**Report on the Deliberation Results**

July 31, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Daichirona for Intramuscular Injection |
| **Non-proprietary Name** | Coronavirus (SARS-CoV-2) RNA Vaccine |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | January 13, 2023 |

**Results of Deliberation**

In its meeting held on July 31, 2023, the Second Committee on New Drugs concluded that the product may be approved 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 drug product and its drug substance are both classified as powerful drugs.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information on the product at the current moment, the applicant is required to (a) promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, (b) submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and (c) take necessary actions to ensure the proper use of the product.
3. The applicant is required to submit results of the ongoing Japanese clinical study of the product to PMDA as soon as they become available and take necessary actions to make the latest efficacy and safety data of the product easily accessible to healthcare professionals and vaccine recipients.
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 latest efficacy and safety data of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

**Review Report**

July 19, 2023
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** | Daichirona for Intramuscular Injection |
| **Non-proprietary Name** | Coronavirus (SARS-CoV-2) RNA Vaccine |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | January 13, 2023 |
| **Dosage Form/Strength** | Injection: Each vial contains 0.15 mg of ufrenmeran. |
| **Application Classification** | Prescription drug (1) Drug with a new active ingredient |
| **Items Warranting Special Mention** | Priority review in accordance with "Handling of regulatory reviews of drugs, medical devices, *in vitro* diagnostics, and regenerative medical products in association with the emergence of COVID-19" (Administrative Notice dated April 13, 2020, by the Pharmaceutical Evaluation Division and Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)<br>A prior assessment consultation was conducted on the product. |
| **Reviewing Office** | Office of Vaccines and Blood Products |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of disease caused by 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**

A single dose of 0.6 mL is injected intramuscularly as a booster dose.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information on the product at the current moment, the applicant is required to (a) promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, (b) submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and (c) take necessary actions to ensure the proper use of the product.
3. The applicant is required to submit results of the ongoing Japanese clinical study of the product to PMDA as soon as they become available and take necessary actions to make the latest efficacy and safety data of the product easily accessible to healthcare professionals and vaccine recipients.
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 latest efficacy and safety data of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

**Attachment**

# Review Report (1)

June 12, 2023

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** | Daichirona for Intramuscular Injection |
| **Non-proprietary Name** | Coronavirus (SARS-CoV-2) RNA Vaccine |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | January 13, 2023 |
| **Dosage Form/Strength** | Injection: Each vial contains 0.15 mg of ufrenmeran. |

**Proposed Indication**

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

**Proposed Dosage and Administration**

A single dose of 0.6 mL is injected intramuscularly as a booster dose.

**Table of Contents**



**List of Abbreviations**

See Appendix.

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

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a single-stranded positive-chain ribonucleic acid (RNA) virus belonging to the family *Coronaviridae* in the order *Nidovirales* and was identified as a new coronavirus infectious and pathogenic in human in 2019 (*Lancet.* 2020;395:565-74, *Nat Microbiol.* 2020;5:536-44. etc.).

The disease caused by SARS-CoV-2 infection (COVID-19) was designated as a Public Health Emergency of International Concern (PHEIC)[1)] by the World Health Organization (WHO) in January 2020, and as of June 4 2023, >750 million people have been infected with SARS-CoV-2 worldwide (COVID-19 Weekly Epidemiological Update).[2)] Against the global COVID-19 pandemic, a certain number of therapeutic drugs and preventive vaccines have been developed in addition to various infection control measures, leading to increased population immunity, and the death toll has shifted to a decreasing trend. Based on the trend, on May 5, 2023, the WHO stated that COVID-19 was no longer considered as a PHEIC.[3)] However, since SARS-CoV-2 is still prevalent with the emergence of variants with varied infectivity and transmissibility, measures against COVID-19 are still needed. In Japan, under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Law), COVID-19's category was reclassified from a class of the "Novel Influenza and other diseases" (equivalent to Class 2) to Class 5 on May 8, 2023, but the government decided to continue the official SARS-CoV-2 vaccination program for FY2023 ("Revisions of medical care delivery system and government support associated with the classification change of novel coronavirus infection under the Infectious Diseases Control Law [in Japanese]" dated March 10, 2023, decided by the Novel Coronavirus Response Headquarters). Omicron variant emerged at the end of 2021 and brought the world into a pandemic in 2022. It differs from Wuhan-Hu-1 strain (the original strain) in antigenicity and thus can evade the immunity induced by the vaccines administered in the vaccination program starting in 2021, resulting in decreased efficacy of the vaccines. To address repeated waves of SARS-CoV-2 infection and the decreased efficacy of vaccines, several booster vaccination programs have been implemented to reactivate the immune response. Furthermore, bivalent vaccines with increased immunogenicity against Omicron variant have been used for booster vaccination.

Vaccines approved for prevention of COVID-19 in Japan as of June 12, 2023 are Comirnaty Intramuscular Injection (Pfizer Japan Inc.), Vaxzevria Intramuscular Injection (AstraZeneca K.K.), Spikevax Intramuscular Injection (Moderna Japan Co., Ltd.), Nuvaxovid Intramuscular Injection (Takeda Pharmaceutical Company Limited), and Jcovden Intramuscular Injection (Janssen Pharmaceutical K.K). In September 2022, a booster vaccination program using Omicron-variant-adapted bivalent vaccines was started. Under the official vaccination programs with these vaccine products (except Jcovden Intramuscular Injection), approximately 80% of the Japanese

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

2) https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---8-june-2023 (last accessed on June 9, 2023)

3) https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic (last accessed on June 9, 2023)

population have completed the primary series of a vaccine against SARS-CoV-2 and approximately 70% have completed the first booster dose.[4)]

Although currently more than 2 years have passed since market launch of the vaccine products against SARS-CoV-2, most of the vaccine products supplied in Japan are imported, and the Omicron-variant-adapted vaccine products currently available for distribution are all imported. The COVID-19 global pandemic is still ongoing with continuous emergence of new variants. To ensure that vaccines adapted to new variants can be promptly developed and supplied in Japan, Japan should acquire the ability to develop and produce vaccines internally, as stated in the government's "Strategy for Strengthening the Vaccine Development and Production System" (adopted by the Cabinet on June 1, 2021).

Daichirona is a vaccine made of a messenger RNA (mRNA) encoding receptor-binding domain (RBD) of the spike protein (S protein) of SARS-CoV-2 (the original strain), which is encapsulated in lipid nanoparticles (LNPs). Daichirona has been developed as an mRNA vaccine to be manufactured in Japan, supported by the "Vaccine development project" of the Japan Agency for Medical Research and Development (AMED) and the "Urgent improvement project for vaccine manufacturing systems" of the Ministry of Health, Labour and Welfare (MHLW). A phase I/II/III study in Japanese adults demonstrated the efficacy and safety of Daichirona administered as a booster dose, and the applicant has submitted an application for marketing approval. As of June 2023, Daichirona is not approved outside Japan.

## 2. Quality and Outline of the Review Conducted by PMDA

### 2.1 Active substance

MAFB-7566a, the active substance of Daichirona, is mRNA encoding RBD of the S protein. It includes the 5' cap structure and poly A sequence, and all cytidine and uridine residues are replaced by 5-methylcytidine and 5-methyluridine residues, respectively.

#### 2.1.1 Generation and control of cell substrate

A cell bank of *Escherichia coli* (*E. coli*) is used to generate the template deoxyribonucleic acid (DNA) (MAFB-7563a), a raw material of Daichirona. A master cell bank (MCB) of *E. coli* was generated from *E. coli* (JM109 strain) transfected with a circular plasmid DNA containing genes encoding [redacted], signal peptide of the S protein, RBD, and poly A tail. A working cell bank (WCB) was then generated from the MCB after [redacted] subcultures.

MCB and WCB were subjected to characterization (absence of [redacted], [redacted], [redacted], DNA sequence, identification, [redacted], and [redacted]) and to purity tests.

4) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (released on June 6, 2023) (last accessed on June 9, 2023)

### 2.1.2 Manufacturing process

The manufacturing process of the active substance consists of *in vitro* transcription, [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

[redacted], [redacted], [redacted], and [redacted] were defined as critical steps.

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

### 2.1.3 Safety evaluation of adventitious agents

The manufacturing process of the active substance involves the use of the following raw materials of biological origin: [redacted] in [redacted] and casein peptone, which is added as [redacted] in the preparation of [redacted]. Casein peptone is manufactured from milk of healthy cattle through a process including autoclave at [redacted]°C for ≥[redacted] minutes to inactivate/remove potential pathogens, and has been confirmed to meet the Standards for Biological Ingredients.

### 2.1.4 Manufacturing process development

Table 1 shows major changes made to the manufacturing process of the active substance during development. The active substance used in non-clinical studies were manufactured by Process a, the active substance used in clinical studies were manufactured by Process b or c, and the active substance used in the commercial product is manufactured by Process d. In response to each change of the manufacturing process, the quality attributes of the pre-change and post-change active substances were assessed and demonstrated to be comparable.

**Table 1. Major changes in the manufacturing process of the active substance**

| Manufacturing process | Changes |
|---|---|
| From Process a to Process b | • Change of [redacted]<br>• [redacted]<br>• Change of [redacted] ([redacted] → [redacted]) |
| From Process b to Process c | • Change of [redacted]<br>• [redacted]<br>• Change of [redacted]<br>• Change of conditions of [redacted]<br>• Change of conditions of [redacted]<br>• Change of conditions of [redacted] and [redacted]<br>• Addition of [redacted] ([redacted])<br>• Change of conditions of [redacted] |
| From Process c to Process d | • Change of conditions of [redacted]<br>• Change of conditions of [redacted] |

### 2.1.5 Characterization

#### 2.1.5.1 Structure and characteristics

The active substance was subjected to characterization shown in Table 2.

**Table 2. Parameters and methods for characterization**

| Parameter | | Test method |
|---|---|---|
| Primary structure | RNA sequence | Sanger sequencing |
| | 5'-cap structure | Reverse-phase chromatography and mass spectrometry after RNase H treatment |
| | Poly A tail length | [redacted], [redacted] |
| Higher order structure | Tertiary structure | Circular dichroism spectroscopy |
| | [redacted] | [redacted] electrophoresis |
| Physicochemical property | Ultraviolet spectroscopy | Ultraviolet-visible spectrophotometry |
| Biological property | *In vitro* biological activity ([redacted]) | Cell-based assay ([redacted]) |

### 2.1.5.2 Product-related substances/product-related impurities

The product-related substance is [redacted] (Substance A).

The product-related impurities are [redacted] (Impurity A and Impurity B), unmodified 5'-cap, varied poly-A tail form, double-strand RNA, and altered transcripts. [redacted] (Impurity A and Impurity B), unmodified 5'-cap, varied poly-A tail form, and double-strand RNA are appropriately controlled by specifications for the active substance. The altered transcripts are controlled within a certain range by the consistent manufacturing process.

### 2.1.5.3 Process-related impurities

The process-related impurities are *E. coli*-derived impurities (host cell protein and DNA), enzymes ([redacted], [redacted], [redacted], and [redacted]), template DNA, nucleotides ([redacted], [redacted], [redacted] and [redacted]), and a capping reagent ([redacted]). The *E. coli*-derived impurities, enzymes, nucleotides, and capping reagent were shown to be adequately removed through the manufacturing process. The residual proteins (enzymes, etc.) are appropriately controlled by the specifications for the active substance, and host cell protein, DNA, and template DNA are appropriately controlled by the in-process control for the active substance.

### 2.1.6 Control of active substance

The proposed specifications for the active substance include a description (appearance), identification (1) (sequencing: polymerase chain reaction [PCR] and [redacted] electrophoresis), identification (2) (electrophoresis time: [redacted] electrophoresis), pH, purity (1) (mRNA purity: [redacted] electrophoresis), purity (2) (double-strand RNA: [redacted]), percent 5'-capped form (liquid chromatography), poly A tail length distribution ([redacted]), residual proteins (bicinchoninic acid method), bacterial endotoxins, microbial limit, and content (ultraviolet-visible spectrophotometry).

### 2.1.7 Stability of active substance

Table 3 shows a summary of the main stability studies for the active substance.

**Table 3. Summary of main stability studies for the active substance**

| | Manufacturing process for the active substance | Number of batches | Storage condition | Test period | Storage form |
|---|---|---|---|---|---|
| Long-term | Process c | 3 | −70°C ± 10°C | 9 months[a)] | [redacted] |
| | Process d | 3 | | 0 months[a)] | bag |

a) The stability testing is ongoing and continued for 24 months.

The active substance manufactured by Process c under the long-term storage condition showed no definite time-dependent changes in the parameters tested throughout the period tested. The active substance met the specifications. The mRNA purity was tested by the method for identification ([redacted]) in the specifications for the active substance until [redacted] months. After [redacted] months, it was [redacted]. A stability study is ongoing, which evaluates the active substance manufactured by Process d (commercial process) at a production scale for validation.

Based on the above, the applicant proposed a shelf life of 9 months for the active substance stored in a [redacted] bag at −80°C to −60°C.

## 2.2 Vaccine product

### 2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is an aqueous injection, and each vial (1.5 mL) contains 150 μg of the active substance (MAFB-7566a) for 2 doses (0.6 mL per dose). The vaccine product contains T168-1857a, cholesterol, 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), polyethylene glycol $(PEG)_{2000}$-DMG, sucrose, L-histidine, and water for injection as excipients. Of note, T168-1857a, cholesterol, DSPC, and $PEG_{2000}$-DMG are components of LNPs, which encapsulate the active substance.

### 2.2.2 Manufacturing process

The manufacturing process of the vaccine product consists of [redacted], [redacted], [redacted], liquid preparation (mixing), concentration adjustment, sterile filtration, filling, clamping, testing, and labeling/packaging/storage.

[redacted] and [redacted] are defined as critical steps.

The manufacturing process of the vaccine product was subjected to process validation at a commercial scale.

### 2.2.3 Manufacturing process development

Table 4 shows major changes made to the manufacturing process of the vaccine product during development. The vaccine product used in non-clinical studies were manufactured by Process A, the vaccine product used in clinical studies were manufactured by Process B or C, and the commercial vaccine product is manufactured by Process C. In response to each change of the manufacturing process, the quality attributes of the pre-change and post-change vaccine products were assessed and demonstrated to be comparable.

**Table 4. Major changes in the manufacturing process of the vaccine product**

| Manufacturing process | Changes |
|---|---|
| From Process A to Process B | • Change of [redacted]<br>• Change of [redacted]<br>• Changes of [redacted] and [redacted] ([redacted] → [redacted]) |
| From Process B to Process C | • Change of [redacted]<br>• [redacted]<br>• Change of [redacted] ([redacted] → [redacted])<br>• Addition of [redacted] ([redacted] → [redacted] and [redacted]) |

### 2.2.4 Control of vaccine product

The proposed specifications for the vaccine product include description (appearance), identification (1) (electrophoresis time check: [redacted] electrophoresis), identification (2) ([redacted]: [redacted]), ratio of osmolality, pH, purity (mRNA purity: [redacted] electrophoresis), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, lipid content (liquid chromatography), percent encapsulation ([redacted]), particle size (dynamic light scattering), strength ([redacted]), and titer ([redacted]).

### 2.2.5 Stability of vaccine product

Table 5 shows a summary of the main stability studies for the vaccine product.

**Table 5. Summary of main stability studies for the vaccine product**

| | Manufacturing process of active substance | Manufacturing process of vaccine product | Number of batches | Storage condition | Test period | Storage form |
|---|---|---|---|---|---|---|
| Long-term | Process c | Process C | 3 | 5°C ± 3°C | 6 months[a)] | Glass vial |
| | Process d | Process C | 3 | | 0 months[a)] | |

a) The stability testing is ongoing and continued for 12 months.

The vaccine product manufactured by Process C using the Process c-derived active substance under the long-term storage condition showed an increase in Impurity A for mRNA purity during the period tested. No definite time-dependent changes were observed for the other parameters tested, and the vaccine product met the specifications. A stability study is ongoing, which evaluates the vaccine product manufactured by Process C using the Process d-derived active substance at a production scale for validation.

Based on the above, the applicant proposed a shelf life of 6 months for the vaccine product stored in a glass vial at 2°C to 8°C.

## 2.R Outline of the review conducted by PMDA

At present, based on the submitted data, PMDA has concluded that there are no critical quality problems that may affect evaluation of non-clinical or clinical study results of Daichirona. PMDA has instructed the applicant to submit (a) a rationale for the acceptance criteria for purity (mRNA purity) of the vaccine product and (b) results of the ongoing long-term testing of the active substance and vaccine product. The review results are described in the Review Report (2).

### 2.R.1 Novel excipients

The vaccine product contains the excipient T168-1857a, which has never been used before, and the excipients DSPC and $PEG_{2000}$-DMG, which are permitted for use in accordance with the “Handling of

excipients that are permitted only for specific drug products or under specific conditions" (Administrative Notice dated June 23, 2009). However, DSPC and $PEG_{2000}$-DMG in the vaccine product have different specifications from those for the permitted ones. PMDA has concluded that the use of the excipients T168-1857a, DSPC, and $PEG_{2000}$-DMG in vaccines for preventing infections is acceptable but their use as excipients should not serve as a precedent for other products to be developed in the future.

### 2.R.1.1 Specifications and stability

Based on the submitted data, PMDA has concluded that the specifications and stability for T168-1857a, DSPC, and $PEG_{2000}$-DMG have no particular problems.

### 2.R.1.2 Safety

Based on the submitted data, PMDA has concluded that safety problems related to the excipients are unlikely to occur when Daichirona is used at the clinical dosage.

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

The applicant submitted the data on primary pharmacodynamics of Daichirona in the form of results from studies in mice, rats, and cynomolgus monkeys. The dose of Daichirona represents an amount of RNA.

### 3.1 Primary pharmacodynamics

Table 6 shows a summary of the studies submitted (evaluation data).

**Table 6. Summary of primary pharmacodynamics studies**

| Animal species<br>Sex | Number of animals | Dosage regimen<br>(intramuscular route for all doses) | Main endpoints | Attached document CTD |
|---|---|---|---|---|
| BALB/c mice<br>Female | 10/group | • 2 doses of Daichirona (0.03, 0.3, or 3 μg) or placebo[a)] or adjuvanted RBD protein[b)] 3 weeks apart | Immunogenicity[c)] | 4.2.1.1-1<br>4.2.1.1-2<br>4.2.1.1-3 |
| SD rat/<br>Wistar rat<br>Female | SD rat:<br>4 for negative control<br>6/group for Daichirona<br>Wistar rat:<br>2/group | • 2 doses of Daichirona (5 or 15 μg) or placebo[a)] 2 weeks apart | Immunogenicity[d)] | 4.2.1.1-4 |
| Cynomolgus monkey<br>Male and female | 2/sex/group | • 2 doses of Daichirona 100 μg or placebo[a)] 3 weeks apart<br>• Intranasal and intratracheal inoculation of the original strain[g)] at $10^6$ $TCID_{50}$/animal 3 weeks after the second dose | Protection from infection[e),f)] | 4.2.1.1-5 |

a) Placebo: Formulation buffer (10 mM histidine, 300 mM sucrose, pH 7.0)
b) Adjuvanted RBD protein: RBD protein 1.0 μg/body adjuvanted with alum 100 μg/body
c) Day of sampling: 2 weeks after the second dose
d) Days of sampling: 2, 4, 6, and 9 weeks after the first dose in SD rats; 2, 4, and 7 weeks after the first dose in Wistar rats
e) Days of sampling (swab): 2, 4, 6, and 8 days after exposure to virus
f) Days of sampling (organ): 8 and 9 days after exposure to virus
g) SARS-CoV-2 USA_WA1/2020

### 3.1.1 Immunogenicity of Daichirona (CTD 4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-3, and 4.2.1.1-4)

BALB/c mice (n = 10 females/group) received 2 doses of Daichirona (0.03, 0.3, or 3 μg), placebo, or adjuvanted RBD protein 3 weeks apart. Serum neutralizing antibody titer anti-RBD immunoglobulin

G (IgG) titer against SARS-CoV-2 USA_WA1/2020 (the original strain) were determined. In addition, RBD-specific cytokine production and T-cell response were evaluated using mouse spleen cells.

Daichirona induced production of neutralizing antibodies in a dose-dependent manner, and the neutralizing antibody titer was positively correlated with anti-RBD IgG titer.

The RBD IgG2a/IgG1 titer ratio was higher in the Daichirona groups than in the adjuvanted RBD protein group. Daichirona 0.3 and 3 μg led to significantly high interferon-gamma (IFN-γ)/interleukin (IL)-5 ratio and IFN-γ/IL-13 ratio, showing helper T cell (Th1)-dominant T-cell response.

SD rats (n = 6 females/group for Daichirona, n = 4 females/group for placebo) and Wister rats (n = 2 females/group) received 2 doses of Daichirona (5 or 15 μg) or placebo 2 weeks apart, and serum anti-RBD IgG titer was determined.

In both animal species, the anti-RDB IgG titer reached a plateau 4 weeks after the first dose of Daichirona and then gradually decreased until the last sampling point (9 weeks after the first dose in SD rats and 7 weeks after that in Wister rats).

### 3.1.2 Infection-preventing response of Daichirona (CTD 4.2.1.1-5)

Cynomolgus monkeys (n = 2/sex/group) received 2 doses of Daichirona (100 μg) or placebo 21 days apart, and immune response and infection-preventing response after exposure to SARS-CoV-2 were evaluated. SARS-CoV-2 USA_WA1/2020 (the original strain) at $10^6$ $TCID_{50}$ was intratracheally or intranasally administered 3 weeks after the second dose. Viral RNA amounts in a nasopharyngeal swab and bronchoalveolar lavage fluid were determined 2, 4, 6, and 8 days after viral exposure. Lung tissues were collected 8 or 9 days after viral exposure, and histopathological examination was performed based on the area of inflammatory lesions.

The viral RNA amounts in nasopharyngeal swabs in the Daichirona group were lower than those in the placebo group, but the viral RNA amount in a bronchoalveolar lavage fluid specimen differed from animal to animal. The histopathological analysis revealed that inflammation in the lung tissue specimens was slight to mild in severity in both groups.

## 3.2 Safety pharmacology

No independent safety pharmacology study of Daichirona was conducted. The applicant explained safety pharmacology of Daichirona based on results from a repeated-dose toxicity study in cynomolgus monkeys. In the study, blood pressure, electrocardiogram, heart rate, respiratory rate, and blood gas components were measured, and the animals were evaluated for the functional observational battery. The applicant stated that these results showed no Daichirona-associated effects on physiological functions of the cardiovascular, respiratory, and central nervous systems (CTD 4.2.3.2-2).

## 3.R Outline of the review conducted by PMDA

### 3.R.1 Mechanism of action of Daichirona

The applicant's explanation about the mechanism of action of Daichirona:
After intramuscular injection of Daichirona in mice, RBD protein was produced in the administration site, regional lymph node, and blood and thereby induced RBD-specific neutralizing antibodies and Th1-dominant RBD-specific cellular immune response (CTD 4.2.1.1-1, CTD 4.2.1.1-2, and CTD 4.2.1.1-3). Daichirona prevented SARS-CoV-2 infection through the upper respiratory tract in cynomolgus monkeys (CTD 4.2.1.1-5).

After Daichirona is injected, the active substance of mRNA encoding RBD of the S protein derived from SARS-CoV-2 is incorporated into host cells and then translated into the RBD protein (which is the target of neutralizing antibodies), thereby inducing humoral immunity and cellular immunity. Daichirona is considered to contribute to prevention of COVID-19 in this manner.

PMDA accepted the applicant's explanation.

### 3.R.2 Risk of Daichirona-associated enhanced disease

The applicant's explanation about a risk of Daichirona-associated enhanced disease:
Although whether the approved COVID-19 vaccines have a risk of enhanced disease remains unclear, a vaccine against SARS-CoV-1 enhances disease in an animal model, suggesting relation to Th2-dominant immune response (*PLoS ONE.* 2012;7:e35421). The risk of COVID-19 vaccine-associated enhanced disease after SARS-CoV-2 infection can be reduced by inducing Th1-dominant immune response (*Vaccine.* 2020;38:4783-91).

In a non-clinical pharmacology study of Daichirona in mice, evaluation of blood RBD IgG2a titer/RBD IgG1 titer, expression of Th1 cytokines, and Th1 cytokine/Th2 cytokine ratio indicated that Daichirona induced Th1-dominant immune response (CTD 4.2.1.1-1, CTD 4.2.1.1-2 and CTD 4.2.1.1-3). Histopathological examination of lung tissues from cynomolgus monkeys that were given Daichirona and then exposed to SARS-CoV-2 showed no worsening of inflammatory findings compared with those given placebo.

Based on the above non-clinical study results, Daichirona is unlikely to induce enhanced disease.

Based on the results of non-clinical pharmacology studies conducted, PMDA considers the risk of Daichirona-associated enhanced disease is low. However, PMDA assesses the risk in humans by reviewing clinical study results as well [see Section 7.R.3].

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

The applicant submitted results from studies in SD rats and cynomolgus monkeys, which evaluated the pharmacokinetics (PK) of MAFB-7566a (mRNA in Daichirona) and T168-1857a and $PEG_{2000}$-DMG (lipid components of LNPs).

Plasma MAFB-7566a concentrations in rats and monkeys were determined by quantitative PCR (lower limit of quantification, 0.001 ng/mL). Plasma T168-1857a and $PEG_{2000}$-DMG concentrations in rats and monkeys were determined by liquid chromatography-tandem mass spectrometry (lower limit of quantification, 10 and 5 ng/mL, respectively). Tissue MAFB-7566a concentrations in rats were determined by quantitative PCR (lower limit of quantification, 0.0317 ng/mL; lower limit of quantification per unit tissue weight, 1.62 ng/g tissue for the femoral bone marrow, 1.34-5.98 ng/g tissue for the thyroid, and 0.983 ng/g tissue for the other tissues).

Unless otherwise specified, PK parameters are expressed as the mean.

## 4.1 Absorption

### 4.1.1 Four-week intermittent intramuscular dose study in rats and monkeys (CTD 4.2.3.2-1, 4.2.3.2-2)

Rats (n = 8/sex/group) intramuscularly received 3 doses of Daichirona at 5, 15, or 50 µg RNA/body every 2 weeks, and monkeys (n = 3/sex/group) intramuscularly received 3 doses of Daichirona at 10, 30, or 100 µg RNA/body every 2 weeks. Plasma concentrations of MAFB-7566a, T168-1857a, and $PEG_{2000}$-DMG were determined. Table 7 shows PK parameters. $C_{max}$ and AUC of MAFB-7566a, T168-1857a, and $PEG_{2000}$-DMG mostly increased with increasing dose but decreased with increasing number of doses. Some of $C_{max}$ and AUC in the low dose groups in rats and monkeys were higher in males than in females, but generally there was no trend of a remarkable difference between males and females.

