in subjects without prior SARS-CoV-2 infection[7] (20,998 in the Comirnaty group, 21,096 in the placebo group) and 91.1% [88.8, 93.0] in subjects with and without evidence of prior SARS-CoV-2 infection (22,166 in the Comirnaty group, 22,320 in the placebo group). VE [2-sided 95%CI], classified by the period between the second dose and the onset of COVID-19, was 96.2% [93.3, 98.1] for ≥7 days to <2 months, 90.1% [86.6, 92.9] for ≥2 months to <4 months, and 83.7% [74.7, 89.9] for ≥4 months (in the population receiving at least 1 dose of the study vaccine [23,040 in the Comirnaty group, 23,037 in the placebo group]). VE against severe COVID-19[8] [2-sided 95%CI] in the evaluable efficacy population was 95.3% [71.0, 99.9] in subjects without prior SARS-CoV-2 infection and 95.3% [70.9, 99.9] in subjects with and without evidence of prior SARS-CoV-2 infection. At the initial approval, VE against severe COVID-19 [95%CI] was 95.0% [90.3, 97.6] in subjects without prior SARS-CoV-2 infection and 94.6% [89.9, 97.3] in subjects with and without evidence of prior SARS-CoV-2 infection, and VE [95%CI] against severe COVID-19 was 66.4% [-124.8, 96.3] and 66.3% [-125.5, 96.3], respectively (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021]).

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5) Defined as subjects who received the second dose of study vaccine between 19 and 42 days after the first dose without any significant protocol deviation until 7 days after the second dose.

6) A confirmed COVID-19 case was defined as a subject who has at least 1 of the following symptoms with a positive SARSCoV-2 result by nasopharyngeal swab nucleic acid amplification testing: (a) Pyrexia, (b) new onset or worsening of cough, (c) new onset or worsening of shortness of breath, (d) chills, (e) new onset or worsening of myalgia, (f) new loss of taste or smell, (g) sore throat, (h) diarrhoea, and (i) vomiting

7) "Prior SARS-CoV-2 infection" is defined as SARS-CoV-2 infection confirmed before the first dose until 7 days after the second dose of study vaccine.

8) Severe COVID-19 was defined as having at least 1 of the following conditions in subjects with symptoms meeting the definition of COVID-19: (a) Clinical signs at rest suggesting severe systemic disease (respiratory rate ≥30/min, heart rate ≥125/min, SpO_2 ≤93% or PaO_2/FiO_2 <300 mmHg), (b) respiratory failure (requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO]), (c) shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors), (d) acute renal, hepatic, or neurologic dysfunction, (e) admission to an ICU, and (f) death.

Immunogenicity results:
Geometric mean titer (GMT) [2-sided 95% CI] of the neutralizing antibody at 6 months after the second dose of Comirnaty 30 μg in the phase I part was 54.7 [24.7, 121.1] in subjects 18 to 55 years of age (N = 10) and 29.0 [19.4, 43.5] in subjects 65 to 85 years of age (N = 11). These values were lower than the GMTs at 1 month after the second dose (179.2 [102.3, 313.8] in subjects 18 to 55 years of age [N = 11] and 151.6 [58.6, 392.1] in subjects 65 to 85 years of age [N = 11]).

Furthermore, the relationship between the timing of Comirnaty vaccination and occurrence of COVID-19 was investigated during the upsurge of Delta variant (July 1, 2021 through August 31, 2021). In Study C4591001, subjects were randomized to receive the primary series of Comirnaty or placebo. Subjects in the placebo group who wished to receive, and were eligible for, Comirnaty were allowed to receive Comirnaty in an unblinded manner if either of the following occurred: (a) Comirnaty or any other SARS-CoV-2 vaccine was approved in the country or region of the subject during the follow-up period after the second dose of the study vaccine; or (b) 6 months had passed since the second dose of the study vaccine. Using the data from ≥16 year-old subjects extracted on September 2, 2021, a post hoc analysis was conducted to compare the incidence rate of COVID-19 between the population receiving 2 doses of Comirnaty during the early period of the study (18,727 subjects who were randomized to Comirnaty group and thus received Comirnaty) and the population receiving 2 doses of Comirnaty at a later stage of the study (17,748 subjects who were randomized to the placebo group and later received Comirnaty). The median duration between the second dose of Comirnaty and July 1, 2021 was 10.1 months (≥8 months in approximately 97% of subjects) in the "early" vaccine recipients and 4.8 months (<6 months in approximately 90% of subjects) in the "late" vaccine recipients. The incidence rate of COVID-19 was higher in the "early" vaccine recipients (70.3/1,000 person years) than in the "late" vaccine recipients (51.6/1,000 person years). Severe COVID-19 was observed in 3 subjects, all of whom were "early" vaccine recipients.

(b) Reports from foreign countries

In the United States and Israel, the primary vaccination with Comirnaty was started in December 2020, and, as of October 19, 2021, 56% and 64%, respectively, of the entire population have completed a primary series of a SARS-CoV-2 vaccine (https://ourworldindata.org/covid-vaccinations#frequently-asked-questions [last accessed on October 19, 2021]). However, the effectiveness against SARS-CoV-2 infection and against COVID-19 waned approximately 6 to 8 months after the second dose in both countries. (*MMWR Morb Mortal Wkly Rep.* 2021;70:1163-6, medRxiv preprint doi: https://doi.org/10.1101/2021.07.29.21261317, https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf [last accessed on October 19, 2021]).
Comirnaty has been reported to remain highly effective against COVID-19-associated hospitalization and severe COVID-19 (*MMWR Morb Mortal Wkly Rep.* 2021;70:1306-11, *MMWR Morb Mortal Wkly Rep.* 2021;70:1156-62), whereas its effectiveness against severe COVID-19 in people ≥65 years of age has been reported to decline over time.

(COVID-19 Weekly Data. Division of Epidemiology Public Health Services 11/08/2021 (https://www.gov.il/BlobFolder/reports/vpb-12082021/he/files_publications_corona_vpb-12082021-01.pdf [last accessed on October 19, 2021]).

Although several therapeutic agents are currently available for the treatment of COVID-19, disease prevention by SARS-CoV-2 vaccines continues to have an important role under the current situation of persistent COVID-19 pandemic.

It is unknown how long the efficacy of the primary series of Comirnaty against COVID-19 lasts, but the post hoc analysis of Study C4591001 and reports from foreign countries suggest that the efficacy of Comirnaty wanes over time. Also, the follow-up data of Study C4591001 shows a decrease in the neutralizing antibody titer over time. A survey of healthcare professionals showed that the decrease in the neutralizing antibody titer was correlated with SARS-CoV-2 infections (breakthrough infections) in those who have been vaccinated with Comirnaty (*N Engl J Med.* 2021;385:1474-84). This suggests that restoring the declined neutralizing antibody titer by a booster dose may enhance the preventive effect against COVID-19.

In order to evaluate the usefulness of a booster dose of Comirnaty, a sub-study of Study C4591001 was conducted to investigate the immunogenicity and safety of the booster dose in subjects who had received the primary series approximately 6 months previously [see Section 7.1]. Results confirmed that the booster dose elicited a high neutralizing antibody titer against SARS-CoV-2. These results, together with the already demonstrated efficacy of primary series of Comirnaty and foreign reports on neutralizing antibody titers against Delta variant and on booster dose, show that the booster dose of Comirnaty is expected to be effective [see Section 7.R.2]. Further, the safety profile of the booster dose in the sub-study of Study C4591001 was similar to that of the primary series, with no serious safety concerns [see Section 7.R.3].

These findings show the clinical significance of providing a booster dose of Comirnaty to individuals who received the primary series of Comirnaty approximately 6 months previously, because it prevents COVID-19 caused by breakthrough infection, thereby providing a high preventive effect against COVID-19 even in the midst of prevalence of Delta variant.

