Report on the Deliberation Results

November 28, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Kostaive Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Meiji Seika Pharma Co., Ltd.
Date of Application	April 28, 2023

Results of Deliberation

In its meeting held on November 27, 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 vaccine product and its active 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 information on the product is limited at present, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product.
3. Results of the ongoing Japanese clinical studies of the product should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients.
4. The efficacy and safety data of the product will be accrued with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

Review Report

November 9, 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	Kostaive Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Meiji Seika Pharma Co., Ltd.
Date of Application	April 28, 2023
Dosage Form/Strength	Lyophilized powder for injection in a vial for reconstitution before use: Each vial contains 0.10 mg of Zapomeran.
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Items Warranting Special Mention	Priority review in accordance with "Handling on regulatory reviews of drugs, medical devices, *in vitro* diagnostics, and regenerative medical products for the time being associated with COVID-19" (Administrative Notice dated April 13, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [PSEHB/PED], and the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [PSEHB/MDED]). A prior assessment consultation was conducted on the product.
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

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

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

Indication

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

Dosage and Administration

The product is dissolved in 10 mL of physiological saline (Japanese Pharmacopoeia grade).
As the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 4 weeks apart.
As the booster dose, a single dose of 0.5 mL is injected intramuscularly.

Approval Conditions

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

Attachment

Review Report (1)

October 6, 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	Kostaive Intramuscular Injection (changed from "COVID-19 Vaccine Meiji Injection" [the name proposed at the application])
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Meiji Seika Pharma Co., Ltd.
Date of Application	April 28, 2023[1)]
Dosage Form/Strength	Lyophilized powder for injection in a vial for reconstitution before use: Each vial contains 0.10 mg of Zapomeran.

Proposed Indication

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

Proposed Dosage and Administration[1)]

The product is suspended in 10 mL of physiological saline (Japanese Pharmacopoeia grade).
Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 4 weeks apart.
Booster dose: A single dose of 0.5 mL is injected intramuscularly.

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List of Abbreviations

See Appendix.

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1) The application for the proposed dosage and administration pertaining to the booster dose was submitted on June 30, 2023.

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

Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) is a single-stranded positive-chain ribonucleic acid (RNA) virus belonging to the family *Coronaviridae* and the order *Nidovirales*. In 2019, the virus was found to infect humans and identified as a pathogenic virus (*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)[2)] by the World Health Organization (WHO) in January 2020, and as of August 25, 2023, >770 million people were infected with SARS-CoV-2 worldwide.[3)] Multiple therapeutic agents and preventive vaccines were developed against the global COVID-19 pandemic, which together with various anti-infection measures, led to improvements in herd immunity and decreased the infection-caused deaths globally. On the basis of the above, the WHO declared the end of PHEIC on May 5, 2023.[4)] However, given that SARS-CoV-2 epidemic is still ongoing, that variants with altered infectivity and transmissibility have emerged, that even individuals with previous infections can be susceptible to re-infection, and that some patients have reported long-COVID (sequelae to the infection), there is an ongoing need for dealing with COVID-19. In Japan, the category of COVID-19 under the Infectious Disease Act was reclassified from "pandemic influenza (novel influenza or re-emerging influenza)" to "Class 5 infectious diseases" on May 8, 2023, while special temporary vaccination of SARS-CoV-2 vaccine is continued throughout the fiscal year 2023.[5)] The Omicron variant, which emerged at the end of 2021 and became endemic globally throughout 2022, is different from the original strain antigenically thereby evading immunity induced by the administration of original strain-derived vaccines which was initiated in 2021, resulting in decreased efficacy of the vaccine. In response to recurrent outbreaks and the waning effectiveness of vaccines, multiple booster doses of the vaccine have been administered to reactivate the immune response. Starting from September 2022, the booster doses of bivalent vaccines with increased antigenicity against the Omicron variant were given and, from September 2023, administration of the monovalent vaccine against strain XBB.1.5 was initiated.[6)] As of September 2023, there are a number of reports on EG.5 variants derived from strain XBB.1 lineage.

As of October 1, 2023, the following vaccines have been approved for the prevention of disease caused by SARS-CoV-2 infection (COVID-19) in Japan: RNA vaccines (Comirnaty, Spikevax, Daichirona), recombinant spike protein (S-protein) vaccine (Nuvaxovid), and adenovirus vector vaccine (Vaxzevria). As a result of the special temporary vaccination with these vaccines, approximately 80% of the Japanese people have completed the primary series of SARS-CoV-2 vaccine, and approximately 70% have completed the first booster dose.[7)]

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2) The term Public Health Emergency of International Concern is defined as follows in the International Health Regulation (IHR) of WHO:
(a) An extraordinary situation that is determined to constitute a public health risk to other states through the international spread of disease, and
(b) An extraordinary situation that is determined to potentially requires a coordinated international response

3) Weekly epidemiological update on COVID-19 - 1 September 2023 https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

4) 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

5) Material 1 presented at the 55th Subcommittee meeting on basic vaccination policy of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (September 8, 2023)

6) "Future vaccination against COVID-19 (No. 6) (in Japanese)" [Administrative Notice dated August 4, 2023, issued by the Office of Counsellor for Vaccination, Health Service Division, Health Service Bureau, Ministry of Health, Labour and Welfare]

7) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (last accessed on October 3, 2023)

Kostaive is a self-amplifying messenger RNA (samRNA) vaccine developed by Arcturus Therapeutics in the US aimed at prevention of COVID-19, and is formulated in lipid nanoparticles (LNPs).

Recently, the applicant submitted applications for marketing approval of Kostaive[1)] with the claim that the efficacy, safety, and immunogenicity of the primary series and booster dose of Kostaive have been confirmed in clinical studies including the foreign phase I/II/III study (Study ARCT-154-01, ongoing in Vietnam) and the Japanese phase III study (Study ARCT-154-J01). Kostaive has not been approved in foreign countries as of October 2023.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Active substance

mRNA-2105 (active ingredient, zapomeran), an active substance of Kostaive, is a samRNA encoding replicase proteins (non-structural protein [nsP]1, nsP2, nsP3, and nsP4) of Venezuelan equine encephalitis virus (VEEV) origin and the full-length of S-protein (S1 and S2) derived from SARS-CoV-2 (of the original strain). mRNA-2105 also contains a 5'-terminal cap structure, 5' untranslated region (UTR), UTR between reading frames, 3'UTR, and 3'-terminal poly A chain.

S-protein has undergone substitution of 6 amino acid residues (D614G, R682G, R683S, R685S, K986P, and V987P) for enhanced immunogenicity. The replicase protein has undergone [redacted] amino acid substitutions ([redacted] at [redacted] and [redacted] at [redacted]). Mutation of [redacted] at [redacted] reduces the cytotoxic effect of the replicase protein, thereby contributing to the prolongation of S-protein expression. The mutation of [redacted] at [redacted] allows constitutive expression of [redacted], enhancing RNA-replicating efficacy and contributing to an increase in S-protein expression level.

2.1.1 Generation and control of cell substrate

The linear plasmid deoxyribonucleic acid (DNA), one of the raw materials of Kostaive, is generated by the use of a cell bank of *Escherichia coli* (*E. coli*). The master cell bank (MCB) of *E. coli* was prepared from *E. coli* transfected with plasmid DNA encoding 5' UTR, replicase protein, UTR between reading frames, S-protein, 3'UTR, and poly A chain. No WCB has been prepared.

The MCB was subjected to characterization (appearance, identity of host cells, absence of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) and to purity tests.

2.1.2 Manufacturing process

The manufacturing process for the active substance consists of mRNA synthesis, [redacted], [redacted] chromatography, [redacted] chromatography, [redacted] filtration/[redacted] filtration, [redacted] filtration, [redacted] filling, and packaging/labeling/testing/storage.

Critical step is [redacted].