**Table 7. PK parameters in rats and monkeys**

| PK parameters | Day | Rat | | | | | | Monkey | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5 µg/body | | 15 µg/body | | 50 µg/body | | 10 µg/body | | 30 µg/body | | 100 µg/body | |
| | | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| MAFB-7566a | | | | | | | | | | | | | |
| $C_{max}$ | 1 | 5.87 | 5.74 | 27.5 | 28.5 | 77.0 | 107 | 8.55 | 0.674 | 7.11 | 11.8 | 59.8 | 40.1 |
| (ng/mL) | 29 | 2.13 | 0.032 | 6.92 | 2.24 | 50.3 | 41.0 | 0.006 | 0.000 | 0.002 | 0.005 | 0.078 | 0.010 |
| AUC | 1 | 60.8 | 26.3 | 112 | 179 | 362 | 1070 | 109 | 9.38 | 85.7 | 173 | 810 | 628 |
| (ng·h/mL) | 29 | 1.22 | 0.149 | 7.79 | 1.94 | 25.7 | 140 | 0.076 | 0.000 | 0.018 | 0.090 | 0.992 | 0.145 |
| $T_{max}$ | 1 | 0.3 | 1.0 | 1.0 | 1.0 | 0.3 | 1.0 | 3.0 | 2.8 | 8.7 | 5.0 | 6.8 | 5.8 |
| (h) | 29 | 0.3 | 1.0 | 0.3 | 0.3 | 0.3 | 1.0 | 15.5 | NC | 7.0 | 15.5 | 12.6 | 13.8 |
| T168-1857a | | | | | | | | | | | | | |
| $C_{max}$ | 1 | 32.2 | 37.4 | 356 | 179 | 592 | 676 | 79.8 | 4.2 | 94.6 | 181 | 621 | 662 |
| (ng/mL) | 29 | 10.5 | 0.0 | 54.8 | 24.1 | 354 | 248 | 0.0 | 0.0 | 9.0 | 12.6 | 49.7 | 26.3 |
| AUC | 1 | 417 | 206 | 1340 | 1730 | 3350 | 9920 | 1150 | 48.3 | 1630 | 2810 | 9400 | 9590 |
| (ng·h/mL) | 29 | 5.3 | 0.0 | 66.9 | 62.8 | 375 | 1250 | 0.0 | 0.0 | 134 | 145 | 860 | 387 |
| $T_{max}$ | 1 | 0.3 | 1.0 | 1.0 | 1.0 | 1.0 | 7.0 | 5.0 | 7.0 | 8.7 | 7.0 | 4.6 | 7.0 |
| (h) | 29 | 0.3 | NC | 0.3 | 0.3 | 0.3 | 1.0 | NC | NC | 7.0 | 7.0 | 13.8 | 13.8 |
| $PEG_{2000}$-DMG | | | | | | | | | | | | | |
| $C_{max}$ | 1 | 0.0 | 0.0 | 12.2 | 7.1 | 45.7 | 31.4 | 6.8 | 0.0 | 14.5 | 13.3 | 50.7 | 32.9 |
| (ng/mL) | 29 | 0.0 | 0.0 | 5.1 | 2.0 | 34.8 | 12.6 | 4.9 | 3.4 | 17.5 | 16.1 | 47.9 | 33.8 |
| AUC | 1 | 0.0 | 0.0 | 46.1 | 26.9 | 114 | 89.6 | 22.8 | 0.0 | 153 | 161 | 555 | 447 |
| (ng·h/mL) | 29 | 0.0 | 0.0 | 2.5 | 1.0 | 22.5 | 45.5 | 63.5 | 39.1 | 227 | 192 | 646 | 417 |
| $T_{max}$ | 1 | NC | NC | 1.0 | 1.0 | 0.3 | 0.3 | 1.0 | NC | 1.0 | 3.0 | 2.2 | 7.0 |
| (h) | 29 | NC | NC | 0.3 | 0.3 | 0.3 | 1.0 | 1.0 | 7.0 | 7.0 | 7.0 | 5.8 | 7.0 |

AUC: 24 hours
NC: Not calculated

## 4.2 Distribution

### 4.2.1 Biodistribution study in rats (CTD 4.2.2.3-1)

A single dose of Daichirona 40 µg RNA/body was administered intramuscularly (thigh) to rats (n = 3/sex/time point), and MAFB-7566a concentrations in plasma and the following tissues were

determined at 6 time points between 1 and 336 hours post-dose: muscle (administration site), popliteal lymph node, axillary lymph node, spleen, liver, lung, kidney, pancreas, brain, heart, femoral bone marrow, thymus, thyroid, stomach, duodenum, jejunum, ileum, testis, and ovary. To investigate accumulation in tissues after repeated doses, 2 doses of Daichirona 40 μg RNA/body were intramuscularly administered to 3 male rats 2 weeks apart, and MAFB-7566a concentrations in plasma and the tissues were determined at 1 hour after the second dose.

MAFB-7566a concentration in the muscle at the administration site peaked (66,700 ng/g tissue) at 1 hour after the single intramuscular dose and then decreased to below the lower limit of quantitation by 336 hours post-dose. MAFB-7566a concentrations in the popliteal lymph node, axillary lymph node, and spleen peaked (10,600, 3,720, and 2,020 ng/g tissue, respectively) at 7, 24, and 24 hours post-dose, respectively. They then decreased to 1,200, 417, and 302 ng/g tissue, respectively, at 336 hours post-dose. MAFB-7566a concentrations in the other tissues and plasma were lower than those in the above tissues and decreased to below the lower limit of quantitation by 24 to 72 hours post-dose.

The MAFB-7566a concentration ratios at 1 hour (second dose/first dose) were 92.4, 17.4, 5.48, 2.56, and 2.38, respectively, in the axillary lymph node, thyroid, brain, popliteal lymph node, and spleen. In the other organs and tissues, the MAFB-7566a concentrations at 1 hour after the second dose were similar to or lower than the values after the first dose.

### 4.3 Metabolism

No study for metabolism of Daichirona was conducted.

### 4.4 Excretion

No study for excretion of Daichirona was conducted.

## 4.R Outline of the review conducted by PMDA

### 4.R.1 Non-clinical pharmacokinetics of Daichirona

The applicant's explanation about non-clinical pharmacokinetics of Daichirona:

Since mRNA is large in molecular mass and negatively charged, its cell membrane permeability and tissue distribution are considered limited (*Nat Rev Drug Discov.* 2014;13:759-80, *Pharmaceutics.* 2020;12:102). In addition, mRNA in a living body is rapidly degraded by ribonuclease with a half-life of <30 minutes to 1 hour or several hours at longest (*DNA Res.* 2009;16:45-58). In view of these attributes of mRNA, Daichirona is designed to improve tissue distribution and stability required for immunity induction by encapsulating mRNA in LNPs. Intramuscularly injected Daichirona is incorporated into immune cells mainly in the lymphatic system or muscles, and thereby enters the regional lymph nodes. Daichirona is then distributed in the spleen, etc. via distal lymph nodes and circulation blood, and incorporated into immune cells in spleen tissue, etc. The mRNA concentration in the thyroid is <1% of those in the muscle at the injection site and in popliteal lymph nodes, and no toxicological findings related to the thyroid were obtained in non-clinical studies. Therefore, there is no concern about accumulation of Daichirona. The concentration in the brain was below the lower limit of quantification in 2 of 3 animals tested, and no accumulation was observed [see Section 4.2.1].

Cholesterol and DSPC contained in LNPs of Daichirona are naturally occurring lipids found in mammalian cell membranes and considered to be metabolized and excreted, as with endogenous lipids.

A pharmacokinetics study was conducted to investigate the distribution, metabolism, and excretion of T168-1857a contained in LNPs of Daichirona. In the study, rats received a single intramuscular dose of LNP-mRNA. (The LNP, prepared using radiolabeled T168-1857a, encapsulated mRNA different from that in Daichirona.) The radioactivity concentrations in the muscle, lymph nodes, lymph fluid, spleen, and liver were relatively high, and those in the other tissues were comparable to or lower than that in blood. Of the radioactive administered, 22.9% were excreted into urine, expired air, and feces until 168 hours post-dose, and the rest mainly remained in the muscle at the administration site and lymph nodes. In the muscle, not only T168-1857a but also its ester-hydrolyzed metabolites were observed (see CTD 4.2.2.3-2 and 4.2.2.4-1).

The distribution, metabolism, and excretion of $PEG_{2000}$-DMG contained in LNPs of Daichirona were not investigated. However, an *in vitro* study and an *in vivo* study (intravenously administered to rats or monkeys) of $PEG_{2000}$-C-DMG, a structural analog, showed that $PEG_{2000}$-C-DMG was distributed mostly in the liver and spleen, scarcely metabolized, and excreted mainly into feces via bile (Review Report of Onpattro for Intravenous Infusion 2 mg/mL dated May 16, 2019).

Distribution of Daichirona in the placenta was not investigated, but according to a clinical research of approved mRNA vaccines (Comirnaty Intramuscular Injection [Comirnaty] and Spikevax Intramuscular Injection [Spikevax]), mRNA was not detected in maternal blood, cord blood, or the placenta in pregnant women (*Nat Commun.* 2022;13:4422). A reproductive and developmental toxicity study of Daichirona in rats demonstrated that the clinical dose had an adequate safety margin. If Daichirona crossed the placenta, its effect is considered negligible. Transfer of Daichirona into milk was not investigated, but according to a clinical research of approved mRNA vaccines, mRNA was detected in milk at low concentrations (1.3-11.7 pg/mL) (*JAMA Pediatr*. 2022;e223581). On the other hand, no anti-SARS-CoV-2 IgG antibodies were detected in blood of breast-fed infants (*Front Immunol.* 2021;12:777103). Daichirona is not considered to be distributed into milk to an extent enough to induce immunogenicity in the infants.

PMDA considers it possible to understand pharmacokinetic attributes of Daichirona to a certain extent from the submitted non-clinical pharmacokinetics study results.

## 5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data on toxicity of Daichirona in the form of results from repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and local tolerance studies of Daichirona.

### 5.1 Single-dose toxicity

No single-dose toxicity study of Daichirona was conducted, but toxicity of a single dose of Daichirona (acute toxicity) was evaluated from the results obtained after the first dose in repeated intramuscular

dose toxicity studies in rats and cynomolgus monkeys (CTD 4.2.3.2-1 and 4.2.3.2-2). No deaths occurred after administration of Daichirona. Rats showed a transient increase in body temperature (1.42°C in males and 0.35°C in females).

## 5.2 Repeated-dose toxicity

Repeated intramuscular dose toxicity studies of Daichirona were conducted in rats and cynomolgus monkeys (Table 8). Main findings were inflammatory changes at the administration site.

**Table 8. Repeated-dose toxicity studies of Daichirona**

| Test system | Route of administration | Treatment period | Dose (μg RNA[d]/body) | Main findings | NOAEL (μg RNA/body) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male and female SD rats | Intramuscular | 4 weeks (3 doses[a),b)]) + 4-week withdrawal | 0,[c)] 5, 15, or 50 | ≥5: Myofiber degeneration/necrosis at the administration site, inflammatory cell infiltration and edema, and increases in white blood cells, neutrophils, eosinophils, fibrinogen, and Cxcl10<br>≥15: Bleeding at the administration site, APTT prolonged<br>50: Decreased platelets<br>These findings were reversible. | 50 | 4.2.3.2-1 |
| Male and female cynomolgus monkeys | | 4 weeks (3 doses[a),c)]) + 4-week withdrawal | 0,[e)] 10, 30, or 100 | ≥10: Inflammatory cell infiltration and edema at the administration site, and increases in fibrinogen and C-reactive protein<br>≥30: Increased IL-6<br>100: Myofiber degeneration/necrosis at the administration site, and increased neutrophils<br>These findings were reversible. | 100 | 4.2.3.2-2 |

a) Administered in the thigh (1 or 2 sites) on Days 1, 15, and 29
b) In a pharmacology study of Daichirona in SD rats (CTD 4.2.1.1-4), production of IgG against the RBD protein was observed from Week 2 to Week 9 after the first intramuscular dose.
c) In a pharmacology study of Daichirona in cynomolgus monkeys (CTD 4.2.1.1-5), neutralizing antibodies against SARS-CoV-2 were observed on Day 42 after the first intramuscular dose.
d) Daichirona: 0.212 mg RNA/mL
e) Vehicle: 10 mM histidine, 300 mM sucrose, pH 7.0

## 5.3 Genotoxicity

*In vitro* and *in vivo* genotoxicity studies of Daichirona were conducted (Table 9), and Daichirona was considered negative for genotoxicity.

**Table 9. Genotoxicity**

| Type of study | | Test system | S9 (treatment) | Dose | Study results | Attached document CTD |
|---|---|---|---|---|---|---|
| *In vitro* | Bacterial reverse mutation assay | *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA* | -/+ (48 hours) | 0,[a)] 0,[b)] 0.291, 0.582, 1.16, 2.33, 4.66, 9.31, 18.6, 37.3, 74.5, 149 μg RNA/plate | Negative | 4.2.3.3.1-1 |
| | *In vitro* mammalian cell micronucleus assay | Human Lymphoblasts (TK6) | -/+ (3 hours)<br>- (24 hours) | 0,[c)] 0.663, 1.33, 2.65, 5.30, 10.6, 15.9, 21.2 μg RNA/mL | Negative | 4.2.3.3.1-2 |
| *In vivo* | Rodent micronucleus assay | Male SD rat Bone marrow | | 0,[c)] 12.5, 25, 50 μg RNA/body (single intramuscular dose) | Negative | 4.2.3.3.2-1 |

a) PBS
b) Untreated
c) Vehicle: 10 mM histidine, 300 mM sucrose, pH 7.0

## 5.4 Carcinogenicity

Since Daichirona is not used continuously for ≥6 months in clinical settings, no carcinogenicity studies of Daichirona have been conducted.

## 5.5 Reproductive and developmental toxicity

A reproductive and developmental toxicity study of Daichirona was conducted in rats (Table 10). Daichirona was not considered to raise safety concerns for parent animals or offspring.

**Table 10. Reproductive and developmental toxicity**

| Type of study | Test system | Route of administration | Treatment period | Dose (μg RNA[c]/body) | Main findings | NOAEL (μg RNA/body) | Attached document CTD |
|---|---|---|---|---|---|---|---|
| Embryo-fetal development and pre- and post-natal development, including maternal function | Female SD rats | Intramuscular | 20 days before mating to 1 day after delivery (3 or 4 doses[a),b)]) | 0,[d)] 5, 15, or 50 | Maternal animals: None<br>Embryos/fetuses: None<br>F1 offspring: None | 50 | 4.2.3.5.2-1 |

a) Administered in the thigh (1 or 2 sites) 20 and 6 days before mating, Gestation Day 6, and 1 day after delivery
b) In a pharmacology study of Daichirona in SD rats (CTD 4.2.1.1-4), production of IgG against the RBD protein was observed from Week 2 to Week 9 after the first intramuscular dose.
c) Daichirona: 0.212 mg RNA/mL
d) Vehicle: 10 mM histidine, 300 mM sucrose, pH 7.0

## 5.6 Local tolerance

A local irritation study of intramuscular doses of Daichirona was conducted in rabbits (Table 11). Daichirona was well tolerated in the administration site.

**Table 11. Local tolerance**

| Test system | Administration site | Test method | Main findings | Attached document CTD |
|---|---|---|---|---|
| Male JW rabbits | Intramuscular[a)] | 3 doses[c)] of Daichirona (100 μg RNA/body)[b)] or formulation buffer were administered at the same site. The administration site was then examined histopathologically. | Bleeding at the administration site, edema, cell infiltration, fibrogenesis, mineral deposition, etc.<br>These findings were reversible.[d)] | 4.2.3.6-1 |

a) Daichirona 0.48 mL/site was administered to one site of the vastus lateralis muscle (left leg, Daichirona; right leg, vehicle)
b) Vehicle: 10 mM histidine, 300 mM sucrose, pH 7.0
c) Administered on Days 1, 15, and 29
d) 2-week withdrawal

## 5.7 Genotoxicity of novel excipients

The novel excipients contained in Daichirona (T168-1857a and $PEG_{2000}$-DMG) were subjected to *in vitro* genotoxicity studies (Table 12) and are considered negative for genotoxicity.

**Table 12. Genotoxicity**

| Test article | Type of study | | Test system | S9 (treatment) | Dose | Study results | Attached document CTD |
|---|---|---|---|---|---|---|---|
| T168-1857a | *In vitro* | Bacterial reverse mutation assay | *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA* | -/+ (48 hours) | 0,[a] 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250,[b] 2500,[b] 5000[b] µg/plate | Negative | 4.2.3.7.7-1 |
| | | *In vitro* mammalian cell micronucleus assay | Human Lymphoblasts (TK6) | -/+ (3 hours)<br>- (24 hours) | 0,[a] 31.3, 62.5, 125, 250, 500 µg/mL | Negative | 4.2.3.7.7-2 |
| $PEG_{2000}$-DMG | | Bacterial reverse mutation assay | *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA* | -/+ (48 hours) | 0,[a] 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500,[b] 5000[b] µg/plate | Negative | 4.2.3.7.7-3 |
| | | *In vitro* mammalian cell micronucleus assay | Human Lymphoblasts (TK6) | -/+ (3 hours)<br>- (24 hours) | 0,[a] 7.81, 15.6, 31.3, 62.5, 125, 250 µg/mL | Negative | 4.2.3.7.7-4 |

a) Vehicle: DMSO
b) Test article precipitated

### 5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that Daichirona has no particular toxicological problems.

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

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

For evaluation of PK of Daichirona, plasma MAFB-7566a concentrations were determined by quantitative PCR. The concentrations of cationic lipid and PEG lipid, component lipids of LNPs, were determined by liquid chromatography-tandem mass spectrometry. Anti-drug antibodies (ADAs) against PEG lipid were measured by ligand-binding assay.

For evaluation of immunogenicity of Daichirona, blood anti-SARS-CoV-2 neutralizing antibody titers were determined by a cytopathic effect assay. Blood anti-RBD IgG titers, IgG subclass (IgG1-IgG4) titers, and cytokine concentrations were determined by enzyme-linked immunosorbent assay (ELISA).

### 6.2 Clinical pharmacology

The applicant submitted clinical pharmacology evaluation data in the form of results from Japanese phase I/II study (Study DS5670-A-J101 [Study J101]) and Japanese phase II study (Study DS5670-116 [Study 116]). Unless otherwise specified, PK parameters are expressed as the mean (± standard deviation [SD]).

### 6.2.1 Japanese phase I/II study (CTD 5.3.5.1-1, Study J101, ongoing since March 2021, data cut-off on [redacted], 20[redacted])

In this study, 2 doses of Daichirona 10, 30, 60, or 100 μg or placebo was administered intramuscularly, 28 days apart, to 80 Japanese healthy adults aged ≥20 years and <65 years (16 per group) and 62 Japanese healthy elderly aged ≥65 years and <75 years (9-15 per group). Of them, 64 healthy adults and 47 healthy elderly, excluding the placebo group, underwent blood sampling. The plasma MAFB-7566a, cationic lipid, and PEG lipid concentrations were determined at 7 to 9 time points between baseline (before the first dose) and Day 28 after the first dose, and at 7 to 9 time points between baseline (before the second dose) and Day 28 after the second dose. PK parameters were then calculated.

The MAFB-7566a concentrations in healthy adults peaked (0.001 ± 0.002 ng/mL in the 10 μg group, 0.005 ± 0.007 ng/mL in the 30 μg group, 0.015 ± 0.021 ng/mL in the 60 μg group, 0.050 ± 0.042 ng/mL in the 100 μg group) at approximately 2 to 4 hours (median in each dose group) after the first dose. In healthy elderly, the MAFB-7566a concentrations peaked (0.003 ± 0.003 ng/mL in the 10 μg group, 0.011 ± 0.020 ng/mL in the 30 μg group, 0.019 ± 0.011 ng/mL in the 60 μg group, 0.077 ± 0.167 ng/mL in the 100 μg group) at approximately 1 to 2 hours (median in each dose group) after the first dose. In both healthy adults and healthy elderly, the MAFB-7566a concentrations fell below the detection limit before the second dose, and the mean $C_{max}$ and $AUC_{last}$ after the second dose were similar to or lower than those after the first dose.

The cationic lipid concentrations in the 10 μg and 30 μg groups were below the detection limit at all the time points in both healthy adults and healthy elderly. The concentrations were near the detection limit (≤6.33 ng/mL) in some subjects receiving 60 μg at 1 to 24 hours post-dose and in some subjects receiving 100 μg at 2 to 72 hours post-dose, but they were below the detection limit at the other time points.

The PEG lipid concentrations were below the detection limit at most of the time points.

### 6.2.2 Japanese phase II study (CTD 5.3.5.2-1, Study 116, ongoing since November 2021, data cut-off in [redacted] 20[redacted])

A total of 80 Japanese healthy adults aged ≥20 years and <65 years (40 per group) were enrolled and intramuscularly received 2 doses of Daichirona 30 or 60 μg 28 days apart (1 subject in the 60 μg group discontinued the study after the first dose). Of the enrolled subjects, 20 (10 per group) underwent blood sampling. The plasma MAFB-7566a, cationic lipid, and PEG lipid concentrations were determined at 7 time points between baseline (before the first dose) and Day 7 after the first dose, and at 7 time points between baseline (before the second dose) and Day 7 after the second dose. PK parameters were then calculated.

The MAFB-7566a concentrations peaked (0.03 ± 0.02 ng/mL in the 30 μg group, 0.08 ± 0.10 ng/mL in the 60 μg group) at approximately 14 to 23 hours (median in each dose group) after the first dose and fell below the detection limit before the second dose. The mean $C_{max}$ and $AUC_{last}$ after the second dose were lower than those after the first dose.

In the 30 μg group, the cationic lipid concentrations were below the detection limit at most of the time points after the first and second doses. In the 60 μg group, the concentrations were at or near the detection limit (≤11 ng/mL) at 1 to 72 hours post-dose but below the detection limit at 168 hours.

The PEG lipid concentrations were below the detection limit at all time points.

### 6.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that clinical pharmacology evaluation of Daichirona has no particular problems.

### 6.R.1 ADA

The applicant's explanation about ADAs against PEG lipid:

In the ADA analysis set (80 healthy adults [16 per group] and 62 healthy elderly [9-15 per group] in Study J101, 80 subjects [40 per group] in Study 116), the incidence[5)] of ADAs against PEG lipid contained in Daichirona was evaluated. In Study J101, ADA incidences in healthy adults were 68.8% (11 of 16 subjects) in the Daichirona 10 μg group, 87.5% (14 of 16 subjects) in the 30 μg group, 81.3% (13 of 16 subjects) in the 60 μg group, 75.0% (12 of 16 subjects) in the 100 μg group, and 0% (0 of 16 subjects) in the placebo group, and ADA incidences in healthy elderly were 64.3% (9 of 14 subjects) in the Daichirona 10 μg group, 64.3% (9 of 14 subjects) in the 30 μg group, 70.0% (7 of 10 subjects) in the 60 μg group, 88.9% (8 of 9 subjects) in the 100 μg group, and 0% (0 of 15 subjects) in the placebo group. In Study 116, ADA incidences were 82.5% (33 of 40 subjects) in the 30 μg group and 90.0% (36 of 40 subjects) in the 60 μg group.

Subgroup analyses by the ADA development status were performed to evaluate the effects of ADAs on the PK, serum SARS-CoV-2 neutralization activity, and safety of Daichirona.

In Study J101, comparisons of the mean $C_{max}$ and $AUC_{last}$ of MAFB-7566a after the first dose between subjects with and without ADAs showed no consistent trends. However, the mean $C_{max}$ and $AUC_{last}$ of MAFB-7566a after the second dose tended to be lower in subjects with ADAs than in those without ADAs in multiple dose groups of Study J101. Cationic lipid was not detected in many groups, precluding the comparison of its mean $C_{max}$ and $AUC_{last}$, but data for comparison were available from healthy adults receiving 100 μg; in this population, the mean $C_{max}$ and $AUC_{last}$ of cationic lipid after the second dose tended to be lower in subjects with ADAs than in those without ADAs. In Study 116, evaluation was limited because of the small number of subjects without ADAs, but the mean $C_{max}$ and $AUC_{last}$ of MAFB-7566a and cationic lipid did not remarkably differ between subjects with and without ADAs.

Blood anti-SARS-CoV-2 neutralization activity tended to be higher in subjects with ADAs than in subjects without ADAs in both Studies J101 and 116.

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5) Development of ADAs was defined as the following 3 cases where:
- ADAs were negative at baseline but became positive after the dose.
- ADAs were positive at baseline, and the ADA titer increased 4-fold from baseline after the dose.
- ADA titer at baseline was missing, and ADAs were found positive after the dose.

The incidence of adverse events did not definitely differ according to the ADA development status in either Study J101 or 116, except unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out in Study 116. In Study 116, the incidence of unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out was as follows:

- Subjects with ADAs: 33.3% (11 of 33 subjects) in the Daichirona 30 μg group and 47.2% (17 of 36 subjects) in the 60 μg group
- Subjects without ADAs: 0% (0 of 7 subjects) in the 30 μg group and 0% (0 of 4 subjects) in the 60 μg group.

The following are unsolicited adverse events for which a causal relationship to the study vaccine in subjects with ADAs in Study 116:

Body temperature increased in 14 subjects, injection site erythema in 12 subjects, injection site pruritus in 9 subjects, injection site swelling in 7 subjects, injection site induration in 6 subjects, injection site pain in 3 subjects, and injection in 3 subjects

Most of the events were mild or moderate and all resolved. Severe events were injection site erythema in 2 subjects and pyrexia in 1 subject, all of which occurred 10 to 13 days after the first dose of Daichirona and persisted for 24 to 27 days (injection site erythema) and 3 days (pyrexia).

The causal relationship between ADA development and blood anti-SARS-CoV-2 neutralization activity remains unknown, but ADA development is not considered to negatively affect the efficacy. In Study 116, the incidence of unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out was higher in subjects with ADAs than in subjects without ADAs, but the difference may be accidental in view of the following findings:

(a) The number of subjects without ADAs in Study 116 was small.
(b) The events that occurred in subjects with ADAs were adverse events generally reported after vaccination, and were mostly mild or moderate and transient.
(c) In Study J101, the incidence of unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out did not definitely differ between subjects with and without ADAs.

In conclusion, ADAs are highly likely to develop after Daichirona vaccination and may lead to decreased plasma MAFB-7566a and cationic lipid concentrations after the second dose, but the clinical effects on the efficacy and safety are considered to be limited.

PMDA considers that the information available up to the current moment does not suggest any clinically relevant concerns associated with ADA development. However, if a new finding about the effect of ADAs on vaccination becomes available, the necessity of safety measures, etc. should be considered, for the following reasons:

(a) Unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out tended to occur more frequently in subjects with ADAs than in subjects without ADAs, although this evaluation has limitations owing to the small sample size.

(b) In recipients of the other mRNA vaccines containing PEG lipid as with Daichirona, the effects of ADAs against PEG lipid on the efficacy and safety remain unclear (*Vaccine.* 2022;40:6114-24, *ACS Nano.* 2022;16:11769-80, etc.).

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

The applicant submitted efficacy and safety evaluation data in the form of results from 1 study and reference data in the form of results from 2 studies (see Table 13).