PMDA's view:
At the Expert Discussion during the review process for the initial approval of Comirnaty, the expert advisers commented that the necessity of a booster dose should be investigated when the duration of vaccine efficacy is established based on the post-marketing data [Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021]). At the current moment, there is neither established index for judging the duration of the preventive effect of Comirnaty nor an established threshold of the neutralizing antibody titer with a preventive effect. The follow-up data from Study C4591001 showed a decrease in the neutralizing antibody titer at 6 months after the primary series of Comirnaty, but whether the decreased level is insufficient for preventing COVID-19 remains unknown. How long the primary series of Comirnaty remains effective is also unclear. Nevertheless, a post hoc analysis during the period of Delta predominance in Study C4591001 showed,

albeit as a preliminary result, that the incidence rate of COVID-19 was higher in the "early" vaccine recipients than in the "late" vaccine recipients, possibly partly due to the decline in the neutralizing antibody titer over time.

Some foreign countries or regions are introducing a booster dose after the primary series of SARS-CoV-2 vaccine as a public health measure. The status of the booster dose of Comirnaty in major countries and regions is as follows:

Israel:
On July 30, 2021, a booster dose was started in elderly people who had received the second dose of Comirnaty at least 5 months previously, and the age range for the booster dose is being expanded (*N Engl J Med.* 2021;385:1393-400).

United States:
On September 22, 2021, emergency use authorization was granted for a booster dose of Comirnaty administered at ≥6 months after the second dose of the primary series of Comirnaty in the following populations: (a) ≥65 years of age, (b) 18 to 64 years of age at a high risk of severe COVID-19, and (c) 18 to 64 years of age who are frequently exposed to SARS-CoV-2 because of occupational or institutional setting, with a resultant increased risk of severe COVID-19 and other serious COVID-19-associated complications.

Taking into account that Delta variant is the predominant strain and that cases of COVID-19 are increasing in the United States, Centers for Disease Control and Prevention (CDC) recommends a booster dose in the following populations because it is consider to help enhance the preventive effect against severe COVID-19 in those with high risk of exposure to SARS-CoV-2 or with high risk of complications associated with severe SARS-CoV-2
(https://www.cdc.gov/media/releases/2021/p0924-booster-recommendations-.html [last accessed on October 19, 2021]):

- People aged 65 years and older and residents in long-term care settings should receive a booster dose of Comirnaty.
- People aged 50–64 years with underlying medical conditions should receive a booster dose of Comirnaty.
- People aged 18–49 years with underlying medical conditions may receive a booster dose of Comirnaty, based on their individual benefits and risks
- People aged 18-64 years who are at increased risk for COVID-19 exposure and transmission because of occupational or institutional setting may receive a booster dose of Comirnaty, based on their individual benefits and risks.

EU:
On October 5, 2021, an extension of the conditional marketing approval was granted to allow individuals ≥18 years of age who have completed the primary series to receive a booster dose at least 6 months after the second dose of Comirnaty. European Medicines Agency (EMA) states that each

country may issue official recommendations on the use of booster dose, based on the efficacy and safety data.
(https://www.ema.europa.eu/en/news/comirnaty-spikevax-ema-recommendations-extra-doses-boosters [last accessed on October 19, 2021]).

In Japan, the vaccination program of the primary series of SARS-CoV-2 vaccines has been implemented rapidly and, as of October 19, 2021, the number of newly infected people are decreasing (https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html [last accessed on October 19, 2021]). However, the recent resurgence of SARS-CoV-2 infection in foreign countries that had started a SARS-CoV-2 vaccination program ahead of Japan, suggests that a large scale outbreak of SARS-CoV-2 infection may occur and put the medical system under heavy strain in Japan even after most of the Japanese people have completed the primary series of a SARS-CoV-2 vaccine and several treatment options against COVID-19 have become available. A booster dose may restore the declined preventive effect against the onset of COVID-19 due to various causes, such as the decreased neutralizing antibody titer over time and the prevalence of new variants. Therefore, a booster dose should be considered as a measure for protecting the medical system against the potential outbreak of SARS-CoV-2 in Japan.

Results of the clinical studies, etc., suggest that the booster dose of Comirnaty provides a certain degree of effectiveness [see Section 7.R.2], with the acceptable safety profile [see Section 7.R.3]. However, the benefit/risk balance of the booster dose varies depending on the epidemic situation of COVID-19, the prevalent strain, and the presence of risk factors for severe COVID-19 in individuals; it is also different from the benefit/risk balance of the primary series, which is basically indicated for all individuals ≥12 years of age.

The effectiveness of the primary series in preventing SARS-CoV-2 infection and COVID-19 has been reported to wane over time, but the effectiveness in preventing severe COVID-19 has been reported to last at a high level regardless of variants (*Lancet.* 2021;398:1377-80). In the population ≥65 years of age, however, the preventive effect against severe COVID-19 has been reported to wane.
(COVID-19 Weekly Data. Division of Epidemiology Public Health Services 11/08/2021
(https://www.gov.il/BlobFolder/reports/vpb-12082021/he/files_publications_corona_vpb-12082021-01.pdf [last accessed on October 19, 2021]).
A booster dose will have a certain clinical significance for preventing severe COVID-19 and serious outcomes in individuals at high risk of severe COVID-19, including elderly people. However, given the current status of SARS-CoV-2 vaccination, SARS-CoV-2 epidemic, etc., in Japan, it is not urgently needed to give a booster dose to all of those who have completed the primary series.

Thus, the necessity of a booster dose should be judged by taking into account the epidemic status of SARS-CoV-2, the prevalent strain, risk factors of severe COVID-19 in each individual, the extent of exposure to SARS-CoV-2, etc., based on the benefit/risk balance of the booster dose.

7.R.2 Efficacy

7.R.2.1 Protocol of Study C4591001

The applicant's explanation about the plan for the sub-study of Study C4591001:
During the follow-up period after the primary series in Study C4591001, the study protocol was amended to include a sub-study to investigate the immunogenicity and safety of a booster dose of Comirnaty in subjects 18 to 55 years of age who had received the second dose approximately 6 months previously [see Section 7.11].

The sub-study was planned in accordance with the "Appendix 2: Evaluation of vaccines to address emerging SARS-CoV-2 variants" of FDA's "Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19" (February 2021 version available at the time of the planning).[9)] FDA confirmed to the applicant that the Appendix was applicable also to the development of booster vaccination with the same vaccine used for the primary series.

The timing of the booster dose was set at 6 months after the second dose of Comirnaty because the booster dose of other vaccines against infectious diseases is mostly given 6 months after the initial vaccination.

The eligible age range for the sub-study was set between 18 to 55 years in accordance with the Appendix of the FDA Guidance. Since the primary series of Comirnaty is approved for individuals ≥12 years of age, results of the sub-study can be extrapolated to the age ranges outside 18 to 55 years.

In accordance with the Appendix of FDA Guidance, the non-inferiority of the booster dose to the second dose was to be evaluated based on the following primary endpoints:

(a) Geometric mean ratio (GMR) of the neutralizing antibody titer at 1 month after the booster dose to the titer at 1 month after the second dose.
(b) Difference in the neutralizing antibody response rate between 1 month after the booster dose and 1 month after the second dose.

A survey of healthcare professionals has reported that SARS-CoV-2 infection in those who had received the primary series of Comirnaty was correlated with a decline in the neutralizing antibody titer (*N Engl J Med.* 2021;385:1474-84), suggesting that restoring the neutralizing antibody titer by the booster dose of Comirnaty may enhance the preventive effect against COVID-19. This sub-study does not plan to evaluate the efficacy of a booster dose. However, given the high effectiveness achieved by the primary series of Comirnaty, the booster dose can be considered effective if the immunogenicity (evaluated based on the protocol prepared in accordance with the Appendix of FDA Guidance) at 1 month after the booster dose is non-inferior to that at 1 month after the second dose.

As for the success criterion for GMR, FDA stated (at the discussion with the applicant) that GMR data with a low point estimate would be difficult to interpret. Therefore, a criterion for the point estimate of GMR was established with a 1.5-fold non-inferiority margin.

9) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19 (last accessed on October 19, 2021)

PMDA's view:
As for the method for evaluating the efficacy of booster dose, no threshold of neutralizing antibody titer has been established for evaluating the efficacy of SARS-CoV-2 vaccines. However, it is becoming clear that the neutralizing antibody titer after receiving a SARS-CoV-2 vaccine is correlated with the COVID-19-preventive effect (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11). In Japan, "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1): Evaluation of vaccines against variants" (dated April 5, 2021, issued by Office of Vaccines and Blood Products, PMDA) states that the efficacy of a booster dose against variants can be evaluated by comparing the immunogenicity of the booster dose and the primary series of the same vaccine. Thus, it is acceptable to employ the above principles in evaluating the efficacy of the booster dose in individuals who have completed the primary series of the same SARS-CoV-2 vaccine.

Since the primary series of Comirnaty has demonstrated the COVID-19-preventive effect, the following policy of the applicant is acceptable to a certain extent: To explain the efficacy of a booster dose of Comirnaty by demonstrating the non-inferiority of the booster dose to the second dose in terms of immunogenicity in the sub-study of Study C459100. However, the efficacy of Comirnaty should be evaluated, also by taking account of (a) the immunogenicity against variants after the booster dose and (b) data on the usefulness of the booster dose from foreign countries.

The efficacy, safety, and immunogenicity of primary series of Comirnaty were demonstrated in subjects including those 16 to 17 years of age and elderly people. It is therefore reasonable to extrapolate the efficacy and safety of the booster dose in subjects 18 to 55 years of age to other age groups. However, the age range eligible for the booster dose should be determined in a comprehensive manner, based also on the post-marketing safety data on the primary series of Comirnaty, the status of approval and the progress of vaccination program in foreign countries, and other information [see Section 7.R.4].

Appropriateness of the timing of the booster dose and its dosage regimen is discussed in Section 7.R.4.

7.R.2.2 Efficacy of booster dose

The applicant's explanation about the efficacy of the booster dose of Comirnaty:

(a) Immunogenicity results in sub-study of Study C4591001

In the phase II/III part, the booster dose of Comirnaty was not inferior in immunogenicity to the second dose, as demonstrated in the following endpoints:

(a) GMR of the neutralizing antibody titer at 1 month after the booster dose to the titer at 1 month after the second dose.
(b) Difference in the neutralizing antibody response rate between 1 month after the booster dose and 1 month after the second dose.

The neutralizing antibody titer after the booster dose far exceeded the titer after the second dose [see Section 7.1.2].

As for the immunogenicity against variants, Table 8 shows the neutralizing antibody titer against Beta variant (which was evaluated in an exploratory manner in phase I part and was prevalent when the sub-study was planned) and Delta variant (which is currently prevalent). Against both variants, the neutralizing antibody titer was higher after the booster dose than after the second dose.

Table 8. Neutralizing antibody titer in phase I part[a] (all-available immunogenicity population)

Viral strain used for neutralizing antibody titer measurement	18 to 55 years of age (N = 11)			65 to 85 years of age (N = 12)		
	GMT [2-sided 95%CI]		GMR [2-sided 95%CI] ("after booster dose"/ "after second dose")	GMT [2-sided 95%CI]		GMR [2-sided 95%CI] ("after booster dose"/ "after second dose")
	After booster dose	After second dose		After booster dose	After second dose	
Reference strain and Beta variant						
Reference strain	2119.0 [1229.1, 3653.4]	386.6 [247.4, 604.0]	5.48 [3.18, 9.46]	2031.9 [1232.6, 3349.3]	261.4 [151.9, 450.0]	7.77 [5.25, 11.51]
Beta variant	1546.4 [888.1, 2692.4]	102.9 [56.5, 187.4]	15.02 [8.27, 27.28]	1566.8 [875.2, 2804.7]	75.5 [30.3, 188.4]	20.75 [9.61, 44.78]
Reference strain and Delta variant						
Reference strain	1546.4 [896.9, 2666.0]	310.1 [203.3, 473.0]	4.99 [2.81, 8.84]	1612.7 [875.5, 2970.8]	195.9 [114.7, 334.4]	8.23 [5.08, 13.35]
Delta variant	1321.0 [698.5, 2498.3]	241.0 [180.1, 322.4]	5.48 [3.12, 9.65]	1478.9 [734.9, 2975.8]	123.4 [70.2, 216.9]	11.99 [5.73, 25.08]

a) Neutralizing antibody titer was determined by plaque reduction neutralization test using SARS-CoV-2 (reference strain) and SARS-CoV-2 with spike protein gene substituted by the gene of Beta or Delta variant.

Some reports showed that the antibody induced by Comirnaty had a lower neutralizing activity against Beta and Delta variants than against the reference strain (*N Engl J Med.* 2021; 384: 1466-8, *Nature.* 2021; 596: 273-5). In the sub-study, the neutralizing antibody titer against Beta and Delta variants after the booster dose of Comirnaty was lower than the titer against the reference strain after the booster dose, but was sufficiently higher than the titer against the reference strain after the second dose.

In elderly people, the neutralizing antibody titers against the reference strain and Beta and Delta variants were higher after the booster dose of Comirnaty than after the second dose (Table 8).

COVID-19 did not occur in any subject after the booster dose either in phase I or phase II/III part. One subject without prior SARS-CoV-2 infection before the booster dose became positive for SARS-CoV-2 nucleocapsid-binding antibody, but showed no symptoms.

(b) Results of epidemiological study outside Japan

There are following reports on the effectiveness of the booster dose of Comirnaty:

On the basis of data from 1,137,804 people ≥60 years of age who had received the primary series of Comirnaty ≥5 months previously (extracted from the database of the Israel Ministry of Health [last accessed on September 2, 2021]), a comparison of the rates of SARS-CoV-2 infection and severe COVID-19 was made between the population who received a booster dose ≥12 days previously and those not receiving a booster dose, during the period from June 30 through August 31, 2021 (*N Engl J Med.* 2021;385:1393-400). The rates of SARS-CoV-2 infection and severe COVID-19 were 11.3 and 19.5 times lower, respectively, in the population receiving a booster dose than in the population without a booster dose.

This result suggests the preventive effect of the booster dose of Comirnaty against SARS-CoV-2 infection and severe COVID-19 under the prevalence of Delta variant, although the data were only from individuals ≥60 years of age.

Thus, the booster dose of Comirnaty is expected to be effective, as judged by the following findings:

(a) The high efficacy of the primary series of Comirnaty has been demonstrated.
(b) The sub-study of Study C4591001 demonstrated the non-inferiority of the booster dose to the second dose in terms of "GMR of the neutralizing antibody titer against the reference strain" and "the difference in antibody response rate."
(c) An exploratory study showed that the neutralizing antibody titers against Beta and Delta variants were higher after the booster dose than after the second dose.
(d) Reports from Israel suggest the effectiveness of the booster dose of Comirnaty.

The neutralizing activity in serum after vaccination with Comirnaty against Beta and Delta variants, Alfa and Gamma variants (classified as variants of concern [VOCs] by the World Health Organization [WHO] as of October 2021), and Lambda variant (classified as a variant of interest [VOI] as of October 2021), has been reported to be similar to that against the reference strain (Alfa and Gamma variants, *N Engl J Med.* 2021;384:1466-8; Lambda variant, *bioRxiv preprint doi*: https://doi.org/10.1101/2021.09.13.460163). This suggests the efficacy of a booster dose of Comirnaty against those variants. The neutralizing activity against Mu variant (classified as a VOI by WHO) is currently being evaluated.

A randomized, observer-blind, placebo-controlled, parallel-group study is ongoing since July 2021, to evaluate the booster dose of Comirnaty in approximately 10,000 individuals ≥16 years of age who have received the primary series of Comirnaty ≥6 months previously. The study will investigate the safety and the preventive effect against the onset of COVID-19 and severe COVID-19.

