Report on the Deliberation Results

February 12, 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	December 18, 2020

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 February 12, 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, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The vaccine product and its active substance are both classified as powerful drugs.

**Japanese Accepted Name (modified INN)*

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
3. 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.
4. 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.
5. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and who have provided written informed consent through the vaccine screening questionnaire in advance.
6. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If new data, etc., submitted in accordance with approval conditions 2, 3, or 4, necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

Report on Special Approval for Emergency

February 8, 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	December 18, 2020
Dosage Form/Strength	Injection: each vial contains 0.225 mg of Tozinameran
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Tozinameran is a mRNA encoding full length of spike protein analog (Lys986Pro, Val987Pro) of SARS-CoV-2. Tozinameran is a single-stranded RNA consisting of 4284 nucleotide residues including the 5' cap structure and poly A sequence in which all uridine residues are replaced by N^1-methylpseudouridine residues.

Structure

The nucleotide sequence of tozinameran is as follows:

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GAGAAYAAAC  YAGYAYYCYY  CYGGYCCCCA  CAGACYCAGA  GAGAACCCGC    50
CACCAYGYYC  GYGYYCCYGG  YGCYGCYGCC  YCYGGYGYCC  AGCCAGYGYG   100
YGAACCYGAC  CACCAGAACA  CAGCYGCCYC  CAGCCYACAC  CAACAGCYYY   150
ACCAGAGGCG  YGYACYACCC  CGACAAGGYG  YYCAGAYCCA  GCGYGCYGCA   200
CYCYACCCAG  GACCYGYYCC  YGCCYYYCYY  CAGCAACGYG  ACCYGGYYCC   250
ACGCCAYCCA  CGYGYCCGGC  ACCAAYGGCA  CCAAGAGAYY  CGACAACCCC   300
GYGCYGCCCY  YCAACGACGG  GGYGYACYYY  GCCAGCACCG  AGAAGYCCAA   350
CAYCAYCAGA  GGCYGGAYCY  YCGGCACCAC  ACYGGACAGC  AAGACCCAGA   400
GCCYGCYGAY  CGYGAACAAC  GCCACCAACG  YGGYCAYCAA  AGYGYGCGAG   450
YYCCAGYYCY  GCAACGACCC  CYYCCYGGGC  GYCYACYACC  ACAAGAACAA   500
CAAGAGCYGG  AYGGAAAGCG  AGYYCCGGGY  GYACAGCAGC  GCCAACAACY   550
GCACCYYCGA  GYACGYGYCC  CAGCCYYYCC  YGAYGGACCY  GGAAGGCAAG   600
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CAGGGCAACY YCAAGAACCY GCGCGAGYYC GYGYYYAAGA ACAYCGACGG 650
CYACYYCAAG AYCYACAGCA AGCACACCCC YAYCAACCYC GYGCGGGAYC 700
YGCCYCAGGG CYYCYCYGCY CYGGAACCCC YGGYGGAYCY GCCCAYCGGC 750
AYCAACAYCA CCCGGYYYCA GACACYGCYG GCCCYGCACA GAAGCYACCY 800
GACACCYGGC GAYAGCAGCA GCGGAYGGAC AGCYGGYGCC GCCGCYYACY 850
AYGYGGGCYA CCYGCAGCCY AGAACCYYCC YGCYGAAGYA CAACGAGAAC 900
GGCACCAYCA CCGACGCCGY GGAYYGYGCY CYGGAYCCYC YGAGCGAGAC 950
AAAGYGCACC CYGAAGYCCY YCACCGYGGA AAAGGGCAYC YACCAGACCA 1000
GCAACYYCCG GGYGCAGCCC ACCGAAYCCA YCGYGCGGYY CCCCAAYAYC 1050
ACCAAYCYGY GCCCCYYCGG CGAGGYGYYC AAYGCCACCA GAYYCGCCYC 1100
YGYGYACGCC YGGAACCGGA AGCGGAYCAG CAAYYGCGYG GCCGACYACY 1150
CCGYGCYGYA CAACYCCGCC AGCYYCAGCA CCYYCAAGYG CYACGGCGYG 1200
YCCCCYACCA AGCYGAACGA CCYGYGCYYC ACAAACGYGY ACGCCGACAG 1250
CYYCGYGAYC CGGGGAGAYG AAGYGCGGCA GAYYGCCCCY GGACAGACAG 1300
GCAAGAYCGC CGACYACAAC YACAAGCYGC CCGACGACYY CACCGGCYGY 1350
GYGAYYGCCY GGAACAGCAA CAACCYGGAC YCCAAAGYCG GCGGCAACYA 1400
CAAYYACCYG YACCGGCYGY YCCGGAAGYC CAAYCYGAAG CCCYYCGAGC 1450
GGGACAYCYC CACCGAGAYC YAYCAGGCCG GCAGCACCCC YYGYAACGGC 1500
GYGGAAGGCY YCAACYGCYA CYYCCCACYG CAGYCCYACG GCYYYCAGCC 1550
CACAAAYGGC GYGGGCYAYC AGCCCYACAG AGYGGYGGYG CYGAGCYYCG 1600
AACYGCYGCA YGCCCCYGCC ACAGYGYGCG GCCCYAAGAA AAGCACCAAY 1650
CYCGYGAAGA ACAAAYGCGY GAACYYCAAC YYCAACGGCC YGACCGGCAC 1700
CGGCGYGCYG ACAGAGAGCA ACAAGAAGYY CCYGCCAYYC CAGCAGYYYG 1750
GCCGGGAYAY CGCCGAYACC ACAGACGCCG YYAGAGAYCC CCAGACACYG 1800
GAAAYCCYGG ACAYCACCCC YYGCAGCYYC GGCGGAGYGY CYGYGAYCAC 1850
CCCYGGCACC AACACCAGCA AYCAGGYGGC AGYGCYGYAC CAGGACGYGA 1900
ACYGYACCGA AGYGCCCGYG GCCAYYCACG CCGAYCAGCY GACACCYACA 1950
YGGCGGGYGY ACYCCACCGG CAGCAAYGYG YYYCAGACCA GAGCCGGCYG 2000
YCYGAYCGGA GCCGAGCACG YGAACAAYAG CYACGAGYGC GACAYCCCCA 2050
YCGGCGCYGG AAYCYGCGCC AGCYACCAGA CACAGACAAA CAGCCCYCGG 2100
AGAGCCAGAA GCGYGGCCAG CCAGAGCAYC AYYGCCYACA CAAYGYCYCY 2150
GGGCGCCGAG AACAGCGYGG CCYACYCCAA CAACYCYAYC GCYAYCCCCA 2200
CCAACYYCAC CAYCAGCGYG ACCACAGAGA YCCYGCCYGY GYCCAYGACC 2250
AAGACCAGCG YGGACYGCAC CAYGYACAYC YGCGGCGAYY CCACCGAGYG 2300
CYCCAACCYG CYGCYGCAGY ACGGCAGCYY CYGCACCCAG CYGAAYAGAG 2350
CCCYGACAGG GAYCGCCGYG GAACAGGACA AGAACACCCA AGAGGYGYYC 2400
GCCCAAGYGA AGCAGAYCYA CAAGACCCCY CCYAYCAAGG ACYYCGGCGG 2450
CYYCAAYYYC AGCCAGAYYC YGCCCGAYCC YAGCAAGCCC AGCAAGCGGA 2500
GCYYCAYCGA GGACCYGCYG YYCAACAAAG YGACACYGGC CGACGCCGGC 2550
YYCAYCAAGC AGYAYGGCGA YYGYCYGGGC GACAYYGCCG CCAGGGAYCY 2600

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GAYYYGCGCC   CAGAAGYYYA   ACGGACYGAC   AGYGCYGCCY   CCYCYGCYGA   2650
CCGAYGAGAY   GAYCGCCCAG   YACACAYCYG   CCCYGCYGGC   CGGCACAAYC   2700
ACAAGCGGCY   GGACAYYYGG   AGCAGGCGCC   GCYCYGCAGA   YCCCCYYYGC   2750
YAYGCAGAYG   GCCYACCGGY   YCAACGGCAY   CGGAGYGACC   CAGAAYGYGC   2800
YGYACGAGAA   CCAGAAGCYG   AYCGCCAACC   AGYYCAACAG   CGCCAYCGGC   2850
AAGAYCCAGG   ACAGCCYGAG   CAGCACAGCA   AGCGCCCYGG   GAAAGCYGCA   2900
GGACGYGGYC   AACCAGAAYG   CCCAGGCACY   GAACACCCYG   GYCAAGCAGC   2950
YGYCCYCCAA   CYYCGGCGCC   AYCAGCYCYG   YGCYGAACGA   YAYCCYGAGC   3000
AGACYGGACC   CYCCYGAGGC   CGAGGYGCAG   AYCGACAGAC   YGAYCACAGG   3050
CAGACYGCAG   AGCCYCCAGA   CAYACGYGAC   CCAGCAGCYG   AYCAGAGCCG   3100
CCGAGAYYAG   AGCCYCYGCC   AAYCYGGCCG   CCACCAAGAY   GYCYGAGYGY   3150
GYGCYGGGCC   AGAGCAAGAG   AGYGGACYYY   YGCGGCAAGG   GCYACCACCY   3200
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CAYAYGYGCC   CGCYCAAGAG   AAGAAYYYCA   CCACCGCYCC   AGCCAYCYGC   3300
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CACCCAYYGG   YYCGYGACAC   AGCGGAACYY   CYACGAGCCC   CAGAYCAYCA   3400
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AYCGACCGGC   YGAACGAGGY   GGCCAAGAAY   CYGAACGAGA   GCCYGAYCGA   3650
CCYGCAAGAA   CYGGGGAAGY   ACGAGCAGYA   CAYCAAGYGG   CCCYGGYACA   3700
YCYGGCYGGG   CYYYAYCGCC   GGACYGAYYG   CCAYCGYGAY   GGYCACAAYC   3750
AYGCYGYGYY   GCAYGACCAG   CYGCYGYAGC   YGCCYGAAGG   GCYGYYGYAG   3800
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AGGGCGYGAA   ACYGCACYAC   ACAYGAYGAC   YCGAGCYGGY   ACYGCAYGCA   3900
CGCAAYGCYA   GCYGCCCCYY   YCCCGYCCYG   GGYACCCCGA   GYCYCCCCCG   3950
ACCYCGGGYC   CCAGGYAYGC   YCCCACCYCC   ACCYGCCCCA   CYCACCACCY   4000
CYGCYAGYYC   CAGACACCYC   CCAAGCACGC   AGCAAYGCAG   CYCAAAACGC   4050
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YGCCAGCCAC   ACCCYGGAGC   YAGCAAAAAA   AAAAAAAAAA   AAAAAAAAAA   4200
AAAAGCAYAY   GACYAAAAAA   AAAAAAAAAA   AAAAAAAAAA   AAAAAAAAAA   4250
AAAAAAAAAA   AAAAAAAAAA   AAAAAAAAAA   AAAA                     4284
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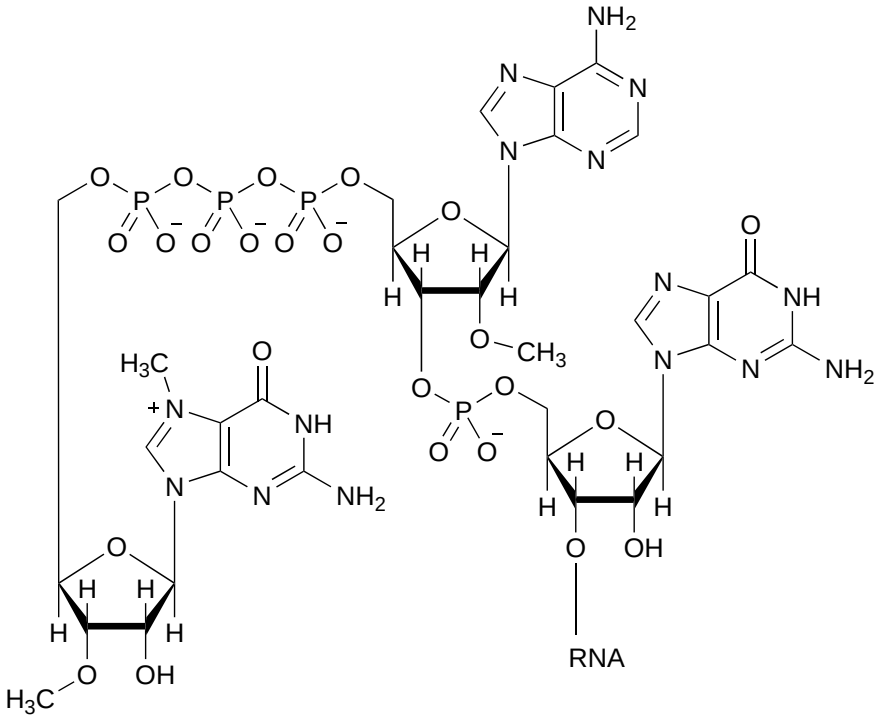
A = adenosine; C = cytidine; G = guanosine, Y = N^1-methylpseudouridine

1-3: 5’ cap structure

55-3879: Protein-coding region

4175-4204, 4215-4284: PolyA transcription slips

5’ Cap structure



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.
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

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

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

Indication

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

Dosage and Administration

The product is diluted with 1.8 mL of physiological saline (Japanese Pharmacopoeia grade), and 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
3. 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.
4. 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.
5. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and who have provided written informed consent through the vaccine screening questionnaire in advance.
6. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If new data, etc., submitted in accordance with approval conditions 2, 3, or 4, necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

Attachment

Report on Special Approval for Emergency (1)

January 29, 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 (for more than one injection) (proposed name)
Non-proprietary Name	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Active ingredient: Tozinameran)
Applicant	Pfizer Japan Inc.
Date of Application	December 18, 2020
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)

Proposed Dosage and Administration

The product is diluted with 1.8 mL of physiological saline (Japanese Pharmacopoeia grade), and usually 2 doses (0.3 mL each) are injected intramuscularly, 3 weeks apart.

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List of Abbreviations

See Appendix.

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

Coronavirus is a single-stranded positive-chain RNA virus belonging to the family *Coronaviridae* and the order *Nidovirales*. Four types of human coronavirus (HCoV), HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, have been known to routinely infect humans causing common cold. In recent years, two types of zoonotic coronavirus causing severe pneumonia have been identified: Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) identified in 2003 and Middle East respiratory syndrome (MERS) corona virus (MERS-CoV) in 2012.

On December 31, 2019, the World Health Organization (WHO) received a report of the outbreak of pneumonia of unknown cause in Wuhan City, Hubei Province, China and, on January 12, 2020, reported that the pneumonia was caused by a novel coronavirus (WHO: https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en [as of January 21, 2021]). On January 30, 2020, WHO declared that the occurrence of novel coronavirus-related pneumonia in Wuhan City, Hubei Province, China is a "Public Health Emergency of International Concern"[1)] (https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-healthregulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) (as of January 21, 2021). On February 11, 2020, WHO named the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by SARS-CoV-2 as coronavirus disease (COVID-19) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirusdisease-(covid-2019)-and-the-virus-that-causes-it [as of January 21, 2021]). As of January 17, 2021, a total of 93,217,287 people have been infected globally, with a total death toll of 2,014,957. The following are regional percentages of infection cases and deaths of the total global numbers (according to the WHO regional classification): 44% (infection cases) and 47% (deaths) in Americas; 33% and 33% in Europe, 13% and 9% in South-Eastern Asia; 6% and 6% in Eastern Mediterranean; 2% and 3% in Africa; and 1% and 1% in Western Pacific. (https://www.who.int/publications/m/item/weekly-epidemiological-update---19-january-2021) (as of January 21, 2021).

In Japan, the first patient with SARS-CoV-2-related pneumonia was identified on January 15, 2020. On February 1, 2020, COVID-19[2)] was classified as a Designated Infectious Disease[3)] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease[4)] pursuant to the Quarantine Act. On April 7, 2020, the Japanese government declared a state of emergency based on the amended Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response; the declaration was lifted on

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[1)] The term Public Health Emergency of International Concern is defined as follows in the International Health Regulations of WHO:
(a) An extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease
(b) An extraordinary event which is determined to potentially require a coordinated international response

[2)] Limited to the disease caused by the novel coronavirus of genus *Betacoronavirus* that was reported as transmissible to humans to WHO from the People's Republic of China in January 2020

[3)] The term Designated Infectious Disease means already known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, and Novel Influenza Infection, etc.) specified by Cabinet Order as a disease which would be likely to seriously affect the health of the public in the event of its spread if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).

[4)] The term Quarantinable Infectious Disease means diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).

May 25, 2020.[5)] The number of newly infected people (those positive for polymerase chain reaction [PCR] test) tended to decline for a while but, from around October 2020, showed an increasing tendency again, leading to the declaration of the second state of emergency on January 7, 2021.[6)]

As of January 19, 2021, 332,231 people have been infected in Japan, with a death toll of 4,547. In addition to these figures, 2,082 people tested positive at airport quarantine, and 15 people tested positive after returning to Japan by international charter flights. In total, 334,328 people are reported to have been infected, with a death toll of 4,548, including 1 patient who died after testing positive at airport quarantine. Furthermore, 712 people were infected and 13 of them died among the passengers on the cruise ship "Diamond Princess," which arrived at Yokohama port on February 3, 2020, (https://www.mhlw.go.jp/stf/newpage_16163.html [as of January 21, 2021]).

The early symptoms of COVID-19 are similar to those of influenza and common cold; this makes it difficult to differentiate the former from the latter during the early phase of the onset. The incubation period from the exposure to SARS-CoV-2 to symptom onset is 1 through 14 days, usually around 5 days (https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations [as of January 21, 2021]). Patients with COVID-19 become infectious before symptom onset and especially highly infectious early after the onset. Further, some patients are asymptomatic. This is considered to be the cause of community transmission, making it difficult to control the transmission. Many patients present with symptoms including fever, cough, malaise, dyspnea, taste disorder, and dysosmia. Approximately 80% of patients have mild symptoms and recover within approximately 1 week, approximately 20% of patients experience aggravated pneumonia symptoms, approximately 5% of patients progress to acute respiratory distress syndrome or multi-organ failure that requires ventilator support, and approximately 2% to 3% of patients die (*JAMA* 2020; 323: 1239-42). As of January 20, 2021, remdesivir is the only drug approved in Japan for the treatment of COVID-19. Dexamethasone can be used under the approved indication. However, even with treatments with these drugs, the number of infected people, patients in serious conditions, and fatal cases keep rising, putting the medical system under severe strain. In order to control the expansion of the infection, COVID-19 prevention by SARS-CoV-2 vaccine is eagerly awaited. Vaccine development is thus an urgent need.

As of the end of January 2021, no vaccines or drugs have been approved for the prevention of COVID-19.

Comirnaty is a vaccine containing mRNA encoding S-protein of SARS-CoV-2 as the active ingredient. The base sequence of the mRNA is optimized for continuous and efficient translation into the encoded target protein. The mRNA is encapsulated in lipid nanoparticles (LNPs) to prevent RNA degradation within the body and to allow mRNA transfection into cells. The development of Comirnaty as a vaccine to prevent COVID-19 was initiated in [redacted] 2020 by BioNTech in Germany and Pfizer in the United States. A foreign clinical study (Study

[5)] Initially, the state of emergency was limited to Saitama, Chiba, Tokyo, Kanagawa, Osaka, Hyogo, and Fukuoka prefectures, but temporarily expanded to cover the whole Japan.
[6)] As of January 20, 2021, the state of emergency covers Tochigi, Saitama, Chiba, Tokyo, Kanagawa, Gifu, Aichi, Kyoto, Osaka, Hyogo, and Fukuoka prefectures.

C4591001) was initiated in April 2020 and a Japanese clinical study (Study C4591005) in October 2020. Both studies are ongoing as of January 20, 2021.

In the United States, Comirnaty was granted Emergency Use Authorization on December 11, 2020 for the prevention of COVID-19, based on its effect to prevent COVID-19 and on the safety data at 2 months after Dose 2 in foreign Study C4591001. In EU, the vaccine was granted conditional approval on December 21, 2020.

On December 18, 2020, Pfizer Japan Inc. filed a marketing application for the approval of Comirnaty under the following backgrounds:

(i) Comirnaty was granted Emergency Use Authorization by U.S. Food and Drug Administration (FDA).
(ii) Comirnaty was under review in EU at the time of application in Japan.
(iii) Japanese Study C4591005 was ongoing to evaluate the immunogenicity and safety of Comirnaty.

Part of the results of Japanese Study C4591005 was submitted during this review process.

This report contains the result of review conducted based on the data submitted by the applicant, in accordance with the "Handling of drugs under the review process for Special Approval for Emergency (Request)" (PSEHB/PED Notification 1217-2, dated December 17, 2020).

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

Comirnaty is a vaccine made of an mRNA encoding spike protein (S1 [carboxy-terminal region of S protein containing RBD] and S2 [amino-terminal region of S protein containing the membrane-spanning region] subunits) of SARS-CoV-2, encapsulated in LNP.

2.1 Active substance

Tozinameran (BNT162b2) is an mRNA encoding S protein (S1 and S2 subunits) of SARS-CoV-2 (isolate Wuhan-Hu-1). It is designed to have substitution of 2 amino acid residues (K986P and V987P) so that S protein exists in an optimal prefusion conformation. The mRNA contains a 5' terminal cap structure; a sequence for enhancing translation ([redacted]); a signal sequence for endoplasmic reticulum transport ([redacted]), a sequence for stabilizing RNA ([redacted]); and poly (A) tail. All uridine (UTP) residues are replaced by $^{m1}\Psi$ residues to repress immunogenicity against mRNA and enhance translation.

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

A cell bank is used for the preparation of the template deoxyribonucleic acid (DNA), a raw material for tozinameran. Plasmid DNA encoding [redacted], [redacted], S1 and S2 proteins, [redacted], and poly (A) tail was introduced into *Escherichia coli* (strain [redacted]) and, after cloning, a master cell bank (MCB) was prepared. A working cell bank (WCB) was then prepared from the MCB after [redacted] subcultures.

MCB and WCB were subjected to characterization (absence of [redacted] and [redacted], identification of host cells, viability, [redacted], restriction enzyme analysis, [redacted], and gene sequence) and to purity tests.

When a new WCB is generated, its conformity to the above characterization and purity tests will be confirmed.

2.1.2 Manufacturing process

The active substance is manufactured by *in vitro* transcription using the linear template DNA as the template and [redacted], adenosine triphosphate (ATP), cytidine triphosphate (CTP), N^1-methylpseudouridine triphosphate ($^{m1}\Psi$TP), and guanosine triphosphate (GTP) as substrates.

The manufacturing process for the active substance consists of *in vitro* transcription, [redacted], [redacted], [redacted], and [redacted], all of which were defined as critical steps. The linear template DNA is prepared by the following process: After cultivation of the WCB, recovered bacterial cells (*Escherichia coli*) are lysed to obtain circular plasmid DNA, which is purified by [redacted], [redacted], and [redacted] and treated [redacted]. The control parameters for the linear template DNA are description (turbidity, color), pH, absorbance ([redacted]), restriction enzyme analysis (integrity of [redacted]), purity, residual protein, microbial limit, and endotoxin.

The commercial scale manufacturing process of the active substance was subjected to process validation.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin are used in the manufacturing process of the active substance. The raw materials of biological origin used for the preparation of the raw material were tested for the contamination with adventitious agents. [redacted] used for the preparation of MCB and WCB is derived from healthy [redacted]. Pathogens were inactivated by heating at ≥[redacted]°C for ≥[redacted] minutes and at ≥[redacted]°C for ≥[redacted], and by drying at ≥[redacted]°C.

2.1.4 Manufacturing process development (comparability)

The following are main changes in the manufacturing process during the development of the active substance: The active substance used for nonclinical and clinical studies are manufactured by Process 1, and the active substance in the proposed commercial formulation by Process 2. In Process 1, the active substance is manufactured by *in vitro* transcription of the template DNA prepared by [redacted], followed by [redacted] and purification through [redacted]. In Process 2, the active substance is manufactured by *in vitro* transcription of the linear template DNA prepared from the plasmid DNA, followed by [redacted], [redacted], and purification through [redacted] and [redacted]. The comparability of quality attributes between pre-change and post-change active substances has been demonstrated.

Quality by design (QbD) approach was used in the development of the manufacturing process of the active substance [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and characteristics

The active substance was subjected to characterization shown in Table 1.

Table 1. Parameters and methods for characterization

Parameter		Test method
Primary structure	RNA sequence	Oligonucleotide mapping (IP-RP-HPLC/ESI/MS/MS or LC-MS/MS) after RNase T1 digestion
		Next-generation sequencing (NGS)
	5' cap structure	IP-RP-HPLC-UV/ESI MS and LC-UV/MS after RNase H digestion
	Poly (A) tail	IP-RP-HPLC-UV/ESI MS and LC-UV/MS after RNase T1 digestion
Higher order structure	Higher order structure	Circular dichroism spectroscopy

2.1.5.2 Product-related substances/product-related impurities

The product-related impurity is double-stranded RNA, which is adequately controlled by the specifications for the active substance.

2.1.5.3 Process-related impurities

Process-related impurities are template DNA, process-related Impurity A, process-related Impurity B, ATP, CTP, GTP, $^{m1}\Psi$TP, process-related Impurity C, process-related Impurity D, process-related Impurity E, magnesium acetate, calcium chloride, ammonium sulfate, Triton X-100, Tris HCl buffer, glycerol, sodium chloride, potassium chloride, process-related Impurity F, process-related Impurity G, and process-related Impurity H.

Residual template DNA is adequately controlled by the specifications for the active substance. Process-related Impurities A and B were shown to be completely removed during the manufacturing process. ATP, CTP, GTP, $^{m1}\Psi$TP, process-related Impurity C, process-related Impurity D, process-related Impurity E, magnesium acetate, calcium chloride, ammonium sulfate, Triton X-100, Tris HCl buffer, glycerol, sodium chloride, potassium chloride, process-related Impurity F, process-related Impurity G, and process-related Impurity H were shown to pose no safety concern at the vaccination dose even if they were not removed by the purification process.

2.1.6 Control of active substance

The proposed specifications for the active substance include content specification, description, identification (reverse transcription PCR [RT-PCR]), pH, purity (double-strand RNA [immunoblotting] and template DNA [quantitative polymerase chain reaction (qPCR)]), 5' cap (reverse phase high performance liquid chromatography [HPLC]), poly (A) chain (ddPCR), RNA integrity (capillary gel electrophoresis), endotoxin, microbial limits, and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of active substance

Table 2 shows the summary of the main stability tests for the active substance.