The process validation of the manufacturing process for the active substance was conducted on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

Materials of biological origin are used in the raw materials for mRNA synthesis and in the [redacted] process in the manufacturing process of the active substance. [redacted], [redacted], [redacted], and [redacted], which are the raw materials used in the process of mRNA synthesis, are synthesized using [redacted] enzymes of rabbit and porcine origin. These enzymes conform to the Standards for Biological Ingredients, and these [redacted] solutions have undergone treatment with activated charcoal and virus removal filtration to remove viruses at preparation. [redacted] which is used in [redacted] process is purified by a porcine heparin affinity column. The heparin conforms to the Standards for Biological Ingredients. Raw materials have undergone the following virus inactivation processes: Hydrochloric acid, high pH, thermal oxidation (hydrogen peroxide), and oxidation at neutral pH by peracetic acid (those supplied by Company A), or treatments with sodium hydroxide and potassium permanganate (those supplied by Company B).

2.1.4 Manufacturing process development

During the development of the active substance, the manufacturing process was changed from Process a to Process b. The main change was the addition of [redacted] process in the manufacturing process.

The active substance used in non-clinical studies was manufactured by Process a, in clinical studies by Process a or b, and the active substance for the proposed vaccine product is manufactured by Process b. For the process changes, comparability between pre-change and post-change active substance has been demonstrated.

The following table shows the types of S-protein encoded by the active substances (mRNA-2002, mRNA-2105, and mRNA-2106) of the drug development candidates (ARCT-021, ARCT-154 [Kostaive], and ARCT-165 [vaccine for variants]) and mutations introduced.

Table 1. Names of mRNAs and vaccine products, and types of S-protein and mutations introduced

Active substance developed	Investigational ingredient code of vaccine product	Type and mutation of S-protein-encoding gene[a)]	Main uses
mRNA-2002	ARCT-021	Original strain (WA1/2020 lineage)	Quality, non-clinical, and clinical studies
mRNA-2105 (zapomeran)	ARCT-154 (Kostaive)	Contains the following mutations to the original strain (WA1/2020 lineage): • D614G (mutation in B1 lineage of the original strain) • K986P, V987P, R682G, R683S, R685S	Quality, non-clinical, and clinical studies
mRNA-2106	ARCT-165	Contains the following mutations to Beta variant (B1.351 lineage): • D614G (mutation in B1 lineage of the original strain) • K986P, V987P, R682G, R683S, R685S	Clinical studies

a) The amino acid sequence of VEEV replicase is the same in all active substances developed.

2.1.5 Characterization

2.1.5.1 Structure and characteristics

The active substance was subjected to characterization tests described in Table 2.

Table 2. Parameters for characterization

Test item		Test method
Primary structure	RNA sequence	Sanger sequencing, [redacted]
	5'-cap structure, poly A chain length distribution	[redacted]-HPLC and [redacted]
Physicochemical property	Ultraviolet absorption spectrum	Ultraviolet-visible spectrophotometry
Biological property	*In vitro* bioactivity ([redacted])	Cell-based assay ([redacted] and [redacted])

2.1.5.2 Product-related substances/product-related impurities

The product-related impurity is Impurity A, which is adequately controlled by the specifications for the active substance.

No product-related substances have been identified.

2.1.5.3 Process-related impurities

Residual plasmid DNA, Impurity B, Impurity C, and elemental impurities were identified as process-related impurities. Residual plasmid DNA, Impurity B, and Impurity C are adequately controlled by the specifications for the active substance. Elemental impurities were shown to be completely removed during the manufacturing process.

2.1.6 Control of active substance

The proposed specifications for the active substance include description, identification ([redacted] electrophoresis and [redacted]), pH, 5'-end capping rate ([redacted]), poly A chain ([redacted]), purity (mRNA [electrophoresis], [redacted] [[redacted]], residual plasmid DNA [[redacted]], and [redacted] [[redacted]]), content (ultraviolet-visible spectrophotometry), bacterial endotoxin, microbial limit, and potency ([redacted]).

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 the main stability studies for the active substance

Study	Manufacturing process of active substance	Number of batches	Storage condition	Test period	Storage form
Long-term testing	Process b	3	≤−60°C	18 months[a)]	[redacted] container with [redacted] cap

a) The stability testing is ongoing and continued for 36 months.

In the long-term testing, no clear changes were observed in the quality attributes in test parameters submitted so far. 5'-end capping rate and poly-A chain were not investigated in the stability study shown in Table 3.

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is a lyophilized vaccine product containing, in each glass vial (12 mL), 0.10 mg of the active ingredient zapomeran. It is a multi-dose product to be used after dissolution in 10 mL of physiological saline (allowing extraction of sixteen 5.0-μg doses).

The vaccine product contains, as excipients, di(pentadecan-8-yl)4,4'-((((3-(dimethylamino)propyl) thio)carbonyl)azanediyl)dibutyrate (ATX-126), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, 1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene (PEG2000-DMG), trometamol, sodium chloride, sucrose, potassium sorbate, and polyoxyethylene (160) polyoxypropylene (30) glycol. ATX-126, DSPC, cholesterol, and PEG2000-DMG are components of LNP encapsulating the active substance.

2.2.2 Manufacturing process

The manufacturing process of the vaccine product consists of dissolution, [redacted], [redacted] filtration/[redacted] filtration, filtration, storage, [redacted] filtration, filling, [redacted], [redacted], and labeling/packaging/testing/storage.

Critical steps are [redacted], [redacted], [redacted], and [redacted].

The process validation of the manufacturing process was conducted on a commercial scale.

2.2.3 Manufacturing process development

Main changes in the manufacturing process during the development of the vaccine product are as shown in Table 4. The vaccine product development was conducted on the vaccine product (ARCT-021) using mRNA-2002 as the active substance. ARCT-154 (Kostaive) and ARCT-021 are manufactured by the same manufacturing process; the only difference is the active substance mRNA used.

The vaccine product used in non-clinical and clinical studies was manufactured by Process A and Process B, and the proposed vaccine product is manufactured by Process B. With the process changes from Process A to Process B, the quality attributes were evaluated before and after the changes. The results confirmed the comparability.

Table 4. Main changes in the manufacturing process of the vaccine product

Manufacturing process	Changes
Process A to Process B	• Changes in components and [redacted] (from [redacted] to [redacted]) • Optimization of [redacted] in [redacted] and addition of [redacted] process • [redacted]

2.2.4 Control of vaccine product

The proposed specifications for the vaccine product include description, appearance of solution, pH, identification (electrophoresis and liquid chromatography), foreign insoluble matter, insoluble particulate matters, purity (mRNA [[redacted] electrophoresis]), water content, enclosure rate (fluorometry), osmotic pressure, time to re-dissolution, particulate size (dynamic light scattering), polydispersity index (dynamic light scattering), residual solvent (ethanol), uniformity of dosage unit,

lipid content ([redacted]-HPLC), total lipid content, mRNA content ([redacted]-HPLC), lipid-to-mRNA ratio, bacterial endotoxin, sterility, and potency ([redacted]).

2.2.5 Stability of vaccine product

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

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

Study	Manufacturing process of vaccine product	Number of batches	Storage condition	Test period	Storage form
Long-term testing	Process B	4	−20 ± 5˚C	18 months[a)]	Glass vial with [redacted] rubber cap
Photostability testing	Process B	1	Overall illuminance of ≥1.2 million lx•h, and integrated near ultraviolet energy of ≥200 W•h/m^2, 5 ± 3˚C		

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

The long-term testing showed no clear changes in quality attributes throughout the study period. The photostability testing showed that the vaccine product was photolabile.

On the basis of the above, the applicant proposed a shelf life of 18 months for the vaccine product when stored at −20 ± 5°C in a glass vial with [redacted] rubber stopper as the primary container and placed in a carton to protect it from light.

2.R Outline of the review conducted by PMDA

PMDA has asked the applicant to evaluate the 5'-end capping rate and poly A chain in the stability study of the active substance. Results of the review will be described in the Review Report (2), based on which the shelf life will be determined.

On the basis of the data submitted so far, PMDA concluded that there was no quality problem affecting the evaluation of non-clinical and clinical studies of Kostaive.