PMDA's view:
Study C4591001 had already demonstrated that the primary series of Comirnaty was highly effective in preventing COVID-19. The sub-study of Study C4591001 demonstrated the non-inferiority of the booster dose of Comirnaty to the second dose in terms of "GMR of the neutralizing antibody titer" and "the difference in the antibody response rate" against the reference strain. The neutralizing antibody titer was several times higher after the booster dose than after the second dose. Also, an exploratory study showed that the neutralizing antibody titers against Beta and Delta variants were higher after the booster dose than after the second dose. There are only a limited number of reports that evaluated the efficacy of the booster dose based on clinical events such as occurrence of COVID-19. Also, it should be noted that the target populations and the observation period are limited. Interactions of various factors may affect the evaluation of effectiveness. With these premises, some reports suggest that the booster dose tends to decrease the incidences of SARS-CoV-2 infection and severe COVID-19. A comprehensive evaluation of the above findings suggests a certain level of effectiveness of the booster dose of Comirnaty.

At present, only short-term data on immunogenicity after the booster dose are available, with no data on changes over time in the neutralizing antibody titer after the booster dose or on the duration of efficacy. The number of countries and regions introducing a booster vaccination program is gradually increasing, and therefore the effectiveness and other findings of the booster dose will be continuously reported. Relevant information should be collected and additional actions should be considered such as providing new findings to healthcare professionals. When results are obtained from the ongoing randomized, observer-blind, placebo-controlled, parallel-group study of the booster dose, additional actions, such as providing information to healthcare professionals, should be considered.

As novel variants are emerging one after another, it is necessary to watch for the occurrence and prevalence of new variants, to collect information on the efficacy and immunogenicity of Comirnaty against variants, and to take actions appropriately depending on the situations.

7.R.3 Safety

7.R.3.1 Safety profile

The applicant's explanation about the safety of the booster dose of Comirnaty in the sub-study of Study C4591001:

The incidence of reactogenicity events observed within 7 days after the booster dose in the phase II/III part was compared with that after the primary series in subjects ≤55 years of age. Results are shown in Table 9. The incidence of events after the booster dose was similar to that observed after the second dose. No events of Grade ≥3 occurred more frequently after the booster dose than after the second dose. The median time to the onset of events (days after the booster dose) was 1 day for local reaction, 2 to 4 days for systemic reactions, with the median duration of 1 to 2 days for both local and systemic reactions, showing no clear difference from the tendency observed after the second dose.

Table 9. Incidence of reactogenicity events within 7 days after each dose of Comirnaty (phase II/III part, safety analysis population, ≤55 years of age)

	Booster dose		Primary series (CTD 5.3.5.1.2)			
Dose #	Third		First		Second	
Age range	18-55		16-55			
No. of subjects analyzed	289		2,899		2,682	
Event terms	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3
Local reactions (total)	240 (83.0)	-	2,444 (84.3)	-	2,108 (78.6)	-
Injection site pain	240 (83.0)	1 (0.3)	2,426 (83.7)	39 (1.3)	2,101 (78.3)	39 (1.5)
Swelling	23 (8.0)	1 (0.3)	184 (6.3)	6 (0.2)	183 (6.8)	7 (0.3)
Redness	17 (5.9)	0	156 (5.4)	7 (0.2)	151 (5.6)	11 (0.4)
Systemic reactions (total)	223 (77.2)	-	1,979 (68.3)	-	2,034 (75.8)	-
Fatigue	184 (63.7)	13 (4.5)	1,431 (49.4)	41 (1.4)	1,649 (59.4)	142 (5.3)
Headache	140 (48.4)	3 (1.0)	1,262 (43.5)	33 (1.1)	1,448 (54.0)	91 (3.4)
Myalgia	113 (39.1)	4 (1.4)	664 (22.9)	15 (0.5)	1,055 (39.3)	62 (2.3)
Chills	84 (29.1)	3 (1.0)	479 (16.5)	15 (0.5)	1,015 (37.8)	69 (2.6)
Arthralgia	73 (25.3)	1 (0.3)	342 (11.8)	5 (0.2)	638 (23.8)	27 (1.0)
Diarrhoea	25 (8.7)	0	309 (10.7)	3 (0.1)	269 (10.0)	6 (0.2)
Pyrexia[a)]	25 (8.7)	1 (0.3)	119 (4.1)	8 (0.3)	440 (16.4)	40 (1.5)
Vomiting	5 (1.7)	0	34 (1.2)	0	58 (2.2)	4 (0.1)

Number of subjects with events (%)

a) Not graded in the study. In this table, pyrexia of >38.9°C was handled as Grade ≥3.

In the phase II/III part, the incidence of adverse events and adverse reactions occurring within 1 month after the booster dose of Comirnaty was 14.4% (44 of 306 subjects) and 7.8% (24 of 306 subjects),

respectively. The main adverse event was lymphadenopathy (5.2% [16 of 306 subjects]), which occurred more frequently than after the primary series (0.4% [83 of 21,926 subjects], CTD 5.3.5.1.2). Lymphadenopathy in all 16 subjects was considered to be related to Comirnaty. It occurred mainly in the axillary lymph nodes 1 to 4 days after the booster dose, but resolved within 5 days in most of the subjects. Grade ≥3 lymphadenopathy was observed in 1 subject; the outcome was "recovered." The increase in the incidence of lymphadenopathy after the booster dose appears to be related to the high neutralizing antibody titer exceeding the level after the second dose. In most subjects, the event was mild and resolved without requiring any treatment, suggesting that the event does not prevent the introduction of a booster dose. Reactogenicity events are likely to occur in association with immune response. The trend of the occurrence of reactogenicity events was similar to that observed after the second dose, as described above.

Table 10 shows the incidence of reactogenicity events observed within 7 days after the booster dose of Comirnaty in subjects 65 to 85 years of age in the phase I part, versus after the primary series. The incidences of headache, myalgia, and arthralgia after the booster dose were higher than those after the second dose, but were lower than those in non-elderly subjects in the phase I part (Table 3) and the phase II/III part (Table 9), showing a similar tendency as observed after the primary series. No adverse events were reported within 1 month after the booster dose in the phase I part.

Table 10. Incidence of reactogenicity events within 7 days after each dose of Comirnaty (phase I part, safety analysis population, 65 to 85 years of age)

	Booster dose		Primary series (CTD 5.3.5.1.1 at initial application)			
Dose #	Third		First		Second	
No. of subjects analyzed	12		12		12	
Event terms	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3
Local reactions (total)	8 (66.7)	-	9 (75.0)	-	8 (66.7)	-
Injection site pain	8 (66.7)	0	9 (75.0)	0	8 (66.7)	0
Swelling	0	0	0	0	0	0
Redness	0	0	0	0	0	0
Systemic reactions (total)	8 (66.7)	-	3 (25.0)	-	7 (58.3)	-
Fatigue	5 (41.7)	0	3 (25.0)	0	5 (41.7)	0
Headache	5 (41.7)	0	0	0	3 (25.0)	0
Myalgia	4 (33.3)	0	0	0	3 (25.0)	0
Chills	2 (16.7)	0	0	0	2 (16.7)	0
Arthralgia	2 (16.7)	0	0	0	1 (8.3)	0
Diarrhoea	0	0	0	0	0	0
Pyrexia[a)]	0	0	0	0	1 (8.3)	0
Vomiting	0	0	0	0	0	0

Number of subjects with events (%)
a) Not graded in the study. In this table, pyrexia of >38.9°C was handled as Grade ≥3.

A serious adverse event (acute myocardial infarction) was observed in 1 subject in the phase II/III part; its causal relationship to Comirnaty was ruled out.

Thus, in the sub-study of Study C4591001, reactogenicity events occurred in most subjects and lymphadenopathy also occurred as a common event. Most of the events, however, were mild to moderate in severity and resolved within a short period after the booster dose. The safety profile of the booster dose of Comirnaty was similar to that after the primary series, suggesting that the booster dose is unlikely to pose any serious safety concerns.