**Table 13. List of clinical studies for efficacy and safety**

| Data category | Region | Study | Phase | Population | No. of subjects enrolled | Dosage regimen | Objective |
|---|---|---|---|---|---|---|---|
| Evaluation | Japan | Study 146 | I/II/III | Healthy adults aged ≥18 years who completed the primary series of a SARS-CoV-2 vaccine (Comirnaty or Spikevax) ≥6 months before | Part 1: 485<br>Part 2: 4,518 | Part 1:<br>*Dose-titration part*<br>A single intramuscular dose of Daichirona (10, 30, or 60 μg) or placebo<br><br>*Parallel-group part*<br>A single intramuscular dose of Daichirona (10, 30, or 60 μg), Comirnaty (30 μg of tozinameran), or Spikevax (50 μg of elasomeran)<br><br>Part 2:<br>A single intramuscular dose of Daichirona (60 μg), Comirnaty (30 μg of tozinameran), or Spikevax (50 μg of elasomeran) | Efficacy (immunogenicity)<br>Safety |
| Reference | Japan | Study J101 | I/II | Healthy adults aged ≥20 and <75 years without previous SARS-CoV-2 vaccination | Healthy adult cohort: 80<br><br>Healthy elderly cohort: 62 | 2 intramuscular doses of Daichirona[a] (10, 30, 60, or 100 μg) or placebo 4 weeks apart | Safety<br>PK |
| | Japan | Study 116 | II | Healthy adults aged ≥20 and <65 years without previous SARS-CoV-2 vaccination | Part 1: 6<br>Part 2: 74 | 2 intramuscular doses of Daichirona (30 or 60 μg) 4 weeks apart | Safety<br>PK |

a) The vaccine product used in Study J101 was different in titer from that used in Study DS5670-146 (Study 146) and Study 116.

No summary of results from Study J101, submitted as the reference data, is presented here, because the vaccine product used in Study J101 had a lower titer than those used in Study DS5670-146 (Study 146) and Study 116.

### 7.1 Japanese phase I/II/III study (CTD 5.3.5.1-2; Study 146; Study period, Part 1 ongoing since January 2022 [data cut-off on [redacted], 20[redacted]], Part 2 ongoing since May 2022 [data cut-off on [redacted], 20[redacted]])

#### 7.1.1 Part 1

A randomized, observer-blind,[6)] placebo-controlled (dose-titration part) and active-comparator parallel-group (parallel-group part) study was conducted to evaluate the safety, tolerability, and immunogenicity of a booster dose of Daichirona in healthy adults aged ≥18 years who had completed the primary series comprised of 2 doses of Comirnaty or Spikevax ≥6 months before with no history

6) Subjects, investigators, sub-investigators, clinical research coordinators, nurses, monitors, sponsor, and persons who perform antibody titer assay were blinded.

of SARS-CoV-2 infection, at 18 study centers in Japan. Target sample size of Part 1 was 48 subjects in the dose-titration part (36 in the Daichirona group, 12 in the placebo group) and 480 subjects in the parallel-group part (360 in the Daichirona group, 120 in the active-comparator group).

In the dose-titration part, Daichirona 10, 30, or 60 μg or placebo (physiological saline) was intramuscularly administered. In the parallel-group part, Daichirona 10, 30, or 60 μg or the active comparator (Comirnaty or Spikevax)[7] was intramuscularly administered.

Part 1 was comprised of the primary Comirnaty cohort and primary Spikevax cohort according to the vaccine product used in the primary series. Each primary cohort was further comprised of the healthy adult cohort (≥18 years and <65 years) and healthy elderly cohort (≥65 years). In the dose-titration part, 12 subjects were included in each cohort and then randomly assigned to receive Daichirona or placebo in a ratio of 3:1 in each of the Daichirona 10, 30, and 60 μg dose groups. In the parallel-group part, 120 subjects were included in each cohort and then randomly assigned to receive Daichirona 10, 30, or 60 μg or the active comparator (Comirnaty or Spikevax) in a ratio of 1:1:1:1.

In the dose-titration part, all of the 48 randomized subjects received the study vaccine and were included in the safety analysis set and full analysis set (FAS). In the parallel-group part, all of the 437 randomized subjects received the study vaccine and were included in the safety analysis set[8] and FAS. The breakdown of the 437 subjects is as follows:

The primary Comirnaty cohort: 120 each in the healthy adult cohort and healthy elderly cohort

The primary Spikevax cohort: 120 in the healthy adult cohort and 77 in the healthy elderly cohort (19 in the Daichirona 10 μg group, 19 in the Daichirona 30 μg group, 19 in the Spikevax group, and 20 in the Daichirona 60 μg group)

In both parts, the primary efficacy (immunogenicity) analysis set was the FAS, and the immunogenicity analysis was performed using data only from subjects without SARS-CoV-2 infection[9] at the time of sampling for immunogenicity assay.

The median interval (range) between the second dose of the primary series and the booster dose in FAS was as follows:

The dose-titration part: 6.456 (6.08-8.94) months in the Daichirona group and 6.456 (5.85-14.26) months in the placebo group in the healthy adult cohort and 7.047 (6.31-7.62) months in the Daichirona group and 7.129 (6.34-7.89) months in the placebo group in the healthy elderly cohort

The parallel-group part: 6.686 (6.05-14.92) months in the Daichirona group, 6.719 (6.05-14.72) months in the Comirnaty group, and 6.604 (6.11-11.79) months in the Spikevax group in the healthy adult cohort and 7.294 (6.24-11.89) months in the Daichirona group, 7.146 (6.31-14.88) months in the Comirnaty group, and 7.294 (6.60-11.86) months in the Spikevax group in the healthy elderly cohort

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7) The active comparator was Comirnaty in the primary Comirnaty cohort or Spikevax in the primary Spikevax cohort.

8) One subject in the Daichirona 30 μg group in the healthy adult cohort in the primary Spikevax cohort wrongly received Spikevax and thus was included in the Spikevax group in the safety analysis set.

9) Subjects who met both (a) and (b) simultaneously at the sampling time point for immunogenicity assay were included in the analysis
(a) Tested negative for anti-SARS-CoV-2 antibody until the sampling time point for immunogenicity assay; and
(b) Had not experience COVID-19 until the sampling time point for immunogenicity assay.

Tables 14 and 15 show results of immunogenicity including geometric mean fold rise (GMFR)[10] in blood anti-SARS-CoV-2 (the original strain) neutralizing antibody titer on Day 28 after study vaccination, the primary efficacy endpoint. Since the dose-titration part was mainly intended to evaluate the safety, only results in the parallel-group part are shown here.

**Table 14. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody in healthy adults (FAS) (parallel-group part)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 10 μg N = 30 | Daichirona 30 μg N = 30 | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 10 μg N = 30 | Daichirona 30 μg N = 30 | Daichirona 60 μg N = 30 | Spikevax N = 30 |
| Baseline | | | | | | | | |
| n | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| GMT [two-sided 95% CI][a)] | 24.953 [17.695, 35.190] | 28.006 [19.621, 39.975] | 23.286 [16.541, 32.781] | 28.655 [17.642, 46.543] | 43.938 [32.935, 58.617] | 46.017 [36.120, 58.625] | 31.060 [22.834, 42.250] | 38.699 [23.776, 62.988] |
| Day 28 after study vaccination | | | | | | | | |
| n | 29 | 30 | 27 | 29 | 29 | 27 | 30 | 29 |
| GMT [two-sided 95% CI][a)] | 858.711 [504.963, 1460.273] | 798.388 [527.058, 1209.399] | 922.935 [628.184, 1355.988] | 922.546 [711.056, 1196.939] | 668.116 [489.935, 911.097] | 1049.343 [799.091, 1377.968] | 836.092 [582.880, 1199.302] | 592.848 [460.224, 763.690] |
| GMFR [two-sided 95% CI][a)] | 34.784 [22.228, 54.434] | 28.508 [19.545, 41.580] | 41.877 [29.063, 60.340] | 37.832 [26.566, 53.876] | 15.438 [10.095, 23.607] | 23.819 [18.319, 30.969] | 26.918 [20.024, 36.186] | 16.984 [11.639, 24.784] |
| Antibody response rate[b)] | | | | | | | | |
| n | 29 | 30 | 27 | 29 | 29 | 27 | 30 | 29 |
| No. of subjects with antibody response | 28 | 30 | 26 | 29 | 27 | 27 | 30 | 28 |
| Antibody response rate (%) [two-sided 95% CI][c)] | 96.6 [82.2, 99.9] | 100 [88.4, 100.0] | 96.3 [81.0, 99.9] | 100 [88.1, 100.0] | 93.1 [77.2, 99.2] | 100 [87.2, 100.0] | 100 [88.4, 100.0] | 96.6 [82.2, 99.9] |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity

a) The two-sided 95% confidence interval (CI) was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.

b) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer

c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

[10] Ratio of the post-dose neutralizing antibody titer to the baseline neutralizing antibody titer

**Table 15. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer in healthy elderly (FAS) (parallel-group part)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 10 μg N = 30 | Daichirona 30 μg N = 30 | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 10 μg N = 19 | Daichirona 30 μg N = 19 | Daichirona 60 μg N = 20 | Spikevax N = 19 |
| Baseline | | | | | | | | |
| n | 30 | 30 | 30 | 30 | 19 | 19 | 20 | 19 |
| GMT [two-sided 95% CI][a)] | 14.844 [11.773, 18.716] | 22.227 [16.169, 30.554] | 16.094 [12.655, 20.466] | 17.049 [13.645, 21.302] | 30.552 [22.293, 41.872] | 26.876 [19.704, 36.657] | 28.660 [19.301, 42.558] | 27.877 [18.781, 41.380] |
| Day 28 after study vaccination | | | | | | | | |
| n | 29 | 30 | 29 | 29 | 19 | 18 | 20 | 19 |
| GMT [two-sided 95% CI][a)] | 303.601 [196.608, 468.820] | 719.412 [445.157, 1162.632] | 789.773 [569.710, 1094.841] | 621.874 [457.955, 844.466] | 575.968 [376.567, 880.958] | 832.856 [517.947, 1339.227] | 1296.868 [781.768, 2151.362] | 814.476 [499.247, 1328.745] |
| GMFR [two-sided 95% CI][a)] | 21.048 [13.606, 32.560] | 32.366 [21.011, 49.860] | 48.009 [37.795, 60.983] | 36.047 [28.831, 45.068] | 18.852 [13.294, 26.732] | 32.633 [20.608, 51.676] | 45.250 [31.426, 65.154] | 29.216 [20.043, 42.589] |
| Antibody response rate[b)] | | | | | | | | |
| n | 29 | 30 | 29 | 29 | 19 | 18 | 20 | 19 |
| No. of subjects with antibody response | 28 | 29 | 29 | 29 | 18 | 18 | 20 | 19 |
| Antibody response rate (%) [two-sided 95% CI][c)] | 96.6 [82.2, 99.9] | 96.7 [82.8, 99.9] | 100 [88.1, 100.0] | 100 [88.1, 100.0] | 94.7 [74.0, 99.9] | 100 [81.5, 100.0] | 100 [83.2, 100.0] | 100 [82.4, 100.0] |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity
a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.
b) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

Safety observation periods are shown below. Severity of an adverse event was graded according to the scale defined based on the Food and Drug Administration (FDA) guidance: Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007.

- Solicited adverse events were collected for 7 days after study vaccination[11)]
  - Adverse events at the injection site (redness, swelling, induration, pain, warmth, and pruritus)
  - Systemic adverse events (pyrexia, malaise, headache, rash [systemic/local], and myalgia)
- Unsolicited adverse events were collected for 28 days after study vaccination[11)]
- Serious adverse events were collected between the time of informed consent and Week 52 after study vaccination[12)]

**(a) Dose-titration part**

In the dose-titration part, incidences of solicited adverse events at the injection site were as follows:

<u>The healthy adult cohort:</u>

- The primary Comirnaty cohort: 100% (3 of 3 subjects) in each of the Daichirona 10, 30, and 60 μg groups and 0% (0 of 3 subjects) in the placebo group
- The primary Spikevax cohort: 100% (3 of 3 subjects) in each of the Daichirona 10 and 60 μg groups, 66.7% (2 of 3 subjects) in the 30 μg group, and 0% (0 of 3 subjects) in the placebo group

11) Subjects recoded in an electronic diary (a) the status of solicited adverse events (yes/no and, if yes, the description of the event) for 7 days after study vaccination and (b) the description of unsolicited adverse events, if occurred, for 28 days after study vaccination. The investigator or sub-investigator identified and assessed adverse events by checking entries in the electronic diaries and interview sheets of the subjects.

12) The investigator or sub-investigator identified and assessed serious adverse events by checking the electronic diaries (only for 28 days after study vaccination) and interviewing the subjects.

The healthy elderly cohort:

- The primary Comirnaty cohort: 0% (0 of 3 subjects) in the Daichirona 10 μg group, 100% (3 of 3 subjects) in each of the 30 μg and 60 μg groups, and 0% (0 of 3 subjects) in the placebo group
- The primary Spikevax cohort: 100% (3 of 3 subjects) in each of the Daichirona 10, 30, and 60 μg groups and 0% (0 of 3 subjects) in the placebo group

Incidences of solicited systemic adverse events were as follows:

The healthy adult cohort:

- The primary Comirnaty cohort: 33.3% (1 of 3 subjects) in each of the Daichirona 10, 30, and 60 μg groups and 0% (0 of 3 subjects) in the placebo group
- The primary Spikevax cohort: 66.7% (2 of 3 subjects) in the Daichirona 10 μg group, 33.3% (1 of 3 subjects) in each of the 30 μg and 60 μg groups, and 0% (0 of 3 subjects) in the placebo group

The healthy elderly cohort:

- The primary Comirnaty cohort: 0% (0 of 3 subjects) in each of the Daichirona 10, 30, and 60 μg groups, and the placebo group
- The primary Spikevax cohort: 33.3% (1 of 3 subjects) in each of the Daichirona 10 and 30 μg groups, 66.7% (2 of 3 subjects) in the 60 μg group, and 0% (0 of 3 subjects) in the placebo group

Incidences of unsolicited adverse events were as follows:

The healthy adult cohort:

- The primary Comirnaty cohort: 33.3% (1 of 3 subjects) in the Daichirona 10 μg group, 0% (0 of 3 subjects) in each of the 30 and 60 μg groups, and 66.7% (2 of 3 subjects) in the placebo group
- The primary Spikevax cohort: 33.3% (1 of 3 subjects) in each of the Daichirona 10 and 60 μg groups, 66.7% (2 of 3 subjects) in the 30 μg group, and 0% (0 of 3 subjects) in the placebo group

Of these, the events occurring in 33.3% (1 of 3) of subjects in the placebo group in the primary Comirnaty cohort and in all the subjects in the primary Spikevax cohort were assessed as adverse reactions (i.e., adverse events for which a causal relationship to the study vaccine could not be ruled out).

The healthy elderly cohort:

- The primary Comirnaty cohort: 0% (0 of 3 subjects) in each of the Daichirona 10 and 60 μg groups and 33.3% (1 of 3 subjects) in each of the 30 μg group and placebo group
- The primary Spikevax cohort: 33.3% (1 of 3 subjects) in each of the Daichirona 10 and 60 μg groups, 66.7% (2 of 3 subjects) in the 30 μg group, and 0% (0 of 3 subjects) in the placebo group

Of these, the events occurring in all the subjects in the primary Spikevax cohort were assessed as adverse reactions.

In the dose-titration part, no serious adverse events occurred.

**(b) Parallel-group part**

Tables 16 and 17 show solicited adverse events reported within 7 days after study vaccination in the parallel-group part.

**Table 16. Solicited adverse events in healthy adults (safety analysis set)**

| MedDRA PT | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 10 µg N = 30 | Daichirona 30 µg N = 30 | Daichirona 60 µg N = 30 | Comirnaty N = 30 | Daichirona 10 µg N=30 | Daichirona 30 µg N = 29 | Daichirona 60 µg N = 30 | Spikevax N = 31 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | 25 (83.3) | 24 (80.0) | 29 (96.7) | 28 (93.3) | 22 (73.3) | 27 (93.1) | 29 (96.7) | 29 (93.5) |
| Erythema | 0 | 1 (3.3) | 3 (10.0) | 2 (6.7) | 0 | 1 (3.4) | 4 (13.3) | 7 (22.6) |
| Swelling | 1 (3.3) | 1 (3.3) | 2 (6.7) | 2 (6.7) | 1 (3.3) | 6 (20.7) | 6 (20.0) | 6 (19.4) |
| Induration | 2 (6.7) | 1 (3.3) | 2 (6.7) | 5 (16.7) | 2 (6.7) | 6 (20.7) | 3 (10.0) | 5 (16.1) |
| Pain | 23 (76.7) | 24 (80.0) | 29 (96.7) | 28 (93.3) | 21 (70.0) | 26 (89.7) | 28 (93.3) | 28 (90.3) |
| Warmth | 4 (13.3) | 5 (16.7) | 7 (23.3) | 8 (26.7) | 5 (16.7) | 12 (41.4) | 14 (46.7) | 13 (41.9) |
| Pruritus | 0 | 4 (13.3) | 5 (16.7) | 2 (6.7) | 4 (13.3) | 2 (6.9) | 10 (33.3) | 11 (35.5) |
| Systemic adverse events | 7 (23.3) | 13 (43.3) | 20 (66.7) | 23 (76.7) | 14 (46.7) | 13 (44.8) | 23 (76.7) | 24 (77.4) |
| Pyrexia | 2 (6.7) | 3 (10.0) | 15 (50.0) | 11 (36.7) | 2 (6.7) | 5 (17.2) | 9 (30.0) | 11 (35.5) |
| Malaise | 4 (13.3) | 9 (30.0) | 17 (56.7) | 18 (60.0) | 9 (30.0) | 8 (27.6) | 16 (53.3) | 17 (54.8) |
| Headache | 5 (16.7) | 6 (20.0) | 14 (46.7) | 9 (30.0) | 9 (30.0) | 7 (24.1) | 13 (43.3) | 14 (45.2) |
| Rash | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (3.2) |
| Myalgia | 1 (3.3) | 2 (6.7) | 5 (16.7) | 13 (43.3) | 4 (13.3) | 3 (10.3) | 4 (13.3) | 9 (29.0) |

N = Number of subjects analyzed, n = Number of subjects with events, Medical Dictionary for Regulatory Activities (MedDRA)/J Ver. 24.1

The following severe solicited adverse events occurred in the healthy adult cohort:

- Adverse events at the injection site in 2 subjects in the Daichirona 30 µg group, 3 subjects in the 60 µg group, and 2 subjects in the Spikevax group.
- Systemic adverse events in 2 subjects (malaise and malaise/headache in 1 subject each) in the 60 µg group and 1 subject (malaise) in the Spikevax group.

**Table 17. Solicited adverse events in healthy elderly (safety analysis set)**

| MedDRA PT | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 10 μg N = 30 | Daichirona 30 μg N = 30 | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 10 μg N = 19 | Daichirona 30 μg N = 19 | Daichirona 60 μg N = 20 | Spikevax N = 19 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | 14 (46.7) | 22 (73.3) | 26 (86.7) | 26 (86.7) | 14 (73.7) | 15 (78.9) | 20 (100) | 17 (89.5) |
| Erythema | 0 | 1 (3.3) | 2 (6.7) | 2 (6.7) | 1 (5.3) | 0 | 3 (15.0) | 5 (26.3) |
| Swelling | 1 (3.3) | 1 (3.3) | 0 | 2 (6.7) | 1 (5.3) | 0 | 5 (25.0) | 6 (31.6) |
| Induration | 1 (3.3) | 1 (3.3) | 2 (6.7) | 3 (10.0) | 1 (5.3) | 1 (5.3) | 3 (15.0) | 4 (21.1) |
| Pain | 13 (43.3) | 20 (66.7) | 24 (80.0) | 24 (80.0) | 13 (68.4) | 15 (78.9) | 19 (95.0) | 15 (78.9) |
| Warmth | 2 (6.7) | 3 (10.0) | 8 (26.7) | 8 (26.7) | 3 (15.8) | 4 (21.1) | 8 (40.0) | 6 (31.6) |
| Pruritus | 2 (6.7) | 2 (6.7) | 3 (10.0) | 3 (10.0) | 0 | 1 (5.3) | 3 (15.0) | 3 (15.8) |
| Systemic adverse events | 5 (16.7) | 7 (23.3) | 11 (36.7) | 9 (30.0) | 2 (10.5) | 4 (21.1) | 12 (60.0) | 8 (42.1) |
| Pyrexia | 1 (3.3) | 0 | 5 (16.7) | 3 (10.0) | 0 | 0 | 3 (15.0) | 4 (21.1) |
| Malaise | 0 | 5 (16.7) | 6 (20.0) | 4 (13.3) | 1 (5.3) | 2 (10.5) | 9 (45.0) | 6 (31.6) |
| Headache | 5 (16.7) | 1 (3.3) | 6 (20.0) | 1 (3.3) | 0 | 1 (5.3) | 3 (15.0) | 4 (21.1) |
| Rash | 0 | 0 | 0 | 0 | 0 | 1 (5.3) | 0 | 0 |
| Myalgia | 0 | 3 (10.0) | 1 (3.3) | 4 (13.3) | 1 (5.3) | 3 (15.8) | 4 (20.0) | 3 (15.8) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 24.1

The following severe solicited adverse events occurred in the healthy elderly cohort:

- Adverse events at the injection site in 2 subjects in the Daichirona 60 μg group.
- Systemic adverse events in 0 subjects.

Tables 18 and 19 show unsolicited adverse events and adverse reactions reported by ≥2 subjects in any group in the parallel-group part.

**Table 18. Unsolicited adverse events and adverse reactions in healthy adults (safety analysis set)**

| MedDRA PT | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 10 μg N = 30 | Daichirona 30 μg N = 30 | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 10 μg N = 30 | Daichirona 30 μg N = 29 | Daichirona 60 μg N = 30 | Spikevax N = 31 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events | 5 (16.7) | 5 (16.7) | 7 (23.3) | 8 (26.7) | 8 (26.7) | 8 (27.6) | 8 (26.7) | 7 (22.6) |
| Injection site erythema | 0 | 2 (6.7) | 1 (3.3) | 2 (6.7) | 3 (10.0) | 5 (17.2) | 6 (20.0) | 3 (9.7) |
| Injection site swelling | 1 (3.3) | 1 (3.3) | 3 (10.0) | 3 (10.0) | 0 | 3 (10.3) | 3 (10.0) | 2 (6.5) |
| Injection site induration | 0 | 0 | 0 | 0 | 1 (3.3) | 3 (10.3) | 3 (10.0) | 0 |
| Axillary pain | 1 (3.3) | 0 | 0 | 4 (13.3) | 0 | 0 | 0 | 0 |
| Injection site pruritus | 0 | 2 (6.7) | 0 | 0 | 0 | 1 (3.4) | 1 (3.3) | 0 |
| Lymphadenopathy | 0 | 0 | 1 (3.3) | 0 | 1 (3.3) | 0 | 1 (3.3) | 2 (6.5) |
| Pharyngitis bacterial | 0 | 0 | 0 | 0 | 0 | 2 (6.9) | 0 | 0 |
| Arthralgia | 0 | 0 | 2 (6.7) | 0 | 0 | 0 | 0 | 0 |
| Adverse reactions | 4 (13.3) | 4 (13.3) | 7 (23.3) | 8 (26.7) | 4 (13.3) | 5 (17.2) | 8 (26.7) | 6 (19.4) |
| Injection site erythema | 0 | 2 (6.7) | 1 (3.3) | 2 (6.7) | 3 (10.0) | 5 (17.2) | 6 (20.0) | 3 (9.7) |
| Injection site swelling | 1 (3.3) | 1 (3.3) | 3 (10.0) | 3 (10.0) | 0 | 3 (10.3) | 3 (10.0) | 2 (6.5) |
| Injection site induration | 0 | 0 | 0 | 0 | 1 (3.3) | 3 (10.3) | 3 (10.0) | 0 |
| Axillary pain | 1 (3.3) | 0 | 0 | 4 (13.3) | 0 | 0 | 0 | 0 |
| Injection site pruritus | 0 | 2 (6.7) | 0 | 0 | 0 | 1 (3.4) | 1 (3.3) | 0 |
| Lymphadenopathy | 0 | 0 | 1 (3.3) | 0 | 1 (3.3) | 0 | 1 (3.3) | 2 (6.5) |
| Arthralgia | 0 | 0 | 2 (6.7) | 0 | 0 | 0 | 0 | 0 |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 24.1

**Table 19. Unsolicited adverse events and adverse reactions in healthy elderly (safety analysis set)**

| MedDRA PT | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 10 μg N = 30 | Daichirona 30 μg N = 30 | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 10 μg N = 19 | Daichirona 30 μg N = 19 | Daichirona 60 μg N = 20 | Spikevax N = 19 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events | 6 (20.0) | 3 (10.0) | 5 (16.7) | 7 (23.3) | 5 (26.3) | 4 (21.1) | 6 (30.0) | 7 (36.8) |
| Injection site erythema | 2 (6.7) | 1 (3.3) | 2 (6.7) | 1 (3.3) | 1 (5.3) | 1 (5.3) | 2 (10.0) | 3 (15.8) |
| Injection site induration | 1 (3.3) | 0 | 1 (3.3) | 0 | 2 (10.5) | 1 (5.3) | 2 (10.0) | 4 (21.1) |
| Injection site swelling | 0 | 0 | 2 (6.7) | 0 | 1 (5.3) | 1 (5.3) | 1 (5.0) | 1 (5.3) |
| Adverse reactions | 4 (13.3) | 1 (3.3) | 5 (16.7) | 3 (10.0) | 4 (21.1) | 1 (5.3) | 6 (30.0) | 6 (31.6) |
| Injection site erythema | 2 (6.7) | 1 (3.3) | 2 (6.7) | 1 (3.3) | 1 (5.3) | 1 (5.3) | 2 (10.0) | 3 (15.8) |
| Injection site induration | 1 (3.3) | 0 | 1 (3.3) | 0 | 2 (10.5) | 1 (5.3) | 2 (10.0) | 4 (21.1) |
| Injection site swelling | 0 | 0 | 2 (6.7) | 0 | 1 (5.3) | 1 (5.3) | 1 (5.0) | 1 (5.3) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 24.1

In the parallel-group part, no serious adverse events occurred.

### 7.1.2 Part 2

A randomized, observer-blind,[13] active-comparator, non-inferiority study was conducted to evaluate the immunogenicity and safety of a booster dose of Daichirona in healthy adults aged ≥18 years who had completed the primary series comprised of 2 doses of Comirnaty or Spikevax ≥6 months before with no history of SARS-CoV-2 infection (target sample size of Part 2, 4,500 subjects [3,000 in the Daichirona group, 1,500 in the active-comparator group]) at 18 study centers in Japan.

Daichirona 60 μg or the active comparator (Comirnaty or Spikevax)[14] was intramuscularly administered.