2.R.1 Novel excipients

The vaccine product contains, as excipients, ATX-126 which has not been previously used and potassium sorbate which has not been previously used for intramuscular injection. Cholesterol, DSPC, and PEG2000-DMG are included in excipients that are permitted for use in specific products in accordance with "Handling of excipients that are permitted only for use in specific drug products or under specific conditions" (Administrative Notice dated June 23, 2009). The route of administration, the maximum daily dose, etc., are within the range of the use experiences with approved infection-preventive vaccines. On the basis of the following investigations, PMDA has concluded that the use of excipients ATX-126, cholesterol, DSPC, and PEG2000-DMG in infection-preventive vaccines, but their use should not be handled as a precedent for other products to be developed in the future.

2.R.1.1 Specifications and stability

PMDA has concluded that there is no particular problem in the specifications and stability of ATX-126, potassium sorbate, cholesterol, DSPC, and PEG2000-DMG.

2.R.1.2 Safety

The applicant explained the single-dose toxicity, repeated-dose toxicity, and reproductive and developmental toxicity of ATX-126 and potassium sorbate based on the results of the toxicity studies on Kostaive or ARCT-021 (CTD 4.2.3.2-02, 4.2.3.2-03, and 4.2.3.5.3-01). The applicant also explained that these novel excipients pose no safety concerns regarding genotoxicity, taking into account the data of previous use experiences with different route of administration and from the results of genotoxicity assessment based on structure-activity relationship (rule-based method based on professional experience and statistics-based method).

On the basis of the submitted data, PMDA concluded that neither ATX-126 nor potassium sorbate is likely to cause safety problems at the clinical dosage regimen of Kostaive.

PMDA also concluded that cholesterol, DSPC, and PEG2000-DMG are unlikely to pose safety problems, taking into account the results of the toxicity studies of Kostaive.

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

The applicant submitted the results of primary pharmacodynamic studies on Kostaive conducted in mice, cynomolgus monkeys, and rhesus monkeys.

3.1 Primary pharmacodynamics

Table 6 shows a summary of major studies submitted.

Table 6. Summary of primary pharmacodynamics studies

Animal species, sex	Number of animals	Dosage regimen (Intramuscular administration in all studies. The dose is expressed in the amount of RNA.)	Main endpoints	CTD
BALB/c mice, female	5/group	Kostaive (2 μg), ARCT-021[a] (2 μg), or placebo was administered once.	Immunogenicity	4.2.1.1-01
Cynomolgus monkeys, male	2-4/group	Kostaive (7.5 μg), ARCT-021 (7.5 μg), or placebo was administered twice, 28 days apart.	Immunogenicity	4.2.1.1-02
C57BL6 mice, female	5/group	• ARCT-021 (0.2, 2, or 10 μg) or placebo was administered once. • ARCT-021 (0.2, 2, or 10 μg) or placebo was administered once, followed by the second dose at the same dose after 30 days.	Immune response	4.2.1.2-02 and 4.2.1.2-03
K18-hACE2 mice,[b] female	5/group	ARCT-021 (2 or 10 μg) or placebo was administered once, followed by intranasal administration of the original strain after 30 days.	Efficacy in preventing SARS-CoV-2 infection	4.2.1.2-06
Rhesus monkeys, male and female	4-5/group	• ARCT-021 (5 or 20 μg) or placebo was administered twice, 28 days apart. • ARCT-021 (20 or 40 μg) was administered once, followed by intranasal and intratracheal administration of the original strain after 42 days.	Efficacy in preventing SARS-CoV-2 infection	4.2.1.2-08

Placebo: Phosphate-buffered saline (PBS)

a) See Table 1 in Section 2.1.4 for the site of the differences in the encoded protein. The sequence of S-protein is derived from the original strain (ARCT-021) and from the original strain with D614G mutation (Kostaive).

b) C57BL6 transgenic mice engineered to express human angiotensin-converting enzyme 2 (hACE2)

3.1.1 Immunogenicity tests (CTD 4.2.1.1-01 and 4.2.1.1-02)

(a) Following a single-dose administration of Kostaive (2 μg[8]), ARCT-021 (2 μg), or placebo to BALB/c mice (n = 5 females/group), serum anti-S-protein antibody and receptor binding-inhibitory

[8] Amount of RNA. The same applies hereinafter unless specified otherwise.

activity were evaluated against the original strain, Alpha variant (B.1.1.7 lineage), Beta variant (B.1.351 lineage), and Gamma variant (P.1 lineage) at multiple time points up to Day 56 after administration. Induction of anti-S-protein antibody and receptor binding-inhibitory activity was observed in the Kostaive group and the ARCT-021 group.

(b) Kostaive (7.5 μg), ARCT-021 (7.5 μg), or placebo was administered to cynomolgus monkeys (n = 2-4 males/group) twice 28 days apart, and immune responses (anti-S-protein antibody, receptor binding-inhibitory antibody, neutralizing antibody, and cellular immunity) against the original strain, Alpha variant (B.1.1.7 lineage), Beta variant (B.1.351 lineage), and Gamma variant (P.1 lineage) were evaluated at multiple time points up to Day 56.

- Induction of anti-S-protein antibody, receptor binding-inhibitory activity, and neutralizing antibody against all strains was clearly demonstrated in the Kostaive group after the first dose and in the ARCT-021 group after the second dose. The neutralizing antibody titer on Day 56 was higher in the Kostaive group than in the ARCT-021 group against all strains investigated.
- Cellular immunity induction against all strains was observed both in the Kostaive group and in the ARCT-021 group compared with the placebo group, as demonstrated by interferon-gamma (IFN-γ)-producing cells counted by enzyme-linked immunospot assay (ELISpot).

3.1.2 Cellular immune response and prevention of SARS-CoV-2 infection (CTD 4.2.1.2-02, 4.2.1.2-03, 4.2.1.2-06, and 4.2.1.2-08)

(a) ARCT-021 (0.2, 2, or 10 μg) or placebo was administered to C57BL6 mice (n = 5 females/group), followed by the second dose at the same dose after 30 days. T cells (CD4+, CD8+, and their subpopulations) within the spleen 7 days after the first dose and 20 days after the second dose was analyzed for immunoglobulin G (IgG) subclass and IFN-γ-producing cell count by flow cytometry and ELISpot, respectively. On the basis of the results of T helper type 1/T helper type 2 (Th1/Th2) cytokine profile assessment, ARCT-021 induced Th1-dominant immune response in Th1/Th2 balance.

(b) A single dose of ARCT-021 (2 or 10 μg) or placebo was administered to K18-hACE2 mice (n = 5 females/group), followed by intranasal inoculation of the original strain (5×10^4 median tissue culture infectious dose [$TCID_{50}$] or 5×10^5 $TCID_{50}$) after 30 days. Clinical symptoms, viral titer (brain and lung, plaque method), and lung histology up to 5 or 14 days after inoculation at 5×10^5 $TCID_{50}$ and viral titer (lung and brain, plaque method and RNA level) on 5 days after inoculation at 5×10^4 $TCID_{50}$ were evaluated. Results confirmed suppression of clinical symptoms and viral growth in the ARCT-021 group.

(c) Rhesus monkeys (n = 4-5/sex/group) received intramuscularly ARCT-021 (5 or 20 μg) or placebo twice 28 days apart, or ARCT-021 (20 or 40 μg) as a single dose, followed by intranasal and intratracheal inoculation of the original strain (1×10^6 $TCID_{50}$ and 0.5×10^6 $TCID_{50}$, respectively) at 42 days after the first dose. After the inoculation, monkeys were evaluated for clinical symptoms, viral titer (nasopharyngeal swab and bronchoalveolar lavage fluid, plaque assay), neutralizing antibody titer (receptor binding-inhibitory activity, microneutralization method), serum cytokine

levels, cytokine expression in T cells, etc. Results confirmed the suppressive effect against clinical symptoms and against viral growth in the ARC-021 group.

The applicant considers that the above results with ARCT-021 are applicable to the evaluation of Kostaive because of the similarity of S-protein expressed.

3.2 Safety pharmacology

No independent safety pharmacology study on Kostaive was conducted. On the basis of the assessment in the repeated-dose toxicity study in rabbits, the applicant explains that Kostaive has no effect on the cardiovascular system, the respiratory system, or the central nervous system (CTD 4.2.3.2).