PMDA's view:
The currently available data from the sub-study of Study C4591001 demonstrate that the safety profile of the booster dose of Comirnaty is similar to that of the primary series. PMDA therefore concludes that there are no serious safety concerns associated with the booster dose, at this moment.

However, because of the limited number of subjects evaluated in the sub-study, information should be collected continuously in Japan and from foreign countries, and appropriate actions should be taken based on the information obtained.

Reactogenicity events affecting activities of daily living occurred in many subjects after the booster dose as after the primary series of Comirnaty. Lymphadenopathy occurred more frequently after the booster dose than after the primary series. Therefore, information regarding these events, including the timing of onset and duration, should be provided appropriately to healthcare professionals and to vaccine recipients.

The safety in specific populations and individual events are described in the following sections.

7.R.3.2 Safety in individuals with underlying diseases

PMDA's view on the safety of a booster dose of Comirnaty in individuals with underlying diseases:
The phase II/III part of Study C4591001 and the sub-study enrolled subjects with underlying diseases (diseases included in Charlson Comorbidity Index) and obesity (body mass index [BMI] ≥30 kg/m^2), a risk factor of severe COVID-19. During the review process for the approval of the primary series, the safety of the primary series in subjects with underlying diseases was confirmed to be similar to that in the entire study population, although their underlying diseases were in relatively stable conditions (Comirnaty Intramuscular Injection: Report on Special Approval for Emergency [dated February 8, 2021]). The safety profile in the entire population after the booster dose was similar to that after the primary series, although the sub-study of the booster dose enrolled a small number of subjects and therefore provides only limited data on the subpopulation [see Section 7.R.3.1]. This suggests that the safety profile of Comirnaty does not significantly differ between the booster dose and the primary series in subjects with underlying diseases as well, based on the follow-up data to date.

The first Periodic Safety Update Report (PSUR) on postmarketing safety information regarding the primary series of Comirnaty (published on August 19, 2021; reporting period from December 19 2020 through June 18, 2021) showed higher incidences of severe reactogenicity events in individuals with underlying diseases than in those without. However, at present, these results are unlikely to suggest any particular risk of the primary series in this population because the underlying diseases may have contributed to the severe events.

Based on the above, PMDA concluded that, at the current moment, there are no evident safety concerns affecting the appropriateness of the booster dose in individuals with underlying diseases.

7.R.3.3 Other

7.R.3.3.1 Myocarditis/pericarditis

The postmarketing data on Comirnaty, etc., raise concerns regarding the risk of myocarditis/pericarditis occurring after administration of an mRNA vaccine against SARS-CoV-2.

The applicant's explanation about myocarditis/pericarditis:
Myocarditis/pericarditis occurring after administration of the primary series of Comirnaty was evaluated mainly in the 6th Summary Monthly Safety Report (SMSR) (published on June 13, 2021; reporting period from April 30 through May 31, 2021). The safety database of the applicant includes 495 reported events of myocarditis (260) and pericarditis (235) (Medical Dictionary for Regulatory Activities [MedDRA] preferred terms). A total of 18 events of myocarditis were definitively diagnosed (level 1) by the Brighton Collaboration case definition criteria (v.1.4.2). The age and sex of patients with the reported myocarditis/pericarditis were consistent with those of patients with common myocarditis/pericarditis, and the incidences of the reported cases did not exceed the expected background rates, although only limited information is available regarding viral infection and other factors in the reported cases of myocarditis/pericarditis. Based on the comprehensive assessment of the incidences following ≥6 hundred million doses of Comirnaty, the applicant concludes that no data have shown the relationship between Comirnaty and myocarditis or pericarditis. Related information is being collected after the above report and being reported in monthly SMSR, but there have been no new safety concerns.

Myocarditis and pericarditis[10)] reported spontaneously between December 1, 2020 and September 30, 2021 (European Economic Area [EEA] and USA) were subjected to calculation of O/E ratio by age range and sex, using various background rates (risk window: 14 and 21 days after vaccination). Results are shown in Tables 11 and 12. According to the analysis based on the report in the United States, O/E ratio exceeded 1 in young males and females when a low background rate was used, and in young males when an intermediate or high background rate was used. According to the analysis based on the report from EEA, O/E ratio exceeded 1 in almost all age ranges and in both sexes when a low background rate was used, and in younger age groups when an intermediate or high background rate was used.

[10)] MedDRA preferred terms: myocarditis, eosinophilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, autoimmune myocarditis, immune-mediated myocarditis, pericarditis, autoimmune pericarditis, pericarditis adhesive, pericarditis constrictive, pleuropericarditis

Table 11. O/E ratio of myocarditis by age group (cumulative) [2-sided 95% CI] (United States)

Background rate	Low [a)]		Mid [b)]		High [a)]	
Age	Male	Female	Male	Female	Male	Female
Risk window: 14 days						
≤17 years	31.012 [22.155, 42.229]	12.375 [2.552, 36.166]	3.383 [2.417, 4.607]	0.225 [0.046, 0.658]	1.802 [1.287, 2.454]	0.697 [0.144, 2.038]
18-24 years	4.101 [2.943, 5.563]	2.324 [0.934, 4.788]	2.581 [1.853, 3.502]	0.391 [0.157, 0.805]	0.562 [0.404, 0.763]	0.378 [0.152, 0.779]
25-49 years	1.196 [0.862, 1.617]	2.088 [1.338, 3.107]	0.674 [0.486, 0.911]	0.342 [0.219, 0.508]	0.198 [0.143, 0.268]	0.379 [0.243, 0.563]
50-59 years	0.365 [0.099, 0.934]	1.246 [0.570, 2.365]	0.138 [0.038, 0.352]	0.275 [0.126, 0.521]	0.071 [0.019, 0.183]	0.349 [0.160, 0.663]
60-69 years	0.408 [0.150, 0.887]	0.965 [0.463, 1.774]	0.220 [0.081, 0.478]	0.325 [0.156, 0.597]	0.201 [0.074, 0.438]	0.340 [0.163, 0.625]
≥70 years	0.451 [0.195, 0.888]	0.537 [0.146, 1.375]	0.264 [0.114, 0.521]	0.117 [0.032, 0.300]	0.304 [0.131, 0.600]	0.107 [0.029, 0.273]
Risk window: 21 days						
≤17 years	21.360 [15.328, 28.977]	11.088 [3.021, 28.389]	2.330 [1.672, 3.161]	0.202 [0.055, 0.516]	1.241 [0.891, 1.684]	0.625 [0.170, 1.599]
18-24 years	3.159 [2.321, 4.200]	1.562 [0.628, 3.217]	1.989 [1.461, 2.644]	0.263 [0.106, 0.541]	0.433 [0.318, 0.576]	0.254 [0.102, 0.523]
25-49 years	0.861 [0.628, 1.152]	1.578 [1.040, 2.296]	0.485 [0.354, 0.650]	0.258 [0.170, 0.376]	0.143 [0.104, 0.191]	0.286 [0.189, 0.416]
50-59 years	0.245 [0.067, 0.628]	0.930 [0.446, 1.711]	0.092 [0.025, 0.237]	0.205 [0.098, 0.377]	0.048 [0.013, 0.123]	0.261 [0.125, 0.480]
60-69 years	0.320 [0.128, 0.659]	0.648 [0.311, 1.192]	0.172 [0.069, 0.355]	0.218 [0.105, 0.401]	0.158 [0.063, 0.325]	0.228 [0.110, 0.420]
≥70 years	0.341 [0.156, 0.647]	0.361 [0.098, 0.924]	0.200 [0.091, 0.379]	0.079 [0.021, 0.202]	0.230 [0.105, 0.437]	0.072 [0.020, 0.184]

a) Background rate given in ACCESS (vACcine Covid-19 monitoring readinESS)/VAC4EU (Vaccine monitoring Collaboration for Europe) (last accessed on August 27, 2021) (https://vac4eu.org/covid-19-tool/, as of October 19, 2021)
Low, PHARMO HOSP (Netherlands); High, ARS (Italy)

b) *J Intern Med.* 2007;262:545-54

Table 12. OE ratio of myocarditis by age group (cumulative) [2-sided 95% CI] (EEA)