Part 2 was comprised of the primary Comirnaty cohort and primary Spikevax cohort according to the vaccine product used in the primary series. In each cohort, subjects were randomly assigned to receive Daichirona 60 μg or the active comparator (Comirnaty or Spikevax) in a ratio of 2:1 using the age category (≥18 years and <65 years; or ≥65 years) as a stratification factor. The first 213 subjects enrolled in each cohort[15] (142 in the Daichirona group and 71 in the Comirnaty group in primary Comirnaty cohort; 142 in the Daichirona group and 71 in the Spikevax group in primary Spikevax cohort) were included in the immunogenicity evaluation set.

In total, 4,518 subjects were randomized[16] (2,311 in the primary Comirnaty cohort [1,540 in the Daichirona group, 771 in the Comirnaty group], 2,207 in the primary Spikevax cohort [1,473 in the Daichirona group, 734 in the Spikevax group]). Among them, 4,511 subjects (2,307 in the primary Comirnaty cohort [1,538 in the Daichirona group, 769 in the Comirnaty group], 2,204 in the primary Spikevax cohort [1,469 in the Daichirona group, 735 in the Spikevax group]) received the study vaccine and were included in the safety analysis set[17] and efficacy-evaluable FAS. Of them, 4,496 subjects (2,297 in the primary Comirnaty cohort [1,531 in the Daichirona group, 766 in the Comirnaty group], 2,199 in the primary Spikevax cohort [1,468 in the Daichirona group, 731 in the Spikevax group]) were included in the efficacy-evaluable per-protocol set (PPS); the remaining 15 subjects were excluded because of critical protocol deviations. In addition, the immunogenicity-evaluable PPS included 421 subjects (209 in the primary Comirnaty cohort [140 in the Daichirona group, 69 in the Comirnaty group], 212 in the primary Spikevax cohort [142 in the Daichirona group, 70 in the Spikevax group]).

In the safety analysis set, the median interval (range) between the second dose of the primary series and the booster dose was as follows:

- The primary Comirnaty cohort: 8.9 (5.3-19.9) months in the Daichirona group and 8.9 (6.0-19.7) months in the Comirnaty group

13) Subjects, investigators, sub-investigators, clinical research coordinators, nurses, monitors, sponsor, and persons who performed antibody titer assay were blinded.
14) The active comparator was Comirnaty in the primary Comirnaty cohort or Spikevax in the primary Spikevax cohort.
15) The number of subjects required to demonstrate non-inferiority of Daichirona to the active comparator with the non-inferiority margin of 0.67 at a one-sided significance level of 1.25% for the power of 90% in view of dropout of 5% on the assumption that GMFR ratios of Daichirona to the active comparators (Comirnaty and Spikevax) were both 1.10 with the SD of common logarithm of the GMFR being 0.405. Of note, Bonferroni correction was applied to adjustment of multiplicity of the test.
16) Three subjects were randomized twice and given 2 subjects numbers. All of them discontinued the study under the first subject number before study vaccination and then received the study vaccine under the second subject number (2 subjects in the Daichirona group in the primary Comirnaty cohort and 1 subject in the Daichirona group in the primary Spikevax cohort).
17) One subject in the primary Spikevax cohort and 2 subjects in the primary Comirnaty cohort were included in the Daichirona group.

- The primary Spikevax cohort: 9.3 (6.2-16.1) months in the Daichirona group and 9.3 (6.1-16.2) months in the Spikevax group

In the immunogenicity-evaluable PPS, the median interval (range) between the second dose of the primary series and the booster dose was as follows:

- The primary Comirnaty cohort: 7.9 (6.0-18.4) months in the Daichirona group and 8.0 (6.0-12.6) months in the Comirnaty group
- The primary Spikevax cohort: 8.3 (6.2-10.5) months in the Daichirona group and 8.6 (6.4-10.2) months in the Spikevax group

The primary efficacy endpoint was GMFR in blood anti-SARS-CoV-2 (the original strain) neutralizing antibody titer on Day 28. The secondary endpoints were geometric mean titer (GMT) of blood anti-SARS-CoV-2 (the original strain) neutralizing antibody titer on Day 28 and antibody response rate.

Table 20 shows results of the primary and secondary endpoints for immunogenicity on Day 28. The lower limit of two-sided 97.5% confidence interval (CI) of GMFR ratio (Daichirona/active comparator [Comirnaty or Spikevax]) for neutralizing antibody titer against the original strain exceeded 0.67, the non-inferiority limit, for both Comirnaty and Spikevax. Thus the predetermined success criteria for non-inferiority were achieved.

**Table 20. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer (immunogenicity-evaluable PPS)**

| | Primary Comirnaty cohort | | Primary Spikevax cohort | |
|---|---|---|---|---|
| | Daichirona N = 140 | Comirnaty N = 69 | Daichirona N = 142 | Spikevax N = 70 |
| Baseline | | | | |
| n | 140 | 69 | 142 | 70 |
| GMT [two-sided 95% CI][a)] | 24.292 [20.431, 28.882] | 29.468 [21.614, 40.175] | 62.576 [50.873, 76.971] | 45.185 [34.608, 58.995] |
| Day 28 | | | | |
| n | 137 | 66 | 136 | 69 |
| GMT [two-sided 95% CI][a)] | 1345.327 [1153.683, 1568.806] | 951.373 [768.559, 1177.672] | 2078.015 [1795.209, 2405.372] | 1096.038 [878.747, 1367.058] |
| GMFR [two-sided 95% CI][a)] | 58.690 [49.643, 69.386] | 38.044 [29.704, 48.726] | 36.074 [29.292, 44.426] | 25.402 [19.163, 33.671] |
| Adjusted GMFR [two-sided 95% CI][a)] | 57.700 [50.330, 66.149] | 39.410 [32.365, 47.989] | 38.864 [33.687, 44.837] | 21.932 [17.935, 26.819] |
| Adjusted GMFR ratio [two-sided 97.5% CI][b)] | 1.464 [1.112, 1.927] | | 1.772 [1.335, 2.353] | |
| Antibody response rate[c)] | | | | |
| n | 137 | 66 | 136 | 69 |
| No. of subjects with antibody response | 133 | 65 | 129 | 64 |
| Antibody response rate (%) [two-sided 95% CI][d)] | 97.1 [92.7, 99.2] | 98.5 [91.8, 100.0] | 94.9 [89.7, 97.9] | 92.8 [83.9, 97.6] |
| Difference in antibody response rate [two-sided 95% CI][e)] | −1.4 [−5.9, 5.4] | | 2.1 [−4.4, 11.1] | |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity

a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.

b) GMFR ratio (Daichirona/comparator) was calculated based on an analysis-of-covariance model using common logarithm of neutralization activity as an explained variable, dose group as an explanatory variable, and common logarithm of baseline neutralization activity as a covariate. For estimation of the interval, two-sided 97.5% CI was calculated by applying Bonferroni correction to evaluate non-inferiority in each cohort.

c) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer

d) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

e) The two-sided 95% CI was calculated according to an age-stratified Newcombe-Wilson score method.

For safety, the observation period and severity grading in Part 2 were the same as those in Part 1.

Table 21 shows solicited adverse events reported within 7 days after study vaccination.

**Table 21. Solicited adverse events (safety analysis set)**

| MedDRA PT | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona N = 1,538 | | Comirnaty N = 769 | | Daichirona N = 1,469 | | Spikevax N = 735 | |
| | All | Severe | All | Severe | All | Severe | All | Severe |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | 1,440 (93.6) | 43 (2.8) | 727 (94.5) | 14 (1.8) | 1,411 (96.1) | 56 (3.8) | 700 (95.2) | 39 (5.3) |
| Erythema | 152 (9.9) | 15 (1.0) | 74 (9.6) | 1 (0.1) | 194 (13.2) | 20 (1.4) | 140 (19.0) | 13 (1.8) |
| Swelling | 222 (14.4) | 13 (0.8) | 118 (15.3) | 2 (0.3) | 248 (16.9) | 16 (1.1) | 176 (23.9) | 11 (1.5) |
| Induration | 150 (9.8) | 6 (0.4) | 82 (10.7) | 0 | 156 (10.6) | 6 (0.4) | 117 (15.9) | 4 (0.5) |
| Pain | 1,420 (92.3) | 9 (0.6) | 709 (92.2) | 6 (0.8) | 1,380 (93.9) | 10 (0.7) | 688 (93.6) | 13 (1.8) |
| Warmth | 609 (39.6) | 15 (1.0) | 345 (44.9) | 7 (0.9) | 757 (51.5) | 21 (1.4) | 425 (57.8) | 13 (1.8) |
| Pruritus | 258 (16.8) | 0 | 128 (16.6) | 0 | 277 (18.9) | 2 (0.1) | 152 (20.7) | 0 |
| Systemic adverse events | 1,051 (68.3) | 68 (4.4) | 538 (70.0) | 33 (4.3) | 1,156 (78.7) | 82 (5.6) | 599 (81.5) | 53 (7.2) |
| Pyrexia | 521 (33.9) | 42 (2.7) | 276 (35.9) | 17 (2.2) | 626 (42.6) | 44 (3.0) | 349 (47.5) | 30 (4.1) |
| Malaise | 851 (55.3) | 30 (2.0) | 447 (58.1) | 17 (2.2) | 984 (67.0) | 38 (2.6) | 498 (67.8) | 29 (3.9) |
| Headache | 591 (38.4) | 8 (0.5) | 319 (41.5) | 6 (0.8) | 677 (46.1) | 10 (0.7) | 358 (48.7) | 13 (1.8) |
| Rash | 25 (1.6) | 0 | 8 (1.0) | 1 (0.1) | 22 (1.5) | 0 | 17 (2.3) | 0 |
| Myalgia | 316 (20.5) | 6 (0.4) | 180 (23.4) | 7 (0.9) | 342 (23.3) | 10 (0.7) | 191 (26.0) | 9 (1.2) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0

Table 22 shows unsolicited adverse events and adverse reactions reported by ≥2% of subjects in any group.

**Table 22. Unsolicited adverse events and adverse reactions (safety analysis set)**

| MedDRA PT | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Adverse events | | Adverse reactions | | Adverse events | | Adverse reactions | |
| | Daichirona N = 1,538 | Comirnaty N = 769 | Daichirona N = 1,538 | Comirnaty N = 769 | Daichirona N = 1,469 | Spikevax N = 735 | Daichirona N = 1,469 | Spikevax N = 735 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events/adverse reactions | 523 (34.0) | 279 (36.3) | 396 (25.7) | 220 (28.6) | 563 (38.3) | 267 (36.3) | 449 (30.6) | 201 (27.3) |
| Injection site erythema | 132 (8.6) | 78 (10.1) | 128 (8.3) | 78 (10.1) | 209 (14.2) | 65 (8.8) | 207 (14.1) | 65 (8.8) |
| Injection site swelling | 103 (6.7) | 52 (6.8) | 103 (6.7) | 52 (6.8) | 142 (9.7) | 61 (8.3) | 141 (9.6) | 61 (8.3) |
| Injection site induration | 91 (5.9) | 54 (7.0) | 91 (5.9) | 54 (7.0) | 101 (6.9) | 63 (8.6) | 100 (6.8) | 63 (8.6) |
| Pyrexia | 59 (3.8) | 27 (3.5) | 53 (3.4) | 26 (3.4) | 46 (3.1) | 16 (2.2) | 35 (2.4) | 13 (1.8) |
| COVID-19 | 25 (1.6) | 14 (1.8) | 0 | 0 | 29 (2.0) | 12 (1.6) | 0 | 0 |
| Injection site pruritus | 19 (1.2) | 2 (0.3) | 17 (1.1) | 2 (0.3) | 31 (2.1) | 2 (0.3) | 29 (2.0) | 2 (0.3) |
| Lymphadenopathy | 21 (1.4) | 18 (2.3) | 21 (1.4) | 18 (2.3) | 25 (1.7) | 10 (1.4) | 25 (1.7) | 10 (1.4) |
| Axillary pain | 26 (1.7) | 19 (2.5) | 24 (1.6) | 19 (2.5) | 19 (1.3) | 11 (1.5) | 19 (1.3) | 10 (1.4) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0

The reported serious adverse events included 3 events in 2 of 3,007 subjects in the Daichirona group (cerebral infarction in 1 subject and ovarian cyst ruptured/uterine leiomyoma in 1 subject), 2 events in 2 of 769 subjects in the Comirnaty group (meniscus injury and hepatic function abnormal in 1 subject each), and 1 event in 1 of 735 subjects in the Spikevax group (cholecystitis). All of the events were unrelated to the study vaccine.

### 7.2 Japanese phase II study (CTD 5.3.5.2-1; Study 116; Study period, ongoing since November 2021; data cut-off on [redacted], 20[redacted])

An open-label, uncontrolled, dose-titration (Part 1) and randomized, double-blind,[18] parallel-group (Part 2) study was conducted to evaluate the safety, tolerability, and immunogenicity of Daichirona in healthy adults aged ≥20 years and <65 years who had not previously received SARS-CoV-2 vaccine with no history of SARS-CoV-2 infection (target sample size; 6 subjects in Part 1, 74 subjects in Part 2) at 2 study centers in Japan.

In both parts, 2 doses of Daichirona 30 or 60 μg was intramuscularly administered 28 days apart.

In both parts, subjects were assigned to receive Daichirona 30 or 60 μg in a ratio of 1:1 (randomly assigned in Part 2). Of 80 subjects enrolled (6 in Part 1 [3 each in the Daichirona 30 and 60 μg groups], 74 in Part 2 [37 each in the Daichirona 30 and 60 μg groups]), 79 subjects received 2 doses of the study vaccine. The remaining 1 subject in the Daichirona 60 μg group[19] in Part 2 did not. All of the 80 subjects were included in the safety analysis set and immunogenicity analysis set.

Safety observation periods are shown below. Severity of an adverse event was graded according to the scale defined based on the FDA guidance (Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007) as done in Study 146.

- Solicited adverse events were collected for 7 days each after the first and second study vaccinations[11]
  - Adverse events at the injection site (redness, swelling, induration, pain, warmth, and pruritus)
  - Systemic adverse events (pyrexia, malaise, headache, rash [systemic /local], myalgia)
- Unsolicited adverse events were collected between the time of first study vaccination and Day 28 after the second study vaccination.[11]
- Serious adverse events were collected between the time of informed consent and Month 12 after the second study vaccination or the last sampling time point for ADA follow-up assay, whichever comes later.

Table 23 shows solicited adverse events reported within 7 days after each study vaccination.

[18] All the individuals concerned (subjects, staff such as investigators at the study centers, and sponsor) were blinded, except for the independent statistics manager, independent statistics experts, staff who administered the study vaccine, study vaccine storage manager, open-label study vaccine storage assistant, and manager/staff in charge of study vaccine allocation.

[19] In Part 2, 1 subject in the Daichirona 60 μg group withdrew the consent after the first study vaccination and discontinued the study without receiving the second dose of the study vaccine.

**Table 23. Solicited adverse events within 7 days after each study vaccination (safety analysis set)**

| MedDRA PT | First dose | | Second dose | |
|---|---|---|---|---|
| | Daichirona 30 μg N = 40 | Daichirona 60 μg N = 40 | Daichirona 30 μg N = 40 | Daichirona 60 μg N = 40[a)] |
| | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | 34 (85.0) | 36 (90.0) | 34 (85.0) | 32 (80.0) |
| Erythema | 0 (0.0) | 1 (2.5) | 2 (5.0) | 6 (15.0) |
| Swelling | 1 (2.5) | 1 (2.5) | 0 (0.0) | 3 (7.5) |
| Induration | 1 (2.5) | 3 (7.5) | 0 (0.0) | 1 (2.5) |
| Pain | 34 (85.0) | 36 (90.0) | 34 (85.0) | 32 (80.0) |
| Warmth | 5 (12.5) | 7 (17.5) | 5 (12.5) | 7 (17.5) |
| Pruritus | 1 (2.5) | 2 (5.0) | 3 (7.5) | 6 (15.0) |
| Systemic adverse events | 22 (55.0) | 23 (57.5) | 18 (45.0) | 30 (75.0) |
| Pyrexia | 0 (0.0) | 4 (10.0) | 3 (7.5) | 8 (20.0) |
| Malaise | 6 (15.0) | 10 (25.0) | 9 (22.5) | 17 (42.5) |
| Headache | 3 (7.5) | 7 (17.5) | 4 (10.0) | 16 (40.0) |
| Rash | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Myalgia | 18 (45.0) | 19 (47.5) | 13 (32.5) | 19 (47.5) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 24.1

a) The safety analysis set included 1 subject who withdrew the consent after the first study vaccination and therefore did not receive the second study vaccination.

Table 24 shows unsolicited adverse events and adverse reactions reported by ≥2 subjects in either group.

**Table 24. Unsolicited adverse events and adverse reactions between the first study vaccination and Day 28 after the second study vaccination (safety analysis set)**

| MedDRA PT | Adverse events | | Adverse reactions | |
|---|---|---|---|---|
| | Daichirona 30 μg N = 40 | Daichirona 60 μg N = 40 | Daichirona 30 μg N = 40 | Daichirona 60 μg N = 40 |
| | n (%) | n (%) | n (%) | n (%) |
| Body temperature increased | 5 (12.5) | 9 (22.5) | 5 (12.5) | 9 (22.5) |
| Injection site erythema | 4 (10.0) | 8 (20.0) | 4 (10.0) | 8 (20.0) |
| Injection site pruritus | 2 (5.0) | 7 (17.5) | 2 (5.0) | 7 (17.5) |
| Injection site swelling | 0 | 7 (17.5) | 0 | 7 (17.5) |
| Injection site induration | 1 (2.5) | 5 (12.5) | 1 (2.5) | 5 (12.5) |
| COVID-19 | 2 (5.0) | 1 (2.5) | 0 | 0 |
| Injection site pain | 1 (2.5) | 2 (5.0) | 1 (2.5) | 2 (5.0) |
| Injection site warmth | 1 (2.5) | 2 (5.0) | 1 (2.5) | 2 (5.0) |
| Nausea | 0 | 2 (5.0) | 0 | 2 (5.0) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 24.1

No serious adverse events occurred in either group.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Clinical data package and review policy

The applicant's explanation about clinical data package:

Daichirona was developed for booster vaccination rather than for the primary series, for the following reasons:

Around the time when Study 146 started, SARS-CoV-2 vaccines had already been approved in Japan and the vaccination program using the vaccines was rapidly progressing. This meant that many people would have received booster vaccination when Daichirona is granted marketing approval. Further, >70% of the population aged ≥18 years in Japan had already completed the

primary series,[20] making it difficult to develop Daichirona for the primary series for this age group in Japan.

Reports on approved SARS-CoV-2 vaccines gradually revealed that blood anti-SARS-CoV-2 neutralizing antibody titer achieved by vaccination was correlated with prevention of COVID-19 (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11). In view of the reports, the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 3): Evaluation of the vaccines based on immunogenicity" (dated October 22, 2021, issued by PMDA) (hereinafter, "Principles [Appendix 3]") states that the efficacy of a vaccine can be evaluated using an immunogenicity bridging approach, which evaluates vaccine efficacy based on immunogenicity using an approved SARS-CoV-2 vaccine with proven efficacy in preventing COVID-19 as an active comparator. In Part 2 of Study 146, non-inferiority of Daichirona to Comirnaty and Spikevax was evaluated using immunogenicity-based endpoints. In Part 2 of Study 146, subjects had completed the primary series and thus had certain neutralizing antibody titer before the booster vaccination, and the neutralizing antibody titer after the booster vaccination would be influenced by both study vaccination and neutralizing antibody titer before vaccination. The primary endpoint in Part 2 of Study 146 was therefore GMFR, and the secondary endpoints were GMT and antibody response rate.

Since the present application was intended to obtain an approval of Daichirona used as a booster dose in individuals who had completed the primary series of a vaccine against SARS-CoV-2 (the original strain), the applicant decided to evaluate the efficacy and safety of Daichirona using results from Study 146 as the evaluation data.

PMDA's view:
The applicant firstly developed Daichirona as a booster dose vaccine. This development strategy is understandable because, when Study 146 started, >70% of the population in Japan had completed the primary series of a SARS-CoV-2 vaccine. In addition, in accordance with the "Principles (Appendix 3)," the applicant decided to evaluate Daichirona according to the predetermined success criteria based on the immunogenicity bridging approach, using approved SARS-CoV-2 vaccines with proven efficacy in preventing COVID-19 as the active comparators. PMDA considers this decision is acceptable, in view of the following:

(1) When Study 146 started, multiple SARS-CoV-2 vaccines had already been approved.
(2) As cited in "Principles (Appendix 3)," a clinical study to demonstrate the non-inferiority of a study vaccine to an approved SARS-CoV-2 vaccine in prevention of COVID-19 requires approximately 2- to 3-fold person-years follow-up than a placebo-controlled trial. (*Clin Trials.* 2021;18:335-42).
(3) Owing to the limited feasibility of placebo-controlled studies, consensus was reached for the necessity of clinical studies using an immunogenicity bridging approach (International Coalition of Medicines Regulatory Authorities [ICMRA] COVID-19 Virus Variants Workshop. June 24, 2021[21]).

[20] https://info.vrs.digital.go.jp/dashboard/ (last accessed on June 9, 2023)
[21] http://www.icmra.info/drupal/en/covid-19/24june2021 (last accessed on June 9, 2023)

The primary efficacy endpoint in Study 146 was GMFR. PMDA considers the applicant's explanation understandable to a certain extent but decided to review the efficacy of Daichirona using data not only on the primary endpoint but also on the secondary endpoints of GMT and neutralizing antibody response rate, because the "Principles (Appendix 3)" states the following:

> The primary immunogenicity endpoint should be GMT. However, a non-inferiority study using GMT as the primary endpoint should also evaluate the neutralizing antibody response rate as the primary endpoint in order to demonstrate the non-inferiority of a study vaccine to an active comparator.

In addition, even in a study where vaccine efficacy is evaluated according to an immunogenicity bridging approach, clinical events should be examined to support the immunogenicity-based efficacy evaluation. In view of the importance of such events, PMDA decided to review the incidence of COVID-19 in Study 146 wherever possible.

Since experience with Daichirona vaccination is limited, PMDA decided to review the safety of Daichirona using not only data from Study 146 but also the safety information from clinical studies for the primary series (Studies J101 and 116: reference data submitted).

### 7.R.2 Efficacy

The applicant's explanation about the efficacy of Daichirona as a booster dose:

Based on results in Part 1 of Study 146, the dose 60 μg dose of Daichirona was selected for Part 2 of Study 146. Subjects who had completed the primary series of an approved SARS-CoV-2 vaccine received Daichirona or the active comparator (Comirnaty or Spikevax), and a comparison of the immunogenicity against SARS-CoV-2 (the original strain) on Day 28 after the booster dose was made between Daichirona and the active comparator (Comirnaty or Spikevax). In both the primary Comirnaty cohort and primary Spikevax cohort, Daichirona was shown to be non-inferior to the active comparator (Comirnaty or Spikevax) in GMFR in blood SARS-CoV-2 (the original strain) neutralizing antibody titer on Day 28 [see Section 7.1.2].

The efficacy by age:

The number of healthy elderly subjects was very small. The immunogenicity evaluation by age therefore included not only healthy elderly subjects eligible for the immunogenicity-evaluable PPS but also those who were not eligible for the PPS but met all the requirements for the immunogenicity-evaluable PPS, except for the requirement "the first 213 subjects enrolled in Part 2 necessary for the immunogenicity evaluation." As shown in Table 25, the results did not present any definite difference between healthy adults and healthy elderly.

**Table 25. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer by age group (immunogenicity-evaluable PPS[a]) (Part 2 of Study 146)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Healthy adult | | Healthy elderly | | Healthy adult | | Healthy elderly | |
| | Daichirona N = 133 | Comirnaty N = 67 | Daichirona N = 90 | Comirnaty N = 45 | Daichirona N = 139 | Spikevax N = 68 | Daichirona N = 29 | Spikevax N = 13 |
| Baseline | | | | | | | | |
| n | 133 | 67 | 90 | 45 | 139 | 68 | 29 | 13 |
| GMT [two-sided 95% CI][b)] | 25.269 [21.131, 30.217] | 30.261 [22.038, 41.554] | 25.243 [17.950, 35.500] | 28.780 [20.212, 40.981] | 61.995 [50.525, 76.069] | 45.792 [34.899, 60.085] | 70.654 [38.966, 128.114] | 61.274 [27.941, 134.371] |
| Day 28 | | | | | | | | |
| n | 130 | 64 | 82 | 42 | 133 | 67 | 28 | 13 |
| GMT [two-sided 95% CI][b)] | 1367.897 [1171.214, 1597.609] | 973.321 [782.968, 1209.951] | 1491.014 [1137.166, 1954.967] | 1254.776 [901.567, 1746.362] | 2108.455 [1818.471, 2444.683] | 1096.201 [874.617, 1373.924] | 2626.100 [1523.745, 4525.957] | 1501.714 [865.947, 2604.252] |
| GMFR [two-sided 95% CI][b)] | 57.494 [48.390, 68.311] | 38.048 [29.476, 49.114] | 75.779 [58.270, 98.549] | 44.128 [31.273, 62.268] | 37.029 [30.349, 45.181] | 25.099 [18.783, 33.538] | 42.012 [21.808, 80.932] | 24.508 [11.453, 52.445] |
| Antibody response rate[c)] | | | | | | | | |
| n | 130 | 64 | 82 | 42 | 133 | 67 | 28 | 13 |
| No. of subjects with antibody response | 126 | 63 | 81 | 39 | 127 | 62 | 25 | 12 |
| Antibody response rate (%) [two-sided 95% CI][d)] | 96.9 [92.3, 99.2] | 98.4 [91.6, 100.0] | 98.8 [93.4, 100.0] | 92.9 [80.5, 98.5] | 95.5 [90.4, 98.3] | 92.5 [83.4, 97.5] | 89.3 [71.8, 97.7] | 92.3 [64.0, 99.8] |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity

a) The healthy elderly cohorts not only healthy elderly subjects eligible for the immunogenicity-evaluable PPS also those who were not eligible for the immunogenicity-evaluable PPS but met all the requirements for the PPS, except for "the first 213 subjects enrolled in Part 2 necessary for the immunogenicity evaluation."

b) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.

c) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer

d) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

A post hoc analysis was performed to evaluate the efficacy in subjects who had at least 1 pre-existing disease (including past history) when enrolled in Part 2 of Study 146. Table 26 shows the efficacy in subjects with pre-existing disease(s) (including subjects with underlying disease[s] at high risk of severe COVID-19 or with high risk factor[s] for severe COVID-19[22)]) and those without. The GMFR ratio tended to be higher in subjects with pre-existing disease(s) than in those without in both the primary Comirnaty cohort and primary Spikevax cohort; this shows that the efficacy of Daichirona would not be reduced in subjects with pre-existing disease(s).

[22)] Underlying diseases at high risk of severe COVID-19 or high risk factors for severe COVID-19 were defined as the medical conditions presented in the minutes of the 44th Subcommittee meeting on basic vaccination policy of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (held on March 18, 2021) or in Guidelines for Diagnosis and Treatment of COVID 19, ver. 9.0 (February 10, 2023).