3.R Outline of the review conducted by PMDA

Kostaive is expected to show efficacy in preventing SARS-CoV-2 infection from the results of the primary pharmacodynamics studies submitted. Results of the safety pharmacology study submitted show no particular safety concerns on Kostaive.

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

No non-clinical pharmacokinetic study of Kostaive has been conducted. The applicant submitted the data on the pharmacokinetics of Kostaive, in the form of results of the biodistribution in mice and rabbits of LNP formulation (ARCT-021) manufactured from mRNA-2002 as the active substance.

mRNA-2002 concentration in mouse and rabbit plasma and tissues was measured by chemiluminescence analysis using sandwich nucleic hybridization and signal amplification with branched DNA technology.[9)] ATX-126 in mouse and rabbit plasma and tissues was measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS),[10)] S-protein in mouse plasma and tissues was measured by Jess simple western blotting.[11)]

The concentrations of mRNA-2002, ATX-126, and S-protein are expressed in mean ± standard deviation (SD), unless specified otherwise.

4.1 Absorption

No absorption study has been conducted on Kostaive because it is a vaccine. Plasma pharmacokinetics of mRNA-2002, ATX-126, and S-protein was evaluated in a single-dose biodistribution study of ARCT-021 in mice. Section 4.2.1 shows the results.

4.2 Distribution

4.2.1 Biodistribution in single intramuscular administration in mice (CTD 4.2.2.3-02, Reference data)

A single dose of 25 or 50 μg of ARCT-021 was administered intramuscularly to male and female mice (n = 6/sex/time point). At a total of 8 time points within 31 days after administration, plasma, brain, lung,

9) The lower limit of quantification (LLOQ) was 0.49 pg/mL in mouse plasma, 3.0 pg/mL in mouse tissues, 0.49 pg/mL in rabbit plasma, and 3.91 pg/mL in rabbit tissues.
10) The LLOQ was 25.0 ng/mL in mouse and rabbit plasma and 250 to 500 ng/g in mouse and rabbit tissues.
11) The LLOQ was 48 pg/mL in plasma and 12 pg/mL in tissues.

heart, liver, spleen, kidney, rectus femoris muscle (the injection site), lymph nodes (inguinal and popliteal), testis, and ovary[12] were isolated and measured for mRNA-2002, ATX-126, and S-protein.

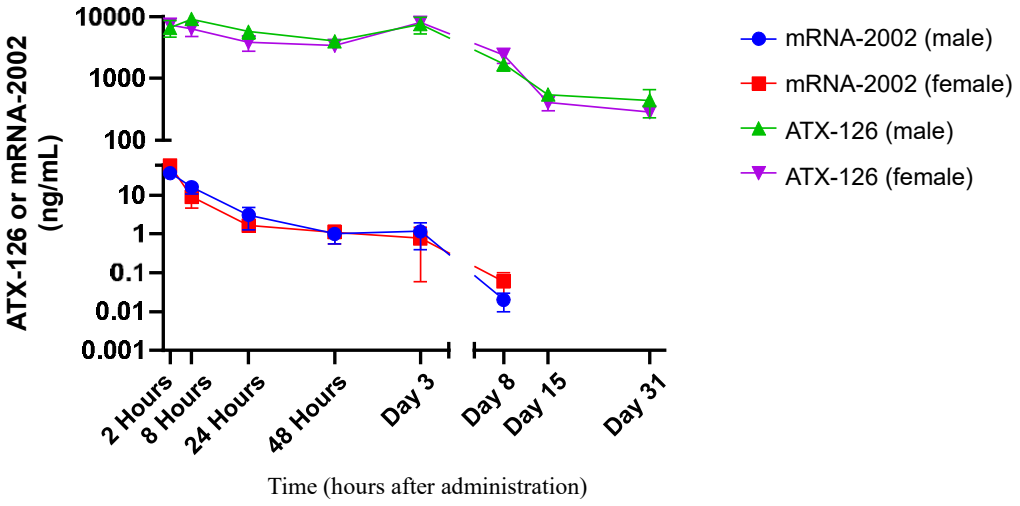
mRNA-2002

mRNA-2002 was detectable in plasma and all tissues at 2 hours after ARCT-021 administration, but was eliminated by Day 31 from plasma and all tissues, except for the following tissues: Muscles in the 25 µg group (11.29 pg/mg in a male [below limit of quantification (BLOQ) in 4 of 5 samples],[13] 17.09 ± 22.65 pg/mg in females [BLOQ in 3 of 5 samples]), muscles in the 50 µg group (27.78 pg/mg in a male [BLOQ in 4 of 5 samples],[13] 14.29 ± 11.56 pg/mg in females [BLOQ in 2 of 5 samples]), and inguinal lymph node (1.39 pg/mg[12] in males and females combined) (Figures 1 and 2).

The mean elimination half-life of mRNA-2002 in muscles in males and females combined was 46 and 70 hours in the 25 and 50 µg groups, respectively.

Since mRNA-2002 was detected in plasma samples, the applicant explains the possibility that distribution in lymph nodes and spleen suggests the whole body exposure and that mRNA-2002 was distributed throughout the body after uptake into immune cells at the injection site (muscle).

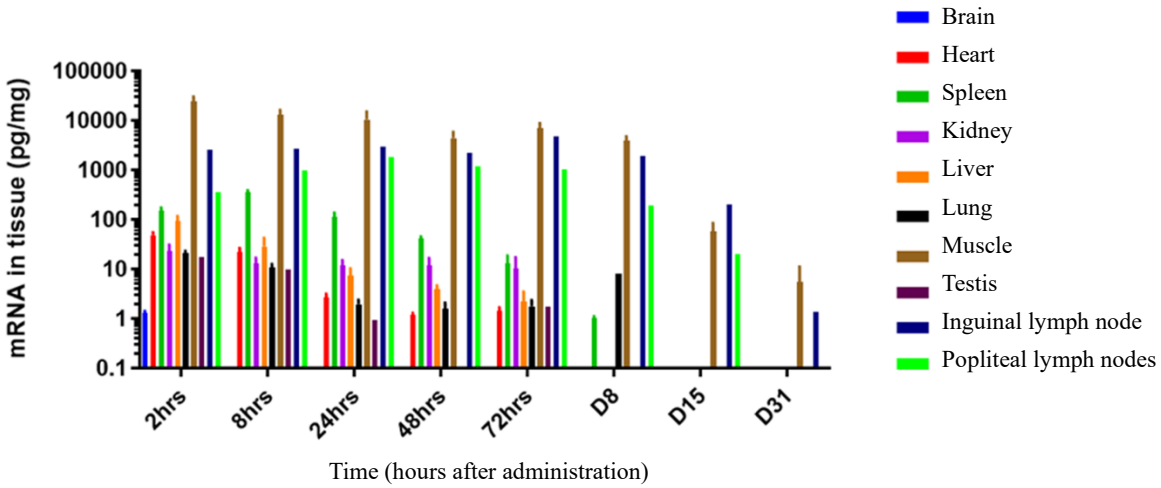
Figure 1. Changes over time in plasma concentration of mRNA-2002 and ATX-126 after a single intramuscular administration of ARCT-021 50 µg in mice



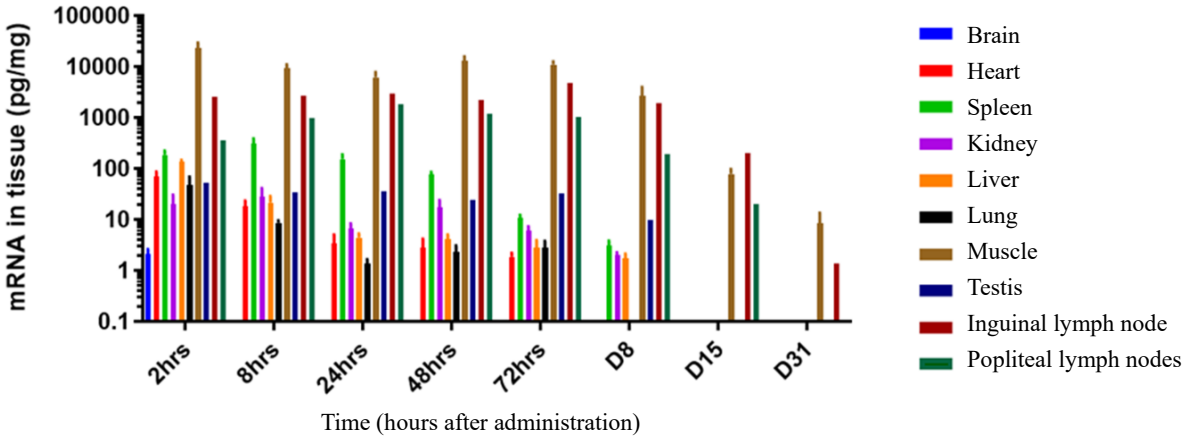
[12] Due to the small sampling size, lymph node, testis, and ovary were pooled for measurement. The measurement is not exactly an average value because only one measured value was available at each time point.
[13] The measurement is not exactly an average value because only one measured value was available.