Background rate	Low [a)]		Mid [b)]		High [a)]	
Age	Male	Female	Male	Female	Male	Female
Risk window: 14 days						
≤17 years	74.170 [63.378, 86.273]	54.028 [34.249, 81.069]	8.091 [6.914, 9.412]	0.982 [0.623, 1.474]	4.310 [3.683, 5.013]	3.044 [1.930, 4.567]
18-24 years	21.515 [19.317, 23.895]	13.097 [10.086, 16.724]	13.545 [12.161, 15.043]	2.203 [1.696, 2.813]	2.950 [2.649, 3.277]	2.130 [1.640, 2.720]
25-49 years	6.151 [5.571, 6.776]	7.589 [6.478, 8.835]	3.467 [3.140, 3.819]	1.242 [1.060, 1.446]	1.019 [0.923, 1.123]	1.376 [1.175, 1.602]
50-59 years	4.338 [3.497, 5.320]	4.652 [3.590, 5.929]	1.637 [1.319, 2.007]	1.025 [0.791, 1.307]	0.849 [0.685, 1.042]	1.304 [1.006, 1.662]
60-69 years	1.570 [1.099, 2.173]	2.167 [1.509, 3.014]	0.845 [0.592, 1.170]	0.729 [0.508, 1.014]	0.775 [0.543, 1.073]	0.764 [0.532, 1.062]
≥70 years	0.923 [0.650, 1.273]	1.725 [1.155, 2.477]	0.541 [0.381, 0.746]	0.376 [0.252, 0.541]	0.624 [0.439, 0.860]	0.343 [0.230, 0.492]
Risk window: 21 days						
≤17 years	54.243 [46.608, 62.771]	41.688 [27.232, 61.083]	5.917 [5.084, 6.848]	0.758 [0.495, 1.111]	3.152 [2.708, 3.648]	2.349 [1.534, 3.441]
18-24 years	15.147 [13.633, 16.784]	9.367 [7.274, 11.875]	9.536 [8.582, 10.566]	1.575 [1.223, 1.997]	2.077 [1.869, 2.302]	1.523 [1.183, 1.931]
25-49 years	4.660 [4.245, 5.104]	5.583 [4.801, 6.456]	2.626 [2.393, 2.877]	0.914 [0.786, 1.056]	0.772 [0.703, 0.846]	1.013 [0.871, 1.171]
50-59 years	3.188 [2.596, 3.873]	3.736 [2.953, 4.663]	1.203 [0.980, 1.461]	0.824 [0.651, 1.028]	0.624 [0.508, 0.758]	1.047 [0.828, 1.307]
60-69 years	1.341 [0.982, 1.789]	1.698 [1.218, 2.303]	0.723 [0.529, 0.964]	0.571 [0.410, 0.775]	0.662 [0.485, 0.883]	0.598 [0.429, 0.812]
≥70 years	0.734 [0.533, 0.985]	1.431 [1.002, 1.981]	0.430 [0.313, 0.578]	0.312 [0.219, 0.432]	0.496 [0.360, 0.665]	0.284 [0.199, 0.394]

a) Background rate given in ACCESS (vACcine Covid-19 monitoring readinESS)/VAC4EU (Vaccine monitoring Collaboration for Europe) (last accessed on August 27, 2021) (https://vac4eu.org/covid-19-tool/, as of October 19, 2021)
Low, PHARMO HOSP (the Netherlands); High, ARS (Italy)

b) *J Intern Med.* 2007;262:545-54

In the sub-study of Study C4591001, myocarditis or pericarditis after the booster dose of Comirnaty has not been observed up to now.[11)] Myocarditis and pericarditis are potential risks associated with mRNA vaccines against SARS-CoV-2 including Comirnaty, but they do not affect the benefit/risk balance of Comirnaty, and the same holds for the booster dose. Information on myocarditis and pericarditis, including the information obtained following a booster dose, will be collected continuously from the postmarketing settings, clinical studies, research reports, etc., and appropriate actions will be taken as necessary. The applicant plans to conduct a clinical study to evaluate the risk of myocarditis and pericarditis after vaccination with Comirnaty.

PMDA confirmed the following data from Japan and other areas:
CDC analyzed cases of myocarditis or pericarditis that had been reported to VAERS (Vaccine Adverse Event Reporting System) up to August 18, 2021, by vaccine product, sex, dose number, and age (https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/03-COVID-Su-508.pdf [last accessed on October 19, 2021]). Table 13 shows the frequency of myocarditis/pericarditis within 7 days after Comirnaty vaccination per one million doses. The event was reported predominantly in young males, particularly after the second dose.

11) Monitoring of myocarditis/ pericarditis was added to the clinical study protocol on September 7, 2021 (monitoring of clinical symptoms of myocarditis/pericarditis during 4 weeks after the booster dose and, if symptoms are reported, measurement of electrocardiogram, troponin concentration, etc.)

Table 13. Frequency of reports of myocarditis/pericarditis within 7 days after Comirnaty vaccination (per 1,000,000 doses, United States)

	Males and females combined		Males		Females	
Age	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose
12-15 years	2.6	20.9	4.8	42.6	0.5	4.3
16-17 years	2.5	34.0	5.2	71.5	0.0	8.1
18-24 years	1.1	18.5	2.4	37.1	0.0	2.6
25-29 years	1.0	7.2	1.8	11.1	0.3	1.3
30-39 years	0.8	3.4	1.1	6.8	0.6	1.0
40-49 years	0.4	2.8	0.7	4.4	0.1	1.8
50-64 years	0.2	0.5	0.2	0.5	0.3	0.8
≥65 years	0.2	0.3	0.2	0.4	0.2	0.4

Data of "Pfizer" excerpted from Slide No. 13 of
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/03-COVID-Su-508.pdf (last accessed on October 19, 2021).

After the market launch in Japan, a total of 160 suspected cases of myocarditis-related events were reported by the marketing authorization holder between the start of vaccination (February 17, 2021) and October 3, 2021; the reporting frequency tended to be high in males in their twenties (Table 14).

Table 14. Frequency of reports of myocarditis/pericarditis (per 1,000,000 doses, Japan)

	Male		Female	
Age	1st and 2nd doses	2nd dose	1st and 2nd doses	2nd dose
10-19 years	2.38	2.89	1.41	1.00
20-29 years	5.75	10.74	0.65	0.51
30-39 years	1.63	2.00	0.96	0.76
40-49 years	0.98	0.85	0.58	0.43
50-59 years	0.51	0.44	0.94	1.09
60-69 years	1.26	1.03	0.76	0.77
70-79 years	1.19	0.75	0.63	0.38
≥80 years	1.02	0.77	1.11	1.19

Material for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 70th meeting), and the 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (the 19th meeting) (joint meeting) (slide under 1-1-1)
(https://www.mhlw.go.jp/stf/shingi2/0000208910_00032.html) (last accessed on October 19, 2021)

PMDA's view on the risk of myocarditis/pericarditis after vaccination with Comirnaty:
Myocarditis/pericarditis after administration of mRNA vaccine against SARS-CoV-2, including Comirnaty, is reported to occur at a higher frequency in young males than in those of other age ranges, but it is rare and asymptomatic or mild in most cases (*Circulation.* 2021;144:471-84, etc.).