Table 2. Summary of the main stability tests for the active substance

Test	Manufacturing process	Number of batches	Storage condition	Test period	Storage package
Long-term	Process 1	1	-20±5°C	6 months	[redacted] container
Accelerated			5±3°C		
Long-term	Process 1	1	-20±5°C	3 months	[redacted] container
Accelerated			5±3°C		
Long-term	Process 2	4	-20±5°C	3 months	[redacted] container

In the long-term testing, 2 batches manufactured by Process 1 were tested only for RNA integrity and content, and the results showed no clear change throughout the test period. Among consecutive 4 batches manufactured by Process 2, the first batch did not meet the RNA integrity requirements at 2 and 3 months. The applicant explained that the specification limit for RNA integrity was changed from [redacted]% to [redacted]% during the development process, and that this batch had fulfilled the specification limit of [redacted]% (which was effective when the batch was tested) throughout the test period.

In the accelerated testing, 2 batches manufactured by Process 1 were tested only for RNA integrity and content, and the results showed no clear change throughout the test period.

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is a multiple-dose vial formulation manufactured by mixing the diluted active substance and lipid components of LNP (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide [ALC-0159], [(4-hydroxybutyl) azanediyl]bis (hexane-6,1-diyl)bis(2-hexyldecanoate) [ALC-0315], 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and cholesterol) and filling the mixture in vials. Each vial (0.45 mL) contains 0.225 mg of the active substance. Before use, the content is diluted with 1.8 mL of physiological saline to a total volume of 2.25 mL. The vaccine product contains excipients: purified sucrose, sodium chloride, potassium chloride, sodium hydrogenphosphate dihydrate, potassium dihydrogen phosphate, and water for injection.

Comirnaty was submitted for approval as a vial formulation from which 5 doses can be extracted. Currently, a study is ongoing to investigate whether more doses can be extracted. Results are described in Report (2).

2.2.2 Manufacturing process

The vaccine product is manufactured through a process comprised of the following steps: thawing of the active substance, dilution of the active substance, preparation of [redacted], preparation of [redacted], buffer exchange, concentration, filtration, preparation of vaccine product bulk solution, sterile filtration, sterile filling, labeling, packaging, storage, testing, and storage.

The following were defined as critical steps: dilution of the active substance, preparation of [redacted], preparation of [redacted], buffer exchange, concentration, filtration, preparation of vaccine product bulk solution, sterile filtration, sterile filling, labeling, packaging, and storage.

The commercial-scale manufacturing process of the vaccine product is currently being subjected to process validation.

2.2.3 Manufacturing process development

There was a change in manufacturing scale between (a) the manufacturing process of the formulation used in clinical studies and (b) the proposed manufacturing process. The comparability of quality attributes between pre- and post-change vaccine products has been demonstrated.

QbD approach was used in the development of the manufacturing process of the vaccine product [see Section 2.3].

2.2.4 Control of vaccine product

The proposed specifications for the vaccine product include content specification, description, identification (lipids [HPLC] and RNA [RT-PCR]), osmotic pressure, pH, RNA integrity (capillary gel electrophoresis), encapsulated RNA (fluorometry), particle size and polydispersity of particles (dynamic light scattering), endotoxin, extractable volume, insoluble particulate matters, sterility, lipid content (HPLC), and assay (fluorometry). Biological activity ([redacted]) was added during the review process.

2.2.5 Stability of vaccine product

Table 3 shows the summary of the main stability tests for the vaccine product.

Table 3. Summary of the main stability tests for the vaccine product

Test	Manufacturing process of active substance	Number of batches	Storage condition	Study period	Storage package
Long-term	Process 1	2	-70 ± 10°C	6 months	[redacted] rubber-stoppered glass container
Long-term	Process 2	2	-90 to -60°C	3 months	[redacted] rubber-stoppered glass container

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

2.3 QbD

QbD approach was used in the development of the active substance and the vaccine product, and the quality control strategy was developed by doing the following:

- Identification of critical quality attributes (CQAs)

  The following were identified as CQAs because they affect the efficacy and safety of Comirnaty.

  CQAs of the active substance: Description (turbidity and color), pH, RNA integrity, microbial limit, and endotoxin

  CQAs of the vaccine product: Particle size and polydispersity of particles, encapsulated RNA, RNA content, content of lipids (ALC-0159, ALC-0315, DSPC, and cholesterol), *in vitro* expression, RNA integrity, 5' cap structure, and poly (A) tail.

- Process characterization
  Each process was characterized based on the process parameters.
- Establishment of the controlling methods
  Based on the knowledge of the process including the above process characterization, quality attributes of the product, and the results of the stability tests, the control method of the quality attributes of Comirnaty was established by the combination of process parameters control, performance attributes control, and specifications [see Sections 2.1.5.2 and 2.1.5.3 for the control of product-related impurities and process-related impurities].

2.R Outline of the review conducted by PMDA

2.R.1 Changes in the manufacturing process of the active substance

The applicant's explanation about the changes in the manufacturing process of the active substance [see Section 2.1.4]:

Four batches of the active substance manufactured by Process 1 and 5 batches manufactured by Process 2 were compared in terms of the following parameters: Description, pH, identification (RT-PCR), content, RNA integrity (capillary electrophoresis), 5' cap structure (reverse phase HPLC), poly (A) tail (droplet digital polymerase chain reaction [ddPCR]), template DNA (qPCR), double-strand RNA (immunoblotting), and osmotic pressure. Results showed no significant difference. The active substance of Process 2 tended to show lower RNA integrity than that of Process 1, but both active substances met the specifications. Three batches of Process 1 and 1 batch of Process 2 showed a slight difference in the content of poly (A) tail, but all batches conformed to the specifications. The active substances manufactured by both processes showed the identical primary and higher order structure, as revealed by mass spectrometry and optical spectrometry. No significant difference was observed in the percentage of complete RNA with 5' cap structure which is essential for *in vivo* translation of the protein antigen.

The above results show that the active substances manufactured by Process 1 and Process 2 were comparable, without any difference affecting the safety or efficacy.

PMDA accepted the explanation of the applicant.

2.R.2 Foreign insoluble matter

White to grayish white, opaque, amorphous particles were detected in the batch analysis of the vaccine product for "foreign insoluble matter."

The applicant's explanation about the particles:

"White to grayish white, opaque, amorphous particles" were detected in [redacted]% to [redacted]%, and did not show any correlation with the supplier of lipids, manufacturing sites, or filling process. The amount of the particles did not change over time. Analysis of the particles showed that they were RNA and lipids contained in the vaccine product. It also showed that the particles disappeared when the product was diluted with physiological saline,

and that RNA content and the percentage of encapsulated RNA in each batch were similar regardless of the presence or absence of the particles.

These results suggest that the particles in Comirnaty, if any, do not affect the efficacy or safety of Comirnaty.

In rare occasions, the particles are still visible in the solution that has been diluted with physiological saline. Therefore, the package insert will include a precautionary statement to the following effect:

> After diluting Comirnaty with physiological saline, confirm the diluted liquid does not contain particles. Do not use if the liquid contains particles.

PMDA accepted the explanation of the applicant.

2.R.3 Shelf life of active substance and vaccine product

The shelf life of the active substance and the vaccine product proposed by the applicant is 6 months, the same shelf life as in foreign countries.

The applicant's explanation about the shelf life of the active substance and the vaccine product:
The active substances manufactured by Process 1 and Process 2 were shown to be comparable [see Section 2.R.1].

The long-term and accelerated testing of 2 batches of Process 1-derived active substance [see Section 2.1.7] did not show any change in RNA integrity or RNA content. Therefore, the shelf life of the active substance can be defined as 6 months. A long-term testing of 4 batches of Process 2-derived active substances is currently ongoing and will yield stability data beyond 6 months.

As for the shelf-life of the vaccine product, a long-term testing was conducted on 2 batches of the vaccine product containing Process 1-derived active substance. Results showed no significant changes in the main quality attributes (RNA integrity, encapsulated RNA, particle size and polydispersity of particles, RNA content, etc.) up to 6 months. The long-term testing of 2 batches of the vaccine product containing Process 2-derived active substance (Table 3) showed that all quality attributes conformed to the specifications up to 3 months, although no biological activity data are available. Therefore the shelf life of the vaccine product can be defined as 6 months. A long-term testing of 2 batches of the vaccine product containing Process 2-derived active substance, is currently ongoing and will yield stability data beyond 6 months.

PMDA's view:
Additional information is required to confirm the stability of the active substance up to 6 months, for the following reasons:

(i) The long-term testing of 2 batches of Process 1-derived active substance did cover only part of the specifications.

(ii) The number of batches tested was less than 3, the number exemplified in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5C.

Nevertheless, there is no significant stability problem of the active substance at the current moment, for the following reasons:

(i) No significant changes were observed over time in the stability test results submitted.

(ii) In the long-term testing of Process 2-derived active substance, the first batch failed to meet the specification for RNA integrity, but, from the start of the test, RNA integrity of the batch remained at a level close to the lower specification limit ([redacted]%).

(iii) All consecutive 3 batches manufactured after the above batch conformed to the specifications up to 3 months in the long-term testing.

As for the shelf life of the vaccine product, the applicant submitted data from the 6-month long-term testing of only 2 batches. Additional data are required to confirm the stability of the vaccine product up to 6 months. However, all data submitted (including the long-term data up to 3 months of the vaccine product containing Process 2-derived active substance) conformed to all specifications, without any significant change over time.

Comirnaty is manufactured from the active substance common to each country, and supplied to each country. Defining a different shelf life of the active substance and the vaccine product from that in other countries may have an adverse impact on manufacturing and distribution control, and may affect the batches and quantity supplied to Japan. Given the current status of COVID-19 epidemic and the social need for Comirnaty in Japan, at present, there is no choice but to define the shelf life of the active substance and the vaccine product as 6 months, the same period used in foreign countries. Data from the ongoing long-term testing of the active substance and the vaccine product should be submitted to PMDA promptly after the data become available.

Based on the above, the shelf life of the active substance should be 6 months when stored at -20°C ± 5°C in a [redacted] container, and the shelf life of the vaccine product should be 6 months when stored at -90°C to -60°C.

2.R.4 Novel excipients

The vaccine product contains novel excipients of ALC-0159 and ALC-0315, which have never been used before, and DSPC, which is permitted for use in specific products or under specific conditions in accordance with “Handling of excipients that are permitted only for specific drug products or under specific conditions” (Administrative Notice dated June 23, 2009).

The applicant’s explanation about the reason for using the excipients:

ALC-0159 is intended to suppress the interaction between Comirnaty and plasma proteins. ALC-0315 is intended to regulate particle formation and intracellular uptake of Comirnaty and to regulate the release of RNA contained in Comirnaty from the endosome. DSPC is intended to [redacted].

2.R.4.1 Specifications and stability

PMDA concluded that the specifications and the stability of ALC-0159, ALC-0315, and DSPC are acceptable, judging from the data submitted.

2.R.4.2 Safety

The applicant explained single dose toxicity, repeated-dose toxicity, and reproductive toxicity of ALC-0159, ALC-0315, and DSPC based on the results of the toxicity studies of Comirnaty (common technical document [CTD] 4.2.3.2.1, 4.2.3.2.2, and 4.2.3.5.1.1). The applicant also explained that these novel excipients pose no safety concerns regarding genotoxicity, judging from the data of previous use experiences with different route of administration and from the results of genotoxicity assessment based on structure-activity correlation (rule-based method based on professional experience and statistics-based method).

PMDA's view:

The repeated intramuscular dose toxicity study in rats showed effect on the liver (increased blood γ-glutamyltransferase [GGT] and vacuolization of liver cells), but these findings are considered to be of little toxicological significance [see Section 5.R.1]. Since ALC-0159, ALC-0315, and DSPC are essential for ensuring the characteristics of Comirnaty, using these excipients in Comirnaty is acceptable. However, since long-term repeated-dose toxicity of Comirnaty has not been evaluated, the use of these excipients should be limited to the dosage regimen of Comirnaty, and should not be handled as a precedent.

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

Results of primary pharmacodynamics studies were submitted as data of the nonclinical pharmacological studies of Comirnaty.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* antigen expression (CTD 4.2.1.1.1, 4.2.1.1.5)

A mixture of tozinameran (BNT162b2) and transfection reagent was introduced into human embryonic kidney 293 T cells (HEK293T cells), and expression of the antigen (full-length SARS-CoV-2 S protein) was evaluated by Western blotting and by immunofluorometry. Results confirmed that the antigen was expressed in HEK293T cells and localized in the endoplasmic reticulum, suggesting that the antigen was synthesized and processed in the endoplasmic reticulum.

Comirnaty (LNP-encapsulated BNT162b2) or the mixture of tozinameran (BNT162b2) and the transfection reagent was transfected into HEK293T cells, and transfection efficiency and cell viability were evaluated by flow cytometry. Antigen-expressing cells accounted for 98.0% ± 0.2% of the total Comirnaty-transfected cells and 85.1% ± 4.4% of the total tozinameran-transfected cells. The cell viability of Comirnaty-transfected cells and tozinameran-transfected cells was similar to that of control cells (non-transfected cells).

Expi293F cells were engineered to express S protein from DNA encoding the same amino acid sequence encoded by tozinameran. The expressed S protein bound to angiotensin converting enzyme 2 (a receptor on human cells) and to human receptor binding domain (RBD)-neutralizing antibody, and the S protein was expressed on the cell surface.

3.1.2 Immunogenicity test in mice (CTD 4.2.1.1.2)

A single dose of Comirnaty (0.2, 1.0, or 5.0 μg of RNA) was administered intramuscularly to BALB/c mice (8 females per group), and immune response was evaluated. The following results were obtained.

- Study on immunoglobulin G (IgG) antibody specific to S protein S1 subunit and to RBD (enzyme-linked immunosorbent assay [ELISA])

S1-specific IgG antibody and RBD-specific IgG antibody in serum were measured. Results showed dose-dependent production of antigen-specific antibodies at measured time points (7 through 28 days after treatment with Comirnaty).

- Study on neutralizing antibody using pseudovirus (neutralization assay)

Neutralizing antibody in serum was measured using pseudovirus.[7)] Dose-dependent production of the neutralizing antibody was observed at measured time points (14 through 28 days after treatment with Comirnaty).

- IgG subtypes (ELISA)

IgG subtypes (IgG1 and IgG2a) in serum were investigated 28 days after treatment with Comirnaty. Th2-dominant immune response was not observed.

- Cytokine production in spleen cells (Luminex assay and intracellular cytokine staining)[8)]

Spleen cells were treated with Comirnaty and, 28 days later, stimulated with S1 or RBD peptide. The results showed production of interferon-gamma (IFN-γ), tumor necrosis factor - alpha (TNF-α), interleukin 2 (IL-2), IL-6, IL-18, and granulocyte macrophage colony-stimulating factor (GM-CSF). In contrast, production of IL-4, IL-5, and IL-13 was scarce, suggesting Th1-dominant immune response. The cells treated with Comirnaty showed a higher percentage of CD4- or CD8-positive T cells producing IFN-γ, TNF-α, or IL-2, compared with control cells (spleen cells 28 days after being given buffer solution), but showed no significant increase in the percentage of CD4-positive T cells producing IL-4 (IL-4 was evaluated only in CD4-positive T cells).

3.1.3 Challenge test in monkeys (CTD 4.2.1.1.4)

Two doses of Comirnaty were administered intramuscularly 21 days apart to rhesus monkeys (6 males per group) to evaluate immune response and the effect of the vaccine in preventing infection and disease onset after exposure to SARS-CoV-2.

- S1-specific IgG antibody and neutralizing antibody (ELISA and neutralization assay)[9)]

S1-specific IgG antibody and neutralizing antibody in serum were measured 35 days after the second dose of Comirnaty (30 or 100 μg of RNA). Both antibodies were detected (Table 4).

[7)] Vesicular stomatitis virus with a gene encoding SARS-CoV-2-derived S protein

[8)] The amount of cytokine produced was measured by fluorescent antibody testing (Luminex assay), and the number of cytokine-producing cells by intracellular cytokine staining.

[9)] S1-specific IgG antibody was evaluated by ELISA, and neutralizing antibody by neutralization assay using SARS-CoV-2 (strain USA-WA1/2020).

Table 4. S1-specific IgG antibody and neutralizing antibody in serum 35 days after the second dose of Comirnaty

Dose	S1-specific IgG antibody GMC [2-sided 95% CI] (U/mL)	Neutralizing antibody GMT [2-sided 95%CI]
Comirnaty 30 μg	4,236 [1,380, 13,003]	285 [136, 598]
Comirnaty 100 μg	6,317 [3,877, 10,291]	310 [175, 549]
Convalescent serum [a)]	631	94

a) Sera from 38 donors who became asymptomatic ≥14 days after testing positive for SARS-CoV-2 by PCR.

- Cytokine production by peripheral mononuclear cells (Enzyme-linked immunospot [ELISpot] and intracellular cytokine staining)[10)]

Peripheral mononuclear cells isolated from monkeys after administration of Comirnaty (30 or 100 μg of RNA) were stimulated with S protein peptide, to measure the amount of cytokines (IFN-γ and IL-4) produced and the number of cytokine-producing cells. IFN-γ was detected at a high level in peripheral mononuclear cells ≥7 days after the second dose of Comirnaty, whereas only a low level of IL-4 was detected at all time points measured. The number of CD4-positive T cells producing IFN-γ, IL-2, or TNF-α and CD8-positive T cells producing IFN-γ increased at ≥14 days after the first dose of Comirnaty, whereas the number of IL-4-producing CD4-positive T cells increased only marginally. Based on the above, the applicant explained that Th1-dominant immune response was induced in monkeys after administration of Comirnaty.

- Prevention of infection and disease onset after exposure to SARS-CoV-2

Two doses of Comirnaty (100 μg of RNA) or physiological saline were administered to monkeys (6 in Comirnaty group, 3 in control group). At 55 days after the second dose, they were exposed to SARS-CoV-2 (strain USA-WA1/2020, 1.05×10^6 PFU) through the nasal or tracheal route. Table 5 shows the results of the observation and tests after the exposure. The amount of viral RNA detected from the airway was lower in the Comirnaty group than in the control group. The applicant explained that these results showed the effect of Comirnaty in preventing the infection.

[10)] IFN-γ and IL-4 production was evaluated by ELISpot method, and the number of cytokine-producing cells by intracellular cytokine staining.

Table 5. Findings and test results after SARS-CoV-2 exposure

Evaluation item	Comirnaty	Control
Viral RNA (bronchoalveolar lavage fluid, nasal swab, and oropharyngeal swab) [a)]	Bronchoalveolar lavage fluid: Undetectable Nasal swab: Detected on Day 1 (in 5 of 6 animals) Oropharyngeal swab: Detected on Day 1 (3 of 6), Day 3 (2 of 6), and Day 7 or 8 (1 of 6)	Bronchoalveolar lavage fluid: Detected on Day 3 (in 2 of 3 animals) and Day 6 (1 of 3) Nasal swab: Detected on Day 1 (2 of 3), Day 3 (2 of 3), and Day 6 (1 of 3) Oropharyngeal swab: Detected on Day 1 (3 of 3) and Day 10 (1 of 3)
Clinical sign[b)]	No abnormal findings	No abnormal findings
Chest X ray and CT[c)]	Normal or mild abnormal findings of the lung[d)]	Mild to moderate abnormal findings of the lung[d)]
Gross observation[e)]	No abnormal findings	No abnormal findings
Histopathology	Inflammatory cell infiltration in the lung[f)]	Inflammatory cell infiltration in the lung

a) Bronchoalveolar lavage fluid was collected on Day 3 and Day 6 after viral exposure, and Day 7 or 8 (in the Comirnaty group only). Nasal and oropharyngeal swabs were collected on Day 1, 3, and 6 after viral exposure, and Day 7 or 8 in the Comirnaty group and Day 10 in the control group.
b) Body weight, body temperature, oxygen saturation of peripheral artery (SpO_2), and heart rate were measured on Day 1, 3, and 6 after viral exposure, and Day 7 or 8 in the Comirnaty group and Day 10 in the control group.
c) Animals were tested on Day 1, 3, and 6 after viral exposure, and Day 7 or 8 in the Comirnaty group and Day 10 in the control group.
d) Control animals showed mild to moderate interstitial opacities, multiple nodular densities in the soft tissues, and localized alveolar disease along the diaphragmatic surface; these symptoms were the most visible on Day 3 after viral exposure. In the Comirnaty group, such findings were mild, if any, or not observed.
e) Animals were necropsied on Day 7 or 8 after viral exposure
f) In the Comirnaty group, the area of inflammation tended to be smaller than that of the control group, and the inflammation sites were only slightly infiltrated with eosinophils.

3.2 Safety pharmacology

No safety pharmacology study of Comirnaty was conducted. Instead, the safety pharmacology of Comirnaty was evaluated based on clinical signs of rats in the repeated intramuscular dose toxicity study (CTD 4.2.3.2.2). The applicant explained that Comirnaty had no effect on the physiological functions of the cardiovascular, respiratory, central nervous systems, etc.

3.R Outline of the review conducted by PMDA

On the basis of the submitted data and the results of the following reviews, PMDA has concluded that there was no particular problem in the nonclinical pharmacology of Comirnaty.

3.R.1 Mechanism of action of Comirnaty

PMDA asked the applicant to explain the mechanism of action of Comirnaty.

The applicant's explanation:

The *in vitro* studies of Comirnaty demonstrated that S protein is expressed in the host cells [see Section 3.1.1]. Studies in mice and monkeys showed production of neutralizing antibody, Th1-dominant immune response, and an increase in IFN-γ-producing CD8-positive T cells [see Sections 3.1.2 and 3.1.3]. The study on monkeys demonstrated a certain effect of Comirnaty in preventing infection in animals exposed to SARS-CoV-2 [see Section 3.1.3].

The active ingredient of Comirnaty is an mRNA encoding the full-length S-protein of SARS-CoV-2. The mRNA is translated into S-protein, the target of the neutralizing antibody, in the host cell. The S protein then induces humoral and cellular immune response. In this way, Comirnaty is expected to prevent COVID-19.

PMDA accepted the explanation of the applicant.

3.R.2 Neutralizing activity against variants

Various variants of SARS-CoV-2 have been identified after the initiation of the development of Comirnaty. PMDA asked the applicant to explain the neutralizing activity of Comirnaty against the variants.

The applicant's explanation:

At the start of the COVID-19 epidemic, the dominant strain of SARS-CoV-2 had S protein with D614 (aspartic acid at position 614), and the mRNA sequence used in Comirnaty also encodes D614. In contrast, a strain with D614G (aspartic acid at position 614 substituted by glycine) started to increase around February 2020 and, as of November 2020, D614G was considered to be the mutation with the highest cumulative frequency (89.0%) globally.[11)] In addition, more infectious variants with multiple mutations in S protein were isolated in the United Kingdom (VOC-202012/01[12)]) and in South Africa (501Y.V2[13)]).

In order to evaluate the neutralizing activity of sera from Comirnaty recipients against the variants, the following experiment was performed. Nineteen different types of S protein gene with amino acid mutations were prepared from the gene of SARS-CoV-2 isolate Wuhan-Hu-1 (which has the same S protein sequence as that encoded by the mRNA of Comirnaty). Pseudoviruses were prepared by introducing each gene into vesicular stomatitis virus, to evaluate neutralizing activity of sera from Comirnaty recipients against each pseudovirus (Figure 1).

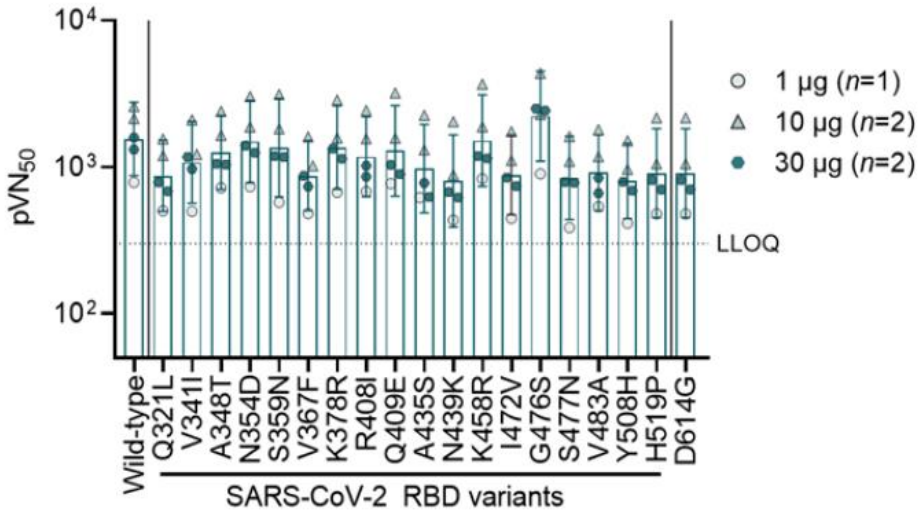

Figure 1. Neutralization assay of pseudoviruses expressing mutant S protein with sera from Comirnaty recipients

The data show pVN_{50} (neutralizing antibody titers with a 50% decrease in pseudovirus-infected cells) of sera from Comirnaty recipients (n = 5) against pseudoviruses (vesicular stomatitis virus) with S protein gene of the wild type SARS-CoV-2 (isolate Wuhan-Hu-1) or with 19 types of S protein genes with amino acid mutations (lower limit of quantitation [LLOQ] = 300).

Results confirmed the neutralizing activity against all of the pseudoviruses. In addition, sera from Comirnaty recipients showed a certain level of neutralizing activity against (i) a pseudovirus with S protein gene with

11) The applicant used results of the analysis of amino acid sequence of 208,147 clinical isolates collected by November 24, 2020 globally from the database containing the information on amino acid sequence of clinical isolates of SARS-CoV-2 (Global Initiative on Sharing All Influenza Data). The cumulative frequency of variants other than D614G in decreasing order: A222V (14.0%), L18F (6.7%), S477N (6.4%), L5F (1.2%), etc. In the analysis of 913 clinical isolates in Japan using the same database, the order was D614G (63.3%), M153T (6.1%), S12F (1.4%), Q613H (1.2%), etc.

12) Deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H

13) L18F, D80A, D215G, L242H, R246I, E484K, K417N, N501Y, D614G, A701V, and I1227V

amino acid mutation N501Y, the mutation common to variants isolated in the United Kingdom and South Africa, (ii) a pseudovirus with S protein gene with several mutations (i.e., K417N, E484K, and N501Y), and (iii) a pseudovirus with S protein gene containing the same mutation as that of the variant isolated in the United Kingdom (https://doi.org/10.1101/2021.01.07.425740, https://doi.org/10.1101/2021.01.15.426911, https://doi.org/10.1101/2021.01.18.426984 (as of January 27, 2021). These results suggest that Comirnaty has a certain level of efficacy against viruses with various S protein mutations. However, some of the currently prevailing SARS-CoV-2 strains include mutants poorly responsive to neutralizing monoclonal antibodies (*Cell.* 2020;182:1284-94), and novel variants may emerge at any time in future. Therefore, the currently available data do not necessarily guarantee the activity of Comirnaty against all variants that may emerge in future. Data on the neutralizing activity of Comirnaty against variants will be collected continuously after the market launch.

PMDA's view:
The study results demonstrated the neutralizing activity of sera from Comirnaty recipients against various pseudoviruses with various S protein gene mutations, including D614G (which has now become the dominant strain). Comirnaty is thus expected to have a certain level of efficacy against various variants prevalent as of January 27, 2021. However, (a) the biological characteristics of SARS-CoV-2 as an RNA virus and (b) a report of a variant poorly responsive to COVID-19 convalescent sera (https://doi.org/10.1101/2021.01.18.427166 [as of January 27, 2021]), suggest that variants evading the immune response induced by Comirnaty may emerge in future epidemics. Data on the neutralizing activity of Comirnaty against variants should be collected continuously after the market launch, and new information obtained should be provided as necessary, and appropriate actions should be taken, such as dissemination of newly acquired information as necessary.

3.R.3 Risk of Comirnaty-associated enhanced disease
PMDA asked the applicant to discuss whether the immune response induced by Comirnaty may enhance the symptoms caused by SARS-CoV-2 infection, compared with symptoms in individuals not receiving the vaccine (risk of vaccine-associated enhanced disease).

The applicant's explanation:
It is currently unclear whether SARS-CoV-2 vaccine has a risk of enhanced disease. A vaccine against SARS-CoV, a virus related to SARS-CoV-2, was reported to have a risk of enhanced disease in animal studies, suggesting the involvement of Th2-dominant immune response (*PLoS ONE.* 2012;7:e35421). Th2-dominant immune response induced by a SARS-CoV-2 vaccine may also enhance disease as with a SARS-CoV vaccine. This suggests that if a SARS-CoV-2 vaccine induces Th1-dominant immune response, vaccine recipients have a low risk of enhanced disease when infected with SARS-CoV-2. (*Vaccine.* 2020;38:4783-91).

In nonclinical pharmacology studies evaluating the immune response of Comirnaty, Comirnaty induced Th1-dominant immune response in both mice and monkeys [see Sections 3.1.2 and 3.1.3]. In the challenge test in monkeys, animals exposed to SARS-CoV-2 after administration of Comirnaty showed a rapid decrease in the amount of viral RNA in the trachea, alveoli, nasal cavity, and oropharynx. Abnormal findings of the lung in

chest X-ray and in CT imaging were milder in Comirnaty group than in the control group. Furthermore, histopathological examination of the lung showed no worsening of "inflammatory findings accompanying eosinophil infiltration," a phenomenon suggestive of Th2-dominant immune response.

Cytokine production induced by Comirnaty in humans was evaluated. In the foreign phase I study (Study BNT162-01, CTD 5.3.5.1.2), peripheral blood mononuclear cells from Comirnaty recipients were stimulated with S protein peptide. Results showed increased production of INF-γ in CD8-positive T cells and INF-γ and IL-2 in CD4-positive T cells, but showed little increase in the production of IL-4, demonstrating Th1-dominant immune response.

These results suggest that Comirnaty is unlikely to pose a risk of enhanced disease.

PMDA accepted the applicant's explanation from the pharmacological point of view. Risk of enhanced disease in humans is further discussed in Section 7.R.3.6.

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

No non-clinical pharmacological study of Comirnaty or tozinameran was conducted.

Instead, nonclinical pharmacology studies were conducted on LNP contained in Comirnaty and on its component lipids ALC-0159 and ALC-0315, and data of their absorption, distribution, metabolism, and excretion were submitted.

ALC-0159 and ALC-0315 concentrations in rat plasma, liver, urine, and feces were measured by LC-MS/MS (lower quantitation limit: 4.88 ng/mL in plasma and urine, 6.592 ng/mL in feces, 19.53 ng/g in the liver). The luciferase gene expression in the mouse body was determined by *in vivo* imaging system. The radioactivity concentration in biological samples following the administration of luciferase-expressing mRNA-[^{3}H]-LNP to rats was measured by liquid scintillation counting. The lower quantitation limits of *in vivo* imaging system and of liquid scintillation counting were not determined.

Pharmacokinetics (PK) parameters are expressed in mean values unless specified otherwise.

4.1 Absorption

4.1.1 Single intravenous dose study of luciferase gene-expressing mRNA-LNP (CTD 4.2.2.2.1)

Luciferase gene-expressing mRNA-LNP (1 mg/kg RNA) was administered to rats (3 males per time point) (1.96 mg/kg ALC-0159 and 15.3 mg/kg ALC-0315), to investigate PK parameters of ALC-0159 and ALC-0315 in plasma and their distribution in the liver. The half-life of ALC-0159 and ALC-0315 in plasma was 1.7 and 1.6 hours, respectively, in the distribution phase and 72.7 and 139 hours in the elimination phase. The plasma concentration of each compound decreased below 1% of the maximum plasma concentration within

24 hours after administration. They were rapidly distributed in the liver within 24 hours after administration, with the estimated distribution rate of approximately 20% and 60%, respectively, of the dose administered.

4.2 Distribution

4.2.1 Biodistribution of luciferase gene-expressing mRNA-LNP (CTD 4.2.2.3.1)

A single dose of luciferase gene-expressing mRNA-LNP (2 μg RNA) was administered intramuscularly to mice (3 females per group), to measure bioluminescence up to 9 days after administration using the *in vivo* imaging system.

The luminescence signal at the administration site and at the liver region was approximately 1.0×10^9 and approximately 5.0×10^7 photons per second (p/s), respectively, at 6 hours after administration (the first measuring time point), and then decreased over time. The luminescence signal at the liver region was undetectable at 48 hours after administration. The luminescence signal at the administration site decreased close to the background level observed in the control group (animals receiving phosphate-buffered physiological saline) at 9 days after administration.

4.2.2 Distribution of luciferase gene-expressing mRNA-[^{3}H]-LNP (CTD 4.2.2.3.2)

A single dose of luciferase gene-expressing mRNA-[^{3}H]-LNP[15)] (50 μg RNA) was administered intramuscularly to rats (3/sex/group), to investigate the tissue distribution of the radioactivity up to 48 hours after administration. The radioactivity concentration at the administration site peaked 1 hour after administration (394 μg lipid eq./g), then decreased over time to 165 μg lipid eq./g 48 hours after administration. The radioactivity was detected, in addition to the administration site, mainly in the liver, spleen, adrenals, and ovary, and the concentration peaked 8 to 48 hours after administration (26, 23, 18, and 12 μg lipid eq./g, respectively, in the liver, spleen, adrenals, and ovary).

4.3 Metabolism

4.3.1 Metabolism of ALC-0159 and ALC-0315 (CTD 4.2.2.4.1 to 4.2.2.4.7)

ALC-0159 or ALC-0315 was added to liver microsomes, S9 fraction, and liver cells of mice, rats, monkeys, and humans (final concentration: 1.5 μmol/L in liver microsomes and S9 fraction, 1.0 μmol/L in liver cells), and the mixture was incubated at 37°C for 2 hours (4 hours for liver cells). At least 90% of ALC-0159 and ALC-0315 remained unchanged in all samples.

ALC-0159 or ALC-0315 was added to S9 fraction, liver cells, and blood of mice, rats, monkeys, and humans (final concentration 10 μmol/L), and the mixture was incubated at 37°C for 24 hours (4 hours in liver cells). Then metabolites were investigated. ALC-0159 with hydrolyzed amide group and ALC-0315 with hydrolyzed ester group were detected in S9 fraction and liver cells of all animal species and in the blood of mice and rats.

[15)] Test substance is luciferase mRNA encapsulated in ^{3}H-labeled LNP (which has the same component and the same quality attributes as LNP contained in Comirnaty, except tritium labeling)

A single dose of luciferase gene-expressing mRNA-LNP was administered intravenously to rats,[16] and metabolites in plasma, urine, feces, and liver samples were measured by ultraperformance liquid chromatography-mass spectrometry up to 14 days after administration. No metabolites of ALC-0159 were detected in any of the samples tested. As for metabolites of ALC-0315, glucuronate conjugate was detected in urine, and hydrolysate of ester group was detected in all samples.

These results suggested that ALC-0159 and ALC-0315 were gradually metabolized by the hydrolysis of ester or amide group.

4.4 Excretion

4.4.1 ALC-0159 and ALC-0315 excretion in urine and feces (CTD 4.2.2.2.1)

A single dose of luciferase gene-expressing mRNA-LNP was administered to rats (3 males), to investigate ALC-0159 and ALC-0315 in feces and urine. Within 336 hours after administration, approximately 47.2% of ALC-0159 and approximately 1.1% of ALC-0315[17] were excreted unchanged in feces. The amount of unchanged ALC-0159 and ALC-0315 in urine was below the lower quantitation limit.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data and the results of the following review, PMDA concluded that there was no particular problem in the nonclinical pharmacokinetics of Comirnaty.

4.R.1 Nonclinical pharmacokinetics of Comirnaty

No nonclinical pharmacokinetic study of Comirnaty was conducted. PMDA asked the applicant to explain the pharmacokinetics of Comirnaty.

The applicant's explanation:

Comirnaty is a formulation consisted of tozinameran (mRNA) encapsulated in LNP. Usually, mRNA administered into the body is rapidly metabolized as with nucleic acid within the body. In contrast, mRNA encapsulated in LNP is taken up by host cells without being metabolized, and serves as a message for protein synthesis. Thus, the pharmacokinetics of mRNA formulation encapsulated in LNP is dependent not on the encapsulated mRNA but on the LNP.

Results of the biodistribution study of luciferase gene-expressing mRNA-LNP injected intramuscularly [see Section 4.2], suggested the following pharmacokinetic characteristics:

> Intramuscularly injected Comirnaty is distributed mainly at the injection site and partially in the whole body (mainly in the liver), and then expresses the protein at each site. However, Comirnaty and the expressed protein are eliminated over time from all sites.

PMDA accepted the explanation of the applicant, and concluded that the pharmacokinetic characteristics of

[16] CTD 4.2.2.2

[17] "Measured amount (μg) of ALC-0159 or ALC-0315 in feces or urine"/"amount (μg) in the dose" × 100

Comirnaty can be understood to a certain extent.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of a repeated-dose toxicity study and a reproductive and developmental toxicity study.

5.1 Single-dose toxicity

No single dose toxicity study of Comirnaty was conducted. Instead, the single dose toxicity (acute toxicity) of Comirnaty was evaluated from the results obtained after the first dose in the repeated intramuscular dose toxicity study in rats (CTD 4.2.3.2.2). After administration of Comirnaty, no death occurred but the following findings were observed: oedema at the injection site, body temperature increased (+0.54℃ in males, +0.42℃ in females), white blood cell count increased, acute phase protein increased, etc.

5.2 Repeated-dose toxicity

A repeated intramuscular dose toxicity study was conducted in rats using Comirnaty and the formulation prior to codon optimization of Comirnaty (BNT162b2 (V8))[18] (Table 6). The main finding was inflammatory change at the injection site.

Table 6. Repeated-dose toxicity study

Test system	Route of administration	Treatment period	Dose (μg RNA/body)	Main findings	No observed adverse effect level (μg RNA /body)	Attached document CTD
Male and female rats (Wistar Han)	i. m.	2 weeks (once weekly, 3 times in total [a]) followed by 3-week recovery period	0, [b] 100 [c]	100 [f]: Body temperature increased, oedema/inflammation of administration site, increases in white blood cells (lymphocytes, monocytes, neutrophils, eosinophils, and basophils), increases in fibrinogen and acute phase protein (α_1-acid glycoprotein, α_2-macroglobulin), GGT increased, hepatocyte vacuolization Reversibility: Yes	100	4.2.3.2.1
			0, [d] 30 [e]	30 [f]: Body temperature increased, oedema/inflammation of administration site, increases in white blood cells (lymphocytes, monocytes, neutrophils, eosinophils, and basophils), increases in fibrinogen and acute phase protein (α_1-acid glycoprotein, α_2-macroglobulin), hepatocyte vacuolization Reversibility: Yes	30	4.2.3.2.2

a) Administered on Day 1, 8, and 15
b) Phosphate-buffer containing 300 mM sucrose
c) BNT162b2 (V8) (2.0 μL/μg RNA)
d) Physiological saline
e) Comirnaty (2.0 μL/μg RNA)
f) Neutralizing antibody was confirmed on Day 17 and 38 after the start of study.

5.3 Genotoxicity

The mRNA contained in Comirnaty is composed of natural nucleic acid, and the novel excipients (ALC-0159, ALC-0315, and DSPC) have no risk of genotoxicity [see Section 2.R.4.2]. Therefore, no genotoxicity study of Comirnaty was conducted.

[18] Comirnaty and BNT162b2 (V8) have been confirmed to have similar qualitative attributes; they encode the same amino acid sequence and have the same 5' cap structure and 3' poly (A) tail.

5.4 Carcinogenicity

Since Comirnaty is not used continuously for ≥6 months, no carcinogenicity study of Comirnaty was conducted.

5.5 Reproductive and developmental toxicity

A reproductive and developmental toxicity study was conducted in rats (Table 7). Comirnaty had no effect on parental animals or on the offspring.

Table 7. Reproductive and developmental toxicity study

Study	Test system	Route of adminis-tration	Treatment period	Dose (μg RNA /body)	Main findings	No observed adverse effect level (μg RNA /body)	Attached document CTD
Fertility and early embryonic development to implantation, effects on pre- and postnatal development, including maternal function	Female rats (Wistar Han)	i. m.	Female: 21 days before mating through gestation day 20 (4 times in total [a])	0,[b] 30[c]	Maternal animals 30 [d]: Decreases in body weight and food consumption Embryos/fetuses 30 [d]: None F1 offspring 30 [d]: None	Maternal animals (general toxicity, fertility): 30 Embryos/fetuses: 30 F1 offspring: 30	4.2.3.5.1.1

a) Administered 21 and 14 days before mating and on gestation day 9 and 20
b) Physiological saline
c) Comirnaty (2.0 μL/μg RNA)
d) Neutralizing antibody was confirmed immediately before mating, on Day 21 after mating (at Caesarean section), and on post-partum day 21 in maternal animals; on gestation day 21 (at Caesarean section) in fetuses; and on post-partum day 21 in F1 offspring.

5.6 Local tolerance

The local tolerance of Comirnaty was evaluated from the results of the repeated intramuscular dose toxicity study in rats (CTD 4.2.3.2.2). Reversible mild to moderate inflammation was observed at the injection site.

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and the results of the following review, PMDA has concluded that there was no particular problem in the toxicity of Comirnaty.

5.R.1 Effect on the liver

The repeated intramuscular dose toxicity study in rats showed an increase in GGT in blood and vacuolization of liver cells. PMDA therefore asked the applicant to discuss the safety of Comirnaty in humans.

The applicant's explanation:

The mechanisms of the GGT increase in blood and the vacuolization of liver cells observed in the repeated intramuscular dose toxicity study in rats are unclear. However, the following findings suggest that vacuoles in liver cells were generated by the uptake of lipids into the liver cells:

(i) The vacuoles are morphologically similar to lipid droplets and are localized in periportal liver cells.
(ii) Distribution of lipid in the liver was confirmed in the nonclinical pharmacokinetic studies of LNP, a component of Comirnaty, in rats [see Sections 4.1 and 4.2].

The increased GGT in blood and the vacuolization of liver cells are both considered to be of little toxicological significance, because (i) both findings were mild and reversible, and (ii) there were no histopathological findings or changes in the laboratory values (blood alanine aminotransferase [ALT], aspartate aminotransferase

[AST], alkaline phosphatase, and total bilirubin) suggestive of Comirnaty-associated injury of the hepatobiliary system.

As for the safety of Comirnaty in humans, Table 8 shows the incidence of adverse events in the hepatobiliary system in the phase II/III part of foreign Study C4591001 [see Section 7.2.2]. No adverse events related to hepatobiliary disorders were reported in Japanese Study C4591005 [see Section 7.1] as of the cut-off date (January 5, 2021).
The above results suggest that Comirnaty is unlikely to have hepatotoxicity in humans.

Table 8. Adverse events of hepatobiliary system in foreign Study C4591001 (safety analysis set, data cut-off November 14, 2020)

	Comirnaty (N = 21,621)	Placebo (N = 21,631)
	n (%)	n (%)
Hepatic and hepatobiliary disorders [a)]	14 (0.1)	5 (0.0)
Cholelithiasis	7 (0.0)	2 (0.0)
Biliary colic	3 (0.0)	0
Cholecystitis	2 (0.0)	0
Bile duct stone	1 (0.0)	0
Cirrhosis alcoholic	1 (0.0)	0
Gallbladder disorder	1 (0.0)	0
Cholecystitis acute	0	3 (0.0)
Hepatic cirrhosis	0	1 (0.0)

N = number of subjects analyzed, n = number of subjects with events
a) Events classified as MedDRA System Organ Class "Hepatic and hepatobiliary disorders"

PMDA's view:
The following view of the applicant is acceptable: The effects on the liver observed in the repeated intramuscular dose toxicity study in rats are of low significance, suggesting that Comirnaty has only a low risk of causing liver toxicity in humans.

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

No relevant studies were conducted.

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

The applicant submitted efficacy and safety evaluation data from 2 clinical studies shown in Table 9. The dose of Comirnaty is expressed as the amount of tozinameran (BNT162b2).

Table 9 Summary of clinical studies (evaluation data)

Region	Study ID	Phase	Population	No. of subjects enrolled	Dosage regimen	Study objective
Japan	C4591005	I/II	Healthy subjects aged 20-85 years	Comirnaty: 120 Placebo: 40	Two doses of Comirnaty 30 μg or placebo, administered intramuscularly 21 days apart.	Safety Tolerability Immunogenicity
Foreign	C4591001	I/II/III	・Phase I part: Healthy subjects aged 18-55 and 65-85 years ・Phase II/III part: Healthy subjects aged ≥12 years	・Phase I part: Three dose levels of Comirnaty or BNT162b1,[a)] stratified by age: 12 per group Placebo: 3 per age group[b)] ・Phase II/III part: Comirnaty: 21,999 Placebo: 21,999	・Phase I part: Two doses of Comirnaty (10, 20, 30 μg), BNT162b1 (10, 20, 30, 100 μg), or placebo, administered intramuscularly 21 days apart. ・Phase II/III part: Two doses of Comirnaty 30 μg or placebo, administered intramuscularly 21 days apart.	・Phase I part: Safety Tolerability ・Phase II/III part: Efficacy Safety

a) BNT162b1: A vaccine candidate containing mRNA that encodes RBD of SARS-CoV-2
b) Subjects stratified into 2 age groups (18-55 and 65-86 years) were assigned to receive one of 3 doses (10, 20, 30 μg) of Comirnaty or BNT162b1. Only subjects aged 18-55 years received BNT162b1 100 μg.

7.1 Japanese Phase I/II Study (CTD 5.3.5.1.2: Study C4591005; study period, ongoing since October 2020; data cutoff date, January 5, 2021)

A randomized, observer-blind,[19)] placebo-controlled, parallel-group study was conducted at 2 study sites in Japan to investigate the safety, tolerability, and immunogenicity of Comirnaty in Japanese healthy subjects aged ≥20 and ≤85 years (target sample size of 160 subjects: 120 in the Comirnaty group; 40 in the placebo group).

Two doses of the study vaccine (Comirnaty 30 μg or placebo) were to be administered intramuscularly, 21 days apart (Day 1 and Day 22 [allowable period: Days 19 to 23]).

All of the randomized 160 subjects (119 in the Comirnaty group; 41 in the placebo group) received at least 1 dose of the study vaccine, and were included in the safety analysis set.

All of the randomized 160 subjects (119 in the Comirnaty group; 41 in the placebo group) received at least 1 dose of the study vaccine, provided immunogenicity results, and were included in the all-available immunogenicity population. The primary immunogenicity analysis set was defined as the evaluable immunogenicity population (i.e., a group of subjects who received Dose 2 within the predefined period, provided immunogenicity results after Dose 2, and were eligible with no significant protocol deviations). The results of this population are being analyzed as of January 29, 2021, and therefore have not yet been submitted. The present report shows the results of the all-available immunogenicity population because they have already been submitted.

In the all-available immunogenicity population, (1) the geometric mean titer (GMT) of serum neutralizing antibody against SARS-CoV-2 at 1 month after Dose 2 and (2) the geometric mean fold rise (GMFR) at 1 month after Dose 2 versus the level before Dose 1 [two-sided 95% CI], were as follows:

[19)] Subjects, investigators, study coordinators, and study staff members (excluding those who prepared or injected the study vaccine) were blinded.

The Comirnaty group: GMT, 489.9 [420.4, 570.9]; GMFR, 48.1 [41.3, 56.0]
The placebo group: GMT, 10.6 [9.8, 11.4]; GMFR, 1.1 [1.0, 1.1]

For the safety, observation periods were defined as follows. The severity of adverse events was assessed based on the FDA guidance regarding the toxicity grading scale in clinical studies of preventive vaccines (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007[20]).

- Reactogenicity events (local reactions[21] [injection site pain, redness, and swelling] and systemic events [pyrexia, fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia]) are collected by the subject diary within 7 days after each dose.
- Adverse events (excluding reactogenicity events collected by the subject diary within 7 days after each dose) are collected during the period from Dose 1 to 1 month after the last dose.
- Serious adverse events are collected during the period from Dose 1 to 12 months after the last dose.

Reactogenicity events that occurred within 7 days after each dose are shown in Table 10.

Table 10 Reactogenicity events within 7 days after each dose (safety analysis set)

	Dose 1		Dose 2	
	Comirnaty (N = 119)	Placebo (N = 41)	Comirnaty (N = 116)	Placebo (N = 41)
	n (%)	n (%)	n (%)	n (%)
Local reactions				
Injection site pain	103 (86.6)	1 (2.4)	92 (79.3)	0
Redness	16 (13.4)	0	12 (10.3)	0
Swelling	15 (12.6)	0	10 (8.6)	0
Systemic events				
Pyrexia	17 (14.3)	0	38 (32.8)	0
Fatigue	48 (40.3)	4 (9.8)	70 (60.3)	1 (2.4)
Headache	39 (32.8)	6 (14.6)	51 (44.0)	5 (12.2)
Chills	30 (25.2)	2 (4.9)	53 (45.7)	1 (2.4)
Vomiting	0	0	1 (0.9)	0
Diarrhoea	6 (5.0)	0	6 (5.2)	1 (2.4)
Myalgia	17 (14.3)	1 (2.4)	19 (16.4)	0
Arthralgia	17 (14.3)	2 (4.9)	29 (25.0)	0

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

Adverse events and adverse reactions (i.e., adverse events for which a causal relationship with the study vaccine cannot be ruled out) were observed in 10.1% (12 of 119 subjects) and 1.7% (2 of 119 subjects), respectively, in the Comirnaty group and 7.3% (3 of 41 subjects) and 0 subjects, respectively, in the placebo group. Adverse events observed in ≥2 subjects were nasopharyngitis (3 subjects in the Comirnaty group; 1 subject in the placebo group) and headache (2 subjects in the Comirnaty group; 1 subject in the placebo group). There have been no reports of adverse events related to SARS-CoV-2 infection or COVID-19.

[20] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (as of January 21, 2021)
[21] Injection site induration was not listed as a local reaction to be collected by the subject diary.

Neither death nor serious adverse events occurred by the data cutoff date (January 5, 2021).

Adverse events leading to study discontinuation (chills, fatigue, injection site pain, arthralgia, and headache) occurred in 1 subject in the Comirnaty group. The injection site pain and headache were severe. All of the events were considered to have a causal relationship with the study vaccine and their outcomes were "recovered."

7.2 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, November 14, 2020 in the Comirnaty 30 µg group; August 24, 2020 in the other groups); Phase II/III Part, ongoing since July 2020 [data cutoff date, November 14, 2020])

7.2.1 Phase I Part

A randomized, observer-blind,[22] placebo-controlled, parallel-group study was conducted to investigate the safety, tolerability, and immunogenicity of Comirnaty in healthy subjects aged ≥18 and ≤55 years and those aged ≥65 to ≤85 years (target sample size of 195 subjects: 156 in the Comirnaty group; 39 in the placebo group) at 4 study sites in the U.S.

Two doses of the study vaccine (Comirnaty 10, 20, 30 µg, or BNT162b1 10, 20, 30, 100 µg, or placebo) were to be administered intramuscularly, 21 days apart (Day 1 and Day 22 [allowable period: Days 19 to 23]). Subjects were randomly assigned to one of 13 groups formed based on age groups and dose levels of Comirnaty or BNT162b1 and placebo (BNT162b1 100 µg was administered only to subjects aged ≥18 and ≤55 years). Comirnaty is mRNA that encodes the total length of SARS-CoV-2 S protein. BNT162b1 is mRNA that encodes the RBD of SARS-CoV-2 S protein.

All of the randomized 195 subjects (15 in each group: 12 receiving Comirnaty or BNT162b1; 3 receiving placebo) received at least 1 dose of the study vaccine and were included in the safety analysis set.

This section describes the results of Comirnaty, the proposed product. The results of BNT162b1 are described in Section 7.3.

For the safety, observation periods were defined as follows. The severity of adverse events was assessed based on the FDA guidance regarding the toxicity grading scale in clinical studies of preventive vaccines (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007[20]).

- Reactogenicity events (local reactions [injection site pain, redness, and swelling] and systemic events [pyrexia, fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia]) are collected by the subject diary within 7 days after each dose.
- Adverse events (excluding reactogenicity events collected by the subject diary within 7 days after each dose) are collected during the period from Dose 1 to 1 month after the last dose.

[22] Sub-investigators, study site staff members, and subjects were blinded.

- Serious adverse events are collected during the period from Dose 1 to 6 months after the last dose.

Reactogenicity events that occurred within 7 days after each dose are shown in Table 11.