Figure 2. mRNA-2002 concentration in tissues after a single intramuscular administration of ARCT-021 50 μg in mice

Male



Female



ATX-126

ATX-126 was detectable at 2 hours after ARCT-021 administration in plasma and all tissues except for brain in the 25 and 50 μg groups[14)] and testis in the 25 μg group (Figure 1 shows ATX-126 concentration in plasma). The tissues containing the highest ATX-126 concentration were muscles (997.2 ± 386.5 μg/g in males and 659.8 ± 157.2 μg/g in females in the 50 μg group) and inguinal lymph nodes (190.0 μg/g in males and females in the 50 μg group[12)]), followed by popliteal lymph nodes. ATX-126 concentration in other tissues was as low as one-tenth to one-three hundredth times that of the tissues with the highest concentration. On Day 31, ATX-126 concentration was <1% of the administered dose in almost all tissues of both dose groups. The mean ATX-126 concentration in liver and muscles was 4% and 3%, respectively, of the administered dose.

The average half-life of ATX-126 in muscles of males and females combined was 32 and 64 days, respectively, in the 25 and 50 μg groups.[15)]

14) Detected at an extremely low concentration in 1 of 20 samples in the 50 μg group.
15) The mean value in females only. ATX-126 concentration in males could not be calculated.

S-protein

S-protein was detectable in muscles, lung, lymph nodes, and ovary of the 25 μg group and in muscles, lymph nodes, ovary, and plasma of the 50 μg group, but undetectable in other tissues. In muscles with the highest S-protein concentration among tissues, S-protein was detectable from approximately 48 hours after administration in both dose groups, reached the peak level at 72 hours or 8 days after administration (12.22 ± 12.84 ng/g in males and 96.92 ± 43.69 ng/g in females in the 50 μg group[16]) and became undetectable on Day 15. In lymph nodes, S-protein was detectable only at a single time point in the 25 μg group, whereas in the 50 μg group, S-protein became detectable from 2 hours after administration and was still detectable on Day 31 (inguinal lymph node, 13.71 ng/g in males and females combined[12]; popliteal lymph nodes, 17.73 ng/g in males and females combined[12]) without showing a clear peak level. In plasma samples as well, S-protein became detectable from 24 hours after administration in the 50 μg group, reached the peak level at 72 hours or 8 days after administration (27.10 ± 23.81 ng/mL in males,[16] 40.48 ± 32.81 ng/mL in females[16]), and was still detectable on Day 31 (8.20 ± 2.84 ng/mL in males,[16] 12.57 ± 19.86 ng/mL in females[16]). S-protein in lung and ovary became detectable from 2 hours after administration; it became undetectable from 8 days after administration in lung and, in the ovary, S-protein level decreased over time, reaching 0.1 ng/g on Day 31.[12]

4.2.2 Biodistribution following the repeated intramuscular administration in rabbits (CTD 4.2.3.2-02)

Phosphate-buffered saline (PBS) or ARCT-021 (20 or 40 μg in the amount of RNA) was administered intramuscularly 3 times at 2-week intervals to rabbits (n = 5/sex in the main study group, n = 2/sex in the withdrawal group) [see Section 5.2]. At necropsy on Day 31 after the first dose (the main study group, 48 hours after the last dose) and on Day 57 (the withdrawal group, Day 28 after the last dose), plasma and tissues[17] were collected and measured for mRNA-2002 and ATX-126 concentrations.

mRNA-2002

Day 31 after the first dose: mRNA-2002 was detectable in the muscle (the administration site) only in 1 animal (female in the 40 μg group, 1.31 pg/mg) and at low levels in the spleen (40 μg group, 1.58 ± 0.82 pg/mg in males, 1.37 ± 0.72 pg/mg in females) depending on the dose administered but was undetectable in other tissues.

Day 57 after the first dose: mRNA-2002 was undetectable in plasma and in all tissues.

ATX-126

ATX-126 was detectable in the plasma, muscle, mesenteric lymph nodes, liver, spleen, and ovary, but not in other tissues. Table 7 shows results in the 40 μg group.

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16) BLOQ level in ≥1 sample.

17) mRNA-2002 was measured in the lung, liver, spleen, muscle (administration site), mesenteric lymph nodes, and ovary. ATX-126 was measured in the plasma, brain, lung, heart, liver, spleen, kidney, muscle (administration site), mesenteric lymph nodes, testis, and ovary. Since ATX-126 in testis was detected only at a low concentration in the tissue distribution study in mice, mRNA-2002 level assessment was not conducted in this tissue. ARCT-021 was administered at 4 different sites of muscles, and samples collected from 2 of these sites were subjected to analysis of mRNA-2002 and ATX-126.

On Day 57, ATX-126 was detectable in the liver, spleen, muscle, and ovary, but no histopathological findings of toxicological significance were observed in any of these tissues.

Table 7. Plasma and tissue concentrations of ATX-126 following a repeated intramuscular administration of ARCT-021 40 µg in rabbits

Tissue	Sex	ATX-126 concentration (mean ± SD) (plasma, ng/mL; tissue, ng/g)	
		Day 31 after the first dose	Day 57 after the first dose
Plasma	Male	47.2 ± 13.5 [a)]	BLOQ
	Female	114.1 ± 51.6	BLOQ
Muscle (Injection site 2)[b)]	Male	*1060* [a)]	BLOQ
	Female	*2000* [a)]	*722* [a)]
Muscle (Injection site 3)[b)]	Male	22200.0 ± 3111.3 [a)]	BLOQ
	Female	*875* [a)]	BLOQ
Mesenteric lymph nodes	Male	BLOQ	BLOQ
	Female	*357* [a)]	BLOQ
Liver	Male	3448.0 ± 288.3	5160.0 ± 1909.2
	Female	4476.0 ± 895.8	3280.0 ± 537.4
Spleen	Male	5426.0 ± 3074.7	5060.0 ± 919.2
	Female	4166.0 ± 1616.7	3255 ± 1237.4
Ovary	Female	455.0 ± 171.7 [a)]	442.0 ± 168.3

Italics, Not exactly the mean because only one measured value was available.
a) BLOQ in ≥1 sample.
b) Of the 3 doses of Kostaive administration, Injection site 2 was the site of the first and the third injections; Injection site 3 was the site of the second injection

4.3 Metabolism (CTD 4.2.2.4-01 to 4.2.2.4-03, Reference data)

Although no study was conducted to evaluate the metabolism of mRNA-2002 and S-protein, it is expected that mRNA-2002 is degraded into small oligomers and mononucleotides, and S-protein into peptides and amino acids. No metabolic study was conducted on DSPC, cholesterol, and PEG2000-DMG, which are components of LNP, because there are use experiences of these excipients with approved drugs.

In vitro metabolism of ATX-126, a novel lipid component of LNP, was evaluated by incubation with mouse, rabbit, monkey, and human liver microsomes and hepatocytes, with rat, rabbit, and human liver S9 fractions, and with rabbit plasma. *In vivo* metabolism of ATX-126 was investigated using mouse plasma, urine, bile, and liver samples. Main results of the studies are summarized below.