**Table 26. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer on Day 28 in subjects with and without pre-existing disease(s) (post hoc analysis, immunogenicity-evaluable PPS) (Part 2 of Study 146)**

| | With pre-existing disease(s) | | | | Without pre-existing disease(s) | | | |
|---|---|---|---|---|---|---|---|---|
| | Primary Comirnaty cohort | | Primary Spikevax cohort | | Primary Comirnaty cohort | | Primary Spikevax cohort | |
| | Daichirona N = 56 | Comirnaty N = 26 | Daichirona N = 41 | Spikevax N = 25 | Daichirona N = 84 | Comirnaty N = 43 | Daichirona N = 101 | Spikevax N = 45 |
| n | 56 | 26 | 39 | 25 | 81 | 40 | 97 | 44 |
| GMT ratio [two-sided 95% CI][a)] | 1.791 [1.180, 2.718] | | 2.144 [1.307, 3.516] | | 1.195 [0.863, 1.655] | | 1.782 [1.315, 2.417] | |
| Adjusted GMFR ratio [two-sided 95% CI][b)] | 1.731 [1.166, 2.570] | | 2.080 [1.279, 3.385] | | 1.305 [0.973, 1.750] | | 1.623 [1.215, 2.170] | |
| Difference in antibody response rate (%) [two-sided 95% CI][c)] | −3.6 [−12.1, 9.6] | | 6.9 [−7.3, 25.2] | | 0.0 [−6.4, 10.6] | | −0.6 [−7.8, 10.4] | |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity

a) GMT ratio (Daichirona/comparator). The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer.

b) GMFR ratio (Daichirona/GMFR). Adjusted according to an analysis of the covariance model. The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer.

c) Difference in antibody response rate (Daichirona − comparator). The two-sided 95% CI was calculated according to a Newcombe-Wilson method.

A case-control research with a test negative design was conducted in the US from December 26, 2021 to June 30, 2022, when Omicron variant was predominant, to investigate the effectiveness of a booster dose against COVID-19-associated hospital admission in individuals who had received the primary series of an approved mRNA SARS-CoV-2 vaccine. The effectiveness for prevention of hospital admission was 65% (95% CI; 58%, 72%) in subjects with underlying diseases and 45% (95% CI; −3%, 71%) in subjects without (*BMJ.* 2022;379:e072065). Therefore, the efficacy of Daichirona can be expected even in individuals with underlying diseases.

**(a) COVID-19 incidence rate**

In Study 146, the secondary endpoint was the COVID-19 incidence rate until Week 52. The incidence rate until Day 28 was submitted for the present application. Cases of COVID-19[23)] that developed on or after Day 7 were evaluated, as in the case of a clinical study of Comirnaty (Foreign Study C4591001).[24)] In Part 2 of Study 146, the primary analysis set of the COVID-19 incidence rate was the efficacy-evaluable PPS. Table 27 shows the COVID-19 incidence rate between Days 7 and 28, and Figures 1 and 2 show the cumulative COVID-19 incidence proportion. Irrespective of the primary series vaccine brand, the results in the Daichirona group was similar to those in the active comparator group. In Part 1 of Study 146 (parallel-group part), COVID-19 occurred in 1 subject in the Daichirona 10 μg group (an adult in the primary Comirnaty cohort) and 2 subjects in the 30 μg group (1 adult and 1 elderly in the primary Spikevax cohort) but did not occur in the other groups.

23) A patient with COVID-19 was defined as an individual who had at least 1 of "pyrexia of ≥37.5°C," "cough," "shortness of breath/suffocation," "fatigue/malaise," "myalgia/systemic pain," "headache," "new dysgeusia/dysosmia," and "pharyngeal pain" and tested positive for SARS-CoV-2 by RT-PCR, antigen testing, or other nucleic acid amplification testing.

24) A clinical study of Comirnaty Intramuscular Injection (phase I part of Foreign Study C4591001) showed that serum anti-SARS-CoV-2 neutralizing antibody titer was remarkably high at ≥7 days after the second study vaccination (*N Engl J Med.* 2020;383:2439-50). Based on this result, in the subsequent phase of the study of Comirnaty (phase II/III part of Foreign Study C4591001), evaluation of prevention of COVID-19 was started on Day 7 (*N Engl J Med.* 2020;383:2603-15).

**Table 27. COVID-19 incidence rate between Days 7 and 28 (efficacy-evaluable PPS) (Part 2 of Study 146)**

| | Primary Comirnaty cohort | | Primary Spikevax cohort | |
|---|---|---|---|---|
| | Daichirona N = 1,531 | Comirnaty N = 766 | Daichirona N = 1,468 | Spikevax N = 731 |
| n | 1,525 | 765 | 1,463 | 729 |
| No. of subjects developing COVID-19 | 21 | 14 | 29 | 13 |
| Observation person-years | 103.76 | 51.99 | 99.25 | 49.34 |
| COVID-19 incidence rate (No. of events per 1,000 person-years)[a] [two-sided 95% CI][b] | 202.40 [125.29, 309.39] | 269.27 [147.21, 451.79] | 292.19 [195.69, 419.64] | 263.50 [140.30, 450.59] |
| COVID-19 incidence rate ratio to active comparator [two-sided 95% CI][c] | 0.75 [0.36, 1.60] | | 1.11 [0.56, 2.32] | |
| Cumulative COVID-19 incidence proportion (%)[d] [two-sided 95% CI][e] | 1.38 [0.90, 2.11] | 1.83 [1.09, 3.07] | 1.98 [1.38, 2.84] | 1.78 [1.04, 3.05] |

N = Number of subjects analyzed, n = Number of subjects evaluated

a) The incidence rate at each time point was calculated by dividing the number of subjects developing COVID-19 during the applicable period by observation person-years in the risk population during the same period.
b) The two-sided 95% CI was calculated based on the Poisson distribution assumption according to an exact method.
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.
d) Cumulative incidence proportion (%) = (1 – proportion of subjects not developing COVID-19 [KM estimate]) × 100
e) The two-sided 95% CI was calculated according to the Greenwood method

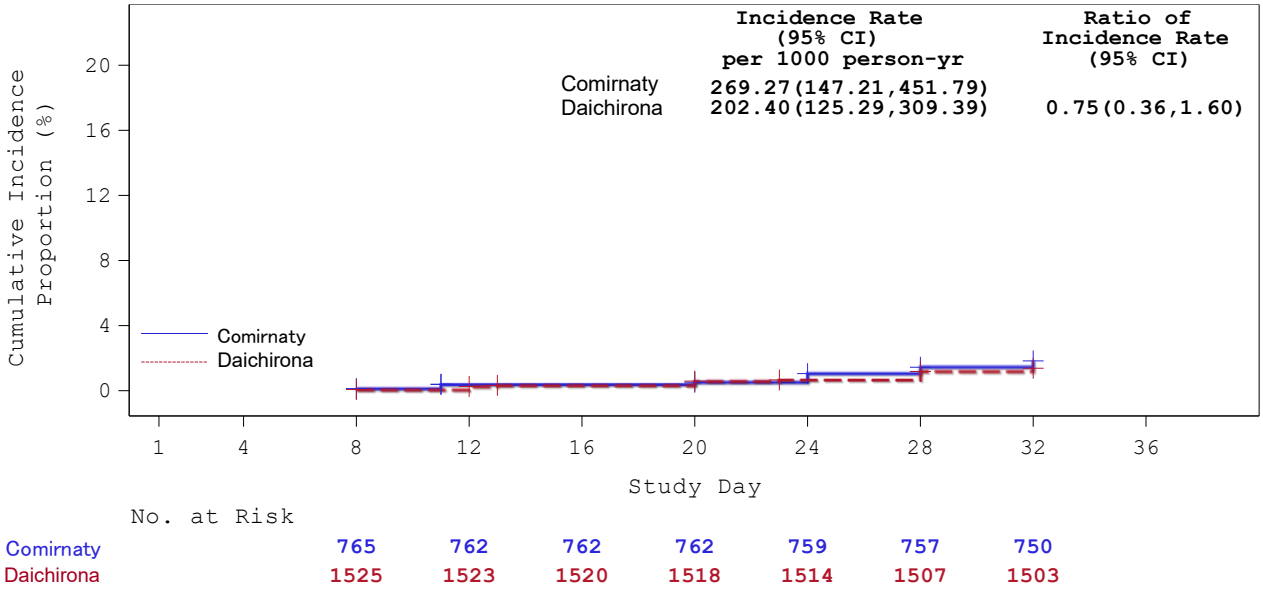


**Figure 1. Cumulative COVID-19 incidence proportion between Days 7 and 28 after study vaccination (primary Comirnaty cohort: Efficacy-evaluable PPS)**

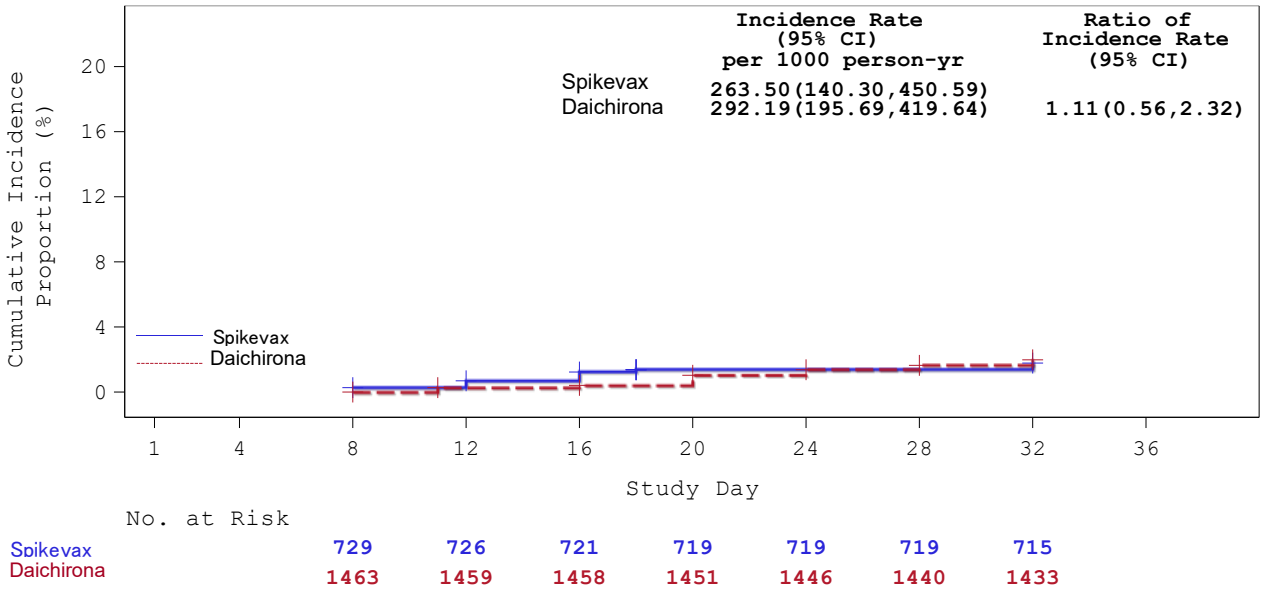


**Figure 2. Cumulative COVID-19 incidence proportion between Days 7 and 28 after study vaccination (primary Spikevax cohort: Efficacy-evaluable PPS)**

**(b) Efficacy against variants**

In Part 1 of Study 146, an exploratory endpoint was immunogenicity against blood anti-SARS-CoV-2 (variants). Tables 28 and 29 show neutralizing antibody titers against Delta variant, a predominant variant at the time of planning of Part 1, and Omicron variant (BA.1 lineage), a predominant variant at the time of application submission. Tables 30, 31, and 32 show neutralizing antibody titers against Omicron variant (BA.4/BA.5, BQ.1.1, and XBB.1.5 lineages), which were exploratory determined using residual specimens. Daichirona booster vaccination increased neutralizing antibody titer against variants (Delta and Omicron [BA.1 and BA.4/BA.5 lineages]) as well, irrespective of brand of the primary series vaccine and age group (adult or elderly). The increased titers were similar to or above those in subjects receiving the active comparator. Neutralizing antibody titers against Omicron variant (BQ.1.1 and XBB.1.5 lineages) increased in some of the subjects who had received the study vaccine.

**Table 28. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer against Delta variant (FAS) (parallel-group part)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Healthy adult | | Healthy elderly | | Healthy adult | | Healthy elderly | |
| | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 60 μg N = 30 | Spikevax N = 30 | Daichirona 60 μg N = 20 | Spikevax N = 19 |
| Baseline | | | | | | | | |
| n | 30 | 30 | 30 | 30 | 30 | 30 | 20 | 19 |
| GMT [two-sided 95% CI][a)] | 8.225 [6.370, 10.620] | 11.223 [7.756, 16.241] | 6.307 [5.545, 7.173] | 8.224 [6.312, 10.716] | 9.882 [8.096, 12.061] | 11.100 [7.126, 17.290] | 8.711 [5.931, 12.794] | 8.191 [6.335, 10.590] |
| Day 28 | | | | | | | | |
| n | 27 | 29 | 29 | 29 | 30 | 29 | 20 | 19 |
| GMT [two-sided 95% CI][a)] | 476.384 [334.337, 678.780] | 382.828 [263.403, 556.397] | 457.980 [332.562, 630.694] | 267.490 [192.709, 371.290] | 288.398 [200.270, 415.307] | 163.866 [123.097, 218.138] | 510.887 [275.764, 946.482] | 162.941 [89.114, 297.929] |
| GMFR [two-sided 95% CI][a)] | 63.924 [46.832, 87.253] | 39.214 [28.642, 53.689] | 72.915 [54.610, 97.356] | 31.971 [22.683, 45.062] | 29.185 [21.034, 40.495] | 16.777 [12.225, 23.024] | 58.647 [36.332, 94.669] | 19.893 [11.425, 34.637] |
| Antibody response rate[b)] | | | | | | | | |
| n | 27 | 29 | 29 | 29 | 30 | 29 | 20 | 19 |
| No. of subjects with antibody response | 27 | 29 | 29 | 28 | 30 | 28 | 20 | 18 |
| Antibody response rate (%) [two-sided 95% CI][c)] | 100.0 [87.2, 100.0] | 100.0 [88.1, 100.0] | 100.0 [88.1, 100.0] | 96.6 [82.2, 99.9] | 100.0 [88.4, 100.0] | 96.6 [82.2, 99.9] | 100.0 [83.2, 100.0] | 94.7 [74.0, 99.9] |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity

a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.

b) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer

c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

**Table 29. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer against Omicron variant (BA.1 lineage) (FAS) (parallel-group part)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Healthy adult | | Healthy elderly | | Healthy adult | | Healthy elderly | |
| | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 60 μg N = 30 | Comirnaty N = 30 | Daichirona 60 μg N = 30 | Spikevax N = 30 | Daichirona 60 μg N = 20 | Spikevax N = 19 |
| Baseline | | | | | | | | |
| n | 30 | 30 | 30 | 30 | 30 | 30 | 20 | 19 |
| GMT [two-sided 95% CI][a)] | 5.878 [4.603, 7.505] | 6.231 [4.373, 8.877] | 5.000 [5.000, 5.000] | 5.000 [5.000, 5.000] | 5.748 [5.266, 6.274] | 7.939 [5.135, 12.274] | 6.486 [5.332, 7.890] | 6.113 [5.206, 7.177] |
| Day 28 | | | | | | | | |
| n | 27 | 29 | 29 | 29 | 30 | 29 | 20 | 19 |
| GMT [two-sided 95% CI][a)] | 162.077 [108.684, 241.701] | 102.820 [77.929, 135.662] | 169.855 [120.041, 240.341] | 79.048 [58.201, 107.362] | 188.092 [134.193, 263.640] | 98.031 [71.744, 133.948] | 226.246 [121.639, 420.812] | 113.139 [66.325, 192.996] |
| GMFR [two-sided 95% CI][a)] | 30.792 [20.805, 45.574] | 19.593 [15.144, 25.349] | 33.971 [24.008, 48.068] | 15.810 [11.640, 21.472] | 32.722 [23.837, 44.918] | 14.366 [10.543, 19.574] | 34.883 [20.351, 59.793] | 18.509 [11.346, 30.194] |
| Antibody response rate[b)] | | | | | | | | |
| n | 27 | 29 | 29 | 29 | 30 | 29 | 20 | 19 |
| No. of subjects with antibody response | 27 | 29 | 29 | 28 | 30 | 28 | 19 | 18 |
| Antibody response rate (%) [two-sided 95% CI][c)] | 100.0 [87.2, 100.0] | 100.0 [88.1, 100.0] | 100.0 [88.1, 100.0] | 96.6 [82.2, 99.9] | 100.0 [88.4, 100.0] | 96.6 [82.2, 99.9] | 95.0 [75.1, 99.9] | 94.7 [74.0, 99.9] |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity

a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.

b) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer

c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

**Table 30. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer against Omicron variant (BA.4/BA.5 lineage) (FAS) (parallel-group part)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Healthy adult | | Healthy elderly | | Healthy adult | | Healthy elderly | |
| | Daichirona 60 μg N = 33 | Comirnaty N = 30 | Daichirona 60 μg N = 33 | Comirnaty N = 30 | Daichirona 60 μg N = 33 | Spikevax N = 30 | Daichirona 60 μg N = 23 | Spikevax N = 19 |
| Baseline | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| GMT [two-sided 95% CI][a)] | 51 [48, 55] | 55 [45, 68] | 50 [50, 50] | 50 [50, 50] | 56 [44, 71] | 62 [46, 83] | 50 [50, 50] | 53 [47, 60] |
| Day 28 | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| GMT [two-sided 95% CI][a)] | 203 [148, 279] | 236 [174, 321] | 229 [147, 358] | 116 [86, 156] | 294 [202, 429] | 181 [122, 268] | 378 [217, 656] | 189 [116, 309] |
| GMFR [two-sided 95% CI][a)] | 3.9 [2.9, 5.4] | 4.3 [3.1, 5.8] | 4.6 [2.9, 7.2] | 2.3 [1.7, 3.1] | 5.2 [3.6, 7.5] | 2.9 [2.2, 3.9] | 7.6 [4.3, 13.1] | 3.6 [2.1, 5.9] |
| Antibody response rate[b)] | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| No. of subjects with antibody response | 16 | 18 | 18 | 6 | 22 | 8 | 15 | 8 |
| Antibody response rate (%) [two-sided 95% CI][c)] | 48.5 [30.8, 66.5] | 60.0 [40.6, 77.3] | 54.5 [36.4, 71.9] | 20.0 [7.7, 38.6] | 66.7 [48.2, 82.0] | 26.7 [12.3, 45.9] | 65.2 [42.7, 83.6] | 42.1 [20.3, 66.5] |

Luciferase assay using pseudo-virus
N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity
a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.
b) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

**Table 31. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer against Omicron variant (BQ1.1 lineage) (FAS) (parallel-group part)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Healthy adult | | Healthy elderly | | Healthy adult | | Healthy elderly | |
| | Daichirona 60 μg N = 33 | Comirnaty N = 30 | Daichirona 60 μg N = 33 | Comirnaty N = 30 | Daichirona 60 μg N = 33 | Spikevax N = 30 | Daichirona 60 μg N = 23 | Spikevax N = 19 |
| Baseline | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| GMT [two-sided 95% CI][a)] | 50 [50, 50] | 52 [48, 56] | 50 [50, 50] | 50 [50, 50] | 57 [44, 73] | 59 [46, 74] | 50 [50, 50] | 50 [50, 50] |
| Day 28 | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| GMT [two-sided 95% CI][a)] | 56 [50, 63] | 63 [54, 74] | 56 [52, 61] | 79 [58, 106] | 63 [50, 78] | 74 [55, 99] | 98 [65, 149] | 84 [57, 123] |
| GMFR [two-sided 95% CI][a)] | 1.1 [1.0, 1.3] | 1.2 [1.0, 1.4] | 1.1 [1.0, 1.2] | 1.6 [1.2, 2.1] | 1.1 [1.0, 1.3] | 1.3 [1.1, 1.5] | 2.0 [1.3, 3.0] | 1.7 [1.1, 2.5] |
| Antibody response rate[b)] | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| No. of subjects with antibody response | 1 | 1 | 0 | 4 | 0 | 1 | 5 | 3 |
| Antibody response rate (%) [two-sided 95% CI][c)] | 3.0 [0.1, 15.8] | 3.3 [0.1, 17.2] | 0.0 [0.0, 10.6] | 13.3 [3.8, 30.7] | 0.0 [0.0, 10.6] | 3.3 [0.1, 17.2] | 21.7 [7.5, 43.7] | 15.8 [3.4, 39.6] |

Luciferase assay using pseudo-virus
N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity
a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.
b) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

**Table 32. GMT, GMFR, and antibody response rate of SARS-CoV-2 neutralizing antibody titer against Omicron variant (XBB.1.5 lineage) (FAS) (parallel-group part)**

| | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Healthy adult | | Healthy elderly | | Healthy adult | | Healthy elderly | |
| | Daichirona 60 μg N = 33 | Comirnaty N = 30 | Daichirona 60 μg N = 33 | Comirnaty N = 30 | Daichirona 60 μg N = 33 | Spikevax N = 30 | Daichirona 60 μg N = 23 | Spikevax N = 19 |
| Baseline | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| GMT [two-sided 95% CI][a)] | 50 [50, 50] | 52 [48, 57] | 50 [50, 50] | 50 [50, 50] | 56 [45, 70] | 57 [47, 69] | 50 [50, 50] | 50 [50, 50] |
| Day 28 | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| GMT [two-sided 95% CI][a)] | 60 [52, 68] | 54 [50, 59] | 59 [53, 66] | 63 [51, 79] | 69 [55, 87] | 61 [49, 77] | 109 [69, 172] | 64 [49, 82] |
| GMFR [two-sided 95% CI][a)] | 1.2 [1.0, 1.4] | 1.0 [1.0, 1.1] | 1.2 [1.1, 1.3] | 1.3 [1.0, 1.6] | 1.2 [1.0, 1.4] | 1.1 [1.0, 1.2] | 2.2 [1.4, 3.4] | 1.3 [1.0, 1.6] |
| Antibody response rate[b)] | | | | | | | | |
| n | 33 | 30 | 33 | 30 | 33 | 30 | 23 | 19 |
| No. of subjects with antibody response | 0 | 0 | 0 | 3 | 1 | 0 | 7 | 1 |
| Antibody response rate (%) [two-sided 95% CI][c)] | 0.0 [0.0, 10.6] | 0.0 [0.0, 11.6] | 0.0 [0.0, 10.6] | 10.0 [2.1, 26.5] | 3.0 [0.1, 15.8] | 0.0 [0.0, 11.6] | 30.4 [13.2, 52.9] | 5.3 [0.1, 26.0] |

Luciferase assay using pseudo-virus
N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity
a) The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer or fold rise in antibody titer.
b) Percentage of subjects who showed a ≥4-fold increase from baseline in neutralizing antibody titer
c) The two-sided 95% CI was calculated according to the Clopper-Pearson method.

PMDA's view:

In Part 2 of Study 146, the results of GMFR, the primary endpoint, demonstrated the non-inferiority of Daichirona to both Comirnaty and Spikevax [see Section 7.1.2]. The results of GMT and antibody response rate, the secondary endpoints, in the Daichirona group were similar to those in the Comirnaty or Spikevax group. When analyzed by age group, results of immunogenicity did not clearly differ between healthy adults and healthy elderly. The efficacy of Daichirona thus can be expected in healthy adults aged ≥18 years, irrespective of their age.

For efficacy against variants, existing SARS-CoV-2 vaccines, which were proven to be highly effective against the original strain, had reduced effectiveness with time in the circumstances where Omicron variant was predominant; the effectiveness against Omicron BA.1 or BA.2 lineage was 35.9% to 71.0% in the population that received only the primary series (*Nat Med.* 2022;28:1063-71, *Nat Commun.* 2022;13:3082, *MMWR.* 2022;71:931-9). Furthermore, in studies for neutralization activity against various variants, the neutralization activity against Omicron variant was lower than that against the original strain (*Nature.* 2022;603:493-6, *N Engl J Med.* 2022;386:698-700, etc.). On the other hand, some reports show that the effectiveness in the population receiving a booster dose tends to be higher than that in the population receiving only the primary series:

- The effectiveness against Omicron variant after a booster dose was 56% to 84% (*MMWR.* 2022;71:931-9).
- The effectiveness against Delta and Omicron variants between 2 and 4 weeks after a booster dose was 94.7% to 96.6% and 64.9% to 73.9%, respectively (*N Engl J Med.* 022;386:1532-46).

The assessment in Study 146 showed that the booster dose of Daichirona also re-increased the neutralizing antibody titer that had decreased with time after the primary series and induced production of neutralizing antibodies against variants (Delta and Omicron [BA.1 and BA.4/BA.5

lineages) to a certain level. The booster dose is expected to have efficacy against not only the original strain but also variants such as Omicron variant to a certain extent.

However, data on the clinical efficacy and long-term efficacy of Daichirona are not available. The applicant is therefore required to continue collecting information after the market launch and promptly provide the obtained information to healthcare professionals. At present, no definite conclusion can be drawn from the results of the COVID-19 incidence rate, the secondary endpoint, because the evaluation period of the COVID-19 incidence rate is very short with a limited number of subjects developing COVID-19 in both Daichirona and active comparator groups; nevertheless, the results available to date suggest that Daichirona does not tend to have a far inferior efficacy than the active comparators, irrespective of the primary series vaccine.

### 7.R.3 Safety

#### 7.R.3.1 Safety profile

Table 33 shows a summary of adverse events in Part 2 of Study 146. No large differences were observed between the Daichirona group and either active comparator group (Comirnaty or Spikevax).

**Table 33. Summary of incidences of adverse events in Part 2 of Study 146 (safety analysis set)**

| | Primary Comirnaty cohort | | Primary Spikevax cohort | |
|---|---|---|---|---|
| Study vaccine | Daichirona n (%) | Comirnaty n (%) | Daichirona n (%) | Spikevax n (%) |
| No. of subjects | 1,538 | 769 | 1,469 | 735 |
| Death | 0 | 0 | 0 | 0 |
| Serious adverse events | 1 (0.1) | 2 (0.3) | 1 (0.1) | 1 (0.1) |
| Solicited adverse events at the injection site | 1,440 (93.6) | 727 (94.5) | 1,411 (96.1) | 700 (95.2) |
| Severe | 43 (2.8) | 14 (1.8) | 56 (3.8) | 39 (5.3) |
| Solicited systemic adverse events | 1,051 (68.3) | 538 (70.0) | 1,156 (78.7) | 599 (81.5) |
| Severe | 68 (4.4) | 33 (4.3) | 82 (5.6) | 53 (7.2) |
| Unsolicited adverse events | 523 (34.0) | 279 (36.3) | 563 (38.3) | 267 (36.3) |
| Severe | 10 (0.7) | 3 (0.4) | 28 (1.9) | 3 (0.4) |

n = Number of subjects with events

**(a) Solicited adverse events**

Table 21 [see Section 7.1.2] shows the incidences of solicited adverse events, which were mostly mild or moderate in severity. The incidences of solicited adverse events occurring after a booster dose of Daichirona were similar in the primary Comirnaty cohort and primary Spikevax cohort.