Table 11 Reactogenicity events within 7 days after each dose (safety analysis set)

Event terms	Dose #	18-55 years old				65-85 years old			
		Comirnaty			Placebo	Comirnaty			Placebo
		10 μg (N = 12)	20 μg (N = 12)	30 μg (N = 12)	(N = 9)	10 μg (N = 12)	20 μg (N = 12)	30 μg (N = 12)	(N = 9)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reactions									
Injection site pain	Dose 1	8 (66.7)	8 (66.7)	11 (91.7)	0	4 (33.3)	7 (58.3)	9 (75.0)	0
	Dose 2	7 (58.3)	10 (83.3)	10 (83.3)	2 (22.2)	4 (33.3)	7 (58.3)	8 (66.7)	1 (11.1)
Redness	Dose 1	0	0	1 (8.3)	0	0	0	0	0
	Dose 2	0	0	0	0	0	0	0	0
Swelling	Dose 1	2 (16.7)	0	0	0	0	0	0	0
	Dose 2	0	0	0	0	0	0	0	0
Systemic events									
Pyrexia	Dose 1	0	0	2 (16.7)	0	0	0	0	0
	Dose 2	0	1 (8.3)	2 (16.7)	0	0	0	1 (8.3)	0
Fatigue	Dose 1	3 (25.0)	5 (41.7)	5 (41.7)	3 (33.3)	1 (8.3)	4 (33.3)	3 (25.0)	2 (22.2)
	Dose 2	4 (33.3)	7 (58.3)	9 (75.0)	5 (55.6)	2 (16.7)	6 (50.0)	5 (41.7)	1 (11.1)
Headache	Dose 1	4 (33.3)	4 (33.3)	6 (50.0)	3 (33.3)	1 (8.3)	3 (25.0)	0	1 (11.1)
	Dose 2	3 (25.0)	4 (33.3)	8 (66.7)	1 (11.1)	4 (33.3)	4 (33.3)	3 (25.0)	1 (11.1)
Chills	Dose 1	0	0	4 (33.3)	0	0	2 (16.7)	0	0
	Dose 2	1 (8.3)	5 (41.7)	7 (58.3)	1 (11.1)	2 (16.7)	1 (8.3)	2 (16.7)	0
Vomiting	Dose 1	0	0	1 (8.3)	0	0	0	0	0
	Dose 2	1 (8.3)	0	0	1 (11.1)	0	0	0	0
Diarrhoea	Dose 1	0	1 (8.3)	1 (8.3)	0	0	0	0	1 (11.1)
	Dose 2	0	0	0	0	0	0	0	1 (11.1)
Myalgia	Dose 1	3 (25.0)	2 (16.7)	3 (25.0)	0	1 (8.3)	1 (8.3)	0	2 (22.2)
	Dose 2	2 (16.7)	5 (41.7)	7 (58.3)	0	1 (8.3)	1 (8.3)	3 (25.0)	1 (11.1)
Arthralgia	Dose 1	1 (8.3)	0	2 (16.7)	0	0	0	0	1 (11.1)
	Dose 2	1 (8.3)	0	2 (16.7)	0	1 (8.3)	1 (8.3)	1 (8.3)	1 (11.1)

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

The incidences of adverse events and adverse reactions are shown in Table 12.

Table 12 Adverse events and adverse reactions other than reactogenicity events within 1 month after the last dose (safety analysis set)

	18-55 years old				65-85 years old			
	Comirnaty			Placebo	Comirnaty			Placebo
	10 μg (N = 12)	20 μg (N = 12)	30 μg (N = 12)	Placebo (N = 9)	10 μg (N = 12)	20 μg (N = 12)	30 μg (N = 12)	(N = 9)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	4 (33.3)	5 (41.7)	5 (41.7)	2 (22.2)	1 (8.3)	2 (16.7)	3 (25.0)	2 (22.2)
Adverse reactions	2 (16.7)	4 (33.3)	3 (25.0)	1 (11.1)	0	1 (8.3)	0	0

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

Neither death nor adverse events leading to study discontinuation occurred by the data cutoff dates (November

14, 2020 in the Comirnaty 30 μg group; August 24, 2020 in the other groups).

A serious adverse event of peripheral nerve injury (originally reported as neuritis) occurred in 1 subject in the Comirnaty 30 μg group. The event was considered unrelated to the study vaccine, and its outcome was "not recovered" as of December 16, 2020.

The following abnormal laboratory values (i.e., abnormal changes of Grade ≥3) were observed: lymphocyte count decreased in 1 subject each in the Comirnaty 10 and 30 μg groups and bilirubin increased in 1 subject in the Comirnaty 10 μg group. All of the events occurred 1 to 3 days after Dose 1 and recovered to a level within the reference range by 6 to 8 days after Dose 1.[23)] The applicant provided the following explanation:

> The events of lymphocyte count decreased observed early after vaccination with Comirnaty were transient (recovered 6 to 8 days after the vaccination). This means that the events were probably due to lymphocyte redistribution, not lymphocyte depletion. Since such abnormal laboratory values have low clinical significance, the applicant decided not to examine laboratory values in the Phase II/III part.

7.2.2 Phase II/III Part

A randomized, observer-blind,[24)] placebo-controlled, parallel-group study was conducted to investigate the efficacy and safety of Comirnaty in healthy subjects aged ≥12 years at 153 study sites in 6 foreign countries (the U.S., Germany, Turkey, Brazil, Argentina, and South Africa). The study originally started in healthy subjects aged 18 to 85 years, but the protocol was modified to include subjects aged ≥16 years to evaluate Comirnaty in a wider range of ages (Protocol Version 6, revised on September 8, 2020). Then the protocol was further modified to add subjects aged 12 to 15 years (Protocol Version 7, revised on October 6, 2020). The original target sample size was 29,286 subjects, which was changed to 43,998 subjects (21,999 each in the Comirnaty and placebo groups), including up to 2,000 subjects aged 12 to 15 years (Protocol Version 6, revised on September 8, 2020). The development for children has been considered separately. Data on the immunogenicity, safety, and tolerability (the primary purposes of this study) in the population aged 12 to 15 years were not available at the time of the marketing application.[25)] The present report therefore evaluates data from subjects aged ≥16 years. (The present application is for the population aged ≥16 years).

Two doses of the study vaccine (Comirnaty 30 μg or placebo) were to be administered intramuscularly, 21 days apart (Day 1 and Day 22 [allowable period: Days 19 to 23]). Subjects were randomized after stratification by age (12 to 15 years, 16 to 55 years, and ≥56 years).

Safety populations:

At least 1 dose of the study vaccine was administered to 43,449 of the 43,548 subjects who had been

23) In the BNT162b1 groups, ≥Grade 3 lymphocyte count decreased was observed in the population aged 18 to 55 years (1 subject receiving 10 μg, 2 subjects receiving 20 μg, 1 subject receiving 30 μg, and 4 subjects receiving 100 μg) and the population aged 65 to 85 years (1 subject receiving 30 μg). All of the subjects experienced the event several days after vaccination and recovered a few days later.

24) Subjects, investigators, subinvestigators, study coordinators, and study staff members (excluding those who prepared or injected the study vaccine) were blinded. The sponsor was also blinded except persons in charge of activities that must be performed in an unblinded manner.

25) As of the data cutoff date, Comirnaty and placebo, respectively, was administered to 49 and 51 subjects aged 12 to 15 years. These subjects were included in the efficacy analysis set, but not in the safety analysis set. It is planned to evaluate the non-inferiority of the 12- to 15-year-old group to the 16- to 25-year-old group in terms of immunogenicity.

randomized by the data cutoff date (November 14, 2020). One subject in the Comirnaty group had not provided consent. The remaining 43,448 subjects (21,720 in the Comirnaty group; 21,728 subjects in the placebo group) were included in the safety analysis set. Among them, 8,183 subjects (4,093 in the Comirnaty group; 4,090 in the placebo group) provided the subject diary and were included in the reactogenicity analysis set.[26)]

Efficacy population:
Of the 43,651 subjects who were randomized by the data cutoff date (November 14, 2020), 3,374 were excluded from analyses (3,111 who did not receive the study vaccine or did not receive Dose 2 within a predefined period, 371[27)] who had significant protocol deviations within 7 days after Dose 2, 62 who were found not to meet the eligibility criteria after randomization, and 1 who had not provided consent [some subjects had more than 1 reason for exclusion]). The remaining 40,277 subjects (20,033 in the Comirnaty group; 20,244 in the placebo group) were included in the evaluable efficacy population,[28)] which was defined as the primary analysis set.

Efficacy results:
The primary endpoint was vaccine efficacy (VE [VE1 and VE2]) based on confirmed COVID-19 cases (COVID-19 cases occurring ≥7 days after Dose 2 per 1,000 person-years).

VE (%) = 100 × (1 – ratio of incidence rate [COVID-19 cases occurring during the follow-up period per 1,000 person-years] of the Comirnaty group to that of the placebo group [IRR]).

- VE1: VE in subjects without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2
- VE2: VE in subjects with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2.

A confirmed COVID-19 case was defined as a subject who has at least 1 symptom suggestive of COVID-19 (pyrexia, new onset or worsening of cough, new onset or worsening of shortness of breath, chills, new onset or worsening of myalgia, new loss of taste or smell, sore throat, diarrhoea, and vomiting) with a positive SARS-CoV-2 result by nasopharyngeal swab nucleic acid amplification testing.

Four interim analyses were planned to assess VE1 and terminate the study early for futility (when at least 32, 62, 92, and 120 confirmed COVID-19 cases are accrued). However, the first interim analysis (when 32 cases were accrued) was not performed for operational reasons. The protocol was then modified during the study period to perform 3 interim analyses (when at least 62, 92, and 120 confirmed COVID-19 cases are accrued) (Protocol Version 9, revised on October 29, 2020). In order to have a <0.025 probability of success of the entire study when the true VE is 30%, efficacy success criteria were predefined for the interim analyses (99.5%) and

26) The protocol states that the subject diary should be collected from at least 6,000 subjects who were first enrolled.
27) Of 371 subjects, 283 had a deviation related to study vaccination, 43 had a deviation from the inclusion/exclusion criteria, 43 had a deviation related to data reliability, 5 used a prohibited concomitant drug, and 3 had a deviation related to sample transportation (some had more than 1 deviation).
28) The evaluable efficacy population was defined as subjects who received Dose 2 of the study vaccine 19 to 42 days after Dose 1 and had no significant protocol deviations within 7 days after Dose 2.

final analysis (98.6%).

The first interim analysis was performed when 94 cases were accrued. In the analysis, the posterior probability of the true VE1 exceeding 30% was > 99.99%, thus greater than the predefined efficacy success criterion (99.5%). ("True VE1 exceeding 30%" was used because the FDA guidance [Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19] states that the lower limit of CI appropriately adjusted for type I error of VE exceeds 30% as a statistical success criterion.) Subsequently, at least 164 confirmed COVID-19 cases (the number planned for the final analysis) were rapidly accrued, and therefore the second and subsequent interim analyses were not performed. The blindness has been maintained after completion of the final analysis.

Table 13 shows VE1 and VE2 when ≥164 confirmed COVID-19 cases were accrued (final analysis). The posterior probability of the true VE exceeding 30% was >99.99% for both VE1 and VE2, thus greater than the predefined efficacy success criterion (98.6%). The two-sided 95% CI (Clopper-Pearson method) of VE1 and VE2 was [90.0, 97.9] and [89.6, 97.6], respectively.

Table 13 Vaccine efficacy against COVID-19 occurring ≥7 days after Dose 2 (evaluable efficacy population)[a)]

		N	Confirmed COVID-19 cases	Total follow-up period (1,000 person-years)	n	VE [95% CI] (%)[b)]	Posterior probability (VE >30%)[b)]
Without prior infection[c)]	Comirnaty	18,198	8	2.214	17,411	VE1: 95.0 [90.3, 97.6]	＞99.99%
	Placebo	18,325	162	2.222	17,511		
With and without prior infection[c)]	Comirnaty	19,965	9	2.332	18,559	VE2: 94.6 [89.9, 97.3]	＞99.99%
	Placebo	20,172	169	2.345	18,708		

N = number of subjects analyzed, n = number of subjects contributing to the follow-up period

a) HIV-positive subjects (68 in the Comirnaty group and 72 in the placebo group in the evaluable efficacy population) are not included in this table because they were to be analyzed separately. The confirmed COVID-19 cases in both the Comirnaty and placebo groups included no HIV-positive subjects with or without prior SARS-CoV-2 infection.

b) Calculated based on the Bayesian beta-binomial distribution model with a beta distribution (0.700102, 1) of minimal amount of information as a prior distribution.

c) Prior SARS-CoV-2 infection prior to 7 days after Dose 2

Safety results:

The severity of adverse events was assessed based on the FDA guidance regarding the toxicity grading scale in clinical studies of preventive vaccines (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007[20)]). In the safety analysis set, the observation period until the data cutoff date (November 4, 2020) was as follows:

- <2 weeks after Dose 2 in 14.9% (6,483 of 43,448 subjects);
- ≥2 and <4 weeks after Dose 2 in 5.6% (2,433 of 43,448 subjects);
- ≥4 and <6 weeks after Dose 2 in 14.9% (6,474 of 43,448 subjects);
- ≥6 and <8 weeks after Dose 2 in 20.7% (8,991 of 43,448 subjects);
- ≥8 and <10 weeks after Dose 2 in 29.1% (12,625 of 43,448 subjects);
- ≥10 and <12 weeks after Dose 2 in 13.0% (5,662 of 43,448 subjects);
- ≥12 and <14 weeks after Dose 2 in 1.8% (780 of 43,448 subjects).

The definition of observation periods:

Reactogenicity analysis set only

- Reactogenicity events (local reactions [injection site pain, redness, and swelling] and systemic events [pyrexia, fatigue, headache, chills, vomiting, diarrhoea, myalgia, and arthralgia]) are collected by the subject diary within 7 days after each dose.

Safety analysis set

- Adverse events (excluding reactogenicity events collected by the subject diary within 7 days after each dose in the reactogenicity analysis set) are collected during the period from Dose 1 to 1 month after the last dose.
- Serious adverse events are collected during the period from Dose 1 to 6 months after the last dose.

Reactogenicity events that occurred within 7 days after each dose are shown in Table 14.

Table 14 Reactogenicity events within 7 days after each dose (reactogenicity analysis set)

	Event terms	Dose 1		Dose 2	
		Comirnaty (N = 4,093)	Placebo (N = 4,090)	Comirnaty (N = 3,758)	Placebo (N = 3,749)
		n (%)	n (%)	n (%)	n (%)
Local reactions	Injection site pain	3,186 (77.8)	488 (11.9)	2,730 (72.6)	372 (9.9)
	Redness	189 (4.6)	45 (1.1)	243 (6.5)	26 (0.7)
	Swelling	250 (6.1)	32 (0.8)	256 (6.8)	16 (0.4)
Systemic events	Pyrexia	111 (2.7)	27 (0.7)	512 (13.6)	14 (0.4)
	Fatigue	1,700 (41.5)	1,172 (28.7)	2,086 (55.5)	756 (20.2)
	Headache	1,413 (34.5)	1,100 (26.9)	1,732 (46.1)	735 (19.6)
	Chills	434 (10.6)	203 (5.0)	1,114 (29.6)	125 (3.3)
	Vomiting	37 (0.9)	37 (0.9)	51 (1.4)	30 (0.8)
	Diarrhoea	402 (9.8)	388 (9.5)	356 (9.5)	276 (7.4)
	Myalgia	738 (18.0)	398 (9.7)	1,260 (33.5)	260 (6.9)
	Arthralgia	406 (9.9)	247 (6.0)	772 (20.5)	170 (4.5)

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

The incidences of adverse events and adverse reactions were 26.7% (5,770 of 21,621 subjects) and 20.7% (4,484 of 21,621 subjects), respectively, in the Comirnaty group and 12.2% (2,638 of 21,631 subjects) and 5.1% (1,095 of 21,631 subjects), respectively, in the placebo group. Table 15 shows adverse events and adverse reactions that occurred in ≥1% of subjects in either group.

Table 15 Adverse events and adverse reactions occurring in ≥1% of subjects in either group within 1 month after the last dose (safety analysis set)

Event terms	Adverse events		Adverse reactions	
	Comirnaty (N = 21,621)	Placebo (N = 21,631)	Comirnaty (N = 21,621)	Placebo (N = 21,631)
	n (%)	n (%)	n (%)	n (%)
Total	5,770 (26.7)	2,638 (12.2)	4,484 (20.7)	1,095 (5.1)
Injection site pain	2 440 (11.3)	322 (1.5)	2,437 (11.3)	316 (1.5)
Pyrexia	1,255 (5.8)	68 (0.3)	1,242 (5.7)	57 (0.3)
Fatigue	1,145 (5.3)	294 (1.4)	1,118 (5.2)	268 (1.2)
Chills	1,111 (5.1)	100 (0.5)	1,103 (5.1)	89 (0.4)
Headache	1,084 (5.0)	345 (1.6)	1,012 (4.7)	249 (1.2)
Myalgia	999 (4.6)	142 (0.7)	971 (4.5)	120 (0.6)
Pain	507 (2.3)	45 (0.2)	502 (2.3)	37 (0.2)
Nausea	238 (1.1)	75 (0.3)	211 (1.0)	50 (0.2)
Arthralgia	224 (1.0)	89 (0.4)	168 (0.8)	30 (0.1)
Diarrhoea	220 (1.0)	166 (0.8)	166 (0.8)	113 (0.5)

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

As of the data cutoff date (November 14, 2020), 2 subjects died in the Comirnaty group (arteriosclerosis and cardiac arrest in 1 subject each) and 4 subjects in the placebo group (unknown cause in 2 subjects; haemorrhagic stroke in 1 subject; myocardial infarction in 1 subject). None of the deaths were related to the study vaccine.

Serious adverse events occurred in 126 of 21,621 subjects (0.6%) in the Comirnaty group and 111 of 21,631 subjects (0.5%) in the placebo group. Among them, 4 subjects in the Comirnaty group had such events for which a causal relationship with the study vaccine could not be ruled out: lymphadenopathy, shoulder injury related to vaccine administration, ventricular arrhythmia, and back pain/pain in legs with radicular paresthesia (this event is not coded by MedDRA) in 1 subject each. The outcomes were “not recovered” for lymphadenopathy, “recovered” for ventricular arrhythmia, and “recovering” for the others.

Adverse events leading to study discontinuation occurred in 37 of 21,621 subjects (0.2%) in the Comirnaty group and 30 of 21,631 subjects (0.1%) in the placebo group. Among them, 16 subjects in the Comirnaty group and 9 subjects in the placebo group (25 in total) had such events for which a causal relationship with the study vaccine could not be ruled out.

The following is a breakdown of the events in the 25 subjects (some subjects had more than 1 event) (a breakdown by group is unavailable because the study is ongoing in a blinded manner):

- Diarrhoea and headache in 3 subjects each;
- Fatigue, injection site pain, urticaria, and dizziness in 2 subjects each;
- Injection site dermatitis, vertigo, injection site swelling, allergy to vaccine, eye pain, abdominal discomfort, muscular weakness, pain in extremity, lymphadenopathy, heart rate irregular, myalgia, paraesthesia oral, nausea, tachycardia, chills, pyrexia, abdominal pain, night sweats, deafness unilateral, exposure during pregnancy, and depression in 1 subject each; and
- Events not coded (redness on the upper body due to vaccine, fatigue) in 2 subjects.

The outcome was “not recovered” for lymphadenopathy and depression in 1 subject each, “unknown” for exposure during pregnancy in 1 subject, and “recovered” or “recovering” for the others.

HIV-positive subjects were not included in the primary safety analysis, and the safety evaluation of HIV-positive subjects was handled as an exploratory analysis. The incidences of adverse events and adverse reactions in HIV-positive subjects were 13.1% (13 of 99 subjects) and 10.1% (10 of 99 subjects), respectively, in the Comirnaty group and 10.3% (10 of 97 subjects) and 0 subjects, respectively, in the placebo group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical Data Package and Review Policy

Rapid development of vaccines against SARS-CoV-2 is needed amid the COVID-19 pandemic. ICMRA,[29] WHO,[30] and the regulatory authorities in various countries[31] have published guidance, etc. to accelerate vaccine development. In Japan PMDA published, on September 2, 2020, the “Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2”[32], which explains the following principles for clinical studies.

- The efficacy of infectious disease preventive vaccines is in principle evaluated using the disease-preventive effect as the primary endpoint. In the current situation in which no surrogate marker for the disease-preventive effect against COVID-19 is known, in principle, clinical trials to assess the preventive effect against COVID-19 must be conducted to evaluate the efficacy of the SARS-CoV-2 vaccine candidate.
- The benefit-risk judgement of any SARS-CoV-2 vaccines can differ depending on the situation of each country/region given that the degree of the COVID-19 epidemic, that the virus may undergo mutation according to the geographic/passage conditions, and that the percentage of severe patients with worsened COVID-19 and the background of the worsening is being investigated in various ways. In addition, ethnic differences might affect the efficacy and safety of the SARS-CoV-2 vaccine. There may therefore be a high need of evaluating the efficacy and safety of the vaccine in Japanese subjects by conducting a clinical trial(s) in Japan, even if a large-scale confirmatory trial is conducted overseas to evaluate the disease-preventive effect.
- When a large-scale confirmatory clinical trial of the vaccine candidate is conducted overseas using the disease-preventive effect as the primary endpoint, it may be sufficient to conduct a Japanese clinical trial to confirm the immunogenicity and safety in Japanese subjects without conducting a confirmatory clinical trial in Japan to evaluate the disease-preventive effect in Japanese subjects.

The applicant planned and conducted a Japanese clinical study to evaluate the immunogenicity and safety of Comirnaty, for the following reasons:

(a) When the applicant planned a Japanese clinical study of Comirnaty, a foreign large-scale confirmatory

29) Global Regulatory Workshop on COVID-19 Vaccine Development (March 18, 2020 and June 22, 2020)
30) “Target Product Profiles for COVID-19 Vaccines, WHO R&D Blueprint, 29 April 2020” and “An international randomised trial of candidate vaccines against COVID-19, WHO R&D Blueprint, 28 May 2020”
31) “Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, CBER FDA, June 2020,” by FDA, “EMA considerations on COVID-19 vaccine approval,” by EMA, and others.
32) https://www.pmda.go.jp/files/000236327.pdf (as of January 21, 2021)

study was ongoing to evaluate the effect of Comirnaty in preventing COVID-19 as the primary endpoint.

(b) A confirmatory clinical study to evaluate the effect in preventing COVID-19 was unfeasible in Japan because of the relatively low prevalence of the disease in Japan.

The clinical data package for the present application includes the foreign phase I/II/III study (foreign Study C4591001) and the Japanese phase I/II study (Japanese Study C4591005) as evaluation data.

PMDA's view:

At present, there is no known surrogate marker for the effect in preventing COVID-19, and the relationship between immunogenicity and the effect in preventing COVID-19 remains unclear. However, since rapid development of vaccines against SARS-CoV-2 is needed, PMDA decided to evaluate the efficacy and safety of Comirnaty in the Japanese population based on the efficacy results of the foreign confirmatory study (foreign Study C4591001) and the immunogenicity and safety results of the Japanese clinical study.

7.R.2 Efficacy

PMDA's conclusion as a result of reviewing the submitted study results (see Sections below for details):

The results of foreign Study C4591001 showed that Comirnaty prevented COVID-19. Comirnaty is expected to have similar efficacy in the Japanese population as well according to the immunogenicity results from foreign Study C4591001 and Japanese Study C4591005.

According to data available at present, however, the long-term efficacy of Comirnaty and its efficacy against SARS-CoV-2 variants remain unknown. The applicant should therefore continue to collect data after the market launch and take appropriate actions, including providing new findings to healthcare professionals.

This conclusion by PMDA will be discussed at the Expert Discussion.

7.R.2.1 Efficacy endpoints

The applicant's explanation about the efficacy endpoints of Comirnaty:

In the Phase II/III part of foreign Study C4591001 (the pivotal clinical study for development of Comirnaty), the primary efficacy endpoint was VE estimated based on confirmed COVID-19 cases occurring ≥7 days after Dose 2 of the study vaccine. A confirmed COVID-19 case was defined as a patient who has at least 1 of the following clinical symptoms with a positive SARS-CoV-2 result by nasopharyngeal swab nucleic acid amplification testing.

Clinical symptoms: Pyrexia, new onset or worsening of cough, new onset or worsening of shortness of breath, chills, new onset or worsening of myalgia, new loss of taste or smell, sore throat, diarrhoea, and vomiting

This definition is consistent with the definition[33)] of COVID-19 shown in the FDA Guidance (Development

33) FDA recommends that the primary or secondary efficacy endpoint of clinical trials (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with at least 1 of the following clinical symptoms: fever or chills, cough, shortness of breath or

and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry[34]). The guidance recommends that the efficacy endpoint be defined as confirmed COVID-19 in clinical studies of SARS-CoV-2 vaccines. The clinical symptoms of COVID-19 presented in the FDA Guidance include fatigue, headache, congestion or runny nose, and nausea, in addition to the symptoms listed above. These additional symptoms, however, are not specific to COVID-19 and therefore were excluded from the definition of "a confirmed COVID-19 case," which was used for the primary efficacy evaluation in foreign Study C4591001.

COVID-19 occurring ≥7 days after Dose 2 was classified as a confirmed COVID-19 case used for primary efficacy evaluation in the Phase II/III part. This evaluation period (≥7 days after Dose 2) was defined for the following reason:

Serum SARS-CoV-2 neutralizing antibody titers increased markedly ≥7 days after Dose 2 during the Phase I part of foreign Study C4591001 (Table 16). This suggests that Comirnaty exerts its efficacy ≥7 days after Dose 2 if neutralizing antibodies play an important role in preventing COVID-19.

Table 16 Serum SARS-CoV-2 neutralizing antibody titers (50% neutralizing antibody titers) (foreign Study C4591001 Phase I part, evaluable immunogenicity population)

	18-55 years old			65-85 years old		
	Comirnaty 10 μg (N = 11)	Comirnaty 20 μg (N = 12)	Comirnaty 30 μg (N = 12)	Comirnaty 10 μg (N = 12)	Comirnaty 20 μg (N = 12)	Comirnaty 30 μg (N = 11)
	GMT [2-sided 95% CI]	GMT [2-sided 95% CI]	GMT [2-sided 95% CI]	GMT [2-sided 95% CI]	GMT [2-sided 95% CI]	GMT [2-sided 95% CI]
Before Dose 1	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]
21 days after Dose 1	16.6 [9.8, 27.9]	18.9 [11.1, 32.3]	14.4 [10.1, 20.4]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	12.0 [9.0, 16.0]
7 days after Dose 2	169 [102, 278]	363 [257, 512]	361 [237, 549][a)]	79.3 [50.6, 125]	79.3 [40.9, 154]	156 [80.4, 302]
14 days after Dose 2	109 [54.7, 217]	292 [179, 476]	162 [109, 239][b)]	111 [81.0, 152][a)]	73.7 [32.8, 166][a)]	214 [106, 433][a)]
1 month after Dose 2	105 [65.1, 171]	252 [144, 441][a)]	144 [104, 199][a)]	69.6 [43.0, 113]	49.6 [23.1, 107][a)]	152 [81.2, 286][a)]

N = number of subjects analyzed

a) Data obtained from 11 subjects, b) Data obtained from 9 subjects.