When ATX-126 was incubated with human liver microsomes, liver S9, and hepatocytes, 2 types of metabolites were generated by oxidation and dehydration. All of the metabolites identified upon incubation with human samples were detected upon incubation with mouse and monkey samples but not upon incubation with rat samples. In these *in vitro* studies, the parent compound ATX-126 was detected as the most abundant ATX-126-related component in all animal species studied, demonstrating the extremely low turn-over rate of ATX-126. LNP formulation containing ATX-126 and small interfering RNA (siRNA) (ATX-LNP siRNA[18)]) was administered intravenously to mice in a single dose, and plasma, urine, bile, and liver samples were collected at 24 hours post-dose and subjected to investigation of *in vivo* metabolism of ATX-126. Results showed that 7 metabolites generated by ester hydrolysis, oxidation, N-demethylation, or dehydration were identified. All of the 7 metabolites were

[18)] Non-target siRNA-containing LNP formation with the same LNP components as those of Kostaive

excreted in urine. All of the 4 types of metabolites identified in plasma, bile, or liver accounted <5% of the total metabolites, except for 1 type of metabolite with an abundance ratio of 5% to 20% in plasma.

4.4 Excretion

No excretion study has been conducted.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following investigations, PMDA concluded that there are no particular problems with non-clinical pharmacokinetics of Kostaive.

4.R.1 Non-clinical pharmacokinetics of Kostaive

The applicant's explanation about the self-amplification of Kostaive, its regulation, and the pharmacokinetics:

The replicon of mRNA-2105 is derived from VEEV, and the sequence encoding the structural protein of VEEV is replaced by the sequence encoding S-protein in mRNA-2105. Therefore, no infectious viral particles are generated by Kostaive administration. Because of the absence of reverse transcriptase, sequences of mRNA-2105 are not incorporated into host cell DNA. Kostaive is an LNP-formulation of mRNA-2105. After intramuscular administration, it is expected to be incorporated by endocytosis into muscle cells and antigen presenting cells (e.g., dendritic cells) at the administration site (*Vaccines. (Basel)* 2019;7(4):122, *Vaccines. (Basel)* 2021;9(2):147, etc.). mRNA-2105 released from LNP into cytoplasm is expected to be amplified by replication mechanisms of VEEV replicase[19)] and translated into S-protein antigen by ribosome within the cell, thereby exhibiting the expected effect. The amplified mRNA and the translated protein within the cell are expected to be degraded and removed by intracellular nuclease and protease (*Vaccines. (Basel)* 2021;9(2):97).

Usually, administered mRNA is rapidly metabolized as is the case with nucleic acid in the body, whereas mRNA encapsulated in LNP is incorporated into cells without being metabolized. The biodistribution of LNP-encapsulated mRNA depends mainly on the components and particle size of LNP but not on the incorporated mRNA itself (*Mol Ther Nucleic Acids.* 2019;15:1-11, *Nanomedicine. (Lond)* 2016;11:673-92). Since Kostaive and ARCT-021 are similar in their components with the identical LNP components and LNP-to-mRNA ratio, tissue distribution and elimination of the components of ARCT-021 [see Sections 4.1 and 4.2] are considered to be extrapolatable to Kostaive.

Metabolism of ATX-126, the novel ionized lipid common to both vaccines, was investigated. Results were as described in Section 4.3.

Placental transfer of Kostaive was discussed based on the results of the fertility studies, embryo-fetal studies, and developmental toxicity studies on ARCT-021 (CTD 4.2.3.5.3-01). mRNA-2002 was undetectable in placenta or fetal tissues in any treatment group studied, except in the plasma (8.19 pg/mL) of a fetus in 1 of 20 samples in the 10 μg group. ATX-126 was detectable in placenta in

[19)] A replicase (including RNA-dependent RNA polymerase) is expressed from mRNA-2105 released into cytoplasm, and the replicase generates minus-chain RNA complementary to mRNA-2105. When mRNA-2105 is resynthesized from the minus chain RNA by replicase, mRNA encoding S-protein is also synthesized (*J Gen Virol.* 2015;96 (9):2483-2500, *Gene Ther.* 2021;28 (3-4):117-129).

the 10 and 20 μg groups (275.0 ± 33.9 ng/g in the 10 μg group, 387.6 ± 117.8 ng/g in the 20 μg group), but not detected in plasma or tissues of fetuses in either of the groups. The above results suggest that ARCT-021 is unlikely to be transferred from maternal animals to fetuses. The same is considered to apply to Kostaive.

PMDA's view:
The explanation about the pharmacokinetics related to distribution and elimination of Kostaive is acceptable mainly based on the results of ARCT-021 studies, and the pharmacokinetics of Kostaive can be understood to a certain extent from the applicant's explanation and the results of the non-clinical pharmacokinetic studies submitted [Sections 4.1 to 4.3]. The samRNA may possibly persist for a longer period in the body compared with conventional non-samRNA, but mRNA has not raised any problem of particular concern such as accumulation; instead, it has been shown that mRNA is eliminated from the body over time. In the biodistribution study in mice, S-protein was detected mainly in the muscle of the administration sites, lymph nodes, and plasma, showing the same distribution pattern as that of mRNA. S-protein showed the tendency of decrease with time, suggesting that it does not persist for an extended period. The lipid ATX-126 has a long half-life and may remain for a long period, while no adverse histopathological findings have been observed in the repeated-dose toxicity study in rabbits [see Section 5.2].

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the following data relating to the toxicity of Kostaive: Repeated-dose toxicity studies on Kostaive as well as repeated-dose toxicity studies and reproductive and developmental toxicity studies on ARCT-021 containing mRNA encoding S-protein with amino acid sequence different from that of S-protein of Kostaive, encapsulated in LNP with the same components as that of Kostaive. ARCT-021 administration resulted in production of anti-S-protein IgG and SARS-CoV-2-neutralizing antibodies in mice and cynomolgus monkeys [see Section 3.1.1], and the applicant considers that these results can be used in the safety evaluation of Kostaive.

5.1 Single-dose toxicity

No single-dose toxicity study of Kostaive was conducted. Instead, the single-dose toxicity (acute toxicity) of Kostaive was evaluated based on the results of the initial dose in the repeated intramuscular dose toxicity study in rabbits (CTD 4.2.3.2-03). No death occurred after vaccination with Kostaive. A transient and mild increase in body temperature was observed.

5.2 Repeated-dose toxicity

Repeated intramuscular dose toxicity studies on Kostaive and ARCT-021 were conducted in rabbits (Table 8). The main finding was inflammatory change at the administration site.

Table 8. Major repeated-dose toxicity studies on Kostaive and ARCT-021

Test substance	Test system	Route of administration	Treatment period	Dose (μg RNA/body)	Main findings	NOAEL (μg RNA/body)	CTD
Kostaive	Male and female rabbits (NZW)	Intra-muscular injection	4 weeks (3 doses[a) b) c)]) + 4-week withdrawal	0,[f)] 16.75, 25.1, or 33.55	≥16.75: Skeletal muscle degeneration and inflammation at the injection site, inflammation of subcutaneous tissue, decrease in erythrocyte parameters (red blood cell count, etc.)/platelet count, increase in neutrophil count/monocyte count/fibrinogen, increase in IP-10/IL-6/MCP-1 Reversible	33.55	4.2.3.2 -03
ARCT-021			4 weeks (3 doses[a) d) e)]) + 4-week withdrawal	0,[g)] 20, or 40	≥20: Skeletal muscle degeneration and inflammation at the injection site, inflammation of subcutaneous tissue, decrease in erythrocyte parameters (red blood cell count, etc.), increase in fibrinogen/CRP, increase in IP-10/IL-6/MCP-1 Reversible	40	4.2.3.2 -02

a) Administered at the back or the lumbar level (1 or 2 sites) on Day 1, 15, and 29 after the start of the study.
b) Production of IgG against S-protein was detected on Day 31 after the start of the study.
c) Volume, 0.5 mL/body
d) Production of IgG against S-protein was detected on Day 15, 29, 31, and 57 after the start of the study.
e) Volume, 0.4 mL/body (20 μg RNA/body group) or 0.8 mL/body (0 or 40 μg RNA/body group)
f) Vehicle, Physiological saline
g) Vehicle, PBS

5.3 Genotoxicity

The mRNA contained in Kostaive consists of natural nucleic acid, and the novel excipients (ATX-126, cholesterol, PEG2000-DMG, and DSPC) pose no genotoxicity concern [see Section 2.R.1.2]. No genotoxicity study on Kostaive has therefore been conducted.