Tables 34 and 35 show time from study vaccination to onset of solicited adverse events and duration of the events in the number of days. The time to onset (days) and duration (days) of solicited adverse events did not clearly differ between the groups.

**Table 34. Time to onset and duration of solicited adverse events (Part 2 of Study 146, primary Comirnaty cohort, safety analysis set)**

| MedDRA PT | Time to onset (days) | | | | Duration (days)[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona (N = 1,538) | | Comirnaty (N = 769) | | Daichirona (N = 1,538) | | Comirnaty (N = 769) | |
| | n | Median [range] | n | Median [range] | n | Median [range] | n | Median [range] |
| Adverse events at the injection site (overall) | 1,440 | 2.0 [1, 6] | 727 | 2.0 [1, 5] | 1,440 | 4.0 [1, 34] | 727 | 4.0 [1, 32] |
| Erythema | 152 | 3.0 [1, 7] | 74 | 3.0 [1, 4] | 152 | 4.0 [1, 29] | 74 | 3.5 [1, 11] |
| Swelling | 222 | 2.0 [1, 7] | 118 | 2.0 [1, 4] | 222 | 3.0 [1, 28] | 118 | 3.0 [1, 15] |
| Induration | 150 | 2.0 [1, 7] | 82 | 2.0 [1, 5] | 150 | 3.0 [1, 25] | 82 | 4.0 [1, 9] |
| Pain | 1,420 | 2.0 [1, 4] | 709 | 2.0 [1, 3] | 1,420 | 4.0 [1, 34] | 709 | 4.0 [1, 32] |
| Warmth | 609 | 2.0 [1, 7] | 345 | 2.0 [1, 4] | 609 | 3.0 [1, 15] | 345 | 3.0 [1, 29] |
| Pruritus | 258 | 4.0 [1, 8] | 128 | 4.0 [1, 7] | 258 | 3.0 [1, 28] | 128 | 2.0 [1, 28] |
| Systemic adverse events (overall) | 1,051 | 2.0 [1, 8] | 538 | 2.0 [1, 8] | 1,051 | 3.0 [1, 42] | 538 | 3.0 [1, 32] |
| Pyrexia | 521 | 2.0 [1, 5] | 276 | 2.0 [1, 7] | 521 | 2.0 [1, 9] | 276 | 2.0 [1, 26] |
| Malaise | 851 | 2.0 [1, 8] | 447 | 2.0 [1, 8] | 851 | 2.0 [1, 42] | 447 | 3.0 [1, 32] |
| Headache | 591 | 2.0 [1, 8] | 319 | 2.0 [1, 8] | 591 | 2.0 [1, 32] | 319 | 2.0 [1, 27] |
| Rash | 25 | 4.0 [1, 8] | 8 | 3.0 [2, 5] | 25 | 3.0 [1, 19] | 8 | 2.0 [1, 15] |
| Myalgia | 316 | 2.0 [1, 7] | 180 | 2.0 [1, 5] | 316 | 2.0 [1, 29] | 180 | 2.0 [1, 28] |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0
a) Adverse events that did not resolve until data cut-off date were handled as events that persisted until Day 29 in the concerned subject.

**Table 35. Time to onset and duration of solicited adverse events (Part 2 of Study 146, primary Spikevax cohort, safety analysis set)**

| MedDRA PT | Time to onset (days) | | | | Duration (days)[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona (N = 1,469) | | Spikevax (N = 735) | | Daichirona (N = 1,469) | | Spikevax (N = 735) | |
| | n | Median [range] | n | Median [range] | n | Median [range] | n | Median [range] |
| Adverse events at the injection site (overall) | 1,411 | 2.0 [1, 6] | 700 | 1.0 [1, 3] | 1,411 | 4.0 [1, 34] | 700 | 4.0 [1, 29] |
| Erythema | 194 | 3.0 [1, 8] | 140 | 3.0 [1, 10] | 194 | 4.0 [1, 34] | 140 | 3.0 [1, 10] |
| Swelling | 248 | 2.0 [1, 6] | 176 | 2.0 [1, 4] | 248 | 3.0 [1, 16] | 176 | 3.0 [1, 12] |
| Induration | 156 | 2.0 [1, 8] | 117 | 2.0 [1, 4] | 156 | 4.0 [1, 18] | 117 | 4.0 [1, 26] |
| Pain | 1,380 | 2.0 [1, 4] | 688 | 2.0 [1, 3] | 1,380 | 4.0 [1, 34] | 688 | 4.0 [1, 29] |
| Warmth | 757 | 2.0 [1, 7] | 425 | 2.0 [1, 5] | 757 | 3.0 [1, 19] | 425 | 3.0 [1, 11] |
| Pruritus | 277 | 4.0 [1, 8] | 152 | 4.0 [1, 7] | 277 | 3.0 [1, 28] | 152 | 3.0 [1, 13] |
| Systemic adverse events (overall) | 1,156 | 2.0 [1, 8] | 599 | 2.0 [1, 7] | 1,156 | 3.0 [1, 29] | 599 | 3.0 [1, 25] |
| Pyrexia | 626 | 2.0 [1, 7] | 349 | 2.0 [1, 6] | 626 | 2.0 [1, 9] | 349 | 2.0 [1, 24] |
| Malaise | 984 | 2.0 [1, 8] | 498 | 2.0 [1, 6] | 984 | 2.0 [1, 29] | 498 | 2.0 [1, 25] |
| Headache | 677 | 2.0 [1, 8] | 358 | 2.0 [1, 8] | 677 | 2.0 [1, 19] | 358 | 2.0 [1, 19] |
| Rash | 22 | 4.0 [1, 6] | 17 | 3.0 [1, 6] | 22 | 3.0 [1, 27] | 17 | 2.0 [1, 7] |
| Myalgia | 342 | 2.0 [1, 5] | 191 | 2.0 [1, 3] | 342 | 2.0 [1, 14] | 191 | 2.0 [1, 12] |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0
a) Adverse events that did not resolve until data cut-off date were handled as events that persisted until Day 29 in the concerned subject.

Severe solicited adverse events at the injection site:

In the primary Comirnaty cohort, severe solicited adverse events at the injection site in the Daichirona group developed until Day 2 (median 1.0 day) and persisted for 3 to 29 days (median 6.0 days) and those in the Comirnaty group developed until Day 2 (median 2.0 days) and persisted for 2 to 8 days (median 6.0 days). As for outcome at the time of data cut-off, the events in 2 subjects (injection site erythema and injection site swelling in 1 subject each) in the Daichirona group did not resolve[25] but the other events resolved. In the primary Spikevax cohort, severe solicited adverse events at the injection site in the Daichirona group developed until Day 2 (median 1.0 day) and persisted for 3 to 34 days (median 8.0 days) and those in the Spikevax group developed until Day 2 (median 2.0 days) and

[25] Injection site erythema in 1 subject resolved on Day 42, and injection site swelling in 1 subject resolved on Day 12.

persisted for 2 to 12 days (median 4.0 days). As for the outcome at the time of data cut-off, the events in 2 subjects (injection site erythema in both) in the Daichirona group did not resolve[26] but the other events resolved.

Severe solicited systemic adverse events:

In the primary Comirnaty cohort, severe solicited systemic adverse events in the Daichirona group developed until Day 3 (median 2.0 days) and persisted for 1 to 19 days (median 4.0 days) and those in the Comirnaty group developed until Day 2 (median 2.0 days) and persisted for 2 to 29 days (median 5.0 days). As for the outcome at the time of data cut-off, the event in 1 subject (myalgia/malaise) in the Comirnaty group did not resolve[27] but the other events resolved. In the primary Spikevax cohort, severe solicited systemic adverse events developed until Day 2 (median 2.0 days) and persisted for 2 to 14 days (median 4.0 days) in the Daichirona group and those in the Spikevax group developed until Day 2 (median 2.0 days) and persisted for 2 to 25 days (median 4.0 days). As for the outcome at the time of data cut-off, the event in 1 subject (malaise) in the Spikevax group did not resolve[27] but the other events resolved.

Table 36 shows delayed adverse events at the injection site and systemic adverse events that occurred between Days 9 and 29. The outcome at the time of data cut-off was as follows:

Adverse events at the injection site:

In the Daichirona group, 11 subjects did not recover,[28] 1 subject was recovering, and all the other subjects recovered. In the Comirnaty and Spikevax groups, all the subjects recovered.

Systemic adverse events:

In the Daichirona group, 2 subjects did not recover,[29] 1 subject was recovering, and all the other subjects recovered. In the Comirnaty and Spikevax groups, 1 (Comirnaty) and 2 (Spikevax) subjects did not recover,[29] and all the other subjects recovered.

Neither serious delayed adverse events at the injection site nor serious systemic adverse events occurred.

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[26] Injection site erythema in 2 subjects resolved on Days 57 and 66, respectively.

[27] One subject in the Comirnaty group (myalgia/malaise) discontinued the study, leaving the final outcome unknown. One subject in the Spikevax group (malaise) recovered on Day 57.

[28] Injection site erythema or injection site swelling in 6 subjects resolved on Days 33 to 46. As of June 8, 2023, injection site pruritus in 2 subjects, injection site erythema in 2 subjects, and injection site induration in 1 subject did not resolve.

[29] Of the events in 2 subjects in the Daichirona group, headache in 1 subject resolved on Day 44 and rash in 1 subject on Day 57. Myalgia in 1 subject in the Comirnaty group resolved on Day 129. Of the events in 2 subjects in the Spikevax group, malaise in 1 subject resolved on Day 33. As of June 8, 2023, 1 subject in the Spikevax group did not recover.

**Table 36. Delayed adverse events at the injection site and systemic adverse events (Part 2 of Study 146, safety analysis set)**

| MedDRA PT | Primary Comirnaty cohort | | | | Primary Spikevax cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona N = 1,538 | | Comirnaty N = 769 | | Daichirona N = 1,469 | | Spikevax N = 735 | |
| | All | Severe | All | Severe | All | Severe | All | Severe |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site (overall) | 48 (3.1) | 5 (0.3) | 3 (0.4) | 0 | 104 (7.1) | 24 (1.6) | 4 (0.5) | 1 (0.1) |
| Erythema | 37 (2.4) | 5 (0.3) | 0 | 0 | 87 (5.9) | 22 (1.5) | 2 (0.3) | 0 |
| Swelling | 16 (1.0) | 2 (0.1) | 0 | 0 | 34 (2.3) | 6 (0.4) | 0 | 0 |
| Induration | 3 (0.2) | 0 | 0 | 0 | 7 (0.5) | 1 (0.1) | 0 | 0 |
| Pain | 0 | 0 | 1 (0.1) | 0 | 3 (0.2) | 0 | 1 (0.1) | 1 (0.1) |
| Warmth | 7 (0.5) | 0 | 0 | 0 | 5 (0.3) | 0 | 0 | 0 |
| Pruritus | 19 (1.2) | 0 | 2 (0.3) | 0 | 31 (2.1) | 1 (0.1) | 2 (0.3) | 0 |
| Systemic adverse events (overall) | 37 (2.4) | 1 (0.1) | 13 (1.7) | 0 | 37 (2.5) | 4 (0.3) | 16 (2.2) | 0 |
| Pyrexia | 10 (0.7) | 1 (0.1) | 1 (0.1) | 0 | 13 (0.9) | 4 (0.3) | 3 (0.4) | 0 |
| Malaise | 7 (0.5) | 0 | 1 (0.1) | 0 | 3 (0.2) | 0 | 5 (0.7) | 0 |
| Headache | 15 (1.0) | 0 | 7 (0.9) | 0 | 20 (1.4) | 0 | 8 (1.1) | 0 |
| Rash | 9 (0.6) | 0 | 3 (0.4) | 0 | 7 (0.5) | 0 | 2 (0.3) | 0 |
| Myalgia | 2 (0.1) | 0 | 1 (0.1) | 0 | 1 (0.1) | 0 | 0 | 0 |

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### (b) Unsolicited adverse events and serious adverse events

For unsolicited adverse events (Table 22) [see Section 7.1.2], the safety profile did not remarkably differ between the Daichirona and active comparator groups. Several serious adverse events occurred as described in Section 7.1.2, but all of them were unrelated to the study vaccine. Daichirona did not cause any situation of particular concern.

### (c) Adverse events by age group

Tables 37 and 38 show (overall and severe) solicited adverse events by age group. The results of pooled data from Parts 1 and 2 are presented because the number of elderly subjects in Study 146 was limited. In both the primary Comirnaty and primary Spikevax cohorts, incidences of solicited adverse events and severe solicited adverse events tended to be lower in elderly than in non-elderly.

**Table 37. Solicited adverse events in the primary Comirnaty cohort by age group (Study 146 [Part 1 and Part 2 pooled], safety analysis set)**

| MedDRA PT | Overall solicited adverse events | | | | Severe solicited adverse events | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 60 µg | | Comirnaty | | Daichirona 60 µg | | Comirnaty | |
| | Healthy adult N = 1,475 | Healthy elderly N = 123 | Healthy adult N = 754 | Healthy elderly N = 75 | Healthy adult N = 1,475 | Healthy elderly N = 123 | Healthy adult N = 754 | Healthy elderly N = 75 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | 1,386 (94.0) | 109 (88.6) | 715 (94.8) | 66 (88.0) | 40 (2.7) | 3 (2.4) | 13 (1.7) | 1 (1.3) |
| Erythema | 144 (9.8) | 13 (10.6) | 72 (9.5) | 6 (8.0) | 14 (0.9) | 1 (0.8) | 1 (0.1) | 0 |
| Swelling | 206 (14.0) | 18 (14.6) | 113 (15.0) | 9 (12.0) | 11 (0.7) | 2 (1.6) | 2 (0.3) | 0 |
| Induration | 132 (8.9) | 22 (17.9) | 81 (10.7) | 9 (12.0) | 5 (0.3) | 1 (0.8) | 0 | 0 |
| Pain | 1,366 (92.6) | 107 (87.0) | 698 (92.6) | 63 (84.0) | 9 (0.6) | 0 | 5 (0.7) | 1 (1.3) |
| Warmth | 582 (39.5) | 42 (34.1) | 332 (44.0) | 29 (38.7) | 15 (1.0) | 0 | 6 (0.8) | 1 (1.3) |
| Pruritus | 247 (16.7) | 19 (15.4) | 120 (15.9) | 13 (17.3) | 0 | 0 | 0 | 0 |
| Systemic adverse events | 1,031 (69.9) | 51 (41.5) | 541 (71.8) | 29 (38.7) | 67 (4.5) | 2 (1.6) | 29 (3.8) | 4 (5.3) |
| Pyrexia | 517 (35.1) | 24 (19.5) | 278 (36.9) | 12 (16.0) | 41 (2.8) | 1 (0.8) | 16 (2.1) | 1 (1.3) |
| Malaise | 840 (56.9) | 34 (27.6) | 449 (59.5) | 20 (26.7) | 30 (2.0) | 1 (0.8) | 15 (2.0) | 2 (2.7) |
| Headache | 583 (39.5) | 28 (22.8) | 321 (42.6) | 8 (10.7) | 8 (0.5) | 0 | 5 (0.7) | 1 (1.3) |
| Rash | 22 (1.5) | 3 (2.4) | 6 (0.8) | 2 (2.7) | 0 | 0 | 0 | 1 (1.3) |
| Myalgia | 308 (20.9) | 14 (11.4) | 181 (24.0) | 16 (21.3) | 5 (0.3) | 1 (0.8) | 5 (0.7) | 2 (2.7) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0

**Table 38. Solicited adverse events in the primary Spikevax cohort by age group (Study 146 [Part 1 and Part 2 pooled], safety analysis set)**

| MedDRA PT | Overall solicited adverse events | | | | Severe solicited adverse events | | | |
|---|---|---|---|---|---|---|---|---|
| | Daichirona 60 μg | | Spikevax | | Daichirona 60 μg | | Spikevax | |
| | Healthy adult N = 1,470 | Healthy elderly N = 49 | Healthy adult N = 753 | Healthy elderly N = 32 | Healthy adult N = 1,470 | Healthy elderly N = 49 | Healthy adult N = 753 | Healthy elderly N = 32 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | 1,413 (96.1) | 47 (95.9) | 720 (95.9) | 26 (81.3) | 57 (3.9) | 4 (8.2) | 41 (5.4) | 0 |
| Erythema | 193 (13.1) | 8 (16.3) | 144 (19.1) | 8 (25.0) | 18 (1.2) | 3 (6.1) | 14 (1.9) | 0 |
| Swelling | 250 (17.0) | 9 (18.4) | 179 (23.8) | 9 (28.1) | 16 (1.1) | 2 (4.1) | 11 (1.5) | 0 |
| Induration | 155 (10.5) | 7 (14.3) | 119 (15.8) | 7 (21.9) | 6 (0.4) | 1 (2.0) | 4 (0.5) | 0 |
| Pain | 1,381 (93.9) | 46 (93.9) | 707 (93.9) | 24 (75.0) | 10 (0.7) | 0 | 13 (1.7) | 0 |
| Warmth | 759 (51.6) | 20 (40.8) | 431 (57.2) | 13 (40.6) | 22 (1.5) | 0 | 14 (1.9) | 0 |
| Pruritus | 277 (18.8) | 13 (26.5) | 159 (21.1) | 7 (21.9) | 2 (0.1) | 0 | 0 | 0 |
| Systemic adverse events | 1,160 (78.9) | 31 (63.3) | 617 (81.9) | 14 (43.8) | 81 (5.5) | 2 (4.1) | 54 (7.2) | 0 |
| Pyrexia | 624 (42.4) | 14 (28.6) | 358 (47.5) | 6 (18.8) | 43 (2.9) | 1 (2.0) | 30 (4.0) | 0 |
| Malaise | 983 (66.9) | 26 (53.1) | 511 (67.9) | 10 (31.3) | 39 (2.7) | 0 | 30 (4.0) | 0 |
| Headache | 686 (46.7) | 7 (14.3) | 368 (48.9) | 8 (25.0) | 11 (0.7) | 0 | 13 (1.7) | 0 |
| Rash | 21 (1.4) | 1 (2.0) | 18 (2.4) | 0 | 0 | 0 | 0 | 0 |
| Myalgia | 342 (23.3) | 8 (16.3) | 198 (26.3) | 5 (15.6) | 9 (0.6) | 1 (2.0) | 9 (1.2) | 0 |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0

### 7.R.3.2 Adverse events of special interest

PMDA reviewed data on shock/anaphylaxis, myocarditis/pericarditis, vaccine-associated enhanced respiratory disease (VAERD)/vaccine-associated enhanced disease (VAED), and Guillain-Barre syndrome, because they have been identified as adverse events and adverse reactions of special interest for the other mRNA vaccines.

**(a) Shock/anaphylaxis**

Preferred terms (PTs) coded to Standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) “Anaphylactic reaction (narrow and broad)” and “Hypersensitivity (narrow)” were collected as adverse events related to shock/anaphylaxis.

In Part 1 of Study 146, adverse events related to shock/anaphylaxis occurred in 3 of 122 subjects (2.5%) in the Daichirona 60 μg group (rash in 2 subjects and urticaria in 1 subject) and 1 of 50 subjects (2.0%) in the Spikevax group (rash). All the events were mild in severity, and a causal relationship to the study vaccine could not be ruled out for any of the events in the Daichirona group. As for the outcome at the time of data cut-off, urticaria in the Daichirona 60 μg group did not resolve but the other events resolved.

In Part 2 of Study 146, adverse events related to shock/anaphylaxis occurred in 105 of 3,007 subjects (3.5%) in the Daichirona 60 μg group (rash in 63 subjects, pruritus in 9 subjects, cough and eczema in 6 subjects each, erythema in 5 subjects, urticaria and injection site rash in 4 subjects each, swelling of eyelid and dyspnoea in 2 subjects each, eye pruritus, ocular hyperaemia, gingival swelling, lip swelling, solar urticaria, hand dermatitis, dermatitis contact, erythema multiforme, chest discomfort, and swelling in 1 subject each [some subjects had more than 1 event]), 20 of 769 subjects (2.6%) in the Comirnaty group (rash in 12 subjects, pruritus in 2 subjects, cough, urticaria, swelling of eyelid, dyspnoea, hand dermatitis, chest discomfort, and asthma in 1 subject each [some subjects had more than 1 event]), and 34 of 735 subjects (4.6%) in the Spikevax group (rash in 18 subjects, cough and

urticaria in 5 subjects each, eczema in 3 subjects, pruritus and dyspnoea in 2 subjects each, eye pruritus, solar urticaria, rhinitis allergic, and oedema in 1 subject each [some subjects had more than 1 event]). Of these, a severe adverse event occurred only in 1 of 769 subjects (0.1%) in the Comirnaty group (rash), but it was unrelated to the study vaccine. Moderate adverse events related to shock/anaphylaxis occurred in 12 of 3,007 subjects (0.4%) in the Daichirona 60 μg group (rash in 7 subjects, urticaria in 2 subjects, pruritus, eye pruritus, ocular hyperaemia, and erythema multiforme in 1 subject each [some subjects had more than 1 event]), 1 of 769 subjects (0.4%) in the Comirnaty group (urticaria in 1 subject), and 4 of 735 subjects (0.5%) in the Spikevax group (rash, cough, pruritus, dyspnoea, and solar urticaria in 1 subject each [some subjects had more than 1 event]). A causal relationship to the study vaccine could not be ruled out for the events in 79 of 3,007 subjects (2.6%) in the Daichirona 60 μg group (rash in 59 subjects, pruritus in 5 subjects, erythema and injection site rash in 4 subjects each, eczema in 3 subjects, cough and dyspnea in 2 subjects each, swelling of eyelid, lip swelling, chest discomfort, and swelling in 1 subject each [some subjects had more than 1 event]), 16 of 769 subjects (2.1%) in the Comirnaty group (rash in 11 subjects, pruritus, cough, swelling of eyelid, dyspnea, and urticaria in 1 subject each), and 22 of 735 subjects (3.0%) in the Spikevax group (rash in 17 subjects, pruritus and urticaria in 2 subjects each, cough, rhinitis allergic, and oedema in 1 subject each [some subjects had more than 1 event]). Of these, the events in the following subjects were moderate: 7 of 3,007 subjects (0.2%) in the Daichirona 60 μg group (rash in 7 subjects), 2 of 769 subjects (0.3%) in the Comirnaty group (rash and urticaria in 1 subject each), and 2 of 735 subjects (0.3%) in the Spikevax group (rash and pruritus in 1 subject each).

The outcome at the time of data cut-off was as follows:

Resolving: The events in 3 subjects in the Daichirona 60 μg group (rash, pruritus, urticaria, and erythema in 1 subject each [some subjects had more than 1 event]) and in 2 subjects in the Spikevax group (pruritus and urticaria in 1 subject each)

Not resolved: The events in 10 subjects in the Daichirona group (cough in 3 subjects, pruritus in 2 subjects, eczema, rash, gingival swelling, lip swelling, and hand dermatitis in 1 subject each), in 2 subjects in the Comirnaty group (urticaria and hand dermatitis in 1 subject each), and in 6 subjects in the Spikevax group (cough, urticaria, and eczema in 2 subjects each) did not resolve.[30)]

Resolved: All the other events

In Study J101, adverse events related to shock/anaphylaxis occurred in 3 of 30 subjects (10.0%) in the Daichirona 30 μg group (dermatitis contact, urticaria, and chest discomfort in 1 subject each), 2 of 26 subjects (7.7%) in the Daichirona 60 μg group (rash in 2 subjects), and 1 of 31 subjects (3.2%) in the placebo group (rhinitis allergic). All the events were mild in severity, and a causal relationship to the study vaccine could not be ruled out for rash in 2 subjects in the Daichirona 60 μg group. As for the outcome at the time of data cut-off, chest discomfort in the Daichirona 30 μg group did not resolve but the other events resolved.

[30)] As of June 8, 2023, all the events resolved, except for events in 2 subjects (lip swelling and pruritus) in the Daichirona group and 2 subjects (cough and urticaria) in the Spikevax group.

In Study 116, adverse events related to shock/anaphylaxis occurred in 1 of 3 subjects (33.3%) in the Daichirona 30 μg group (cough) in Part 1 and 2 of 37 subjects (5.4%) in the Daichirona 60 μg group (cough and chest discomfort in 1 subject each) in Part 2. All the events were mild in severity, and a causal relationship to the study vaccine could not be ruled out for chest discomfort in the Daichirona 60 μg group. All the events resolved.

**(b) Myocarditis/pericarditis, Guillain-Barre syndrome, and VAED/VAERD**

PTs coded to MedDRA High level terms (HLTs) "Noninfectious myocarditis" and "Noninfectious pericarditis" were collected as adverse events related to myocarditis/pericarditis. PTs coded to MedDRA SMQ "Guillain-Barre syndrome (narrow)" were collected as adverse events related to Guillain-Barre syndrome. Adverse events of MedDRA PTs "VAED" and "VARED" as well as severe adverse events of MedDRA PTs "Dyspnoea," "Tachypnoea," "Hypoxia," "COVID-19 pneumonia," "Respiratory failure," and "Acute respiratory distress syndrome" in subjects with confirmed COVID-19 were collected as adverse events related to VAED/VAERD.

In Part 1 and Part 2 of Study 146, Study J101, and Study 116, no adverse events related to myocarditis/pericarditis, Guillain-Barre syndrome, or VAED/VAERD occurred in any group.

The applicant's explanation about the safety of Daichirona based on Sections 7.R.3.1 and 7.R.3.2:

The safety profile of a booster dose of Daichirona did not differ remarkably according to vaccine brand of the primary series or age group (adults or elderly) or did not clearly differ from the safety profile of a booster dose of Comirnaty or Spikevax; Daichirona was thus tolerated. Relatively common solicited adverse events at the injection site were pain and warmth. Relatively common solicited systemic adverse events were malaise, headache, and pyrexia. Most of the adverse events were transient and mild or moderate. Most of the severe adverse events were transient and resolved with or without treatment. There were no serious adverse events for which a causal relationship could not be ruled out. The package inserts for Comirnaty and Spikevax state that attention should be paid to shock/anaphylaxis, myocarditis/pericarditis, Guillain-Barre syndrome, and VAERD/VAED. To date, these adverse events have not been reported in subjects receiving Daichirona, except for adverse events related to shock/anaphylaxis. However, since Daichirona is an mRNA vaccine of the same modality as that of Comirnaty and Spikevax, attention should be paid to a risk of these adverse events as well.

As described above, caution should be raised appropriately based on adverse events reported in the clinical studies of Daichirona and adverse events reported with other vaccines in the same class, but the applicant considers that a booster dose of Daichirona 60 μg is tolerable in individuals aged ≥18 years who have completed the primary series of an approved mRNA SARS-CoV-2 vaccine.