When the antibody titer was less than LLOQ, 0.5 × LLOQ was used for analysis.

PMDA's view:

The effect of Comirnaty in preventing COVID-19 can be evaluated by the endpoints used in foreign Study C4591001. Foreign Study C4591001 was not designed to evaluate the effect of Comirnaty in preventing SARS-CoV-2 infection; this should be noted.

difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea.

34) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19 (as of January 21, 2021)

7.R.2.2 Efficacy against COVID-19

The applicant's explanation about the efficacy of Comirnaty against COVID-19:

(a) Foreign clinical study results

In the Phase II/III part of foreign Study C4591001, the primary endpoints were VE1 (VE in subjects without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2) and VE2 (VE in subjects with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2) in the evaluable efficacy population. The results showed that VE1 was 95.0 [90.3, 97.6]% and VE2 was 94.6 [89.9, 97.3]%. The posterior probability of the true vaccine efficacy exceeding 30% was >99.99% for both VE1 and VE2; this was greater than the efficacy success criterion (98.6%) predefined for the final analysis. The 2-sided 95% CI (Clopper-Pearson method) for VE1 and VE2 was [90.0, 97.9] and [89.6, 97.6], respectively. In the all-available efficacy population, VE1 and VE2 [95%CI] were 95.2 [90.6, 97.7]% and 94.8 [90.2, 97.4]%, respedtively, and the 2-sided 95% CI (Clopper-Pearson method) were [90.3, 98.0] and [89.9, 97.7], respectively.

The major analysis did not cover COVID-19 cases occurring prior to 7 days after Dose 2. The applicant therefore conducted another analysis that covered COVID-19 cases occurring after Dose 1 among all subjects who received at least 1 dose of the study vaccine. VE by onset time of COVID-19 is shown in Table 17. The cumulative incidence curves for COVID-19 occurrence is shown in Figure 2. The Comirnaty and placebo groups showed similar cumulative incidence for COVID-19 occurrence during the period from Dose 1 to approximately 14 days after Dose 1. This suggests that Comirnaty is expected to exert the effect in preventing COVID-19 after Dose 2.

Table 17 VE based on COVID-19 cases occurring after Dose 1
(all subjects who received at least 1 dose of the study vaccine)

		Comirnaty	Placebo	VE [2-sided 95% CI] (%)[a)]
N = number of subjects analyzed		21,669	21,686	
Total follow-up period (1,000 person-years)		4.015	3.982	
Confirmed COVID-19 cases (by time of occurring)	Total period (after Dose 1)	50	275	82.0 [75.6, 86.9]
	Between Dose 1 and before Dose 2	39	82	52.4 [29.5, 68.4]
	Between Dose 2 and 6 days after Dose 2	2	21	90.5 [61.0, 98.9]
	≥7 days after Dose 2	9	172	94.8 [89.8, 97.6]

a) Clopper-Pearson method

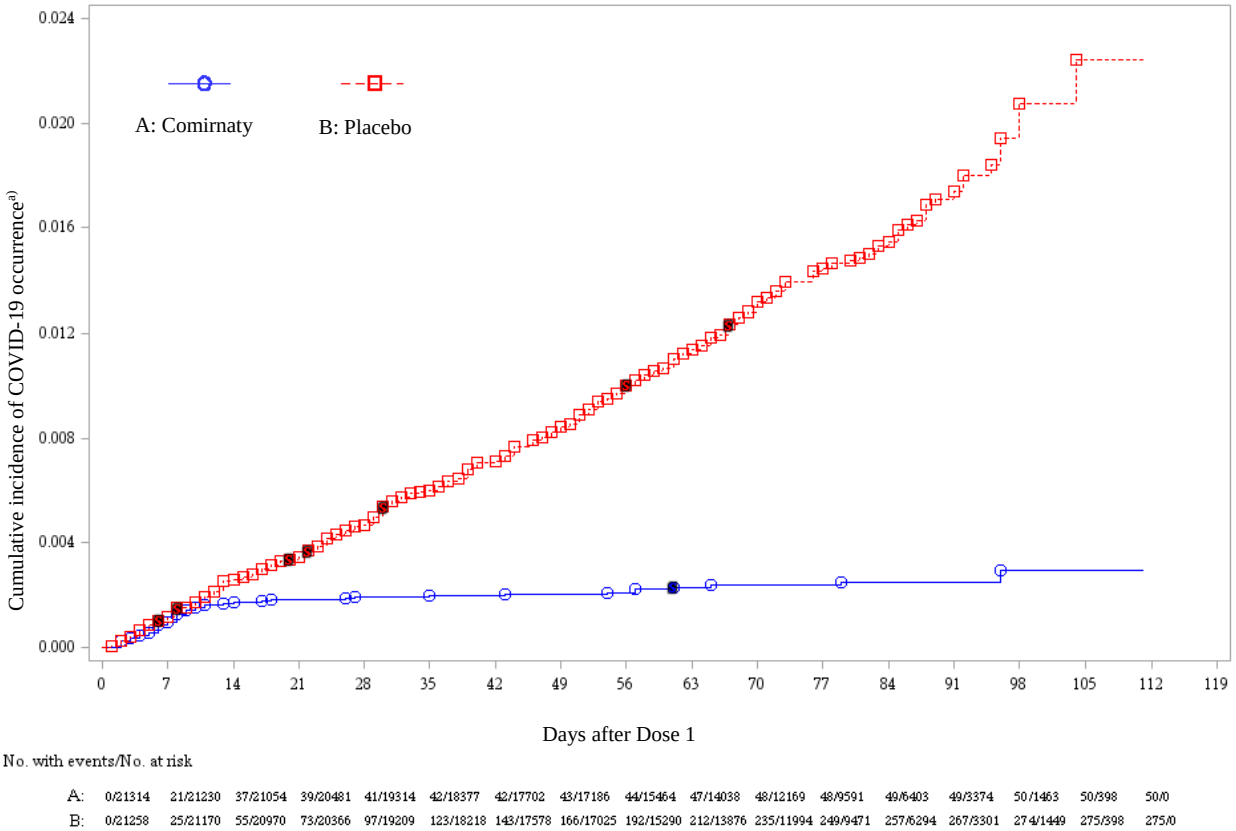

Figure 2 Cumulative incidence curves for COVID-19 occurrence
(all subjects who received at least 1 dose of the study vaccine)

Black points indicate severe COVID-19 cases (1 in the Comirnaty group, 9 in the placebo group; a single black point may indicate more than 1 case).

a) Kaplan-Meier method

The efficacy by subgroup is shown in Table 18 (subjects without evidence of prior SARS-CoV-2 infection) and Table 19 (subjects with and without evidence of prior SARS-CoV-2 infection).

Table 18 Subgroup analysis of vaccine efficacy against COVID-19 occurring ≥7 days after Dose 2 (subjects without evidence of prior SARS-CoV-2 infection in evaluable efficacy population)[a)]

		Comirnaty				Placebo				
		N (%)	Confirmed COVID-19 cases	Total follow-up period (1,000 person-years)	n	N (%)	Confirmed COVID-19 cases	Total follow-up period (1,000 person-years)	n	VE1 [2-sided 95% CI] (%)[b)]
Total		18,198	8	2.214	17,411	18,325	162	2.222	17,511	95.0 [90.0,97.9]
Age	16-19 years	245 (1.3)	0	0.022	218	266 (1.5)	5	0.024	244	100 [−19.0, 100.0]
	20-55 years	10,148 (55.8)	5	1.212	9,679	10,200 (55.7)	109	1.215	9,711	95.4 [88.9, 98.5]
	16-55 years	10,393 (57.1)	5	1.234	9,897	10,466 (57.1)	114	1.239	9,955	95.6 [89.4, 98.6]
	≥56 years	7,759 (42.6)	3	0.980	7,500	7,817 (42.7)	48	0.983	7,543	93.7 [80.6, 98.8]
	16-17 years	66 (0.4)	0	0.002	52	68 (0.4)	0	0.003	55	NE
	18-64 years	14,107 (77.5)	7	1.703	13,497	14,180 (77.4)	143	1.708	13,563	95.1 [89.6, 98.1]
	≥65 years	3,979 (21.9)	1	0.508	3,848	4,035 (22.0)	19	0.511	3,880	94.7 [66.7, 99.9]
Sex	Male	9,288 (51.0)	3	1.124	8,875	9,188 (50.1)	81	1.108	8,762	96.4 [88.9, 99.3]
	Female	8,910 (49.0)	5	1.090	8,536	9,137 (49.9)	81	1.114	8,749	93.7 [84.7, 98.0]
Race	Caucasian	15,091 (82.9)	7	1.889	14,504	15,283 (83.4)	146	1.903	14,670	95.2 [89.8, 98.1]
	Black or African American	1,594 (8.8)	0	0.165	1,502	1,585 (8.6)	7	0.164	1,486	100 [31.2, 100.0]
	Other[c)]	1,513 (8.3)	1	0.160	1,405	1,457 (8.0)	9	0.155	1,355	89.3 [22.6, 99.8]
	Asian	815 (4.5)	1	0.092	764	809 (4.4)	4	0.093	769	74.6 [−156.6, 99.5]
Country	Argentine	2,558 (14.1)	1	0.351	2,545	2,538 (13.8)	35	0.346	2,521	97.2 [83.3, 99.9]
	Brazil	1,231 (6.8)	1	0.119	1,129	1,222 (6.7)	8	0.117	1,121	87.7 [8.1, 99.7]
	U.S.	14,013 (77.0)	6	1.732	13,359	14,178 (77.4)	119	1.747	13,506	94.9 [88.6, 98.2]
At Risk[d)]	Yes	8,388 (46.1)	4	1.025	8,030	8,396 (45.8)	86	1.025	8,029	95.3 [87.7, 98.8]
	No	9,810 (53.9)	4	1.189	9,381	9,929 (54.2)	76	1.197	9,482	94.7 [85.9, 98.6]

N = number of subjects analyzed, n = number of subjects contributing to the follow-up period

a) HIV positive subjects (68 in the Comirnaty group and 72 in the placebo group among the evaluable efficacy population) were analyzed separately and not included in this table.

b) Clopper-Pearson method

c) American Indian, Alaska Native, Asian, Native Hawaiian, Other Pacific Islander, Multiracial, or Not Reported

d) "At risk" is defined as having at least 1 of the Charlson Comorbidity Index or obesity (BMI ≥30 kg/m^2).

Table 19 Subgroup analysis of vaccine efficacy against COVID-19 occurring ≥7 days after Dose 2 (subjects with and without evidence of prior SARS-CoV-2 infection in evaluable efficacy population)[a)]

		Comirnaty				Placebo				
		N (%)	Confirmed COVID-19 cases	Total follow-up period (1,000 person-years)	n	N (%)	Confirmed COVID-19 cases	Total follow-up period (1,000 person-years)	n	VE2 [2-sided 95% CI] (%)[b)]
Total		19,965	9	2.332	18,559	20,172	169	2.345	18,708	94.6 [89.6 ,97.6]
Age	16-19 years	287 (1.4)	0	0.024	242	300 (1.5)	6	0.025	266	100 [8.1 ,100.0]
	20-55 years	11,251 (56.4)	6	1.286	10,411	11,391 (56.5)	114	1.292	10,472	94.7 [88.1 ,98.1]
	16-55 years	11,538 (57.8)	6	1.309	10,653	11,691 (58.0)	120	1.317	10,738	95.0 [88.7 ,98.2]
	≥56 years	8,379 (42.0)	3	1.022	7,892	8,434 (41.8)	49	1.028	7,956	93.8 [80.9 ,98.8]
	16-17 years	77 (0.4)	0	0.003	58	76 (0.4)	1	0.003	61	100 [−3969.9 ,100.0]
	18-64 years	15,549 (77.9)	8	1.799	14,443	15,735 (78.0)	149	1.811	14,566	94.6 [89.1 ,97.7]
	≥65 years	4,291 (21.5)	1	0.530	4,044	4,314 (21.4)	19	0.532	4,067	94.7 [66.8 ,99.9]
Sex	Male	10,197 (51.1)	4	1.183	9,457	10,093 (50.0)	85	1.170	9,342	95.3 [87.6 ,98.8]
	Female	97,68 (48.9)	5	1.149	9,102	10,079 (50.0)	84	1.176	9,366	93.9 [85.2 ,98.1]
Race	Caucasian	16,362 (82.0)	7	1.975	15,294	16,597 (82.3)	153	1.990	15,473	95.4 [90.3 ,98.2]
	Black or African American	1,916 (9.6)	0	0.187	1,758	1,926 (9.5)	7	0.188	1,758	100 [30.4 ,100.0]
	Other[c)]	1,687 (8.4)	2	0.170	1,507	1,649 (8.2)	9	0.167	1,477	78.2 [−5.4 ,97.7]
	Asian	880 (4.4)	1	0.095	796	882 (4.4)	4	0.097	808	74.4 [−158.7 ,99.5]
Country	Argentine	2,683 (13.4)	1	0.366	2,664	2,710 (13.4)	36	0.367	2,684	97.2 [83.5 ,99.9]
	Brazil	1,429 (7.2)	2	0.134	1,274	1,424 (7.1)	8	0.132	1,257	75.4 [−23.5 ,97.5]
	U.S.	15,259 (76.4)	6	1.816	14,141	15,443 (76.6)	124	1.830	14,287	95.1 [89.1 ,98.2]
At Risk[d)]	Yes	366 (1.8)	0	0.015	362	368 (1.8)	1	0.015	363	100 [−3818.9 ,100.0]
	No	9,210 (46.1)	4	1.083	8,584	9,242 (45.8)	87	1.084	8,609	95.4 [87.8 ,98.8]

N = number of subjects analyzed, n = number of subjects contributing to the follow-up period

a) HIV positive subjects (68 in the Comirnaty group and 72 in the placebo group among the evaluable efficacy population) were analyzed separately and not included in this table.

b) Clopper-Pearson method

c) American Indian, Alaska Native, Asian, Native Hawaiian, Other Pacific Islander, Multiracial, or Not Reported

d) "At risk" is defined as having at least 1 of the Charlson Comorbidity Index or obesity (BMI ≥30 kg/m^2).

VE in the race category "Other" (VE1, 89.3%; VE2, 78.2%) and the country category "Brazil" (VE1, 87.7%; VE2, 75.4%) was lower than that in the other subgroups.

A post-hoc analysis was conducted to evaluate the efficacy in subjects at high risk of severe COVID-19.[35)] In the analysis, "at risk" was defined as having at least 1 of the Charlson Comorbidity Index or obesity (BMI ≥30 kg/m^2). VE1 was 95.3% in subjects at risk and 94.7% in subjects not at risk. VE1 analysis (at-risk vs. not at-risk) by age group also showed similar results.

The subgroups analyses showed lower VE in some subgroups than in the other subgroups, but this difference was considered to have no clinical significance because the number of confirmed COVID-19 cases was small in this study.

Japanese Study C4591005 was not designed to evaluate the effect of Comirnaty in preventing COVID-19, but was designed to collect data on the occurrence or diagnosis of COVID-19 during the study period as adverse events. No such adverse events have been reported from the study (data cut-off date, January 5, 2021).

(b) Immunogenicity

Table 20 shows the results of neutralizing antibody titers in the evaluable immunogenicity population and the Dose 2 all-available immunogenicity population enrolled in the Phase II part of foreign Study C4591001 (corresponding to approximately 360 subjects first enrolled in the Phase II/III part). The results from the evaluable immunogenicity population (the primary immunogenicity analysis set) in Japanese Study C4591005 are being analyzed as of January 29, 2021. Table 21 therefore shows the results of all-available immunogenicity population as they have already been obtained. Each population was defined as follows.

Foreign Study C4591001

- Evaluable immunogenicity population:
  A group of subjects who were randomized, received 2 doses of the study vaccine during the predefined period, yielded at least 1 valid and determinate immunogenicity result from blood samples collected during the predefined period, and had no major protocol deviations.
- Dose 2 all-available immunogenicity population
  A group of subjects who were randomized, received at least 1 dose of the study vaccine, and yielded immunogenicity results after Dose 2.

Japanese Study C4591005

- Evaluable immunogenicity population:
  A group of subjects who were randomized, received 2 doses of the study vaccine during the predefined period, yielded immunogenicity results after Dose 2, and had no major protocol deviations.
- All-available immunogenicity population:
  A group of subjects who were randomized, received at least 1 dose of the study vaccine, and yielded immunogenicity results.

35) The Clinical Guidance for COVID-19 (ver. 4.1) (in Japanese) (https://www.mhlw.go.jp/content/000712473.pdf [as of January 21, 2021]) lists the risk factors for severe COVID-19: aged ≥65 years, malignant neoplasm, chronic obstructive pulmonary disease, chronic kidney disease, type 2 diabetes mellitus, hypertension, obesity (BMI ≥30 kg/m^2), smoking and immunodeficiency after solid organ transplantation.

Table 20 Serum SARS-CoV-2 neutralizing antibody titers (50% neutralizing antibody titers) at 1 month after Dose 2 (foreign Study C4591001 Phase II part)

		Age	N	GMT [2-sided 95% CI] (1 month after Dose 2)	GMFR [2-sided 95% CI] (1 month after Dose 2/before Dose 1)
Evaluable immunogenicity population	Comirnaty	All ages	167	316.1 [275.6, 362.6]	31.1 [27.2, 35.5][b)]
		18[a)] to 55 years	80	399.4 [342.1, 466.2]	39.4 [34.0, 45.6]
		56-85 years	87	255.0 [205.7, 316.0]	24.9 [20.2, 30.9][c)]
	Placebo	All ages	167	10.6 [10.0, 11.3]	1.0 [1.0, 1.1]
Dose 2 all-available immunogenicity population	Comirnaty	All ages	176	320.3 [279.8, 366.6]	31.4 [27.5, 35.7][d)]
		18[a)] to 55 years	85	389.3 [334.1, 453.7]	38.4 [33.2, 44.4]
		56-85 years	91	266.9 [215.3, 330.8]	25.9 [21.0, 31.9][e)]
	Placebo	All ages	176	10.6 [10.0, 11.3]	1.0 [1.0, 1.1]
Serum from recovered patients[f)]				319	—

N = number of subjects analyzed. When the antibody titer was less than LLOQ, 0.5 × LLOQ was used for analysis.

a) Subjects aged ≥18 and were eligible at the time of enrollment in the Phase II part.

b) N = 166, c) N = 86, d) N = 175, e) N = 90.

f) Serum collected from 33 donors who became asymptomatic ≥14 days after testing positive for SARS-CoV-2 by PCR

Table 21 Serum SARS-CoV-2 neutralizing antibody titers (50% neutralizing antibody titers) at 1 month after Dose 2 (Japanese Study C4591005)

		Age	N	GMT [2-sided 95% CI] (1 month after Dose 2)	GMFR [2-sided 95% CI] (1 month after Dose 2/before Dose 1)
All-available immunogenicity population	Comirnaty	All ages	119	489.9 [420.4, 570.9]	48.1 [41.3, 56.0]
		20-64 years	97	523.5 [442.0, 619.9]	51.2 [43.3, 60.6]
		65-85 years	22	365.6 [254.6, 525.0]	36.6 [25.5, 52.5]
	Placebo	All ages	41	10.6 [9.8, 11.4][a)]	1.1 [1.0, 1.1][a)]

N = number of subjects analyzed. When the antibody titer was less than LLOQ, 0.5 × LLOQ was used for analysis.

a) N = 40, excluding 1 subject who had not completed the "visit at 1 month after Dose 2" by the time when immunogenicity samples were shipped.

In both studies, compared with the placebo group, the Comirnaty groups had significantly higher GMT (serum SARS-CoV-2 neutralizing antibody titer at 1 month after Dose 2) and significantly higher GMFR (1 month after Dose 2/before Dose 1). In both studies, GMT and GMFR were lower in older subjects (aged 56-85 or 65-85 years) than in younger subjects (aged 16-55 or 20-64 years), but VE in foreign Study C4591001 was similar across all age groups (Table 20 and Table 21).

Foreign Study C4591001 and Japanese Study C4591005 have not yielded immunogenicity data at >1 month after Dose 2. However, another foreign Phase I Study (Study BNT162-01, CTD 5.3.5.1.2) yielded data at 63 days after Dose 2 in subjects aged 18-55 years. The data showed that the serum SARS-CoV-2 neutralizing antibody titer was maintained at 63 days after Dose 2, and GMT in these subjects was 1.3-1.9 times higher than that in patients who recovered from COVID-19.

(c) Efficacy in Japanese population

In the analysis of immunogenicity data, GMT and GMFR for serum SARS-CoV-2 neutralizing antibody titer in Japanese Study C4591005 were comparable to or higher than those in foreign Study C4591001 (Table 20 and Table 21).

In foreign Study C4591001, COVID-19 developed in only 9 of the 21,669 subjects receiving Comirnaty.

Therefore the data from the study are insufficient for investigating the relationship between the effect in preventing COVID-19 and the neutralizing antibody titer. Even with data from the published literature, the relationship has not been established completely. However, the applicant considers that Comirnaty is expected to have similar efficacy in the Japanese population as in foreign Study C4591001, for the following reasons: (a) Japanese subjects in Japanese Study C4591005 had similar elevation of serum SARS-CoV-2 neutralizing titers as in foreign Study C4591001. (b) The efficacy of Comirnaty was demonstrated in foreign Study C4591001 involving subjects from multiple countries, races and ethnic origins.

The relationship between the effect in preventing COVID-19 and the neutralizing antibody titer will be further analyzed.

As described in Section 7.R.1, PMDA decided to evaluate the efficacy in the Japanese population based on the results from the foreign confirmatory study (foreign Study C4591001) as well as based on the immunogenicity results in Japanese subjects from the Japanese clinical study. The data from the evaluable immunogenicity population (the primary immunogenicity analysis set) in Japanese Study C4591005 are being analyzed as of January 29, 2021. In view of the urgent need of reviewing Comirnaty, PMDA decided to use the already submitted data from the all-available immunogenicity population. PMDA confirmed the following findings from the data submitted for the present application.

- The results of foreign Study C4591001 demonstrate the effect of Comirnaty in preventing COVID-19 in the entire study population.
- The races and countries of subjects enrolled in foreign Study C4591001 were biased (Caucasians accounted for 82.8% and persons living in the U.S. for 77.0% of all subjects analyzed), but the analysis results of the study showed no marked difference in the effect in preventing COVID-19 between the races or countries.
- (a) In Japanese Study C4591005, serum SARS-CoV-2 neutralizing antibody titers after Comirnaty vaccination was higher those before vaccination and those in the placebo group.

  (b) The serum neutralizing titers in the all-available immunogenicity population of Japanese Study C4591005 was comparable to or higher than those in the evaluable immunogenicity population and the Dose 2 all-available immunogenicity population of foreign Study C4591001. (This result, however should be interpreted with care because it was from a between-study comparison and the compared populations were defined differently.)

Based on the data above, PMDA considers that Comirnaty is expected to have efficacy in the Japanese population as well.

However, foreign Study C4591001 have not shown the long-term efficacy data of Comirnaty and both foreign Study C4591001 and Japanese Study C4591005 will be continued after the market launch. The subjects in the studies should be monitored until the completion of observation period. The information collected after the market launch should be provided to healthcare professionals in an appropriate manner.

If any new finding is obtained about the relationship between the effect in preventing COVID-19 and the neutralizing antibody titer, appropriate actions (including assessment of the need of additional studies) should be taken.

7.R.2.3 Effect in preventing severe COVID-19

The applicant's explanation about the effect of Comirnaty in preventing severe COVID-19:
Among confirmed COVID-19 cases occurring ≥7 days after Dose 2 during the Phase II/III part of foreign Study C4591001, severe cases were analyzed to evaluate the effect of Comirnaty in preventing severe COVID-19. Severe COVID-19 was defined as having at least 1 of the following conditions, in accordance with the criteria in the FDA Guidance (Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19[36)]).

- 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)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
- Shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg or requiring vasopressors)
- Acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

Among subjects without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2 in the evaluable efficacy population, 1 receiving Comirnaty and 3 receiving placebo had severe COVID-19, with VE1 [95%CI] of 66.4 [−124.8, 96.3]%. The posterior probability of the true VE1 exceeding 30% was 74.29%, which did not meet the predefined success criterion (98.6%). Similar results were obtained in subjects with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2 (VE2 [95%CI]: 66.3 [−125.5, 96.3]%). Among all subjects who received at least 1 dose of the study vaccine, 1 receiving Comirnaty and 9 receiving placebo had severe COVID-19 after Dose 1, with VE [2-sided 95% CI] of 88.9 [20.1, 99.7]%.

These results fail to demonstrate the effect of Comirnaty in preventing severe COVID-19. This is, however, probably due to the small number of severe COVID-19 cases in the study.

PMDA accepts the applicant's explanation and considers that if any new finding is obtained about the effects of Comirnaty or SARS-CoV-2 vaccines in preventing severe COVID-19, appropriate actions should be taken, such as determining the necessity of providing the information as needed.

36) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19 (as of January 21, 2021)

7.R.2.4 Efficacy against variants

PMDA's view on the efficacy against variants:

Since December 2020, new SARS-CoV-2 variants have been reported from various parts of the world, such as the U.K. and South Africa, and have been detected in other countries, including Japan. These variants differ from the strains prevalent during the period of the clinical studies submitted for the present application (see Section 3.R.2). The efficacy of Comirnaty against these variants was not evaluated in the clinical studies. Non-clinical pharmacological assessments of variants are described in Section 3.R.2. Continuous attention should be paid to the emergence and prevalence of variants, information on the efficacy of Comirnaty against variants (including non-clinical evaluation) should continue to be collected, and appropriate actions should be taken according to the situation.