5.4 Carcinogenicity

Since Kostaive is not used clinically continuously for ≥6 months, no carcinogenicity study on Kostaive has been conducted.

5.5 Reproductive and developmental toxicity

A reproductive and developmental toxicity study on ARCT-021 was conducted in rabbits (Table 9). ARCT-021 caused a reduced body weight gain in parental animals, but had no effect on the offspring. The safety margin of the no observed adverse effect level (NOAEL) in parental animals (10 μg RNA/body) was 30 times the recommended clinical dose in body weight ratio. On the basis of the above, the applicant considers that Kostaive is unlikely to pose any safety concern.

Table 9. Reproductive and developmental toxicity studies on ARCT-021

Study	Test system	Route of administration	Treatment duration	Dose (μg RNA/body)	Main findings	NOAEL (μg RNA/body)	CTD
Fertility and early embryonic development to implantation, embryofetal development, pre- and postnatal development, including maternal function	Female rabbits (NZW)	Intra-muscular injection	Female: 28 days before mating to Gestation Day 28 (5 doses in total[a)])	0,[b)] 10,[c)] 20[c)]	Maternal animals[d)] 20: Reduced body weight gain Embryos/fetuses 10, 20[d)]: None F1 offspring 10, 20[d)]: None	Maternal animals (general toxicity, fertility): 10 Embryos/fetuses: 20 F1 offspring: 20	4.2.3.5.3 -01

a) Administered at the back or lumbar level (1 site) on 28 and 14 days before the start of mating and on Gestation Day 0, 14, and 28
b) Vehicle, PBS
c) ARCT-021 (20 μL/μg RNA)
d) In the 20 μg RNA group, production of IgG against S-protein was confirmed in maternal animals 15 days before mating, 29 days after mating (at caesarean section), and 27 days after delivery; fetuses on Gestation Day 29 (at caesarean section), and F1 offspring on Day 27 after delivery.

5.6 Local tolerance

Local tolerance of Kostaive was evaluated based on Draize score and histopathology in the repeated intramuscular dose toxicity study in rabbits (CTD 4.2.3.2-03). No toxicologically significant findings were observed at the administration site of Kostaive.

5.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that there was no particular problem in the toxicity of Kostaive.

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

No clinical pharmacology study has been conducted in the present application.

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

The applicant submitted the efficacy and safety evaluation data in the form of results from 4 studies shown in Table 10.

Table 10. List of clinical studies

Study code (country)	Phase	Population (healthy adults)	No. of subjects enrolled	Dosage regimen[a) b)]	Study objective
Foreign					
ARCT-021-04 (US, Singapore)	II	≥18 years old	Primary series part: 581 A: 146 B: 145 C: 145 D: 145	A: A single dose of ARCT-021 7.5 µg, followed by placebo after 28 days B: 2 doses of ARCT-021 5 µg, 28 days apart C: 2 doses of ARCT-021 7.5 µg, 28 days apart D: 2 doses of placebo, 28 days apart	Immunogenicity Safety
			Booster dose part: 228[20)] ARCT-021: 44 Kostaive: 41 ARCT-165: 42 Placebo: 99	A single dose of Kostaive 5 µg, ARCT-021 5 µg, ARCT-165 5 µg, or placebo was administered 6 months after the second dose of the primary series[c)]	Immunogenicity Safety
ARCT-154-01 (Vietnam)	I/II/III	Part 1 ≥18 to <60 years old Part 2, 3a ≥18 years old	Part 1: 100 Kostaive: 75 Placebo: 25 Part 2: 302 Kostaive: 226 Placebo: 75 Part 3a: 600 Kostaive: 448 Placebo: 152	Part 1: Two doses of Kostaive 5 µg or placebo were administered 28 days apart. At 2 months after the second dose, Kostaive group and placebo group received 2 doses of placebo and Kostaive 5 µg, respectively, 28 days apart. Part 2 and Part 3a: Two doses of Kostaive 5 µg or placebo were administered 28 days apart. At 2 months after the second dose, placebo group received 2 doses of Kostaive 5 µg, 28 days apart. Subjects in the Kostaive group were re-assigned to receive the Kostaive or placebo group at a ratio of 3:1. The new Kostaive group received a single dose of Kostaive 5 µg followed by a single dose of placebo after 28 days, and the new placebo group received 2 doses of placebo.	Immunogenicity Safety
		Part 3b ≥18-year old	16107 Kostaive: 8059 Placebo: 8048	Two doses of Kostaive 5 µg or placebo were administered 28 days apart. At 2 months after the second dose, Kostaive group and placebo group received 2 doses of placebo and Kostaive 5 µg, respectively, 28 days apart.	Efficacy Safety
ARCT-165-01 (Singapore, US, South Africa)	I/II	Individuals aged ≥21 to ≤65 years who had received Comirnaty twice ≥5 months before	Cohort B[21)]: 36 Kostaive: 12 ARCT-021: 12 ARCT-165: 12	A single dose of Kostaive 5 µg, ARCT-021 5 µg, or ARCT-165 5 µg was administered.	Immunogenicity Safety
Japan					
ARCT-154-J01 (Japan)	III	Individuals aged ≥18 years who had received the primary series and the booster dose ≥3 months before	828 Kostaive: 420 Comirnaty: 408	A single dose of Kostaive 5 µg or Comirnaty (tozinameran) 30 µg was administered.	Immunogenicity Safety

a) The dose (µg) is the amount of RNA in each vaccine product unless specified otherwise. Intramuscular injection in all studies. Placebo is physiological saline.
b) ARCT-021 encodes S-protein of the original strain, Kostaive (ARCT-154) encodes S-protein of the original strain containing mutations of B1 lineage (D614G, etc.), and ARCT-165 encodes S-protein of Beta variant (B.1.351 lineage) [see Table 1 in Section 2.1.4].
c) Subjects assigned to group A, B, or C in the primary series part were re-assigned to receive ARCT-021, Kostaive (ARCT-154), ARCT-165 or placebo at a ratio of 1:1:1:1.

In the following are described the outlines of main clinical studies.

[20)] Two subjects (1 each receiving ARCT-021 and vaccination with Kostaive, respectively) who had been assigned to the placebo group in the primary series are included in the total number of subjects.
[21)] Study ARCT-165-01 included Cohort A without a prior SARS-CoV-2 vaccination and Cohort B with a prior SARS-CoV-2 vaccination. Only the data of Cohort B were submitted in the present application.

7.1 Phase II study

7.1.1 Foreign phase II study (CTD 5.3.5.1-03; Study ARCT-021-04; study period, January 2021 to March 2022)

Study ARCT-021-04 consisted of the following 2 parts: (1) The primary series part investigating the safety and immunogenicity of ARCT-021 given as the primary series and (2) the booster dose part administering ARCT-021, Kostaive, ARCT-165, or placebo after 6 months to subjects who had received ARCT-021 or placebo intramuscularly in the primary series part (subjects who had received only placebo in the primary series received either ARCT-021, Kostaive, or ARCT-165).[22] In the following is described the primary series part.

A randomized, observer-blind,[23] placebo-controlled, parallel-group study was conducted to investigate the safety and immunogenicity of ARCT-021 in healthy adults aged ≥18 years without history of SARS-CoV-2 infection[24] (target sample size, 600 subjects [300 aged 18-55 years, 300 aged ≥56 years; 150 each in Groups A, B, C, or D] at 15 study sites in the US and Singapore. Subjects were stratified by age (18-55, ≥56) and randomized. The dosage regimen in each group was as follows:

Group A: A single dose of ARCT-021 7.5 μg, followed by administration of placebo (physiological saline) after 28 days
Group B: 2 doses of ARCT-021 5 μg 28 days apart
Group C: 2 doses of ARCT-021 7.5 μg 28 days apart
Group D: 2 doses of placebo 28 days apart

Of 581 subjects who were enrolled in the study and randomized, 580 subjects (146 in Group A, 145 in Group B, 144 in Group C, and 145 in Group D) received at least 1 dose of the study vaccine and were included in the intention-to-treat (ITT) population and the safety analysis population. Of the subjects in ITT, 577 subjects (143 in Group A, 145 in Group B, 144 in Group C, and 145 in Group D) available with immunogenicity data before and after study vaccination were included in the modified intention-to-treat (mITT) population and subjected to immunogenicity analysis.