PMDA's view:

No large differences were found in the type or incidence of adverse events between Daichirona and the active comparators, Comirnaty and Spikevax. Most of the adverse events reported with Daichirona were mild or moderate and its safety profile did not differ according to age group. Based on the above

findings, PMDA has concluded that a booster dose of Daichirona 60 μg has a tolerable safety profile in individuals aged ≥18 years. However, attention should be paid to the following findings:

(a) The incidence of delayed injection site reaction was higher in the Daichirona group than in the Comirnaty and Spikevax groups.
(b) In subjects receiving a booster dose of Daichirona, some adverse events tended to occur more frequently in the primary Spikevax cohort than in the primary Comirnaty cohort.

Of adverse events of special interest, adverse events related to shock/anaphylaxis that occurred after Daichirona vaccination were all mild or moderate hypersensitivity, and Daichirona is thus tolerable.

Further, attention should be paid to myocarditis/pericarditis, Guillain-Barre syndrome, and VAERD/VAED (which are adverse events of special interest for Comirnaty and Spikevax) and, as proposed by the applicant, caution should be raised about these events, for the following reasons:

(a) These events occur rarely and did not occur in subjects enrolled in the submitted clinical studies of Daichirona, including those receiving the active comparator (Comirnaty or Spikevax). Thus definite risk assessment cannot be made based on the information available to date.
(b) Since Daichirona is an mRNA vaccine of the same modality as that of Comirnaty and Spikevax, these events may also occur in individuals receiving Daichirona.

These adverse events should be closely monitored after the market launch, and appropriate risk assessment and actions such as review of the safety measures should be made in a timely manner.

#### 7.R.3.3 Safety in population with special characteristics

The applicant's explanation about the safety of Daichirona in population with special characteristics:

(a) Individuals with underlying diseases

According to its exclusion criteria, Study 146 excluded individuals with serious cardiovascular, renal, hepatic, hematologic, or neuropsychiatric disease, developmental disorder, thrombocytopenia, or coagulation disorder. A post hoc analysis was performed to evaluate the safety in subjects who had at least 1 pre-existing disease (including medical history) but did not meet the above exclusion criteria when enrolled in Part 2 of Study 146. Of 4,511 subjects in the safety analysis set, 2,059 had pre-existing diseases. Among the pre-existing diseases, the following were deemed as underlying diseases at high risk of severe COVID-19 or high risk factors for severe COVID-19[31)]: respiratory diseases in 63 subjects, cardiac diseases in 220 subjects (including hypertension in 199 subjects), hepatic diseases in 105 subjects, renal diseases in 8 subjects, diabetes mellitus in 120 subjects, hematologic diseases in 6 subjects, malignant tumor in 27 subjects, dyslipidaemia in 390 subjects, and cerebrovascular disease in 1 subject. Table 39 shows incidences of solicited adverse events in the populations with and without pre-existing disease(s). In the population with pre-existing diseases, adverse events including unsolicited adverse events occurred in 96.7% (722 of 747) of subjects in the Daichirona group and 98.7% (366 of 371) of subjects in the Comirnaty group in the primary Comirnaty cohort, and 98.7% (613 of 621) of subjects in the Daichirona group and 98.4% (315 of 320) of subjects in the Spikevax group in the primary Spikevax cohort. In the population without pre-existing diseases, adverse events including unsolicited adverse events occurred in 96.3% (762 of

[31)] Underlying diseases at high risk of severe COVID-19 were defined as the medical conditions presented in the minutes of the 44th Subcommittee meeting on basic vaccination policy of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (held on March 18, 2021) or in Guidelines for Diagnosis and Treatment of COVID 19, ver. 9.0 (February 10, 2023).

791) of subjects in the Daichirona group and 96.5% (384 of 398) of subjects in the Comirnaty group in the primary Comirnaty cohort, and 97.6% (828 of 848) of subjects in the Daichirona group and 96.9% (402 of 415) of subjects in the Spikevax group in the primary Spikevax cohort. Even in view of incidences of individual adverse events, the safety profile did not clearly differ between the populations with and without pre-existing diseases.

Based on the above, Daichirona did not raise any concern of increased incidence and severity of adverse events in subjects with pre-existing diseases.

**Table 39. Solicited adverse events in subjects with and without pre-existing diseases (Part 2 of Study 146, safety analysis set)**

| MedDRA PT | | With pre-existing disease(s) | | | | Without pre-existing disease(s) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Primary Comirnaty cohort | | Primary Spikevax cohort | | Primary Comirnaty cohort | | Primary Spikevax cohort | |
| | | Daichirona N = 747 | Comirnaty N = 371 | Daichirona N = 621 | Spikevax N = 320 | Daichirona N = 791 | Comirnaty N = 398 | Daichirona N = 848 | Spikevax N = 415 |
| | | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | All | 702 (94.0) | 359 (96.8) | 598 (96.3) | 311 (97.2) | 738 (93.3) | 368 (92.5) | 813 (95.9) | 389 (93.7) |
| | Severe | 24 (3.2) | 10 (2.7) | 29 (4.7) | 20 (6.3) | 19 (2.4) | 4 (1.0) | 27 (3.2) | 19 (4.6) |
| Erythema | All | 72 (9.6) | 37 (10.0) | 84 (13.5) | 60 (18.8) | 80 (10.1) | 37 (9.3) | 110 (13.0) | 80 (19.3) |
| | Severe | 5 (0.7) | 0 | 11 (1.8) | 5 (1.6) | 10 (1.3) | 1 (0.3) | 9 (1.1) | 8 (1.9) |
| Swelling | All | 120 (16.1) | 60 (16.2) | 108 (17.4) | 81 (25.3) | 102 (12.9) | 58 (14.6) | 140 (16.5) | 95 (22.9) |
| | Severe | 10 (1.3) | 1 (0.3) | 9 (1.4) | 6 (1.9) | 3 (0.4) | 1 (0.3) | 7 (0.8) | 5 (1.2) |
| Induration | All | 82 (11.0) | 47 (12.7) | 84 (13.5) | 59 (18.4) | 68 (8.6) | 35 (8.8) | 72 (8.5) | 58 (14.0) |
| | Severe | 5 (0.7) | 0 | 4 (0.6) | 2 (0.6) | 1 (0.1) | 0 | 2 (0.2) | 2 (0.5) |
| Pain | All | 691 (92.5) | 351 (94.6) | 585 (94.2) | 307 (95.9) | 729 (92.2) | 358 (89.9) | 795 (93.8) | 381 (91.8) |
| | Severe | 5 (0.7) | 4 (1.1) | 6 (1.0) | 7 (2.2) | 4 (0.5) | 2 (0.5) | 4 (0.5) | 6 (1.4) |
| Warmth | All | 325 (43.5) | 176 (47.4) | 332 (53.5) | 196 (61.3) | 284 (35.9) | 169 (42.5) | 425 (50.1) | 229 (55.2) |
| | Severe | 8 (1.1) | 6 (1.6) | 10 (1.6) | 5 (1.6) | 7 (0.9) | 1 (0.3) | 11 (1.3) | 8 (1.9) |
| Pruritus | All | 131 (17.5) | 70 (18.9) | 124 (20.0) | 73 (22.8) | 127 (16.1) | 58 (14.6) | 153 (18.0) | 79 (19.0) |
| | Severe | 0 | 0 | 2 (0.3) | 0 | 0 | 0 | 0 | 0 |
| Systemic adverse events | All | 530 (71.0) | 256 (69.0) | 493 (79.4) | 266 (83.1) | 521 (65.9) | 282 (70.9) | 663 (78.2) | 333 (80.2) |
| | Severe | 39 (5.2) | 17 (4.6) | 40 (6.4) | 25 (7.8) | 29 (3.7) | 16 (4.0) | 42 (5.0) | 28 (6.7) |
| Pyrexia | All | 271 (36.3) | 139 (37.5) | 271 (43.6) | 164 (51.3) | 250 (31.6) | 137 (34.4) | 355 (41.9) | 185 (44.6) |
| | Severe | 26 (3.5) | 10 (2.7) | 19 (3.1) | 14 (4.4) | 16 (2.0) | 7 (1.8) | 25 (2.9) | 16 (3.9) |
| Malaise | All | 427 (57.2) | 210 (56.6) | 427 (68.8) | 223 (69.7) | 424 (53.6) | 237 (59.5) | 557 (65.7) | 275 (66.3) |
| | Severe | 16 (2.1) | 9 (2.4) | 21 (3.4) | 12 (3.8) | 14 (1.8) | 8 (2.0) | 17 (2.0) | 17 (4.1) |
| Headache | All | 303 (40.6) | 156 (42.0) | 304 (49.0) | 169 (52.8) | 288 (36.4) | 163 (41.0) | 373 (44.0) | 189 (45.5) |
| | Severe | 5 (0.7) | 6 (1.6) | 5 (0.8) | 5 (1.6) | 3 (0.4) | 0 | 5 (0.6) | 8 (1.9) |
| Rash | All | 15 (2.0) | 5 (1.3) | 14 (2.3) | 11 (3.4) | 10 (1.3) | 3 (0.8) | 8 (0.9) | 6 (1.4) |
| | Severe | 0 | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 |
| Myalgia | All | 151 (20.2) | 85 (22.9) | 150 (24.2) | 88 (27.5) | 165 (20.9) | 95 (23.9) | 192 (22.6) | 103 (24.8) |
| | Severe | 2 (0.3) | 4 (1.1) | 3 (0.5) | 5 (1.6) | 4 (0.5) | 3 (0.8) | 7 (0.8) | 4 (1.0) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0

(b) Pregnant and lactating women

In non-clinical reproductive and developmental toxicity studies, Daichirona had no effects on (a) general toxicity and reproductive capacity in maternal animals, (b) offspring development, or (c) pre- and post-natal development in the offspring [see Section 5.5]. In all the clinical studies, however, pregnant women were ineligible, and the safety of Daichirona in pregnant women has not been established. In any of the clinical studies, no pregnancy was reported up to the data-cutoff date of each study. Therefore, the package insert should include a cautionary statement to the following effect: "Daichirona should be used in pregnant or possibly pregnant women only if the expected benefits of vaccination outweigh its possible risks." In addition, since lactating women have not been vaccinated as with pregnant women in clinical studies, the package insert should include the following cautionary statements: (a) "Whether to continue or discontinue lactating should be considered by weighing vaccination benefits against breastfeeding benefits." and (b) "Whether Daichirona transfers into human milk remains unknown."

As described above, the clinical studies of Daichirona conducted so far excluded populations such as (a) and (b) who are classified as populations requiring attention in the package inserts for vaccine products in the same class. On the basis of this fact and according to the "Interim guidelines for vaccination against COVID-19 (in Japanese)" (issued by MHLW on August 1, 2022), the package insert of Daichirona should include cautionary statements similar to those included in the package inserts for the vaccine products in the same class.

PMDA's view:
In Study 146, a comparison between the population with pre-existing diseases and the overall population has raised no safety concerns requiring special attention. Currently, no particular caution is required for individuals with pre-existing diseases. However, experience with Daichirona in subjects with pre-existing diseases is limited, and thus its vaccination would require further attention. Caution should be raised as done for vaccine products in the same class.

Regarding use in pregnant and lactating women, the Center for Disease Control (CDC) in the US recommends pregnant women, including lactating women, to be vaccinated,[32)] because the safety information in pregnant women who had received mRNA vaccine (Comirnaty or Spikevax), obtained from multiple adverse reaction reporting systems such as Vaccine Adverse Event Reporting System (VAERS), has not shown particular safety signals currently, and because pregnant women have a risk of severe COVID-19. In Japan, these women are also encouraged to receive SARS-CoV-2 vaccine in view of the risk of severe COVID-19 in pregnant women (Administrative Notice "Encouragement of COVID-19 vaccination and preventive measures against COVID-19 (in Japanese)" dated August 23, 2021, issued by Immunization Office, Health Service Division, Health Service Bureau, MHLW and Maternal and Child Health Division, Child and Family Policy Bureau, MHLW). In view of the above situations, pregnant and lactating women are expected to receive Daichirona. Although the non-clinical studies has shown no Daichirona-associated safety concerns in dams and offspring, the package insert should include cautionary statements for use in pregnant and lactating women as with the package inserts for vaccine products in the same class, for the following reasons: (1) Daichirona has not been used in pregnant women; (2) transfer of Daichirona into milk has not been investigated and thus remains unknown; and (3) Daichirona has not been used in lactating women.

After the market launch, Daichirona is expected to be used in individuals with various characteristics including populations with special characteristics, which were excluded from the clinical studies. The applicant is required to (a) collect safety information of Daichirona from a wide range of vaccine recipients including individuals in such populations and (b) consider whether additional safety measures should be taken in a timely manner based on the obtained information.

### 7.R.4 Clinical positioning and indication

The proposed indication is "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)."

32) https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html (last accessed on June 9, 2023)

The applicant's explanation about clinical positioning of Daichirona:
Data from the foreign clinical studies of Comirnaty and Spikevax and from Part 2 of Study 146 showed the following results of the efficacy and safety of Daichirona versus Comirnaty and Spikevax (approved vaccines in Japan):

(a) The lower limit of 97.5% CI of GMFR ratio of Daichirona to the active comparator exceeded 0.67, the pre-determined non-inferiority margin, irrespective of vaccine brand of the primary series, demonstrating the non-inferiority of Daichirona to the active comparator [see Section 7.1.2].
(b) Compared with a booster dose of Comirnaty or Spikevax, a booster dose Daichirona did not raise clear concerns about safety. Daichirona was accordingly considered to be tolerable.

Based on the above, Daichirona is considered clinically useful as a booster vaccine in individuals who have completed the primary series of an approved vaccine against SARS-CoV-2.

The primary series of Comirnaty and Spikevax has been demonstrated to induce blood anti-SARS-CoV-2 neutralizing antibodies, to have the consistent efficacy and safety irrespective of age, sex, race, and ethnic group, and to provide ≥90% protection against COVID-19 (*N Engl J Med.* 2020;383:2603-15, *N Engl J Med.* 2021;384:403-16). The immune response induced by vaccination, however, decreases with time (*MMWR.* 2022;71:139-45). This raises a concern about reduced vaccine effectiveness in preventing severe disease, hospitalization, or death due to SARS-CoV-2, especially in individuals who completed the primary series a certain period of time ago, elderly people, and high-risk individuals with underlying diseases. The immune response that has decreased with time after completion of the primary series is restored by booster vaccination, with the blood anti-SARS-CoV-2 neutralizing antibody level exceeding that achieved by the primary series (*N Engl J Med.*2021;385:1627-9, etc.). In response to re-spread of the infection owing to emergence of variants and the above mentioned decreased immune response, Comirnaty and Spikevax have been used for booster vaccination in individuals who completed the primary series in and outside Japan. To date in Japan, original strain-based vaccines of Comirnaty, Spikevax, Nuvaxovid Intramuscular Injection, and Jcovden Intramuscular Injection are approved for booster vaccination in individuals who have completed the primary series. Furthermore, as results of research and development of variant-adapted vaccines, Omicron variant-adapted bivalent vaccines of Comirnaty (original strain/Omicron variant BA.4/BA.5, original strain/Omicron variant BA.1) and Spikevax (original strain/Omicron variant BA.4/BA.5) are approved. A number of SARS-CoV-2 variants have emerged to date. Having the capability to develop and produce mRNA vaccine in Japan is clinically meaningful, because it enables prompt development of vaccine in response to newly obtained genetic information on a virus to be used as the antigen. By doing so, infection control measures can be taken in Japan without being affected by circumstances outside Japan in case of an emergency situation such as an outbreak of an emerging or re-emerging infection or a pandemic.

A phase III Comirnaty-controlled study (Study DS5670-103) was conducted to evaluate the efficacy (immunogenicity) and safety of Daichirona used for the primary series in subjects aged ≥18 years who had not received SARS-CoV-2 vaccine with no history of SARS-CoV-2 infection, but Daichirona was not shown to be non-inferior to Comirnaty. In view of this result, practicality of the original strain vaccine during the Omicron-predominant period and an announcement for changes of use of

SARS-CoV-2 vaccines,[33] the applicant decided not to submit the application of Daichirona for the primary series.

Currently, the applicant is currently developing a variant-adapted bivalent vaccine using Daichirona as a parent vaccine.[34]

PMDA's view:
Multiple vaccines are commercialized and the vaccinated population is globally expanding, but vaccine effectiveness has been shown to decrease with time. Booster vaccination is needed to maintain the effectiveness (*Lancet.* 2021;398:1377-80). In addition, a booster dose of the original strain-based vaccine (monovalent) restored the decreased blood anti-SARS-CoV-2 neutralizing antibody titer in adults and strengthened the clinical effectiveness against COVID-19, hospitalization, and COVID-19-related deaths (*Nat Med.* 2022;28:1042-9, *Nat Med.* 2022;28:1063-71).

Currently, multiple reports are available on the effectiveness of bivalent mRNA vaccines including Omicron variant-adapted vaccines (Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review. March 9, 2023).[35] In Japan, variant-adapted vaccines, Comirnaty and Spikevax (bivalent, original strain/Omicron variant), were approved for booster vaccination in September 2022, and these bivalent vaccines are designated as mRNA vaccines to be used for booster vaccination (HSB Notification No. 0308-15 "Partial revision of 'Vaccination against COVID-19 (instruction) (in Japanese)'" dated March 8, 2023, MHLW). In view of currently prevalent variants and accordingly recommended variant-adapted vaccines, PMDA must say that clinical positioning of Daichirona, the original strain-based vaccine, remains unclear. However, Daichirona is considered clinically meaningful as one of the new vaccine options for prevention of SARS-CoV-2 infection, for the following reasons:

(a) Even a booster dose of the original strain-based vaccine has been reported to prevent severe COVID-19 requiring emergency department visit or hospitalization (*MMWR.* 2022;71:139-45).
(b) A booster dose of Daichirona was shown to induce production of neutralizing antibodies to a certain extent, and thus its efficacy can be expected to some extent.
(c) Having the capability to develop and produce vaccines in Japan is deemed particularly critical to ensure (i) reliable vaccine supply to people in Japan without being affected by circumstances outside Japan and (ii) prompt development and supply of new variant-adapted vaccines ("Strategy for Strengthening the Vaccine Development and Production System" decided by the Cabinet on June 1, 2021).

Based on the above, the indication of Daichirona should be "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as proposed by the applicant. This is the same as the indication of the approved SARS-CoV-2 vaccines. Based on the currently available data, PMDA considers that

[33] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-changes-simplify-use-bivalent-mrna-covid-19-vaccines (last accessed on June 9, 2023)
[34] https://www.daiichisankyo.co.jp/files/news/pressrelease/pdf/202305/20230519_J.pdf, https://www.daiichisankyo.com/files/news/pressrelease/pdf/202305/20230519_E.pdf (last accessed on June 9, 2023)
[35] https://view-hub.org/sites/default/files/2023-03/COVID19%20VE%20Studies_Bivalent%20VE%20Plots.pdf (last accessed on June 9, 2023)

Daichirona is only useful for booster vaccination in individuals who have completed the primary series of an approved SARS-CoV-2 vaccine.

### 7.R.5 Dosage and administration

The proposed dosage and administration is "A single dose of 0.6 mL is injected intramuscularly as a booster dose."

The applicant proposed the following statements as the Precautions Concerning Dosage and Administration:

(1) Daichirona should be used in individuals aged ≥18 years who have completed the primary series or received a booster dose of SARS-CoV-2 vaccine.
(2) The efficacy and safety of Daichirona have not been established in individuals who have received SARS-CoV-2 vaccine other than Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2).
(3) A booster dose of Daichirona should be administered ≥3 months after the last dose of SARS-CoV-2 vaccine.

PMDA's conclusion:

Based on review in Sections 7.R.2 to 7.R.4 and the following sections, the proposed dosage and administration and the proposed Precautions Concerning Dosage and Administration are acceptable. However, the interval from the last dose of a SARS-CoV-2 vaccine should be changed from "≥3 months" to "≥6 months" in the Precautions Concerning Dosage and Administration.

#### 7.R.5.1 Dosage and administration for booster dose

The applicant's explanation about the dosage and administration for the booster dose:

In the parallel-group part in Part 1 of Study 146, booster vaccination with Daichirona increased blood anti-SARS-CoV-2 (the original strain) neutralizing antibody titer, irrespective of brand of the primary series vaccine and the age (adult or elderly cohort); the GMFR in the Daichirona 60 μg group was highest among all groups and thus higher than that in the active comparator groups. The GMT values in the Daichirona 30 μg and 60 μg groups were similar to or above that in the active comparator groups in both adult and elderly cohorts, irrespective of brand of the primary series vaccine. The antibody response rate exceeded 90% in all groups, irrespective of brand of the primary series vaccine and the age (adult or elderly cohort). Based on the above results, the recommended dose of 60 μg was selected for booster vaccination with Daichirona, because the dose is expected to have high efficacy in both adults and elderly irrespective of brand of the primary series vaccine and has not raised any considerable safety concerns.

The results from Part 2 of Study 146 showed that booster vaccination with Daichirona 60 μg is expected to have efficacy [see Section 7.R.2], and that there were no critical concerns regarding its safety profile [see Section 7.R.3]. In the present application, therefore, the dose of 60 μg (or the vaccination volume of 0.6 mL) was selected for booster vaccination with Daichirona.

PMDA's conclusion:

In view of the review in Sections 7.R.2 to 7.R.4, the dose of 60 μg (or the vaccination volume of 0.6 mL) is acceptable for booster vaccination with Daichirona.

### 7.R.5.2 Target population

The applicant's explanation about (a) to (c) regarding the target population of Daichirona:

(a) Age of the target population

The age eligible for booster vaccination with Daichirona is ≥18 years based on the age eligible for Study 146.

The applicant plans to obtain an approval of a variant-adapted vaccine (using Daichirona [monovalent, the original strain] as a parent vaccine), which is currently under development. Individuals aged <18 years will be included in the eligible population for the variant-adapted vaccine.

(b) Use in previously infected individuals

Study 146 excluded individuals with a history of SARS-CoV-2 infection in accordance with the exclusion criteria, and no data are available on the efficacy or safety of Daichirona in previously infected individuals. However, anti-spike protein antibody titer in previously infected individuals was at a certain level before vaccination, but a dose of mRNA SARS-CoV-2 vaccine further increased the titer, exceeding the post-vaccination level in uninfected individuals (*N Engl J Med.* 2021;384:1372-4). A survey in the US conducted from June 2021 to February 2022 showed that vaccine effectiveness of mRNA SARS-CoV-2 vaccine against COVID-19–associated hospitalization was 34.6% (95% CI; 25.5%, 42.5%) after 2 doses and 67.6% (61.4%, 72.8%) after a booster dose in individuals previously infected during the Omicron-predominant period. The vaccination is therefore effective in preventing COVID-19–associated hospitalization in previously infected individuals. The population eligible for vaccination including previously infected individuals is recommended to receive a booster dose to keep themselves highly protected (*MMWR.* 2022;71:549-55). For safety, the incidence of systemic adverse reactions to mRNA SARS-CoV-2 vaccination tended to be higher in previously infected individuals than in previously uninfected individuals, but no adverse reactions requiring hospitalization occurred (*N Engl J Med.* 2021;384:1372-4).

In previously infected individuals, no risks outweighing the benefits from receiving an approved mRNA SARS-CoV-2 vaccine have been identified, and thus vaccination is recommended for previously infected individuals. Daichirona was demonstrated to have the efficacy and safety similar to those of approved mRNA SARS-CoV-2 vaccines, which were used as the active comparators in Study 146. In view of the above current circumstances and findings, the applicant considers that Daichirona can be used in previously infected individuals as with the approved mRNA SARS-CoV-2 vaccines. Of note, the applicant plans to conduct a clinical study that will enroll previously infected individuals. The efficacy and safety in this population can be evaluated based on the results to be obtained from this study.

(c) Vaccination prior to use of Daichirona

Study 146 evaluated the efficacy and safety only of the first booster dose after completion of the primary series (hereinafter, the third dose), but currently people in Japan are receiving the second

booster dose (the fourth dose) and third booster dose (the fifth dose) of other SARS-CoV-2 vaccines. The efficacy and safety of the fourth and subsequent doses of approved mRNA SARS-CoV-2 vaccines have been reported as follows.

According to a survey between December 2021 and August 2022 including 82,229 cases of emergency department visits and hospitalization for COVID-19–like illness in 10 states in the US, the estimated vaccine effectiveness against hospitalization during an Omicron BA.4/BA.5-predominant period was higher in patients after the third or fourth dose than in patients after 2 doses of an original strain-based monovalent vaccine (*JAMA Network Open.* 2023;6:e232598). In the US, approximately 16.80 million people aged ≥50 years received the fourth dose of an mRNA SARS-CoV-2 vaccine between March 29 and July 10, 2022. In individuals who received the same brand of mRNA SARS-CoV-2 vaccine for all doses, incidences of adverse reactions at the injection site and systemic adverse reactions were lower after the fourth dose than after the third dose. Of 8,515 adverse events reported, 94.8% were non-serious (*MMWR.* 2022;71:971-76).

Furthermore, in Study 146, the efficacy and safety of the third dose of Daichirona were similar to those of Comirnaty and Spikevax. In view of this finding in Study 146, the above reports, and current vaccination status, the applicant has proposed that Daichirona should be indicated for not only individuals who completed the primary series but also individuals who received a booster dose without restriction of the number of doses as with the approved mRNA SARS-CoV-2 vaccines of the same modality. Because the efficacy of SARS-CoV-2 vaccines decreases with time (*MMWR.* 2022;71:235-63), and the need of booster vaccination has been recognized, the applicant considers it clinically useful to make Daichirona available without restriction of the number of doses. Of note, the applicant plans to evaluate the efficacy and safety of the fourth and subsequent doses Daichirona n a clinical study to be conducted in the future.

No clinical studies of a booster dose of Daichirona in subjects who previously received non-mRNA SARS-CoV-2 vaccines have been conducted to date, and thus no findings are available on the efficacy or safety of a booster dose of Daichirona in subjects who previously received a SARS-CoV-2 vaccine of a different modality. Some of the Comirnaty or Spikevax recipients received a booster vaccine different from the primary vaccine in modality (i.e., they received Vaxzevria Intramuscular Injection or Jcovden Intramuscular Injection as the primary vaccine and then received a booster dose of Comirnaty or Spikevax, or vice versa) (*Lancet.* 2021;398:2258-76, *N Engl J Med.* 2022;386:1046-57, etc.), raising no concerns about the immunogenicity or safety. In view of the reports on mRNA vaccines of the same modality as that of Daichirona, the applicant considered that the efficacy and safety of Daichirona used for booster vaccination in individuals who previously received non-mRNA SARS-CoV-2 vaccines would not raise significant concerns but decided to present a precautionary statement that the efficacy and safety in such individuals have not been established owing to absence of the data.

PMDA's view:

The applicant's explanation about all of (a) to (c) is acceptable. The applicant proposed that the number of doses of Daichirona should not be restricted. Although no study results of Daichirona are

available that support the proposal, the approved mRNA SARS-CoV-2 vaccines of the same modality have been used without restriction of the number of doses. According to the current SARS-CoV-2 vaccination status in Japan, the number of doses received by each individual differs depending on age and type of occupation. PMDA considers it certainly meaningful to allow people who have completed the primary series of a SARS-CoV-2 vaccine to receive booster vaccination with Daichirona without restriction of the number of doses. When new information becomes available about (a) the use in previously infected individuals and (b) the efficacy and safety of the fourth and subsequent doses of Daichirona, the applicant should provide it to healthcare professionals.