7.R.3 Safety

PMDA's conclusion on the safety of Comirnaty:

The submitted data includes the safety data of Comirnaty. In the Phase II/III part of foreign Study C4591001, safety data were obtained primarily within 1 to 3 months after Dose 2 (77.7% [33,752 of 43,448] of subjects were monitored for ≥4 weeks and <12 weeks after Dose 2). In Japanese Study C4591005, safety data were obtained within 1 month after Dose 2. Thus sufficient long-term safety data have not been obtained. Nonetheless, after reviewing the submitted data (see sections below for details), PMDA has found no serious concern that would affect the approval of Comirnaty.

The applicant should collect the following information after the market launch and promptly collect any data concerning Comirnaty including those from foreign countries and ongoing clinical studies. The applicant should also evaluate new findings obtained to determine the necessity of providing additional precautions and information, and take other appropriate actions.

- Long-term safety following vaccination with Comirnaty
- Safety in vaccine recipients with underlying diseases and characteristics associated with severe COVID-19
- Risk of Comirnaty-associated enhanced disease

This conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3.1 Safety profile

The applicant's explanation about the safety of Comirnaty in clinical studies:

(a) Adverse events

In the first 8,214 subjects (4,108 in the Comirnaty group and 4,106 in the placebo group) enrolled in the Phase II/III part of foreign Study C4591001, data on the predefined local reactions (injection site pain, redness, and swelling) and the predefined systemic events (pyrexia, fatigue, headache, chill, vomiting, diarrhoea, myalgia, and arthralgia) were collected within 7 days after each dose by the subject diary. These were analyzed as reactogenicity events (see Table 22 for the results). Many subjects in the Comirnaty group experienced local reactions (84.7%) and systemic events (77.4%) within 7 days after Dose 1 or Dose 2; these incidences were

higher than those in the placebo group. The incidences of vomiting and diarrhoea in the Comirnaty group were similar to those in the placebo group, but the incidences of the other events were higher in the Comirnaty group than in the placebo group. Most of the events in the Comirnaty group occurred in ≥10% of subjects. The following events of Grade ≥3 occurred in at least 1% of subjects: fatigue, headache, myalgia, chill, and injection site pain. Pyrexia (≥38°C) was not graded for severity, and its incidence in the Comirnaty group by temperature was as follows: 38.0°C-38.4°C in 9.2% (378 subjects); 38.5°C-38.9°C in 4.1% (167 subjects); 39.0°C-40.0°C in 0.9% (35 subjects); and >40.0°C in 0.0% (2 subjects).

Table 22 Reactogenicity events within 7 days after Dose 1 or Dose 2
(reactogenicity analysis set, Phase II/III part of foreign Study C4591001)

	Event terms	All		Grade ≥3	
		Comirnaty (N = 4,108)	Placebo (N = 4,106)	Comirnaty (N = 4,108)	Placebo (N = 4,106)
		n (%)	n (%)	n (%)	n (%)
Local reaction	All	3,481 (84.7)	748 (18.2)	—	—
	Injection site pain	3,455 (84.1)	700 (17.0)	59 (1.4)	2 (0.0)
	Redness	389 (9.5)	64 (1.6)	27 (0.7)	6 (0.1)
	Swelling	430 (10.5)	42 (1.0)	17 (0.4)	4 (0.1)
Systemic event	All	3,181 (77.4)	2,255 (54.9)	—	—
	Pyrexia[a)]	582 (14.2)	38 (0.9)	—[a)]	—[a)]
	Fatigue	2,585 (62.9)	1,461 (35.6)	172 (4.2)	26 (0.6)
	Headache	2,265 (55.1)	1,402 (34.1)	98 (2.4)	40 (1.0)
	Chill	1,312 (31.9)	289 (7.0)	71 (1.7)	3 (0.1)
	Vomiting	84 (2.0)	62 (1.5)	5 (0.1)	1 (0.0)
	Diarrhoea	644 (15.7)	576 (14.0)	12 (0.3)	7 (0.2)
	Myalgia	1,573 (38.3)	549 (13.4)	74 (1.8)	9 (0.2)
	Arthralgia	968 (23.6)	360 (8.8)	34 (0.8)	6 (0.1)

N = number of subjects analyzed, n = number of subjects with events
a) ≥38°C, not graded for severity.

Many of the local reactions occurred on Day 1 to 3 of study vaccination and mostly resolved 1 to 2 days after the onset, although some lasted for approximately 1 month or had unknown outcome. Many of the systemic events occurred on Day 2 to 3 of vaccination and mostly resolved 1 day after the onset, although some lasted for approximately 1 month or had unknown outcome.

Subjects were allowed to use antipyretic or pain medication for symptoms associated with study vaccination (not allowed to use them as prophylaxis). The proportion of subjects who used antipyretic or pain medication at least once was 46.5% (1,909 subjects) in the Comirnaty group and 19.7% (810 subjects) in the placebo group.

The incidence of adverse events within 1 month after the last dose was 26.7% (5,770 of 21,621 subjects) in the Comirnaty group and 12.2% (2,638 of 21,631 subjects) in the placebo group (excluding reactogenicity events collected by the subject diary within 7 days after each dose in the reactogenicity analysis set). Adverse events that occurred in ≥1% of subjects in the Comirnaty group were injection site pain, pyrexia, fatigue, chill, headache, myalgia, pain, nausea, arthralgia, and diarrhoea. All of these events, except for pain, had been predefined as reactogenicity events. Many of the events occurred within 7 days after vaccination, and were considered related to Comirnaty (see Section 7.2.2, Table 15).

Adverse events classified as MedDRA System Organ Class "Nervous system disorders" occurred in 5.9% (1,277 of 21,621 subjects) in the Comirnaty group and 2.3% (501 of 21,631 subjects) in the placebo group (hereinafter the same order shall apply); the events included headache (5.0%, 1.6%), dizziness (0.3%, 0.2%), paresthesia (0.1%, 0.1%), migraine (0.1%, 0.0%), lethargy (0.1%, 0.0%), and others.[37)] There was no Guillain-Barre syndrome or acute disseminated encephalomyelitis. Facial paralysis is discussed in Section 7.R.3.3.

The incidence of lymphadenopathy was 0.3% (70 of 21,621 subjects) in the Comirnaty group and 0.0% (7 of 21,631 subjects) in the placebo group. Among these events, those in 50 subjects in the Comirnaty group and 4 subjects in the placebo group were considered related to the study vaccine. Lymphadenopathy mostly occurred in the arm or neck. Many of the events occurred within 2 to 4 days after study vaccination, but those in 12 subjects in the Comirnaty group and 3 subjects in the placebo group occurred ≥8 days after vaccination (98 days at the latest). One subject in the Comirnaty group experienced lymphadenopathy within 30 minutes of vaccination. The event in 1 subject in the Comirnaty group was serious and considered related to the study vaccine, with the outcome of “not recovered” (data cutoff date: November 14, 2020). Based on these results, lymphadenopathy was considered to be a reactogenicity event attributable to Comirnaty, and will be listed as an event requiring attention in the package insert.

In Japanese Study C4591005, reactogenicity events within 7 days after each dose of the study vaccine were evaluated in all subjects of the safety analysis set. Many subjects in the Comirnaty group experienced local reactions (91.6%) and systemic events (78.2%) within 7 days after Dose 1 or Dose 2; these incidences were higher than those in the placebo group (Table 23). The incidence of vomiting in the Comirnaty group was similar to that in the placebo group, but the incidences of the other events were higher in the Comirnaty group than in the placebo group. Most of the events in the Comirnaty group occurred in ≥10% of subjects. The following events had Grade ≥3 cases: fatigue, injection site pain, headache, chill, and arthralgia. Pyrexia (≥37.5°C) was not graded for severity, and its incidence in the Comirnaty group by temperature was as follows: 37.5°C-37.9°C in 17.6% (21 subjects), 38.0°C-38.4°C in 9.2% (11 subjects), 38.5°C-38.9°C in 8.4% (10 subjects), 39.0°C-40.0°C in 0.8% (1 subject), and >40.0°C in 0 subjects. The incidence of pyrexia was higher in Japanese Study C4591005 (36.1%) than in the Phase II/III part of foreign Study C4591001 (14.2%). In Japanese Study C4591005, however, pyrexia was defined as ≥37.5°C and therefore pyrexia of wider range (particularly the range 37.5°C to 37.9°C) was collected compared with foreign Study C4591001 (≥38°C). This resulted in the higher incidence of pyrexia in Japanese Study C4591005.

37) Other than these events, adverse events with an incidence <0.1% in the Comirnaty group included sciatica (9 subjects); somnolence, dysgeusia, syncope, and presyncope (8 subjects each); tension headache and tremor (7 subjects each); cerebrovascular accident, parosmia, subarachnoid haemorrhage, facial paralysis, and hyperaesthesia (4 subjects each); and hypoaesthesia, burning sensation, sinus headache, transient ischemic attack (3 subjects each), etc.

Table 23 Reactogenicity events within 7 days after Dose 1 or Dose 2 (Safety analysis set, Japanese Study C4591005)

	Event terms	All		Grade ≥3	
		Comirnaty (N = 119)	Placebo (N = 41)	Comirnaty (N = 119)	Placebo (N = 41)
		n (%)	n (%)	n (%)	n (%)
Local reaction	All	109 (91.6)	1 (2.4)	—	—
	Injection site pain	109 (91.6)	1 (2.4)	4 (3.4)	0
	Redness	23 (19.3)	0	0	0
	Swelling	19 (16.0)	0	0	0
Systemic event	All	93 (78.2)	9 (22.0)	—	—
	Pyrexia[a)]	43 (36.1)	0	—[a)]	—[a)]
	Fatigue	75 (63.0)	4 (9.8)	5 (4.2)	0
	Headache	64 (53.8)	8 (19.5)	3 (2.5)	0
	Chill	58 (48.7)	3 (7.3)	3 (2.5)	0
	Vomiting	1 (0.8)	0	0	0
	Diarrhoea	10 (8.4)	1 (2.4)	0	0
	Myalgia	29 (24.4)	1 (2.4)	0	0
	Arthralgia	35 (29.4)	2 (4.9)	2 (1.7)	0

N = number of subjects analyzed, n = number of subjects with events
a) ≥37.5°C, not graded for severity.

Many of the local reactions occurred on Day 1 to 3 of study vaccination, and mostly resolved 1 to 3.5 days after the onset. Many of the systemic events occurred on Day 2 to 4 of study vaccination, and mostly resolved 1 day after the onset.

The proportion of subjects who used antipyretic or pain medication at least once was 37.8% (45 subjects) in the Comirnaty group and 4.9% (2 subjects) in the placebo group.

The incidence of adverse events within 1 month after the last dose was 10.1% (12 of 119 subjects) in the Comirnaty group and 7.3% (3 of 41 subjects) in the placebo group (excluding reactogenicity events collected by the subject diary within 7 days after each dose). Adverse events that occurred in ≥2 subjects in the Comirnaty group were nasopharyngitis (3 subjects) and headache (2 subjects). Headache (2 subjects) was the only adverse event classified as a nervous system disorder. Lymphadenopathy did not occur.

(b) Adverse events after each dose by age

Reactogenicity events after each dose by age are shown in Table 24 (Phase II/III part of foreign Study C4591001) and Table 25 (Japanese Study C4591005).

Table 24 Reactogenicity events within 7 days after each dose
(reactogenicity analysis set, Phase II/III part of foreign Study C4591001)

	Event terms	Dose #	Comirnaty			Placebo		
			All	16 to 55 years	56 to 85 years	All	16 to 55 years	56 to 85 years
			Dose 1 N = 4,093	Dose 1 N = 2,291	Dose 1 N = 1,802	Dose 1 N = 4,090	Dose 1 N = 2,298	Dose 1 N = 1,792
			Dose 2 N = 3,758	Dose 2 N = 2,098	Dose 2 N = 1,660	Dose 2 N = 3,749	Dose 2 N = 2,103	Dose 2 N = 1,646
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reaction	Injection site pain	Dose 1	3,186 (77.8)	1,904 (83.1)	1,282 (71.1)	488 (11.9)	322 (14.0)	166 (9.3)
		Dose 2	2,730 (72.6)	1,632 (77.8)	1,068 (66.1)	372 (9.9)	245 (11.7)	127 (7.7)
	Redness	Dose 1	189 (4.6)	104 (4.5)	85 (4.7)	45 (1.1)	26 (1.1)	19 (1.1)
		Dose 2	243 (6.5)	123 (5.9)	120 (7.2)	26 (0.7)	14 (0.7)	12 (0.7)
	Swelling	Dose 1	250 (6.1)	132 (5.8)	118 (6.5)	32 (0.8)	11 (0.5)	21 (1.2)
		Dose 2	256 (6.8)	132 (6.3)	124 (7.5)	16 (0.4)	5 (0.2)	11 (0.7)
Systemic event	Pyrexia[a)]	Dose 1	111 (2.7)	85 (3.7)	26 (1.4)	27 (0.7)	20 (0.9)	7 (0.4)
		Dose 2	512 (13.6)	331 (15.8)	181 (10.9)	14 (0.4)	10 (0.5)	4 (0.2)
	Fatigue	Dose 1	1,700 (41.5)	1,085 (47.4)	615 (34.1)	1,172 (28.7)	767 (33.4)	405 (22.6)
		Dose 2	2,086 (55.5)	1,247 (59.4)	839 (50.5)	756 (20.2)	479 (22.8)	277 (16.8)
	Headache	Dose 1	1,413 (34.5)	959 (41.9)	454 (25.2)	1,100 (26.9)	775 (33.7)	325 (18.1)
		Dose 2	1,732 (46.1)	1,085 (51.7)	647 (39.0)	735 (19.6)	506 (24.1)	229 (13.9)
	Chill	Dose 1	434 (10.6)	321 (14.0)	113 (6.3)	203 (5.0)	146 (6.4)	57 (3.2)
		Dose 2	1,114 (29.6)	737 (35.1)	377 (22.7)	125 (3.3)	79 (3.8)	46 (2.8)
	Vomiting	Dose 1	37 (0.9)	28 (1.2)	9 (0.5)	37 (0.9)	28 (1.2)	9 (0.5)
		Dose 2	51 (1.4)	40 (1.9)	11 (0.7)	30 (0.8)	25 (1.2)	5 (0.3)
	Diarrhoea	Dose 1	402 (9.8)	255 (11.1)	147 (8.2)	388 (9.5)	270 (11.7)	118 (6.6)
		Dose 2	356 (9.5)	219 (10.4)	137 (8.3)	276 (7.4)	177 (8.4)	99 (6.0)
	Myalgia	Dose 1	738 (18.0)	487 (21.3)	251 (13.9)	398 (9.7)	249 (10.8)	149 (8.3)
		Dose 2	1,260 (33.5)	783 (37.3)	477 (28.7)	260 (6.9)	173 (8.2)	87 (5.3)
	Arthralgia	Dose 1	406 (9.9)	251 (11.0)	155 (8.6)	247 (6.0)	138 (6.0)	109 (6.1)
		Dose 2	772 (20.5)	459 (21.9)	313 (18.9)	170 (4.5)	109 (5.2)	61 (3.7)

N = number of subjects analyzed, n = number of subjects with events
a) ≥38.0°C

Table 25 Reactogenicity events within 7 days after each dose (safety analysis set, Japanese Study C4591005)

	Event terms	Dose #	Comirnaty			Placebo		
			All	20 to 64 years	65 to 85 years	All	20 to 64 years	65 to 85 years
			Dose 1 N = 119	Dose 1 N = 97	Dose 1 N = 22	Dose 1 N = 41	Dose 1 N = 33	Dose 1 N = 8
			Dose 2 N = 116	Dose 2 N = 94	Dose 2 N = 22	Dose 2 N = 41	Dose 2 N = 33	Dose 2 N = 8
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reaction	Injection site pain	Dose 1	103 (86.6)	85 (87.6)	18 (81.8)	1 (2.4)	1 (3.0)	0
		Dose 2	92 (79.3)	76 (80.9)	16 (72.7)	0	0	0
	Redness	Dose 1	16 (13.4)	14 (14.4)	2 (9.1)	0	0	0
		Dose 2	12 (10.3)	8 (8.5)	4 (18.2)	0	0	0
	Swelling	Dose 1	15 (12.6)	13 (13.4)	2 (9.1)	0	0	0
		Dose 2	10 (8.6)	8 (8.5)	2 (9.1)	0	0	0
Systemic event	Pyrexia[a)]	Dose 1	17 (14.3)	17 (17.5)	0	0	0	0
		Dose 2	38 (32.8)	35 (37.2)	3 (13.6)	0	0	0
	Fatigue	Dose 1	48 (40.3)	44 (45.4)	4 (18.2)	4 (9.8)	4 (12.1)	0
		Dose 2	70 (60.3)	62 (66.0)	8 (36.4)	1 (2.4)	1 (3.0)	0
	Headache	Dose 1	39 (32.8)	34 (35.1)	5 (22.7)	6 (14.6)	5 (15.2)	1 (12.5)
		Dose 2	51 (44.0)	43 (45.7)	8 (36.4)	5 (12.2)	5 (15.2)	0
	Chill	Dose 1	30 (25.2)	30 (30.9)	0	2 (4.9)	2 (6.1)	0
		Dose 2	53 (45.7)	50 (53.2)	3 (13.6)	1 (2.4)	1 (3.0)	0
	Vomiting	Dose 1	0	0	0	0	0	0
		Dose 2	1 (0.9)	1 (1.1)	0	0	0	0
	Diarrhoea	Dose 1	6 (5.0)	6 (6.2)	0	0	0	0
		Dose 2	6 (5.2)	6 (6.4)	0	1 (2.4)	1 (3.0)	0
	Myalgia	Dose 1	17 (14.3)	15 (15.5)	2 (9.1)	1 (2.4)	1 (3.0)	0
		Dose 2	19 (16.4)	19 (20.2)	0	0	0	0
	Arthralgia	Dose 1	17 (14.3)	17 (17.5)	0	2 (4.9)	2 (6.1)	0
		Dose 2	29 (25.0)	29 (30.9)	0	0	0	0

N = number of subjects analyzed, n = number of subjects with events
a) ≥37.5°C

In the Phase II/III part of foreign Study C4591001, the incidences of each local reaction and vomiting and diarrhoea (systemic events) after Dose 1 were similar to those after and Dose 2. The incidences of the other systemic events were higher after Dose 2 than after Dose 1. The incidences of all Grade ≥3 events occurring after Dose 1 were <1%, but the incidences of the following Grade ≥3 events occurring after Dose 2 were ≥1%: fatigue (3.8%), headache (2.0%), myalgia (1.7%), and chill (1.6%).

The incidences of each event and Grade ≥3 events were mostly higher in younger subjects than in older subjects. There was no event with a markedly higher incidence in older subjects than in younger subjects.

In the Comirnaty group, the incidence of pyrexia (≥38.0°C) was higher after Dose 2 than after Dose 1, and higher in younger subjects than in older subjects. The incidence of pyrexia >38.9°C was 0.2% after Dose 1 (8 subjects: 6 younger and 2 older subjects) and 0.8% after Dose 2 (32 subjects: 27 younger and 5 older subjects), Pyrexia >40.0°C occurred in 2 subjects (1 older subject after Dose 1 and 1 younger subject after Dose 2). The

median time to onset was Day 2 of vaccination and the median duration was 1 day. The median time to onset and median duration were similar in both age groups and similar with both doses (Dose 1 and Dose 2).

Adverse events that occurred within 1 month after the last dose (excluding reactogenicity events collected by the subject diary within 7 days after each dose in the reactogenicity analysis set) were mostly local reactions or systemic events that were predefined as reactogenicity events. The tendency of incidences of these events by age and dose number (Dose 1 or Dose 2) was similar to that of reactogenicity events. The incidence of adverse events among subjects aged 16 to 17 years was 11.6% (16 of 138 subjects) in the Comirnaty group and 4.8% (7 of 145 subjects) in the placebo group; most of the events in the Comirnaty group were events predefined as reactogenicity events.

The results of adverse events by age and dose number (Dose 1 or Dose 2) in Japanese Study C4591005 tended to be similar to those in the Phase II/III part of foreign Study C4591001.

(c) Serious adverse events

In the phase 1 part of foreign Study C4591001 (data cutoff date: August 24, 2020), no death or serious adverse events occurred. During the additional observation period after Dose 2, peripheral nerve injury was reported in 1 subject receiving Comirnaty 30 μg (this event was originally reported as neurosis) but was considered unrelated to the study vaccine.

In the Phase II/III part of foreign Study C4591001 (data cutoff date: November 14, 2020), serious adverse events occurred in 126 of 21,621 subjects (0.6%) in the Comirnaty group and 111 of 21,631 subjects (0.5%) in the placebo group. Among them, 4 subjects in the Comirnaty group had such events for which a causal relationship with the study vaccine could not be ruled out: lymphadenopathy; shoulder injury related to vaccine administration; ventricular arrhythmia; and back pain/pain in legs with radicular paresthesia (this event is not coded by MedDRA) in 1 subject each. The outcomes were “not recovered” for lymphadenopathy, “recovered” for ventricular arrhythmia, and “recovering” for the others. Death occurred in 2 subjects in the Comirnaty group (arteriosclerosis and cardiac arrest in 1 subject each) and 4 subjects in the placebo group (unknown cause in 2 subjects, haemorrhagic stroke in 1 subject, and myocardial infarction in 1 subject). All of the deaths were considered unrelated to the study vaccine.

Ten subjects died between the data cutoff date and December 29, 2020. (Which group they were assigned to is unknown because the study is currently ongoing in a blinded manner). The causes of death were cardio-respiratory arrest in 2 subjects; and cardiac arrest, cardiac failure congestive, hypertensive heart disease, arteriosclerosis, pneumonia, COVID-19, COVID-19-related pneumonia, gallbladder hypofunction, septic shock, aortic rupture, and diabetes mellitus in 1 subject each (some subjects had more than 1 cause of death). Serious adverse events occurred in 91 subjects, and all were considered unrelated to the study vaccine.

In Japanese Study C4591005 (data cutoff date: January 5, 2021), no death or serious adverse events occurred.

As described above, in the Japanese and foreign clinical studies, reactogenicity events occurred in many subjects, with tendency towards higher incidences in younger subjects than in older subjects. Most of the events, however, were mild or moderate and resolved shortly after vaccination. Further, the incidences of death and serious adverse events were low, and most of the deaths and serious adverse events were considered unrelated to Comirnaty. These results show that Comirnaty is tolerable, with no serious concern about the safety profile in vaccine recipients aged ≥16 years.

PMDA's view:
No sufficient data on the long-term safety after vaccination are available from the submitted data of the Japanese and foreign clinical studies. Nonetheless, the following currently available data have revealed no serious concerns that would affect the approval of Comirnaty:

(a) Many subjects experienced local reactions and systemic events (both collected as reactogenicity events), but these events were mostly mild or moderate and reversible.
(b) The safety profile of Comirnaty in the Japanese and foreign studies had no substantial differences.
(c) The incidences of other adverse events and the incidence by age.

However, the systemic events reported in many subjects may affect daily living, and the following information is important for persons who will receive Comirnaty:

(a) A certain proportion of subjects experienced Grade 3 systemic events and pyrexia ≥37.5°C.
(b) Some adverse events occurred more frequently after Dose 2 than after Dose 1.

The applicant should appropriately provide this information (including the time to and duration of events) to healthcare professionals and vaccine recipients.

The applicant should continue to collect the long-term safety data of Comirnaty after the market launch.

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

7.R.3.2 Shock, anaphylaxis

Serious hypersensitivity reactions associated with Comirnaty have been reported after authorization or market launch outside Japan (see Section 7.R.3.7). PMDA asked the applicant to describe the status of hypersensitivity reactions after vaccination with Comirnaty.

The applicant's response:
In the Phase II/III part of foreign Study C4591001, events classified as MedDRA System Organ Class "Immune system disorders" occurred in 0.1% (26 of 21,621 subjects) in the Comirnaty group and 0.1% (22 of 21,631 subjects) in the placebo group. Of these, the causal relationship to the study vaccine could not be ruled out for the events in 6 subjects in the Comirnaty group (immunisation reaction in 5 subjects and drug hypersensitivity in 1 subject) and 1 subject in the placebo group (allergy to vaccine). All of the events classified as immune system disorders in the Comirnaty group were either mild or moderate, and occurred on Day 1 or 2 of Dose 1

or Dose 2. The incidence of events classified as angioedema and hypersensitivity by MedDRA SMQ (narrow scope) was 0.1% (25 of 21,621 subjects) and 0.7% (144 of 21,621 subjects), respectively, in the Comirnaty group, and 0.1% (23 of 21,631 subjects) and 0.6% (120 of 21,631 subjects) in the placebo group. No allergic reactions occurred immediately (within 30 minutes) after vaccination with Comirnaty.

Serious events occurred in 2 subjects in the Comirnaty group (anaphylactic reaction and drug hypersensitivity in 1 subject each) and 1 subject in the placebo group (anaphylactic shock), but all were considered unrelated to the study vaccine.[38)]

The Phase II/III part of foreign Study C4591001 enrolled subjects with prior non-serious allergy: 5,839 in the Comirnaty group and 5,834 in the placebo group (among them, 15 in the Comirnaty group and 22 in the placebo group had prior anaphylaxis). Among these subjects, allergy-related events related to the study vaccine occurred in 1 subject in the Comirnaty group[39)] (drug hypersensitivity and urticaria) and 1 subject in the placebo group[40)] (allergy to vaccine and pharyngeal swelling); all events were moderate with the outcome of "recovered."

In Japanese Study C4591005, there was no allergy-related events (data cutoff date: January 5, 2021).

See Section 7.R.3.7 for foreign safety information reported after authorization or market launch.

Anaphylaxis including shock has been identified in the clinical studies and foreign safety data obtained after authorization or market launch. The package insert will therefore include a precautionary statement regarding shock and anaphylaxis.

PMDA's view:
PMDA reviewed the status of anaphylaxis including shock identified in the clinical studies and foreign safety data obtained after authorization or market launch, and accepted the applicant's proposal to include a precautionary statement regarding shock and anaphylaxis in the package insert. The following information should also be disseminated:

The past history etc. of vaccine recipients should be checked before vaccination. Recipients should be monitored for a certain period of time after vaccination. If any abnormality is found, appropriate actions should be taken.

7.R.3.3 Facial paralysis (Bell's palsy)

Facial paralysis occurred in 4 subjects in the Comirnaty group in the Phase II/III part of foreign Study C4591001.