Myocarditis-related events after the primary series of mRNA vaccines against SARS-CoV-2, including Comirnaty, were discussed on October 15, 2021 at a joint meeting of the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 70th meeting), and the 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (the 19th meeting) (https://www.mhlw.go.jp/stf/shingi2/0000208910_00032.html (last accessed on October 19, 2021). The meeting concluded that the incidence rate of myocarditis-related events after administration of mRNA vaccine is lower than that of COVID-19-associated myocarditis, and therefore that vaccination with mRNA vaccines can be continued in younger males as well on the condition that precautionary statements are provided in the package insert, etc. (Information for males in their 10s to 20s and their guardians: On myocarditis/pericarditis after vaccination against the novel coronavirus [Ministry of Health, Labour and Welfare] https://www.mhlw.go.jp/content/000844011.pdf [last accessed on October 19, 2021]).

Because of the extremely limited number of individuals who have received a booster dose of Comirnaty, the frequency, severity, and recipient characteristics-dependent risk of myocarditis/pericarditis after a booster dose of Comirnaty are unknown at present. Caution should be raised against myocarditis/pericarditis as in the primary series, and relevant information should continue to be collected from Japanese and non-Japanese cases after a booster dose as well as the primary series. Appropriate measures should be taken based on the information thus obtained.

7.R.3.3.2 Matters related to safety investigations in the primary series of Comirnaty

The applicant has compiled safety information on the primary series of Comirnaty obtained after the market launch in the first PSUR (published on August 19, 2021; reporting period from December 19, 2020 through June 18, 2021). In this PSUR, the applicant reported the following results on the important potential risk (vaccine-associated enhanced disease [VAED]/vaccine-associated enhanced respiratory disease [VAERD][12)]) and the important missing information (safety in pregnant and lactating women), both were identified at the initial approval. The applicant explained that there were no new safety signals and that information will be collected continuously.

(a) VAED/VAERD

A total of 631 cases of suspected VAED/VAERD were reported. In 47 of them, the event occurred early after the first dose, and was therefore considered unrelated to VAED/VAERD. A total of 1,261[13)] serious events were reported in the remaining 584 cases and SARS-CoV-2 infection was confirmed in 425 cases, but definitive diagnosis of VAED/VAERD was not made in any of them.

(b) Vaccination in pregnant and lactating women

There were 1,661 spontaneous reports during pregnancy, including 659 reports related to maternal vaccine exposure during pregnancy (there were no events with clinical symptoms), 945 reports of events with clinical symptoms in mothers, and 57 reports on fetuses/infants. Of the events with clinical symptoms in mothers, the following pregnancy-related events had ≥10 reports: abortion spontaneous (275 reports), vaginal hemorrhage (27), abortion missed (21), and foetal death (16). The breakdown of the reports in fetuses/infants was newborns without congenital anomaly (18 reports), abortion spontaneous (14), newborns with congenital anomaly (9), stillbirth (9), and selective abortion (7).

There were 966 spontaneous reports of lactation (802 on infants and 164 on mothers). Of the reports in infants, 147 were related to events with clinical symptoms. Events reported in ≥10 reports were pyrexia (32 reports), rash (19), diarrhoea (11), infant irritability (11), and malaise (10).

PMDA's view:

"VAED/VAERD" and "safety in pregnant and lactating women," which were identified as the important potential risks and the important missing information, respectively, at the initial approval, were assessed based on the postmarketing safety information. At the current moment, there is no

12) Main retrieval conditions for VAED/VAERD: Report of ≥1 of the following: (a) vaccine associated enhanced disease or vaccine associated enhanced respiratory disease (MedDRA preferred terms), (b) report of ineffective vaccine and more than 1 report of events suggestive of severe or severity-unspecified COVID-19 (dyspnoea, tachypnoea, hypoxia, COVID-19 pneumonia, respiratory failure, acute respiratory distress syndrome, etc. (MedDRA preferred terms).

13) Main events included dyspnoea (180 events), COVID-19 pneumonia (179), diarrhoea (111), respiratory failure (52), and vomiting (50).

information suggestive of safety concerns affecting the benefit/risk balance of Comirnaty. Relevant information regarding the booster dose and data from overseas countries, should be collected continuously, and appropriate actions should be taken based on the information thus obtained.

At the time of the initial approval, there was only limited information on Comirnaty vaccination in pregnant and lactating women. The Japan Society of Obstetrics and Gynecology, the Japan Association of Obstetricians and Gynecologists, and the Japan Society for Infectious Diseases in Obstetrics and Gynecology, published a report for pregnant women, titled "Messenger RNA vaccines against the novel corona virus (2nd report) (in Japanese)" (dated August 14, 2021) (https://www.jsog.or.jp/news/pdf/20210814_COVID19_02.pdf [last accessed on October 19, 2021]), based on the accumulated foreign postmarketing data[14)] and recommendations[15)] related to SARS-CoV-2 vaccines issued by related academic societies outside Japan. In this report, the societies and association in Japan recommend pregnant and lactating women to receive a SARS-CoV-2 vaccine.

7.R.4 Dosage and administration

The proposed dosage and administration for the booster dose is "a single dose of 0.3 mL injected intramuscularly." The "precautions concerning dosage and administration" section of the proposed package insert states that "a booster dose may be administered usually approximately 6 months after the second dose in individuals ≥16 years of age."

As reviewed in Sections "7.R.1 Clinical significance of booster dose," "7.R.2 Efficacy," and "7.R.3 Safety," and in Sections 7.R.4.1 to 7.R.4.3, PMDA reached the following conclusion:

"A single dose of 0.3 mL injected intramuscularly" is acceptable for the booster dose of Comirnaty.

The precautions concerning dosage and administration in the package insert should include a statement that the third dose may be given as a booster dose at ≥6 months after the second dose and that individuals ≥18 years are eligible for the booster dose. The precautions should also include a statement that the necessity of a booster dose should be judged based on the benefit/risk balance, the prevalence status of SARS-CoV-2, and the characteristics of each person [see Section 7.R.1].

7.R.4.1 Dose setting

The applicant's explanation about the dose setting for a booster dose of Comirnaty:
In the plan for the sub-study of Study C4591001, the dose for the booster dose was set at 30 μg, the same dose as in the primary series. The pre-defined immunogenicity criteria were achieved by this dosage regimen, suggesting the effectiveness of the booster dose [see Section 7.R.2]. The safety

14) CDC: Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fclinical-considerations.html#pregnant [last accessed on October 19, 2021])

15) The American College of Obstetricians and Gynecologists: Statement of Strong Medical Consensus for Vaccination of Pregnant Individuals Against COVID-19 (https://www.acog.org/news/news-releases/2021/08/statement-of-strong-medical-consensus-for-vaccination-of-pregnant-individuals-against-covid-19?fbclid=IwAR00YKT64YvN5yq4NwuB-oiIuGs1H2vgPhqsydYsR9ZDAPyXYQpbKk090F4 [last accessed on October 19, 2021]), COVID-19 Vaccines While Pregnant or Breastfeeding (https://s3.amazonaws.com/cdn.smfm.org/media/3040/COVID_vaccine_Patients_JULY_29_2021_final.pdf [last accessed on October 19, 2021])

profile was generally similar to that of the primary series without any serious safety concerns [see Section 7.R.3]. Accordingly, the dose 30 μg (0.3 mL solution) was proposed for the booster dose.

Based on the reviews in Sections 7.R.1, 7.R.2, and 7.R.3, PMDA concludes that 30 μg (0.3 mL solution) is acceptable for the booster dose, the same dose used in the primary series.

7.R.4.2 Timing of booster dose (interval between primary series and booster dose)

The applicant's explanation:

In the sub-study of Study C4591001, the booster dose was given to subjects who had received the second dose approximately 6 months previously (6 to 12 months in phase I part, 5 to 7 months in phase II/III part), because the booster dose of other vaccines against infectious disease is mostly given at 6 months after the first dose. The sub-study results suggested the efficacy of the booster dose and showed a favorable safety profile [see Sections 7.R.2 and 7.R.3]. The median interval (range) between the second dose of Comirnaty and the booster dose was 8.2 (7.9-8.8) months in the population of 18 to 55 years of age and 8.4 (8.2-8.5) months in the population of 65 to 85 years of age in the phase I part; and 6.8 (4.8-8.0) months in the phase II/III part.