### 7.R.5.3 Interval between doses

The applicant's explanation about the interval between the last dose of a SARS-CoV-2 vaccine and a dose of Daichirona:

Study 146 included individuals who had completed the primary series of an approved SARS-CoV-2 vaccine (Comirnaty or Spikevax) ≥6 months before. In the immunogenicity-evaluable PPS in Part 2 of the study, the median interval (range) between the second dose of the primary series and a dose of the study vaccine was 8.1 (6.0-18.4) months. Table 40 shows immunogenicity data in the Daichirona group versus the active comparator groups by the interval between the second dose of the primary series and the booster dose (<8 month and ≥8 month) in Part 2. The results showed that immune responses to Daichirona by the interval did not differ from those to Comirnaty or Spikevax, the approved SARS-CoV-2 vaccines.

**Table 40. Immunogenicity on Day 28 after study vaccination by interval between primary series and study vaccination (immunogenicity-evaluable PPS) (Part 2 of Study 146)**

| | <8 months | | ≥8 months | |
|---|---|---|---|---|
| | Primary Comirnaty cohort | Primary Spikevax cohort | Primary Comirnaty cohort | Primary Spikevax cohort |
| | Daichirona/ Comirnaty | Daichirona/ Spikevax | Daichirona/ Comirnaty | Daichirona/ Spikevax |
| N | 75/37 | 54/26 | 65/32 | 88/44 |
| n | 73/35 | 51/25 | 64/31 | 85/44 |
| GMT ratio [two-sided 95% CI][a)] | 1.203 [0.843, 1.718] | 2.041 [1.417, 2.940] | 1.697 [1.136, 2.535] | 1.814 [1.277, 2.577] |
| Adjusted GMFR ratio [two-sided 95% CI][a)] | 1.168 [0.847, 1.610] | 1.830 [1.280, 2.616] | 1.888 [1.311, 2.718] | 1.757 [1.254, 2.461] |
| Difference in antibody response rate [two-sided 95% CI][e)] | −1.4 [−7.4, 8.6] | 2.1 [−9.5, 19.5] | −1.5 [−10.1, 11.9] | 2.1 [−6.0, 13.9] |

N = Number of subjects analyzed, n = Number of subjects evaluated for immunogenicity

a) GMT ratio = GMT (Daichirona)/GMT (active comparator). The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer.

b) GMFR ratio = GMFR (Daichirona)/GMFR (active comparator). Adjusted according to a covariance model. The two-sided 95% CI was calculated on the assumption of t-distribution for logarithm of the antibody titer.

c) Difference in antibody response rate = (Daichirona) − (active comparator). The two-sided 95% CI was calculated according to a Newcombe-Wilson method.

Table 41 shows solicited adverse events by interval between the second dose of the primary series and the booster dose (<8 months and ≥8 months) in Part 2. No clear differences were observed in incidence of the adverse events between <8 months and ≥8 months.

**Table 41. Solicited adverse events by interval between primary series and study vaccination (Part 2 of Study 146, safety analysis set)**

| MedDRA PT | | <8 months | | | | ≥8 months | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Primary Comirnaty cohort | | Primary Spikevax cohort | | Primary Comirnaty cohort | | Primary Spikevax cohort | |
| | | Daichirona N = 366 | Comirnaty N = 186 | Daichirona N = 219 | Spikevax N = 116 | Daichirona N = 1,172 | Comirnaty N = 583 | Daichirona N = 1,250 | Spikevax N = 619 |
| | | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events at the injection site | All | 342 (93.4) | 176 (94.6) | 210 (95.9) | 109 (94.0) | 1,098 (93.7) | 551 (94.5) | 1,201 (96.1) | 591 (95.5) |
| | Severe | 9 (2.5) | 2 (1.1) | 7 (3.2) | 8 (6.9) | 34 (2.9) | 12 (2.1) | 49 (3.9) | 31 (5.0) |
| Erythema | All | 32 (8.7) | 13 (7.0) | 30 (13.7) | 18 (15.5) | 120 (10.2) | 61 (10.5) | 164 (13.1) | 122 (19.7) |
| | Severe | 3 (0.8) | 0 | 2 (0.9) | 3 (2.6) | 12 (1.0) | 1 (0.2) | 18 (1.4) | 10 (1.6) |
| Swelling | All | 48 (13.1) | 23 (12.4) | 34 (15.5) | 29 (25.0) | 174 (14.8) | 95 (16.3) | 214 (17.1) | 147 (23.7) |
| | Severe | 4 (1.1) | 0 | 2 (0.9) | 3 (2.6) | 9 (0.8) | 2 (0.3) | 14 (1.1) | 8 (1.3) |
| Induration | All | 36 (9.8) | 17 (9.1) | 16 (7.3) | 19 (16.4) | 114 (9.7) | 65 (11.1) | 140 (11.2) | 98 (15.8) |
| | Severe | 2 (0.5) | 0 | 0 | 2 (1.7) | 4 (0.3) | 0 | 6 (0.5) | 2 (0.3) |
| Pain | All | 340 (92.9) | 171 (91.9) | 205 (93.6) | 106 (91.4) | 1,080 (92.2) | 538 (92.3) | 1,175 (94.0) | 582 (94.0) |
| | Severe | 3 (0.8) | 1 (0.5) | 2 (0.9) | 3 (2.6) | 6 (0.5) | 5 (0.9) | 8 (0.6) | 10 (1.6) |
| Warmth | All | 141 (38.5) | 82 (44.1) | 103 (47.0) | 64 (55.2) | 486 (39.9) | 263 (45.1) | 654 (52.3) | 361 (58.1) |
| | Severe | 3 (0.8) | 2 (1.1) | 3 (1.4) | 0 | 12 (1.0) | 5 (0.9) | 18 (1.4) | 13 (2.1) |
| Pruritus | All | 63 (17.2) | 29 (15.6) | 39 (17.8) | 26 (22.4) | 195 (16.6) | 99 (17.0) | 238 (19.0) | 126 (20.4) |
| | Severe | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.2) | 0 |
| Systemic adverse events | All | 233 (63.7) | 138 (74.2) | 166 (75.8) | 94 (81.0) | 818 (69.8) | 400 (68.6) | 990 (79.2) | 505 (81.6) |
| | Severe | 18 (4.9) | 13 (7.0) | 17 (7.8) | 7 (6.0) | 50 (4.3) | 20 (3.4) | 65 (5.2) | 46 (7.4) |
| Pyrexia | All | 120 (32.8) | 68 (36.6) | 84 (38.4) | 49 (42.2) | 401 (34.2) | 208 (35.7) | 542 (43.4) | 300 (48.5) |
| | Severe | 10 (2.7) | 7 (3.8) | 9 (4.1) | 2 (1.7) | 32 (2.7) | 10 (1.7) | 35 (2.8) | 28 (4.5) |
| Malaise | All | 184 (50.3) | 111 (59.7) | 144 (65.8) | 80 (69.0) | 667 (56.9) | 336 (57.6) | 840 (67.2) | 418 (67.5) |
| | Severe | 9 (2.5) | 5 (2.7) | 8 (3.7) | 4 (3.4) | 21 (1.8) | 12 (2.1) | 30 (2.4) | 25 (4.0) |
| Headache | All | 139 (38.0) | 82 (44.1) | 106 (48.4) | 53 (45.7) | 452 (38.6) | 237 (40.7) | 571 (45.7) | 305 (49.3) |
| | Severe | 1 (0.3) | 3 (1.6) | 1 (0.5) | 1 (0.9) | 7 (0.6) | 3 (0.5) | 9 (0.7) | 12 (1.9) |
| Rash | All | 9 (2.5) | 2 (1.1) | 3 (1.4) | 2 (1.7) | 16 (1.4) | 6 (1.0) | 19 (1.5) | 15 (2.4) |
| | Severe | 0 | 0 | 0 | 0 | 0 | 1 (0.2) | 0 | 0 |
| Myalgia | All | 68 (18.6) | 43 (23.1) | 49 (22.4) | 24 (20.7) | 248 (21.2) | 137 (23.5) | 293 (23.4) | 167 (27.0) |
| | Severe | 1 (0.3) | 4 (2.2) | 2 (0.9) | 2 (1.7) | 5 (0.4) | 3 (0.5) | 8 (0.6) | 7 (1.1) |

N = Number of subjects analyzed, n = Number of subjects with events, MedDRA/J Ver. 25.0

Currently, results of long-term efficacy in Study 146 are not available, but the long-term efficacy of mRNA vaccines (monovalent, the original strain) in the same class of Daichirona has been reported as shown below.

A total of 3 doses of Comirnaty (first 2 doses for the primary series and a third dose for booster vaccination) has an estimated vaccine efficacy of 95.3% in preventing infection until 3 months after the booster vaccination (*N Engl J Med.* 2022;386:1910-1921). During an Omicron-predominant period, however, the vaccine efficacy in preventing infection of 3 doses of Comirnaty was 53.4% 1 month after the booster vaccination and then decreased to 16.5% at 3 months (*Nat Commun.* 2022;13:3203). During both Delta- and Omicron-predominant periods, the vaccine efficacy decreased with increasing time after the primary series (*MMWR.* 2022;71:235-63). During an Omicron BA.4/BA.5-predominant period, the vaccine efficacy against COVID-19-associated hospitalization was 68% at 7 to 119 days after a third dose of an mRNA vaccine and then decreased to 36% ≥120 days after the third dose (*JAMA Netw Open.* 2023;6:e232598). The antibody titer also showed a gradual decrease, starting 2 to 3 months after booster vaccination (*N Engl J Med.* 2022;387:2092-2094).

In Study 116 of Daichirona used for the primary series, the neutralizing antibody titer against the original strain decreased with increasing time after the second dose of Daichirona 60 μg; the titer at 6 to 7 months after the second dose was approximately one tenth of the titer at 4 weeks after the second dose. Comirnaty also showed a similar decrease in neutralizing antibody titer against the original strain; the titer around 8 months after the second dose was approximately one tenth of the titer at 4 weeks after the second dose (*Cell Host Microbe.* 2022;30:485-488.e3).

A clinical study of booster vaccination with Spikevax evaluated the safety and immunogenicity of the second booster dose of Spikevax (bivalent, the original strain/Omicron BA.1) administered ≥3 months after the first booster dose of Spikevax (monovalent, the original strain). Therefore, Comirnaty and Spikevax are allowed to be administered at least 3 months after the last dose of a SARS-CoV-2 vaccine.

For Daichirona, since no clinical study results are available for a booster dose administered 3 months after completion of the primary series, no findings have been obtained on the efficacy or safety of a booster dose of Daichirona administered 3 months after completion of the primary series. There are no data on changes in immunogenicity over a period of ≥3 months after completion of the primary series of Daichirona. However, the applicant has proposed that the interval between the last dose of a SARS-CoV-2 vaccine and a Daichirona booster dose should be ≥3 months, as with the other mRNA SARS-CoV-2 vaccines, for the following reasons:

(1) The efficacy of mRNA SARS-CoV-2 vaccines (which have the same modality as Daichirona) tend to decrease with time, and booster doses of the vaccines administered 3 months after the completion of primary series were shown to have efficacy and safety.
(2) In a certain number of countries including Japan, the interval between doses of a SARS-CoV-2 vaccine is set at approximately 3 months.
(3) If the recommended between-dose interval for Daichirona is different from that for the other mRNA SARS-CoV-2 vaccines, confusion may be caused in the clinical practice.

The applicant plans to evaluate the safety of booster vaccination with Daichirona at a between-dose interval of 3 months in a clinical study to be conducted in the future.

PMDA's view:
In Japan, the number of new patients with SARS-CoV-2 infection is not extremely large, and thus the current SARS-CoV-2 infection situation does not require vaccination every 3 months.[36)] No clinical study data are available on Daichirona administered every <6 months, and the efficacy and safety of Daichirona administered every <6 months remain unknown. The approved SARS-CoV-2 vaccines are allowed to be administered every ≥3 months. In view of the current infection situation, however, the between-dose interval for Daichirona should be set at ≥6 months because no study results for a between-dose interval of <6 months have been obtained.

### 7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance, etc. of Daichirona:
A use-results survey (planned sample size, 3,000 individuals; observation period, 3 months) is planned to examine the safety and incidence of COVID-19 after booster vaccination with Daichirona in individuals aged ≥18 years who have received an approved SARS-CoV-2 vaccine in the primary series or for booster vaccination. The planned sample size was set at 3,000 because this number would allow an analysis of the incidence and causes of events related to "shock/anaphylaxis," an important identified risk. The observation period was set at 3 months because the between-dose interval of a SARS-CoV-2 vaccine is ≥3 months. The future target population of a SARS-CoV-2 vaccine would

[36)] https://covid19.mhlw.go.jp/ (last accessed on June 9, 2023)

mainly include the elderly and individuals with underlying disease at high risk of severe COVID-19, but information about use in pregnant women, who were not included in studies during Daichirona development, will be collected as well. The applicant does not plan to supply Daichirona (monovalent, the SARS-CoV-2 original strain) in clinical practice, and is currently developing a variant-adapted vaccine using Daichirona (monovalent, the original strain) as a parent vaccine. The survey will begin when the variant-adapted vaccine becomes available for supply.

PMDA's view on the post-marketing surveillance plan, etc.:
Since the clinical studies of Daichirona have revealed limited information about the safety and clinical efficacy of Daichirona [see Sections 7.R.2 and 7.R.3], PMDA considers it appropriate for the applicant to evaluate the safety of Daichirona in clinical use after the market launch. The proposed sample size and observation period are appropriate in view of incidences of adverse events in individuals who received Daichirona. The proposed use-results survey will be implemented when a variant-adapted vaccine becomes available for supply. The applicant should evaluate the safety including the incidence of COVID-19 events, in view of the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 4): Immunogenicity-based evaluation of variant vaccines modified from parent vaccines and booster vaccines with new active ingredients" (dated July 15, 2021, issued by Office of Vaccines and Blood Products, Pharmaceuticals and Medical Devices Agency). The survey protocol should be reviewed in detail to ensure appropriate collection of information in view of the change (or no change) in the COVID-19 test system and in definite diagnosis of COVID-19 after reclassification of COVID-19 into a Class 5 infectious disease under the Infectious Diseases Control Law.

Regarding the ongoing Study 146, the applicant should evaluate (a) the long-term efficacy and safety, (b) COVID-19 incidence when the final data become available from the study, and (c) the clinical usefulness of Daichirona, and should promptly provide the relevant information to healthcare professionals.

## 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 Review Report (1)

On the basis of the data submitted, PMDA has concluded that Daichirona has efficacy in the prevention of COVID-19, and that Daichirona has acceptable safety in view of its benefits. Daichirona is an mRNA SARS-CoV-2 vaccine (monovalent, the original strain) that is manufactured in Japan and

can be used for booster vaccination. Daichirona is considered clinically meaningful because it ensures reliable vaccine supply in Japan, in anticipation of development of a variant-adapted vaccine using Daichirona as a parent vaccine.

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

**Review Report (2)**

July 18, 2023

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Daichirona for Intramuscular Injection |
| **Non-proprietary Name** | Coronavirus (SARS-CoV-2) RNA Vaccine |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | January 13, 2023 |

**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 conclusions in Sections "7.R.3 Safety," "7.R.4 Clinical positioning and indication," and "7.R.5 Dosage and administration" of the Review Report (1).

### 1.1 Efficacy

At the Expert Discussion, the expert advisors supported PMDA's conclusion in Section "7.R.2 Efficacy" of the Review Report (1) and made the following comments:

- PMDA concluded that, based on results in Study 146, booster vaccination with Daichirona is expected to have efficacy against not only the original strain but also variants such as some Omicron variants (BA.1 and BA.4/BA.5 lineages) to a certain extent. This PMDA's conclusion is acceptable. On the other hand, induction of neutralizing antibodies against the other Omicron variants (BQ.1.1 and XBB.1.5 lineages) by Daichirona is limited [see Tables 31 and 32 in the Review Report (1)]. Against the currently predominant XBB.1 lineage, Daichirona is not expected to be as effective as XBB.1-adapted vaccines,[37)] which are supposed to be used in an upcoming vaccination program that begins in fall or winter 2023.

[37)] The 47th meeting of Subcommittee on Immunization and Vaccines of the Health Sciences Council (held on June 16, 2023) "Vaccines to be used in fall and winter 2023" https://www.mhlw.go.jp/content/10900000/001108705.pdf (last accessed on July 18, 2023)

As discussed at the Expert Discussion, PMDA considers that Daichirona has only limited efficacy against the currently predominant Omicron XBB.1 lineage, and thus the applicant should proceed with development of a variant-adapted vaccine using Daichirona as a parent vaccine without delay.

### 1.2 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion in Section "7.R.6 Post-marketing investigations" of the Review Report (1) and made the following comments:

- Since Study 146 excluded individuals with underlying diseases who are particularly recommended to receive a SARS-CoV-2 vaccine, the post-marketing surveillance, etc. should collect safety information in this population. The obtained information should be extensively provided to healthcare professionals and those concerned in SARS-CoV-2 vaccines.
- It may be good to collect infrequent adverse reactions through not only post-marketing surveillance and spontaneous reports but also a government-initiated pharmacoepidemiologic research that performs overall assessment of various vaccines. Having a pharmacoepidemiologic system containing information about vaccination in Japan will greatly contribute to "Strategy for Strengthening the Vaccine Development and Production System" (decided by the Cabinet on June 1, 2021).

PMDA requested that the applicant take the following actions, and the applicant agreed to take actions appropriately:

- The applicant should evaluate (a) the long-term efficacy and safety, (b) COVID-19 incidence when the final data become available from the ongoing Study 146, and (c) the clinical usefulness of Daichirona, and should appropriately provide the relevant information to those concerned in SARS-CoV-2 vaccination such as healthcare professionals and vaccine recipients.
- After the market launch, Daichirona may be administered to populations whose data from the clinical studies of Daichirona are scarce or unavailable (e.g., individuals with underlying diseases). Therefore, information in the populations should be appropriately collected as well. The obtained results should be promptly provided to those concerned in SARS-CoV-2 vaccination such as healthcare professionals and vaccine recipients.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for Daichirona should include the safety and efficacy specifications presented in Table 42, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 43 and 44.

**Table 42. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Shock and anaphylaxis | • Myocarditis/pericarditis<br>• Guillain-Barre syndrome<br>• Vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD) | • Safety in pregnant and lactating women |
| Efficacy specification | | |
| None | | |

**Table 43. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance<br>• General use-results survey | • Disseminate data gathered during early post-marketing phase vigilance<br>• Organize and disseminate information for healthcare professionals<br>• Organize and disseminate information for vaccine recipients<br>• Periodical publication of the occurrence of adverse reactions |

**Table 44. Outline of general use-results survey (draft)**

| | |
|---|---|
| Objective | To evaluate the safety of Daichirona in clinical use |
| Survey method | Central registry system |
| Population | Individuals aged ≥18 years who receive Daichirona for the first time at least 6 months after receiving another approved SARS-CoV-2 vaccine as the primary series or as a booster dose |
| Observation period | 90 days after the first dose of Daichirona |
| Planned sample size | 3,000 |
| Main survey items | Characteristics of vaccine recipients, exposure to Daichirona, adverse events, COVID-19 onset, etc. |

## 1.3 Quality

### 1.3.1 mRNA purity of the vaccine product

mRNA purity of Daichirona is controlled by a purity test of the vaccine product in which [redacted] electrophoresis is performed; the peak areas of the main peak (full-length mRNA), Impurity A, and Impurity B, calculated by [redacted], are required to meet the acceptance criteria.

Regarding mRNA purity of the vaccine product, the acceptance criteria for the main peak and Impurity A were far different from the corresponding manufacturing results and the measured values of study vaccines used in the clinical studies. PMDA asked the applicant to explain the rationale for the acceptance criteria for the main peak and Impurity A and the policy on the acceptance criteria.

The applicant's explanation:
The acceptance criterion for the main peak in the mRNA purity test [redacted]. The acceptance criterion for Impurity A [redacted]. Whether the established acceptance criterion for Impurity A is appropriate in terms of safety can be explained by Impurity A [redacted]. Based on the theoretical degradation mechanism of nucleic acids, Impurity A is degraded into natural nucleic acid monomers in the body as with mRNA and thus would not affect the safety of Daichirona.

The acceptance criterion for the main peak is lower, and that for Impurity A is higher, than the measured values of study vaccines used in the clinical studies. As described above, however, these acceptance criteria are considered to ensure the efficacy and safety comparable to those of study vaccines used in the clinical studies.

PMDA concluded that the applicant's proposed acceptance criteria, which were established based on the non-clinical study results and theoretical discussion, would not ensure the quality comparable to

that of study vaccines. This conclusion was supported at the Expert Discussion. PMDA accordingly requested that the applicant establish different acceptance criteria for the main peak and Impurity A that can ensure the quality comparable to that of study vaccines. In addition, since mRNA purity tended to decrease during storage of Daichirona, PMDA asked the applicant to explain the control method to ensure appropriate mRNA purity throughout the shelf life.

The applicant's response:
In response to the request from PMDA, the applicant will establish acceptance criteria for the main peak and Impurity A that can ensure the quality comparable to that of study vaccines, taking into account the manufacturing results, the decreasing trend in mRNA purity over time, and the quality of study vaccines at the time of vaccination. To ensure appropriate mRNA purity throughout the shelf life, the applicant will control mRNA purity by monitoring it at release as a part of the control method of the vaccine product.

PMDA accepted the applicant's proposed acceptance criteria for the main peak and Impurity A in the mRNA purity test as well as the control method of mRNA purity.

### 1.3.2 Shelf lives of active substance and vaccine product

The applicant submitted the results of the long-term testing of the active substance and vaccine product, as requested by PMDA in the Review Report (1).

**Table 45. Summary of main stability studies for the active substance**

| | Manufacturing process for the active substance | Number of batches | Storage condition | Test period | Storage form |
|---|---|---|---|---|---|
| Long-term | Process c | 3 | −70°C ± 10°C | 12 months[a)] | [redacted] |
| | Process d | 3 | | 6 months[a)] | [redacted] bag |

a) The stability study is ongoing and continued for 24 months.

**Table 46. Summary of main stability studies for the vaccine product**

| | Manufacturing process for the active substance | Manufacturing process for the vaccine product | Number of batches | Storage condition | Test period | Storage form |
|---|---|---|---|---|---|---|
| Long-term | Process c | Process C | 3 | 5°C ± 3°C | 9 months[a)] | Glass vial |
| | Process d | Process C | 3 | | 6 months[a)] | |

a) The stability study is ongoing and continued for 12 months.

In the Review Report (1), based on results of the long-term testing in Tables 3 and 5, the shelf lives of 9 and 6 months were proposed, respectively, for the active substance and vaccine product when stored in the respective containers under the respective conditions [see Sections 2.1.7 and 2.2.5 in the Review Report (1)].

Then, the applicant submitted results at 12 and 6 months of the currently ongoing long-term testing of the active substances manufactured by Processes c and d, and results at 9 and 6 months of the currently ongoing long-term testing of the vaccine product manufactured by Process C using the Process c- or d-derived active substance.

The applicant's explanation:

Since no changing trend was observed in the quality of the active substance over time during the storage period, the shelf life of the active substance was set at 12 months. Although the specifications for the vaccine product were met, a decreasing trend was found in mRNA purity of the vaccine product during the storage period up to 9 months. Therefore, the shelf life of the vaccine product was set at 7 months.

PMDA's conclusion:
Based on the submitted results of the long-term testing and applicant's explanation, the following shelf lives for the active substance and vaccine product are acceptable:

- Active substance: 12 months, when stored in a [redacted] bag at −80°C to −60°C
- Vaccine product: 7 months, when stored in a glass vial at 2°C to 8°C

However, the applicant should submit the following results of the ongoing long-term testing as soon as they become available:

(a) The results at 12 months of 3 batches of the active substance manufactured by Process d.
(b) The results at 9 months of 3 batches of the vaccine product manufactured by Process C using the Process d-derived active substance.

Of note, the following comment was raised at the Expert Discussion: "Since a decreasing trend was found in mRNA purity during storage at 2°C to 8°C, the applicant should investigate an optimal storage method to enable more stable storage of the product in the future."

PMDA informed the applicant of the comment from the Expert Discussion, and the applicant responded that they would continue to investigate an optimal storage method of the LNP-mRNA vaccine.

## 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 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 5.3.5.1-2) 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, the clinical studies were conducted in accordance with GCP overall, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the following finding

requiring corrective action was identified at a study center, although it did not considerably affect evaluation of the study overall. The finding was notified to the head of the study center.

**Finding requiring corrective action**

Study center

- Error in the information in the agreement for partial outsourcing of duties related to conduct of a clinical study

## 3. Overall Evaluation

As a result of its review, PMDA concludes that the product may be approved for the following indication and the 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**

A single dose of 0.6 mL is injected intramuscularly as a booster dose.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information on the product at the current moment, the applicant is required to (a) promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, (b) submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and (c) take necessary actions to ensure the proper use of the product.
3. The applicant is required to submit results of the ongoing Japanese clinical study of the product to PMDA as soon as they become available and take necessary actions to make the latest efficacy and safety data of the product easily accessible to healthcare professionals and vaccine recipients.
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 latest efficacy and safety data of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| ADA | Anti-drug antibody |
| APTT | Activated partial thromboplastin time |
| CI | Confidence interval |
| Comirnaty | Comirnaty Intramuscular Injection |
| COVID-19 | Coronavirus disease |
| Cxcl10 | C-X-C motif chemokine ligand 10 |
| Daichirona | Daichirona for Intramuscular Injection |
| Day X (after the first dose, second dose, etc.) | The day of vaccination is regarded as Day 1. |
| DNA | Deoxyribonucleic acid |
| ELISA | Enzyme-linked immunosorbent assay |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| GMFR | Geometric mean fold rise: |
| GMT | Geometric mean titer |
| HLT | High level term |
| [redacted] | [redacted] |
| ICMRA | International Coalition of Medicines Regulatory Authorities |
| IFN-γ | Interferon-gamma |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| [redacted] | [redacted] |
| LNP | Lipid nanoparticle |
| MCB | Master cell bank |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRNA | Messenger RNA |
| Original strain | Wuhan-Hu-1 strain |
| PCR | Polymerase chain reaction |
| PEG | Polyethylene glycol |
| PK | Pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PT | preferred term |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| S protein | Spike protein |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome CoronaVirus-2 |
| SMQ | Standardised MedDRA queries |
| Spikevax | Spikevax Intramuscular Injection |
| Study 116 | Study DS5670-116 |
| Study 146 | Study DS5670-146 |
| Study J101 | Study DS5670-A-J101 |
| Th | helper T cell |
| VAED | Vaccine-associated enhanced disease |
| VAERD | Vaccine-associated enhanced respiratory disease |
| VE | Vaccine efficacy |
| WCB | Working cell bank |
| WHO | World Health Organization |