38) The anaphylactic reaction in a subject receiving Comirnaty occurred after bee sting on 8 days after Dose 2. The drug hypersensitivity in a subject receiving Comirnaty occurred on 9 days after Dose 2, and was considered to be caused by an antibiotic. The anaphylactic shock in a subject receiving placebo occurred after the subject was bitten by ants 18 days after Dose 2.
39) A subject with prior tree pollen allergy (anaphylaxis)
40) A subject with prior shellfish and iodine allergy

The applicant's explanation:
In the Phase II/III part of foreign Study C4591001, 4 subjects in the Comirnaty group experienced facial paralysis, and the events in 2 of them were considered related to the study vaccine. Both subjects had mild or moderate facial paralysis, with the outcome of "recovered" or "resolved."

In Japanese Study C4591005, no facial paralysis occurred (data cutoff date: January 5, 2021).

Also, 21 subjects had facial paralysis according to foreign spontaneous reports obtained after authorization or market launch (reporting period: December 1 to 31, 2020) (see Section 7.R.3.7).

According to the applicant's U.S. electronic health record database, the incidence rate of facial paralysis is 77 cases per 100,000 person-years. The incidence of facial paralysis in the clinical studies of Comirnaty was slightly higher than that predicted from the database but within the expected range. According to several literature reports, the incidence rate of facial paralysis is 15 to 30 cases per 100,000 person-years (*NEJM.* 2004; 351:1323-31, *Vaccine.* 2017; 35:1972-83, *J Neurol.* 2020; 267:1896-905, etc.). The incidence of facial paralysis in the clinical studies of Comirnaty was 4.3 times higher than that predicted from the literature reports. At present, the relationship between facial paralysis and Comirnaty is unknown. This issue will continue to be investigated, and a precautionary statement regarding facial paralysis will be included in the package inset.

PMDA reviewed the status of facial paralysis identified in the clinical studies and foreign safety data obtained after authorization or market launch, and accepted the applicant's proposal to include a precautionary statement in the package insert.

7.R.3.4 Safety in individuals with underlying diseases

PMDA asked the applicant to describe the safety of Comirnaty in vaccine recipients with underlying diseases associated with a risk of severe COVID-19 who are in high need of SARS-CoV-2 vaccine.

The applicant's response:
Based on the results of the Phase II/III part of foreign Study C4591001, a post-hoc analysis was performed in subjects with underlying diseases at baseline (diseases presented in the Charlson Comorbidity Index) and subjects with obesity (BMI ≥30 kg/m^2) as a risk factor of severe COVID-19. The analysis population included 8,978 subjects with underlying diseases: 3,443 with chronic lung disease, 3,368 with diabetes mellitus without chronic complications, 237 with diabetes mellitus with chronic complications, 1,561 with malignant diseases, 197 with AIDS/HIV, and subjects with other underlying diseases with a high risk of severe COVID-19 listed in the Clinical Guidance for COVID-19 (ver. 4.1).[41)] Reactogenicity events in this population are shown in Table 26.

Table 26 Reactogenicity events within 7 days after vaccination (subjects with underlying disease or obesity in the reactogenicity analysis set, Phase II/III part of foreign Study C4591001)

	Event terms	All		Grade ≥3	
		Comirnaty	Placebo	Comirnaty	Placebo
		N = 1,986	N = 1,942	N = 1,986	N = 1,942
Local reaction	All	1,631 (82.1)	320 (16.5)	—	—
	Injection site pain	1,614 (81.3)	297 (15.3)	20 (1.0)	1 (0.1)
	Redness	191 (9.6)	32 (1.6)	10 (0.5)	4 (0.2)
	Swelling	204 (10.3)	21 (1.1)	6 (0.3)	2 (0.1)
Systemic event	All	1,486 (74.8)	1,094 (56.3)	—	—
	Pyrexia[a)]	230 (11.6)	25 (1.3)	—[a)]	—[a)]
	Fatigue	1,177 (59.3)	707 (36.4)	68 (3.4)	15 (0.8)
	Headache	1,016 (51.2)	673 (34.7)	36 (1.8)	25 (1.3)
	Chill	523 (26.3)	133 (6.8)	28 (1.4)	2 (0.1)
	Vomiting	44 (2.2)	31 (1.6)	3 (0.2)	1 (0.1)
	Diarrhoea	344 (17.3)	314 (16.2)	9 (0.5)	5 (0.3)
	Myalgia	709 (35.7)	285 (14.7)	30 (1.5)	6 (0.3)
	Arthralgia	455 (22.9)	187 (9.6)	17 (0.9)	2 (0.1)

n (%)
a) ≥38.0°C, not graded for severity.

The incidence of adverse events was 25.0% (2,172 of 8,697 subjects) in the Comirnaty group and 13.0% (1,125 of 8,641 subjects) in the placebo group. Among these events, those occurring in 18.1% (1,575 of 8,697 subjects) in the Comirnaty group and 5.1% (439 of 8,641 subjects) in the placebo group, were considered related to the study vaccine. Adverse events that occurred in ≥1% of subjects in the Comirnaty group were injection site pain, pyrexia, fatigue, chill, headache, myalgia, pain, nausea, arthralgia, and diarrhoea.

The above analysis results were similar to those in the entire study population (see Section 7.R.3.1).

The Ministry of Health, Labour and Welfare is currently discussing which underlying diseases qualify people to receive COVID-19 vaccine earlier than other people.[42)] The Clinical Guidance for COVID-19 (ver. 4.1) (in Japanese)[41)] states that people with the following underlying diseases and characteristics are at high risk of severe COVID-19: malignant tumors, chronic obstructive pulmonary disease, chronic kidney disease, type 2 diabetes mellitus, hypertension, dyslipidaemia, obesity of BMI ≥30 kg/m^2, immunodeficiency secondary to solid organ transplantation, etc. The post-hoc analysis of subjects with underlying diseases in the Phase II/III part of foreign Study C4591001 includes some information about the above diseases, but sufficient information is not available at present. The applicant therefore plans to collect post-marketing safety data of Comirnaty in vaccine recipients who have underlying diseases with a high risk of severe COVID-19.

PMDA's view:
The results of the Phase II/III part of foreign Study C4591001 showed that the safety of Comirnaty in subjects with underlying diseases or obesity was similar to that in the entire study population. The underlying diseases

41) https://www.mhlw.go.jp/content/000712473.pdf (as of January 21, 2021)
42) Document presented at the 43th subcommittee meeting on basic vaccination policy of the Committee on Immunization and Vaccines of the Health Sciences Council (December 25, 2020): https://www.mhlw.go.jp/stf/newpage_15767.html (as of January 21, 2021)

in the study subjects were in a relatively stable state, but people who will receive the vaccine after the market launch are expected to have underlying diseases of various severity. Therefore, collecting information in clinical settings is important. PMDA accepts the applicant's proposal to collect post-marketing safety data of Comirnaty in vaccine recipients with underlying diseases with a high risk of severe COVID-19 who are in high need of Comirnaty.

7.R.3.5 Safety in pregnant women

The applicant's explanation about the safety in pregnant women:

The protocols of clinical studies of Comirnaty excluded pregnant women. However, 23 women participating in the Phase II/III part of foreign Study C4591001 were pregnant, and 9 of them discontinued the study because of pregnancy. The outcomes of pregnancy in these women have not been obtained to date, and will continue to be tracked.

According to foreign spontaneous reports obtained after authorization or market launch (reporting period: December 1 to 31, 2020), 28 pregnant women received Comirnaty, but no particular issues have been identified (see Section 7.R.3.7).

As no particular issues were identified in the reproductive and developmental toxicity studies (see Section 5.5), the applicant considers that pregnant women can receive Comirnaty if the benefits of vaccination outweigh the risks.

PMDA accepts the applicant's explanation. When new findings are obtained from the post-marketing safety data and from pregnancy outcome data in women who received Comirnaty while pregnant in clinical studies, the applicant should consider the necessity of issuing additional precautionary statements and take other appropriate actions.

7.R.3.6 Risk of Comirnaty-associated enhanced disease

The applicant's explanation about the risk of Comirnaty-associated enhanced disease:

In the pharmacological investigation, cytokine production and other changes were evaluated in animals and humans that received Comirnaty. The results showed that the risk of Comirnaty-associated enhanced disease was low (see Section 3.R.3).

It is difficult to evaluate the risk of Comirnaty-associated enhanced disease from the clinical study results, for the following reasons: (a) Only a small number of patients experienced COVID-19 in the clinical studies. (b) Long-term monitoring is necessary to evaluate the risk of Comirnaty-associated enhanced disease, but the currently available data consist mainly of records obtained between 1 and 3 months after Dose 2 (77.7% [33,752 of 43,448] of subjects were monitored for ≥4 weeks and <12 weeks after Dose 2).

Since the risk of Comirnaty-associated enhanced disease in humans is unknown, the applicant will continue to

collect information after the market launch.

PMDA accepts the applicant's explanation. The applicant should continue to collect information, including foreign data, regarding the risk of Comirnaty-associated enhanced disease in humans after the market launch, and should disseminate any new findings promptly.

7.R.3.7 Safety information after authorization or market launch in foreign countries

The applicant's explanation about the safety information after authorization or market launch in foreign countries:

As of December 31, 2020, Comirnaty had obtained conditional marketing approval in 32 countries and tentative approval for emergency supply in 19 counties. Vials for approximately 26,079,300 doses of Comirnaty are estimated to have been shipped by December 31, 2020, 39.3% of them to the United States, 22.4% to the United Kingdom, 18.4% to EU, and 17.9% to Asian counties, among others.

There were 3,615 spontaneous reports during the period (December 1 through 31, 2020) covered by the first Summary Monthly Safety Report (January 13, 2021) on Comirnaty. This revealed 12 effective safety signals (anaphylaxis, injection site redness, injection site swelling, malaise, nausea, vomiting, diarrhoea, hypersensitivity, insomnia, injection site pruritus, pain in extremity, and facial paralysis). Anaphylaxis was classified as an important identified risk, and injection site redness, injection site swelling, malaise, and nausea were classified as identified risks (not important risks), while vomiting and diarrhoea were not considered as risks. Clinical significance of other safety signals was subjected to further evaluations. The above results suggest that the benefit-risk profile of Comirnaty during this reporting period is favorable.

A summary of the main spontaneous reports is shown below.

- **Death**

There were 10 reports of deaths (including 7 medically confirmed cases). The reported event terms were death (5 reports), cardiac arrest (3), cardiac failure (1), diarrhoea (1), and myocardial infarction (1). The deceased persons' ages were 41 through 95 years, with 7 of them aged ≥65 years. The 10 persons included 4 frail patients with underlying diseases,[43)] 1 immunocompromised patient, and 1 hypertensive patient. No sufficient data were available from the remaining 4 persons.

- **Anaphylaxis**

Abnormalities corresponding to anaphylactic reaction in the Standardised MedDRA queries (MedDRA SMQ) (wide or narrow) were reported in 824 individuals (including 613 medically confirmed cases) with a total of 1,245 events, of which 314 were serious. The outcome was death (3 events), not recovered (259), recovered with sequelae (31), recovered or recovering (603), and unknown (350). Of the 3 individuals who died, 2 (reported event term: cardiac arrest) were frail patients with multiple underlying diseases, while no sufficient data were available from the remaining patient.

[43)] In Q & A about "Studies in Support of Special Populations: Geriatrics" (ICH E7 Q&A: Administrative Notice dated September 17, 2010), frail patients are defined as vulnerable geriatric patients at high risk of adverse events (so-called "frail" geriatric patients who are, or are at high risk of being, psychologically or physically vulnerable or under custodial or nursing care).

Events corresponding to anaphylactic reaction in MedDRA SMQ (narrow) were reported in 43 individuals. They consisted of anaphylactic reaction (32 events), anaphylactoid reaction (5), anaphylactic shock (4), circulatory collapse (1), and shock symptom (1). Among the 43 individuals, 13 had a past history of asthma, anaphylaxis, or hypersensitivity.

- **Immune-mediated/autoimmune disorder**

Immune-mediated/autoimmune disorder was reported in 91 individuals (including 68 medically confirmed cases). A total of 92 events were reported, of which 27 were serious. Events reported twice or more were hypersensitivity (42 events), anosmia (31), autoimmune disorder (2), facial paresis (2), and pericarditis (2). The outcome was not recovered (24 events), recovered with sequelae (2), recovered or recovering (31), and unknown (35).

- **Facial paralysis**

Facial paralysis was reported in 21 individuals (including 11 medically confirmed cases). A total of 21 events were reported, of which 14 were serious. The outcome was not recovered (7 events), recovered with sequelae (1), recovered or recovering (4), and unknown (9).

- **Neurological events**

Neurological events were reported in 18 individuals (including 13 medically confirmed cases). A total of 22 events were reported, of which 18 were serious. Events reported twice or more were seizure (6 events), cerebrovascular accident (5), epilepsy (2), generalised tonic-clonic seizure (2), and Guillain-Barre syndrome (2). The outcome was not recovered (4 events), recovered with sequelae (3), recovered or recovering (7), and unknown (8).

- **Enhanced disease**

At the current moment, there is no standardized definition of vaccine-associated enhanced disease. Reports of possible enhanced disease were retrieved from spontaneous reports that met any of the following conditions

Search conditions:
Standard Decreased Therapeutic Response Search AND PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children;

The search retrieved events (in 4 individuals) meeting the above conditions. All individuals had respiratory events (4 events of dyspnoea, 1 event of hypoxia), and 1 had a gastrointestinal event (diarrhoea). All events occurred shortly after vaccination (7 hours through 1 week post dose), and they were mild in 3 individuals but severe in 1. The severe event in 1 individual was not considered to have evidence of enhanced disease, because it occurred within 24 hours after Dose 1 while enhanced disease is generally considered to be caused by an immunological mechanism.

- **Vaccination in frail patients with underlying diseases**[43)]

The spontaneous reports included 274 frail patients with underlying diseases. A total of 1,182 events were reported from this population. Main events were headache (77 events), fatigue (59), pyrexia (46), chills (46),

nausea (46), vaccination site pain (35), and dizziness (32). The outcome was death (4 events), not recovered (92), recovered with sequelae (6), recovered or recovering (130), and unknown (42). Of the 4 individuals who died, 1 had serious heart and lung diseases and died of cardiac arrest (reported event term). Another had a history of heart attack, active heart disease, and malignant tumor and died of cardiac failure and cardiac arrest (reported event terms). The other 2 were elderly persons (aged 84 and 91 years) with a history of dementia and died of unknown cause.

- **Vaccination in pregnant or lactating women**

The spontaneous reports included 28 pregnant women and 39 lactating women.

Exposure to vaccine during pregnancy was reported in 26 of the 28 pregnant women. Nine of the 26 women had non-serious events with clinical symptoms (vaccination site pain [4 events], headache [2], pain in extremity [2], bloody discharge [1], myalgia [1], pain [1], and rhinorrhoea [1]).

Non-serious events were reported in 4 of 39 suckling infants (1 event each of abdominal discomfort, decreased appetite, hypersensitivity, illness, infantile vomiting, infant irritability, sleeplessness, irritability, lethargy, pyrexia, redness, and vomiting). To investigate anaphylaxis in detail, the applicant's safety database was searched using an algorithm to retrieve reports on Comirnaty submitted by January 4, 2021 that included events meeting the definition of anaphylactic reaction (wide or narrow) in MedDRA SMQ.

A total of 81 cases met the definition, of whom 53 were serious. Of the 81 individuals, 18 met level 1 of Brighton Collaboration case definition criteria (*Vaccine.* 2007;25:5675-84),[44)] 26 met level 2, and none met level 3, 21 had no sufficient evidence, and 16 did not meet any of the criteria. The outcome of the 81 individuals was death in 1 individual, not recovered in 14, recovered/recovering or recovered with sequelae in 44, and unknown in 22. In total, 27 individuals had a past history of allergy, hypersensitivity, anaphylactic reaction etc.

Based on the above information, the applicant concluded that Comirnaty has a favorable benefit/risk profile. Anaphylaxis and facial paralysis will be defined as events requiring precautions in the package insert, as described in Sections 7.R.3.2 and 7.R.3.3.

PMDA confirmed the safety information after authorization or market launch in foreign countries. PMDA has also confirmed the following reports regarding serious allergic reactions including anaphylaxis.

In the United States, vaccination with Comirnaty was started in December 14, 2020 under emergency use authorization. During the period between December 14 and 23, 2020, Dose 1 was administered to 1,893,360 individuals, and adverse events in 4,393 vaccine recipients (0.2%) were reported to Vaccine Adverse Event Reporting System (VAERS) (*MMWR Morb Mortal Wkly Rep.* 2021;70:46-51). They included possible serious allergic reactions in 175 vaccine recipients, of whom 21 had anaphylaxis and 86 had non-anaphylactic allergic

[44)] Level 1: ≥1 major dermatologic AND ≥1 major cardiovascular (AND/OR ≥1 major respiratory) criterion
Level 2: (a) ≥1 major cardiovascular AND ≥1 major respiratory criterion
(b) ≥1 major cardiovascular (OR ≥1 major respiratory) criterion AND ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems)
(c) ≥1 major dermatologic AND ≥1 minor cardiovascular (AND/OR ≥1 minor respiratory) criterion
Level 3: ≥1 minor cardiovascular (OR respiratory) criterion AND ≥1 minor criterion from each of ≥2 different systems/categories

reactions. Of 21 vaccine recipients with anaphylaxis, 19 received epinephrine injection. Seventeen vaccine recipients had a past history of allergy (drug, food, insect sting), of whom 7 had a past history of anaphylaxis. Of the 86 vaccine recipients with non-anaphylactic allergic reaction, 56 had a past history of allergy.

In the United Kingdom, 3 cases of serious allergic reactions were reported between December 8, 2020 (launch date of vaccination with Comirnaty under temporary authorization) and December 11, 2020. Two of the 3 vaccine recipients had a past history of food or drug allergy.

PMDA's view:
After the start of vaccination with Comirnaty in December 2020, serious events including deaths have been reported, but causal relationship is unclear at the current moment. Safety data are being collected in foreign countries. The safety of Comirnaty should be continuously evaluated based on the available information, and appropriate actions (e.g., discussing the necessity of additional precautionary advice and information provision) should be taken.

7.R.4 Clinical positioning

PMDA's view on the clinical positioning of Comirnaty.
As of January 20, 2021, 332,231 people in Japan have been infected with SARS-CoV-2 (those testing positive by PCR). Of them, 71,129 had severe COVID-19 and 4,547 died.[45)] Because of the inability to identify all asymptomatic patients, the total number of both symptomatic and asymptomatic patients is presumed to be much greater than the above figure. People in their 20s make up the largest age group, followed by 30s, 40s, and 50s, whereas death and serious disease occurred predominantly in those aged ≥60 years.[46)]

The incubation period from SARS-CoV-2 exposure to symptom onset is 1 to 14 days, usually approximately 5 days.[47)] Patients become infectious before symptoms onset and especially highly infectious early after the onset. This is considered to be the cause of community transmission (Clinical Guidance for COVID-19 [ver. 4.1] [in Japanese] [41)]).

In Japan, an antiviral agent remdesivir was approved on May 7, 2020 for the treatment of disease caused by SARS-CoV-2 infection (COVID-19). Dexamethasone is available for use within the range of the approved indication. Also, other various drugs are used in clinical practice, depending on the symptoms and the severity of the disease (Clinical Guidance for COVID-19 [ver. 4.1] [in Japanese] [41)]). However, despite these treatments, the number of infected people, those with severe COVID-19, and death toll are increasing. Further, some patients have persisting symptoms such as dysosmia, taste disorder, dyspnoea, and alopecia even after viral eradication (*Open Forum Infect Dis.* 2020;7:0faa507.doi:10.1093/ofid/ofaa507). Prevention of COVID-19 is extremely important because (i) as of January 2021, the number of infected people is increasing, leaving the

45) https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html#h2_1(as of January 21, 2021)
46) https://www.mhlw.go.jp/content/10906000/000716059.pdf (as of January 21, 2021)
47) https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations (as of January 21, 2021)

medical care system on the brink of collapse, and (ii) COVID-19 may result in serious conditions or death in some patients. According to "Discussion at the Subcommittee on Novel Coronavirus Disease Control and Interim Summary by the Government (in Japanese),"[48] the objective of vaccination is "to decrease the number of deaths and severe cases due to COVID-19 and thereby to prevent the prevalence of COVID-19." In Japan, however, no vaccine has been approved for the prevention of COVID-19.

Results of the phase II/III part of foreign Study C4591001 demonstrated the effect of Comirnaty in preventing COVID-19. Japanese Study C4591005 showed an increase in neutralizing antibody in serum to the same or higher extent than foreign Study C4591001. Comirnaty is thus considered to be similarly effective in preventing COVID-19 in Japanese people as well [see Section 7.R.2]. There are no safety or tolerability problems that might affect the approval of Comirnaty [see Section 7.R.3]. At the current moment, the long-term efficacy and safety of Comirnaty and its effect in preventing severe COVID-19 are unknown [see Sections 7.R.2 and 7.R.3] and the efficacy of Comirnaty against variants is uncertain [see Section 3.R.2]. Nevertheless, it is clinically significant to make Comirnaty available as the first vaccine against COVID-19 in Japan, because (a) vaccination with Comirnaty is expected to prevent COVID-19 and decrease the number of patients with COVID-19, and (b) as of January 2021, the increasing number of patients is bringing the healthcare system to the verge of collapse.

7.R.5 Indication

PMDA's view on the indication of Comirnaty:

Results of the phase II/III part of foreign Study C4591001 demonstrated the effect of Comirnaty in preventing COVID-19, and Japanese Study C4591005 showed an increase in neutralizing antibody titer in serum to the same or higher extent than foreign Study C4591001. These findings suggest that Comirnaty is expected to have a similar effect in preventing COVID-19 in the Japanese population as well [see Section 7.R.2]. PMDA concluded that the indication of Comirnaty should be "prevention of disease caused by SARS-CoV-2 infection (COVID-19)," as proposed by the applicant, taking account of the description in "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2,"[32] and the indications of approved vaccines.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

The applicant's rationale for the proposed dosage and administration of Comirnaty:

The phase I part of foreign Study C4591001 (a dose-finding study) was conducted to investigate the safety, tolerability, and immunogenicity of Comirnaty (10, 20, or 30 μg), administered twice 21 days apart. The following results were obtained.

- At all dose levels, serum SARS-CoV-2 neutralizing antibody titer increased only slightly on Day 21 after Dose 1, but increased markedly from 7 days after Dose 2 [see Section 7.R.2.1 and Table 16].

[48] https://www.cas.go.jp/jp/seisaku/ful/bunkakai/corona_vaccine_2.pdf (as of January 21, 2021)

- Among older subjects at high risk of severe COVID-19, neutralizing antibody titer was higher in those receiving 30 μg than those receiving 20 μg [see Section 7.R.2.1 and Table 16].
- No safety problems were observed at any dose level.

Based on the above, in the phase II/III part of the study, 2 doses of Comirnaty 30 μg was administered intramuscularly, 21 days apart (allowable period, 19 to 23 days). Results confirmed the efficacy of Comirnaty [see Section 7.R.2], and the applicant concluded that its safety and the tolerability were acceptable [see Section 7.R.3].

The Comirnaty and placebo groups showed similar estimated cumulative incidence for COVID-19 occurrence during the period from Dose 1 to approximately 14 days after Dose 1 in the phase II/III part. Then, the cumulative incidence showed a steady increase in the placebo group but almost no increase in the Comirnaty group, resulting in a large difference after Dose 2 between the 2 groups. [see Section 7.R.2.2]. Although the efficacy of Dose 1 alone was not investigated, the phase I part showed that 2 doses were necessary for inducing the neutralizing antibody. Thus, Dose 1 alone is not considered to provide an adequate long-term effect.

In the phase II/III part, Dose 1 and Dose 2 of Comirnaty were administered 21 days apart (allowable period, 19 to 23 days). The protocol predefined that the evaluable efficacy population should include subjects receiving Dose 2 between 19 and 42 days after Dose 1, and the efficacy analysis in the population demonstrated the effect of Comirnaty in preventing COVID-19 [see Section 7.R.2]. Among the subjects in the evaluable efficacy population, 616 of 18,198 in the Comirnaty group and 659 of 18,325 in the placebo group received Dose 2 between 24 and 42 days after Dose 1.[49)] Among the subjects receiving Dose 2 between 24 and 42 days after Dose 1, there were 1 confirmed COVID-19 case in the Comirnaty group and 4 confirmed COVID-19 cases in the placebo group, with VE [2-sided 95%] of 73.3% [-170%, 99.5%] (VE in subjects without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2).

Thus, Comirnaty is expected to have efficacy in individuals receiving 2 doses of Comirnaty 24 to 42 days apart, although the definitive evaluation is difficult because of the limited number of subjects evaluated.

Japanese Study C4591005 used the same dosage regimen as in the phase II/III part of foreign Study C4591001. The immunogenicity results showed that Comirnaty is expected to be effective in preventing COVID-19 in Japanese people as well [see Section 7.R.2.2], and that there is no safety or tolerability concern unique to Japanese people [see Section 7.R.3].

The applicant therefore considers that the dosage and administration of Comirnaty can be defined based on the results of these clinical studies. When a vial of Comirnaty is diluted with 1.8 mL of physiological saline (JP), 0.3 mL of the solution corresponds to Comirnaty 30 μg. Thus the applicant has proposed the following dosage and administration: “The product is diluted with 1.8 mL of physiological saline (Japanese Pharmacopoeia grade), and usually 2 doses (0.3 mL each) are injected intramuscularly, 3 weeks apart.”

PMDA’s view:

[49)] The period between Dose 1 and Dose 2 was as follows: 24 to 25 days (212 subjects in Comirnaty group, 242 subjects in placebo group; the same order applies hereinafter), 26 to 30 days (264, 273), 31 to 35 days (88, 91), 36 to 40 days (32, 41), and 41 to 42 days (20, 12).

Based on the results of the review on the efficacy [see Section 7.R.2] and safety [see Section 7.R.3], PMDA concluded that the following dosage and administration were acceptable:

After dilution with 1.8 mL of physiological saline, 2 doses of 0.3 mL solution (= Comirnaty 30 μg) each are administered intramuscularly 3 weeks apart.

There is no established evidence for the efficacy of Dose 1 alone or of 2 doses separated by ≥24 days. Comirnaty should be administered twice 3 weeks apart according to the dosage regimen in the clinical studies.

7.R.6.1 Age eligibility

The applicant's explanation about the age eligibility for vaccination with Comirnaty:

Japanese Study C4591005 evaluated the safety, tolerability, and immunogenicity of Comirnaty in Japanese subjects aged 20 through 85 years. In the phase II/III part of foreign Study C4591001, the efficacy and safety of Comirnaty were demonstrated in subjects aged ≥16 years, and the analysis of subgroups stratified by age did not reveal any clinical concerns, suggesting that administering Comirnaty to Japanese people aged ≥16 years is acceptable.