The follow-up data after the primary series in Study C4591001 showed that the neutralizing antibody titer after the primary series of Comirnaty had declined at 6 months after the second dose. Foreign observational studies also reported that the efficacy waned approximately 6 to 8 months after the second dose [see Section 7.R.1].

Accordingly, the applicant concluded that the booster dose should be administered approximately 6 months after the second dose.

PMDA's view:

No definitive conclusion has been reached on the duration of efficacy after the primary series of Comirnaty. Also, there are no data regarding a booster dose administered more than or less than 6 months after the first dose. However, given the results from clinical studies, together with the fact that the booster dose "≥6 months after the second dose of Comirnaty" is approved in the United States and EU, the proposed timing of the booster dose (≥6 months after the second dose of Comirnaty) is acceptable in Japan as well.

However, the actual timing of a booster dose in the vaccination program should be considered separately, because the appropriate timing for a booster dose may differ depending on the risks for COVID-19 in individual persons.

There are no data on the booster dose of Comirnaty in people who have received the primary series of other SARS-CoV-2 vaccines. This should be stated in an appropriate manner in the package insert, etc.

7.R.4.3 Eligible age range

The applicant's explanation about the eligible age range:

Since those ≥12 years of age are eligible for the primary series of Comirnaty, data obtained from subjects 18 to 55 years of age in the sub-study of Study C4591001 were extrapolated to other age ranges [see Section 7.R.2.1]. Then, the age range eligible for the booster dose was determined to be ≥16 years because, in this age range, the safety has been confirmed for at least 6 months after the primary series of Comirnaty.

PMDA's view:

The eligible age range should be ≥18 years, as are the cases with the United States and EU, based on the data submitted and the fact that the present review is conducted based on the "Handling of drugs submitted for Special Approval for Emergency (Request) " (PSEHB/PED Notification No. 1011-1, dated October 11, 2021).

7.R.5 Post-marketing investigations

The applicant's explanation:

Results of Study C4591001 showed that the safety profile of the booster dose of Comirnaty was similar to that of the primary series, with no safety concerns specific to the booster dose. Accordingly, it is unnecessary to collect postmarketing information on the booster dose.

PMDA's view:

Given the limited information on the booster dose of Comirnaty and the lack of information in Japanese people, it is necessary to collect safety information related to the booster dose of Comirnaty in Japan and to disseminate the information in an appropriate manner. PMDA instructed the applicant to consider actions to be taken on the booster dose after the market launch.

The applicant accepted the PMDA's opinion and replied that they would consider collecting safety information in routine clinical practice in Japan.

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 inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Report on Special Approval for Emergency (1)

On the basis of the data submitted, PMDA has concluded that the booster dose of Comirnaty has efficacy in preventing disease caused by SARS-CoV-2 infection (COVID-19) with acceptable safety without serious safety concerns. Making a booster dose of Comirnaty available has a certain clinical significance on the condition that the vaccine is used after assessing the benefit/risk balance based on the prevalence of SARS-CoV-2 and the characteristics of individual recipients.

PMDA has concluded that Comirnaty may be approved if Comirnaty is not considered to have any particular problems based on comments from the Expert Discussion.

Report on Special Approval for Emergency (2)

November 2, 2021

Product Submitted for Approval

Brand Name	Comirnaty Intramuscular Injection
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	September 28, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Clinical significance of booster dose

At the expert discussion, expert advisors supported the PMDA's conclusion presented in Section "7.R.1 Clinical significance of booster dose" of Report (1). Also, they stated that the vaccination program of a booster dose should be accessible to people at high risk of exposure to SARS-CoV-2 and those who wish to receive a booster dose.

1.2 Efficacy and safety

At the expert discussion, the expert advisors supported the PMDA's conclusions presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety," and made the following comments:

- In the press release issued on October, 21, 2021, the applicant published results of the interim analysis on the efficacy of a booster dose of Comirnaty in preventing COVID-19 in a randomized, placebo-controlled, observer-blind, parallel-group study (https://www.businesswire.com/news/home/20211021005491/en/ [last accessed on October 29, 2021]). The results are also likely to support the efficacy of the booster dose of Comirnaty.
- Currently available data are only from limited populations during a short period after the booster dose of Comirnaty. Information on the efficacy, immunogenicity, and safety of the booster dose of Comirnaty should be collected continuously from clinical trials, clinical investigations, and routine clinical practice, and appropriate actions should be taken based on the information thus obtained. In particular, information on the cellular immunity elicited by the booster dose of Comirnaty should be collected and published.

PMDA informed the applicant about the above comments. The applicant responded that they would continue to collect information and take appropriate actions based on the findings obtained.

1.3 Dosage and administration

At the expert discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.4 Dosage and administration."

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions described in Section "7.R.5 Postmarketing investigations" of Report (1).

PMDA has concluded that the risk management plan (draft) for Comirnaty should include the safety specifications presented in Table 15, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 16.

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

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

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

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing clinical study (Study C4591005) • Use-results survey on post-approval early vaccine recipients (healthcare professionals) (follow-up study) (C4591006) • Specified use-results survey on vaccine recipients with underlying diseases who are at high risk of severe COVID-19 (C4591019) • Foreign phase II/III study (Study C4591011) [a)] • Foreign phase II/III study in pregnant women (Study C4591015)	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information for healthcare professionals (a proper use guide for Comirnaty) [a)] • Organize and disseminate information (a brochure) for vaccine recipients and their family members[a)] • Periodical publication of the occurrence of adverse reactions

a) To be conducted for the newly added dosage as well.

As described in Section "7.R.5 Postmarketing investigations" of Report (1), the applicant had explained that they would consider collecting safety information on the booster dose of Comirnaty in routine clinical practice in Japan.

Subsequently the applicant provided the following explanation about their plan about safety data collection:

The safety information on the primary series of Comirnaty (i.e., data until 28 days after the second dose) was collected through a government-led program "Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan" (Health, Labor and Welfare Policy Research Grants, Research on Emerging and Re-emerging Infectious Diseases and Immunization, 2020). If another government-led

surveillance is initiated for the booster dose of Comirnaty in a similar manner, an independent surveillance conducted by the applicant may become redundant in its objective and the target population, possibly posing unnecessary burdens on medical institutions. Accordingly, the applicant will confirm whether the government plans to conduct a cohort surveillance on the booster dose, and then will determine whether or how to collect safety data on the booster dose in clinical practice in Japan.

PMDA accepted the applicant's explanation.

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

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

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

2.2 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.

3. Overall Evaluation

As a result of the above review on the submitted data, PMDA has concluded that the product may be approved for the following dosage and administration, with approval conditions shown below. Although this is an application for a drug with a new dosage, the re-examination period for the present application is the remainder of re-examination period for the initial approval (until February 13, 2029) because it has more than 4 years left.

Indication

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

(No change)

Dosage and Administration

The product is diluted with 1.8 mL of physiological saline (Japanese Pharmacopoeia grade).

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

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

(Underlines donate additions)

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (2) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (3) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.
   (4) The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form and have provided written informed consent through the vaccine screening questionnaire in advance.

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

Appendix

List of Abbreviations

BMI	Body mass index
BNT162b1	A vaccine candidate containing mRNA that encodes RBD of SARS-CoV-2 spike protein
$BNT162b2_{SA}$	A vaccine candidate targeted at Beta variant
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of 1961)
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
EEA	European Economic Area
EMA	European Medicines Agency
FDA	Food and Drug Administration
GMR	Geometric mean ratio
GMT	Geometric mean titer
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960)
PMDA	Pharmaceuticals and Medical Devices Agency
PSUR	Periodic Safety Update Report
RBD	Receptor binding domain
Reference strain	Strain USA-WA1/2020
Report (1)/(2)	Report on Special Approval for Emergency (1)/(2)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMSR	Summary Monthly Safety Report
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine Efficacy
VOC	Variants of concern
VOI	Variants of interest
WHO	World Health Organization