During the study period of the phase II/III part of foreign Study C4591001, the protocol was revised to investigate the immunogenicity, safety, and tolerability in children and adolescents aged 12 to 15 years. Some data of this age group are included in the efficacy analysis, but no sufficient results are available at the current moment. A development plan Comirnaty for children will be discussed after the relevant results become available.

PMDA's view:

Since Japanese Study C4591005 enrolled subjects aged 20 through 85 years, data in Japanese people aged 16 to 19 years are unavailable. However, administering Comirnaty to people aged ≥16 years is acceptable, taking account of (i) the above explanation of the applicant, (ii) the lack of significant difference in the immunogenicity and safety profiles in subjects aged ≥20 years between Japanese Study C4591005 and foreign Study C4591001, and (iii) the current epidemic of COVID-19 in Japan.

7.R.7 Post-marketing investigations

The applicant's plan about the post-marketing investigations of Comirnaty:

Only limited safety data (including long-term data) of Comirnaty in Japanese people can be obtained before the marketing approval [see Section 7.R.3]. Enhanced disease is logically possible in Comirnaty recipients infected with SARS-CoV-2 [see Section 3.R.3]. The applicant therefore plans to conduct a use-results survey to investigate the safety, including the risk of enhanced disease, etc., for 12 months after Dose 2 of Comirnaty. The survey will include all vaccine recipients who consent to a 12-month follow-up after Dose 2 (Health Survey on First Vaccine Recipients among Healthcare Professionals [in Japanese] [https://www.mhlw.go.jp/content/10906000/ 000721004.pdf (as of January 21, 2021)]).

Also, a specified use-results survey (observation period: from Dose 1 to 1 month after Dose 2) in recipients with underlying diseases will be conducted to investigate the safety of Comirnaty in this population, because they are at high risk of severe COVID-19, and because the clinical studies of Comirnaty have not yielded

sufficient safety data in the population [see Section 7.R.3.4].

After the approval of Comirnaty, Japanese Study C4591005 will be reclassified as a postmarketing clinical study to investigate the long-term safety, etc.

In order to facilitate proper use of Comirnaty and ensure the safety, the applicant will conduct the following additional risk minimization activities, namely preparing a list of adverse reactions to Comirnaty at regular intervals and providing it to healthcare professionals.

PMDA's view:
The applicant's postmarketing surveillance plan is acceptable. The applicant should collect information not only from Japan but also from foreign countries (data from the ongoing foreign Study C4591001 and data obtained after authorization or after marketing approval) and, based on the information obtained, should continue to evaluate the safety of Comirnaty, discuss the necessity of providing additional precautions and information, and take other appropriate actions.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.3 Adverse events, etc. in subjects receiving another vaccine candidate (BNT162b1) in clinical studies

The safety data of the BNT162b1 group in Phase I part of foreign Study C4591001 (see Section 7.2.1) are shown below. Dose 1 at 100 µg was administered but Dose 2 at 100 µg was cancelled.[50)] The following tables therefore do not include data on Dose 2 at 100 µg.

Reactogenicity events that occurred within 7 days after each dose are shown in Table 27.

[50)] Severe injection site pain occurred after Dose 1 in subjects aged 18-55 years, and the incidences of fatigue, headache, chills and pyrexia were higher in the 100 µg group than in the 30 µg group. For these and other reasons, Dose 2 at 100 µg was cancelled and replaced by BNT162b1 10 µg or placebo.

Table 27 Reactogenicity events within 7 days after each dose (safety analysis set)

Event terms	Dose #	18-55 years old					65-85 years old			
		BNT162b1				Placebo[a]	BNT162b1			Placebo
		10 µg (N = 12)	20 µg (N = 12)	30 µg (N = 12)	100 µg[a] (N = 12)	(N = 12)[b]	10 µg (N = 12)	20 µg (N = 12)	30 µg (N = 12)	(N = 9)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reactions										
Injection site pain	Dose 1	7 (58.3)	9 (75.0)	12 (100)	12 (100) [1]	2 (16.7)	7 (58.3)	11 (91.7)	11 (91.7)	1 (11.1)
	Dose 2	10 (83.3)	11 (91.7)	12 (100)	—	2 (22.2)	8 (66.7)	9 (75.0)	9 (75.0)	0
Redness	Dose 1	0	0	2 (16.7)	4 (33.3)	0	0	0	0	0
	Dose 2	0	0	2 (16.7)	—	0	0	1 (8.3)	1 (8.3)	0
Swelling	Dose 1	0	3 (25.0)	2 (16.7)	5 (41.7)	0	1 (8.3)	1 (8.3)	2 (16.7)	0
	Dose 2	0	1 (8.3)	3 (25.0)	—	0	1 (8.3)	2 (16.7)	3 (25.0)	0
Systemic events										
Pyrexia	Dose 1	1 (8.3)	0	1 (8.3)	6 (50.0)	0	0	0	3 (25.0)	0
	Dose 2	1 (8.3)	2 (16.7)	9 (75.0)	—	0	0	6 (50.0)	4 (33.3) [1]	0
Fatigue	Dose 1	4 (33.3)	8 (66.7)	6 (50.0)	10 (83.3) [2]	3 (25.0)	2 (16.7)	7 (58.3)	6 (50.0) [1]	4 (44.4)
	Dose 2	8 (66.7) [1]	10 (83.3) [1]	10 (83.3)	—	2 (22.0)	3 (25.0)	7 (58.3) [1]	8 (66.7) [1]	2 (22.2)
Headache	Dose 1	5 (41.7)	6 (50.0)	6 (50.0)	9 (75.0) [1]	3 (25.0)	3 (25.0)	4 (33.3)	6 (50.0)	0
	Dose 2	10 (83.3)	8 (66.7)	12 (100)	—	0	5 (41.7)	9 (75.0) [1]	9 (75.0)	1 (11.1)
Chills	Dose 1	1 (8.3)	3 (25.0)	7 (58.3) [1]	10 (83.3) [1]	0	1 (8.3)	1 (8.3)	2 (16.7)	2 (22.2)
	Dose 2	3 (25.0)	6 (50.0)	8 (66.7)	—	0	3 (25.0)	7 (58.3)	4 (33.3)	0
Vomiting	Dose 1	0	0	0	0	0	0	0	0	0
	Dose 2	0	0	0	—	0	0	0	1 (8.3)	0
Diarrhoea	Dose 1	2 (16.7)	0	1 (8.3)	4 (33.3)	0	1 (8.3)	1 (8.3)	0	0
	Dose 2	0	1 (8.3)	1 (8.3)	—	0	0	1 (8.3)	2 (16.7)	0
Myalgia	Dose 1	1 (8.3)	4 (33.3)	3 (25.0)	7 (58.3) [1]	0	2 (16.7)	2 (16.7) [1]	5 (41.7)	1 (11.1)
	Dose 2	5 (41.7)	9 (75.0)	7 (58.3)	—	0	4 (33.3)	4 (33.3)	4 (33.3)	0
Arthralgia	Dose 1	2 (16.7)	1 (8.3)	0	3 (25.0) [1]	1 (11.1)	2 (16.7)	1 (8.3)	1 (8.3)	0
	Dose 2	4 (33.3)	6 (50.0)	3 (25.0)	—	0	3 (25.0)	3 (25.0)	2 (16.7)	0

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

[ ] = number of subjects with Grade 3 events (or pyrexia >38.9ºC) (No Grade 4 events [or pyrexia >40ºC] occurred).

a) Only data after Dose 1 of BNT162b1 100 µg and matched placebo (no data after Dose 2).

b) N = 9 for Dose 2

The incidences of adverse events and adverse reactions other than reactogenicity events are shown in Table 28.

Table 28 Adverse events and adverse reactions other than reactogenicity events within 1 month after the last dose (safety analysis set)

	18-55 years old						65-85 years old			
	BNT162b1			Placebo	BNT162b1	Placebo	BNT162b1			Placebo
	10 μg (N = 12)	20 μg (N = 12)	30 μg (N = 12)	(N = 9)	100 μg Dose 1[a)] (N = 12)	Dose 1[a)] (N = 3)	10 μg (N = 12)	20 μg (N = 12)	30 μg (N = 12)	(N = 9)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	6 (50.0)	5 (41.7)	6 (50.0)	2 (22.2)	6 (50.0)	1 (33.3)	6 (50.0)	7 (58.3)	3 (25.0)	4 (44.4)
Adverse reactions	3 (25.0)	4 (33.3)	6 (50.0)	1 (11.1)	6 (50.0)	1 (33.3)	3 (25.0)	4 (33.3)	2 (16.7)	1 (11.1)

N = number of subjects analyzed, n = number of subjects with events
a) Follow-up until 3 weeks after Dose 1

There was no death, serious adverse events, or adverse events leading to study discontinuation.

Abnormal laboratory values (i.e., Grade ≥3 abnormal changes) were observed in the following subjects receiving BNT162b1.

The population aged 18-55 years: 1 subject in the 10 μg group, 2 subjects in the 20 μg group, 1 subject in the 30 μg group, and 4 subjects in the 100 μg group.

The population aged 65-85 years: 1 subject in the 10 μg group and 1 subject in the 30 μg group.

All of the abnormal values were detected several days after vaccination and recovered to a level within the reference range a few days later.

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 Comirnaty has efficacy in preventing disease caused by SARS-CoV-2 infection (COVID-19) and acceptable safety in view of its benefits. Comirnaty is the first COVID-19 prevention vaccine applied for marketing approval in Japan. Making Comirnaty available for vaccination is clinically meaningful.

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)

February 8, 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	December 18, 2020

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).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the quality, efficacy, safety, etc., of the product presented in Review Report (1), and made additional comments on the following issues (see sections below).

PMDA discussed the following issues and took actions as necessary.

1.1 Efficacy and indication

At the Expert Discussion, the expert advisors supported PMDA's conclusions described in "Section 7.R.2 Efficacy" and in "Section 7.R.5 Indication" of Report (1), with the following comments.

- Healthcare professionals should be informed that no long-term efficacy data have been obtained from foreign Study C4591001, and that the VE results are short-term data after Dose 2. Long-term efficacy data should be collected. When duration of vaccine efficacy is established, the necessity of additional vaccination should be investigated.
- Foreign Study C4591001 demonstrated the efficacy of Comirnaty. The *in vitro* data available at the current moment do not deny the possibility that Comirnaty has the same efficacy also against SARS-CoV-2 variants. However, since further variants are expected to emerge, the occurrence and spread of variants

should be monitored and *in vitro* neutralizing test, etc., of variants should be conducted. New information obtained should be provided to healthcare professionals and, depending on the situation, necessary actions should be taken.

- No detailed information is available on the effect of Comirnaty in preventing severe COVID-19 from the clinical studies results. However, reduction in the number of COVID-19 patients by Comirnaty is expected to eventually lead to reduction in the number of severe cases and deaths.
- The effect of Comirnaty in preventing SARS-CoV-2 infection was not evaluated in the clinical studies. To prevent the spread of SARS-CoV-2, those who have received Comirnaty should continue basic infection control activities, such as avoiding “Three Cs" (1. Closed spaces. 2. Crowded places. 3. Close-contact settings), washing hands, and coughing manners. This should be communicated to healthcare professionals and vaccine recipients.
- Relationship between immunogenicity and prevention of COVID-19 should be further investigated in future.

PMDA communicated the expert advisors’ comments to the applicant.

The applicant’ response:
The applicant will take appropriate actions regarding the following: (i) Investigation of the postmarketing long-term efficacy and the effect against variants, and (ii) provision of information regarding infection control activities to healthcare professionals and vaccine recipients.

After the Expert Discussion, the applicant submitted the analysis results of the evaluable immunogenicity population, the primary analysis in Japanese Study C4591005 (Table 29). PMDA confirmed that the results were similar to those from the all-available immunogenicity population, which had already been submitted (results of the all-available immunogenicity population are copied from Report (1) 7.R.2.2, Table 21). Also, the results were similar to those from foreign Study C4591001 [Report (1) 7.R.2.2, Table 20]. These data were reported to the expert advisors. No additional comments were made by the expert advisors.

Table 29. Serum SARS-CoV-2 neutralizing antibody titer 1 month after Dose 2 of the study vaccine (antibody titer required for 50% neutralization) (Japanese study C4591005)

			N	GMT [2-sided 95% CI] (1 month after Dose 2)	GMFR [2-sided 95% CI] (1 month after Dose 2/before Dose 1)
Evaluable immunogenicity population	Comirnaty	All ages	116	524.5 [459.7, 598.4]	51.5 [45.2, 58.7]
		20-64 years	94	570.7 [497.6, 654.5]	55.8 [48.7, 63.9]
		65-85 years	22	365.6 [254.6, 525.0]	36.6 [25.5, 52.5]
	Placebo	All ages	40	10.6 [9.8, 11.4]	1.1 [1.0, 1.1]
All-available immunogenicity population	Comirnaty	All ages	119	489.9 [420.4, 570.9]	48.1 [41.3, 56.0]
		20-64 years	97	523.5 [442.0, 619.9]	51.2 [43.3, 60.6]
		65-85 years	22	365.6 [254.6, 525.0]	36.6 [25.5, 52.5]
	Placebo	All ages	41	10.6 [9.8, 11.4][a)]	1.1 [1.0, 1.1][a)]

N = number of subjects analyzed. When the antibody titer was less than LLOQ, 0.5 × LLOQ was used for analysis.
a) N = 40, excluding 1 subject who had not completed the “visit at 1 month after Dose 2” by the time when immunogenicity samples were shipped.

1.2 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusions described in "Section 7.R.3 Safety" of Report (1), with the following comments. The Risk of enhanced disease is described in "Section 1.4 Risk management plan (draft)."

- Most of the adverse events observed after vaccination with Comirnaty in Japanese and foreign clinical studies were mild or moderate, and do not outweigh the benefits of Comirnaty. However, some subjects had systemic events affecting the quality of daily living. Also, the incidence of adverse events was higher after Dose 2 than after Dose 1, and higher in younger subjects than in older subjects. These findings are important information both for healthcare professionals and recipients of Comirnaty. The safety information of Comirnaty, including these findings, should be disseminated. In addition, the following information regarding adverse reactions should be provided to healthcare professionals and vaccine recipients: detailed symptoms, peak onset time after vaccination, duration of symptoms, and actions to be taken when symptoms occur or persist (use of antipyretic or pain medication, symptoms requiring an examination by a physician, etc.).
- Serious allergic reactions such as anaphylaxis have been observed in foreign countries after authorization or marketing approval, warranting particular caution. Precautionary advice should be included in the package insert, and relevant information (peak onset time, initial symptoms etc.) should be provided to healthcare professionals and vaccine recipients. An effective system for vaccination should be established to check past history before vaccination, to monitor vaccine recipients for a certain period after vaccination, and to take appropriate actions when symptoms occur.
- Physicians may be unable to decide whether to administer Comirnaty to individuals with a past history of hypersensitivity. Physicians should be provided with detailed information that allows them to make such a decision.
- The safety database held by the applicant contained 81 cases of adverse events corresponding to anaphylactic reactions, reported after authorization or marketing approval in foreign countries. The 81 cases included 57 women, 27 individuals with a past history of allergy, hypersensitivity, anaphylactic reaction, etc., and 4 individuals with a past history of COVID-19. Risk factors of anaphylaxis, etc., should be analyzed based on data to be collected in future, and important findings obtained from the analysis should be provided to healthcare professionals in an appropriate manner.
- According to reports after authorization or marketing approval, some frail patients with underlying diseases died or experienced adverse events after vaccination with Comirnaty, although the causal relationship to the vaccination is unclear. Sufficient safety data in this patient group have not been accumulated at the current moment. They are considered to be at high risk of severe COVID-19, and have a high need for anti-SARS-CoV-2 vaccination. It is acceptable to administer Comirnaty (i) if the physician judges that the benefits of Comirnaty outweighs the risks and (ii) if the candidate vaccine recipient or his/her authorized representative consents to receive Comirnaty after understanding its efficacy, adverse reactions, etc. Safety data in this patient group should be collected continuously, published promptly, and updated as needed.

PMDA communicated the above comments of the expert advisors to the applicant.

The applicant's reply:
Appropriate actions will be taken for the collection of safety data after the market launch and for information provision to healthcare professionals, vaccine recipients, etc.

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions described in "Section 7.R.6 Dosage and administration" of Report (1), with the following comment.

- Information on how to handle individuals who did not receive Dose 2 at 3 weeks after Dose 1, should be disseminated.

PMDA's view:
As described in "Section 7.R.6 Dosage and administration" of Report (1), the protocol of foreign Study C4591001 defined that 2 doses should be administered 19 to 23 days apart. Some subjects received 2 doses up to 42 days apart, but the efficacy of 2 doses administered ≥24 days apart has not been fully established. The efficacy of Dose 1 alone has not been established either. Therefore, 2 doses of Comirnaty should be administered 3 weeks apart. In routine clinical practice, some recipients may not be able to receive 2 doses 3 weeks apart. Such recipients should be encouraged to receive Dose 2 as soon as possible.

PMDA communicated the above comment of the expert advisors and PMDA's view to the applicant.

The applicant's response:
Information regarding the period between Dose 1 and Dose 2 in the clinical studies and the necessity of Dose 2, will be communicated appropriately to healthcare professionals and to vaccine recipients.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion regarding the risk evaluation of enhanced disease after the market launch.

PMDA's conclusion:

Although evaluating the risk of enhanced disease is an important issue, there are limitations to fully evaluating the risk of enhanced disease in the conventional use-results surveys conducted in routine clinical practice, for the following reasons:

(i) There is no internationally established standard method for evaluating the risk of enhanced disease,[51)] and it is difficult to diagnose enhanced disease from clinical conditions alone of individual patients.

(ii) According to data from foreign Study C4591001, only a small number of subjects developed COVID-19 or severe COVID-19 after receiving Comirnaty, and data on COVID-19 occurring long after the vaccination are unavailable.

For a certain period after marketing, the applicant should analyze the occurrence of COVID-19 and severe COVID-19 over a long time period after the vaccination with Comirnaty, through follow-up data from foreign Study C4591001 and the use-results surveys conducted by the applicant. When new information on how to evaluate the risk of enhanced disease or on the risk of SARS-CoV-2 vaccine-associated enhanced disease become available, the applicant should further investigate how to evaluate the risk of Comirnaty-associated enhanced disease, based on the long-term data after vaccination with Comirnaty.

At the Expert Discussion, the expert advisors supported PMDA's conclusions described in "Section 7.R.7 Post-marketing investigations" of Report (1), with the following comment.

- After the market launch, Comirnaty will be used by a vast number of Japanese people; this will result in collection of massive amount of postmarketing safety data. Collection of the safety data of Comirnaty, evaluation of benefit-risk balance, and publication of the results should be done promptly in a highly transparent manner.

Based on the above comment of the Expert Advisors, PMDA instructed the applicant to collect postmarketing safety data, evaluate the benefit-risk balance, and publish the results without delay. The applicant agreed.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for Comirnaty should include the safety specifications presented in Table 30, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 31, 32, and 33.

[51)] Enhanced disease is defined in the Brighton Collaboration standardized case definition "Vaccine-associated Enhanced Disease: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data" (https://brightoncollaboration.us/vaed/ [as of February 3, 2021]), but specific definitions of cases are not described.

Table 30. Safety and efficacy specifications in the risk management plan (draft)

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

Table 31. 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 [Japanese phase I/II study]) • Use-results survey on post-approval early vaccine recipients (healthcare professionals) (follow-up study) • Specified use-results survey on vaccine recipients with underlying diseases who are at high risk of severe COVID-19 • Foreign clinical studies (Study C4591001 [foreign phase II/III study] and Study C4591015 [foreign phase II/III study in pregnant women])	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information for healthcare professionals (a proper use guide for Comirnaty) • Organize and disseminate information (a brochure) for vaccine recipients • Periodical publication of the occurrence of adverse reactions

Table 32. Outline of use-results survey on healthcare professionals (draft)

Objective	To evaluate the long-term safety up to 12 months after Dose 2 of Comirnaty (conducted as a follow-up study after the completion of the observation period [for approx.1 month after Dose 2] in the advance vaccine recipient health monitoring on healthcare professionals)
Population	Among those eligible for the "first vaccine recipient health monitoring in healthcare professionals," those who have consented to participate in the survey.
Observation period	From the day after the last day of the observation period (for 1 month after Dose 2) in the "first vaccine recipient health monitoring in healthcare professionals" until 12 months after Dose 2
Planned sample size	All who have consented to participate in the survey among those eligible for the "first vaccine recipient health monitoring in healthcare professionals"
Main survey item(s)	Characteristics of vaccine recipients (past history, comorbidity, history of allergy, pregnancy or lactation [women only]), status of vaccination with Comirnaty, use of other vaccines, concomitant drugs, serious adverse events, information on COVID-19 (test for SARS-CoV-2, presence/absence of symptoms [in those testing positive for SARS-CoV-2], date of diagnosis, and treatments given), etc.

Table 33. Outline of specified use-results survey on vaccine recipients at high risk of severe COVID-19 (draft)

Objective	To evaluate the safety in Comirnaty recipients at high risk of severe COVID-19
Survey method	Central registry system
Population	Comirnaty recipients at high risk of severe COVID-19
Observation period	From the day of Dose 1 until 28 days after Dose 2 (approx. 7 weeks)
Planned sample size	1,000 individuals
Main survey items	Characteristics of vaccine recipients (past history, comorbidity, history of allergy, pregnancy or lactation [women only]), status of vaccination with Comirnaty, use of other vaccines, concomitant drugs, adverse events, information on COVID-19 (test for SARS-CoV-2, presence/absence of symptoms [in those testing positive for SARS-CoV-2], date of diagnosis, treatments given), etc.

1.5 Quality

1.5.1 Process validation

The applicant explained that the results of the ongoing process validation of the vaccine product mentioned in Report (1), would be obtained in [redacted], 2021.

PMDA's view:

The analysis of ≥3 batches of the vaccine product, manufactured in the commercial scale and used under emergency use authorization, showed that all batches fulfilled all of the specifications. Under ordinary circumstances, however, process validation should be done on 3 consecutive batches manufactured by the final manufacturing process, to confirm whether Comirnaty is manufactured constantly with the same quality. Under the current epidemic of COVID-19 and the urgent societal need for Comirnaty, there is no choice but to perform such process validation at a later stage. Data form the ongoing process validation of the vaccine product should be submitted to PMDA as soon as they become available.

1.5.2 Number of doses that can be extracted from a single vial

During the review process, an additional study was conducted to check whether 6 doses could be extracted from a single vial, and the results were submitted.

Injection syringes (1 mL) with usual or smaller dead space (10 products that are already or will be marketed in Japan) and needles (6 products) were subjected to a test to check if six 0.3-mL doses could be extracted from a single vial diluted with 2.17 mL of physiological saline. Six doses could be extracted when specific combinations of a syringe and a needle was used.

PMDA confirmed the submitted study results, and instructed the applicant to appropriately inform healthcare professionals about the combinations of a syringe and a needle that can be used to extract 6 doses from a single vial.

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, CTD 5.3.5.1.2) 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 indication and dosage and administration, with approval conditions shown below. Since the

product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The vaccine product and its active substance are both classified as powerful drugs.

Indication

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

Dosage and Administration

The product is diluted with 1.8 mL of physiological saline (Japanese Pharmacopoeia grade), and 2 doses (0.3 mL each) are injected intramuscularly, usually 3 weeks apart.

Approval Conditions

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 1
   The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
   (2) 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.
   (3) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (4) Matters related to Item 4
   The applicant is required to report the quantity sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.

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

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

(5) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If new data, etc., submitted in accordance with approval conditions 1-(1), 2-(2), or 2-(3), necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

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

ALC-0159	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
ALC-0315	[(4-hydroxybutyl) azanediyl]bis (hexane-6,1-diyl)bis(2-hexyldecanoate)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BMI	Body mass index
BNT162b1	mRNA encoding RBD of S protein of SARS-CoV-2
BNT162b2	mRNA encoding the full-length of S protein of SARS-CoV-2
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 February 1, 1961)
CI	Confidence interval
Comirnaty	Comirnaty for intramuscular injection, LNP-encapsulated BNT162b2
COVID-19	Disease caused by SARS-CoV-2 infection (coronavirus disease)
CQA	Critical quality attribute
CTD	Common technical document
CTP	Cytidine triphosphate
ddPCR	Droplet digital polymerase chain reaction
DNA	Deoxyribonucleic acid
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
EMA	European Medicines Agency
ESI MS	ElectroSpray ionization-mass spectrometry
EU	European Union
FDA	Food and Drug Administration
GGT	γ-glutamyltransferase
GMC	Geometric mean concentration
GM-CSF	Granulocyte macrophage colony-stimulating factor
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GTP	Guanosine triphosphate
HEK293T cells	Human embryonic kidney 293 T cells
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IL-2/4/5/6/13/18	Interleukin 2/4/5/6/13/18
IP-RP-HPLC	Ion pair reversed phase-high performance liquid chromatography
IRR	Incidence rate ratio
LLOQ	lower limit of quantitation
LNP	Lipid nanoparticle
$^{m1}\Psi$TP	N^1-methylpseudouridine triphosphate
MCB	Master cell bank

MedDRA	Medical Dictionary for Regulatory Activities
Ministerial Ordinance for Enforcement for Pharmaceuticals and Medical Devices Act	Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance of the Ministry of Health and Welfare No. 1 of February 1, 1961)
mRNA	Messenger RNA
p/s	Photons per second
PaO_2/ FiO_2	Partial pressure of arterial oxygen/Fraction of inspiratory oxygen
PCR	Polymerase chain reaction
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)
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
QbD	Quality by design
qPCR	Quantitative polymerase chain reaction
RBD	Receptor binding domain
Report (1)/(2)	Report on Special Approval for Emergency (1)/(2)
RNA	Ribonucleic acid
RT-PCR	Reverse transcription PCR
S protein	Spike protein
S1	Amino terminal region of S protein containing RBD
S2	Carboxy terminal region of S protein containing the membrane-spanning region
SARS	Severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus
SMQ	Standardised MedDRA queries
SpO_2	Oxygen saturation of peripheral artery
Th1/2	T helper cell type 1/2
TNF-α	Tumor necrosis factor - alpha
Tozinameran	BNT162b2, Tozinameran
UTP	Uridine triphosphate
UV	Ultraviolet
VE	Vaccine efficacy
WCB	Working cell bank
WHO	World Health Organization