Table 11 shows the results of main immunogenicity endpoints.

[22] The primary objective of the study was to compare the safety and immunogenicity of ARCT-021 in the primary series with those of the placebo, thereby to determine the dose and schedule for the phase III study.
[23] The investigator, the study staff at study sites, subjects, and the responsible person of the study-supervising organization were blinded to the study.
[24] Subjects who had a history of positive SARS-CoV-2 test or were clinically diagnosed with COVID-19 were excluded.

Table 11. Neutralizing antibody response in serum against the original strain (mITT)

		Group A (N = 143)	Group B (N = 145)	Group C (N = 144)	Group D (N = 145)
Baseline	n	131	140	134	141
	GMC (IU/mL)[a)]	4.40 [4.03, 4.80]	5.14 [4.47, 5.90]	5.31 [4.57, 6.18]	4.75 [4.30, 5.25]
28 days after the first dose	N	126	130	129	133
	GMC (IU/mL)[a)]	6.42 [5.44, 7.59]	6.84 [5.74, 8.14]	7.61 [6.20, 9.33]	4.53 [4.13, 4.96]
	GMFR[a)]	1.5 [1.2, 1.8]	1.4 [1.1, 1.7]	1.5 [1.2, 1.8]	1.0 [0.9, 1.1]
	No. of subjects with antibody response[b)]	16	14	24	4
	SRR (%)[c)]	12.7 [7.4, 19.8]	10.8 [6.0, 17.4]	18.6 [12.3, 26.4]	3.0 [0.8, 7.5]
28 days after the second dose	N	114	116	117	116
	GMC (IU/mL)[a)]	5.47 [4.61, 6.48]	13.37 [10.65, 16.79]	15.31 [11.89, 19.72]	4.21 [3.89, 4.57]
	GMFR[a)]	1.3 [1.1, 1.6]	2.7 [2.2, 3.5]	2.9 [2.2, 3.7]	0.9 [0.8, 1.0]
	No. of subjects with antibody response[b)]	10	50	50	1
	SRR (%)[c)]	8.8 [4.3, 15.5]	43.1 [33.9, 52.6]	42.7 [33.6, 52.2]	0.9 [0.0, 4.7]

N = Number of subjects analyzed, n = Number of subjects without missing data at the evaluation time point, the numbers in the brackets indicates two-sided 95% confidence interval (CI).
If the antibody titer was below LLOQ, the value 0.5 × LLOQ was used for analysis. If the antibody titer was more than upper limit of quantification (ULOQ) and measured value was unavailable, the value ULOQ was used for analysis (quantification range [LLOQ to ULOQ]: 7.84 to 215.69 [original strain])

a) Two-sided 95% CI was calculated by assuming t-distribution for log-transformed value of antibody concentration or for the log-transformed value of the rate of an antibody titer increase.
b) Number of subjects who met the definition of antibody response (a ≥4-fold increase in antibody titer from the level before the primary series [a half of LLOQ if the titer was below LLOQ]).
c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.

The safety observation period was as follows:

- Solicited adverse events[25)] (local [pain, erythema (redness), swelling (induration), injection site tenderness] and systemic [pyrexia, headache, fatigue, myalgia, arthralgia, nausea, chills, diarrhoea, dizziness, vomiting]) were collected from the subject diary for 7 days after the study vaccination.
- Unsolicited adverse events (adverse events other than solicited adverse events observed within 7 days after the study vaccination) were collected for 28 days after the study vaccination.
- Serious adverse events, adverse events of special interest, and adverse events leading to study discontinuation were collected between the study vaccination and the end of the study.

Table 12 shows solicited adverse events.

[25)] Severity of adverse events were evaluated according to the FDA Guidance (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007), and Grade <1 erythema/redness (<2.5 cm), swelling/induration (<2.5 cm), and pyrexia (37.5℃ to 37.9℃) were rated Grade 0.

Table 12. Solicited adverse events after administration of each dose (ITT)

MedDRA PT	First dose				Second dose			
	Group A N = 142	Group B N = 142	Group C N = 144	Group D N = 146	Group A N = 127	Group B N = 130	Group C N = 137	Group D N = 135
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local (all events)	122 (85.9)	122 (85.9)	128 (88.9)	40 (27.4)	28 (22.0)	95 (73.1)	111 (81.0)	31 (23.0)[d]
Pain	75 (52.8)	69 (48.6)	83 (57.6)	12 (8.2)	10 (7.9)	43 (33.1)	61 (44.5)	8 (5.9)[d]
Erythema (redness)	21 (14.8)	28 (19.7)	16 (11.1)	11 (7.5)	9 (7.1)	19 (14.6)	11 (8.0)	12 (8.9)[d]
Swelling (induration)	16 (11.3)	22 (15.5)	13 (9.0)	8 (5.5)	6 (4.7)	15 (11.5)	6 (4.4)	4 (3.0)[d]
Injection site tenderness	113 (79.6)	107 (75.4)	120 (83.3)	29 (19.9)	19 (15.0)	88 (67.7)	103 (75.2)	21 (15.6)[d]
Systemic (all events)	142 (100.0)	142 (100.0)	143 (99.3)	143 (97.9)[b]	123 (96.9)	129 (99.2)	133 (97.1)[e]	134 (99.3)
Pyrexia[a]	6 (4.2)	3 (2.1)	4 (2.8)[c]	0[c]	1 (0.8)[f]	4 (3.1)[g]	9 (6.6)[h]	0[d]
Headache	61 (43.0)	49 (34.5)	57 (39.6)	28 (19.2)[b]	16 (12.6)	39 (30.0)	56 (40.9)[e]	22 (16.3)
Fatigue	67 (47.2)	52 (36.6)	58 (40.3)	30 (20.5)[b]	18 (14.2)	43 (33.1)	61 (44.5)[e]	29 (21.5)
Myalgia	63 (44.4)	41 (28.9)	57 (39.6)	12 (8.2)[b]	8 (6.3)	45 (34.6)	45 (32.8)[e]	19 (14.1)
Arthralgia	30 (21.1)	22 (15.5)	25 (17.4)	12 (8.2)[b]	4 (3.1)	22 (16.9)	33 (24.1)[e]	13 (9.6)
Nausea	15 (10.6)	12 (8.5)	9 (6.3)	11 (7.5)[b]	7 (5.5)	9 (6.9)	12 (8.8)[e]	7 (5.2)
Chills	41 (28.9)	24 (16.9)	33 (22.9)	3 (2.1)[b]	3 (2.4)	17 (13.1)	31 (22.6)[e]	7 (5.2)
Diarrhoea	17 (12.0)	18 (12.7)	23 (16.0)	14 (9.6)[b]	9 (7.1)	13 (10.0)	15 (10.9)[e]	17 (12.6)
Dizziness	11 (7.7)	14 (9.9)	13 (9.0)	13 (8.9)[b]	9 (7.1)	6 (4.6)	24 (12.4)[e]	9 (6.7)
Vomiting	2 (1.4)	0	0	0[b]	0	0	0[e]	1 (0.7)

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

a) ≥38˚C (oral)

b) N = 145, c) N = 143, d) N = 134, e) N = 136, f) N=123, g) N = 129, h) N = 131

Grade ≥3 local adverse events were observed in 9 subjects (6.3%) in the Group A, 3 subjects (2.1%) in the Group B, and 6 subjects (4.2%) in the Group C after the first dose, and in 4 subjects (2.9%) in the Group C after the second dose. Grade ≥3 systemic adverse events were observed in 9 subjects (6.3%) in the Group A, 2 subjects (1.4%) in the Group B, 1 subject (0.7%) in the Group C, and 1 subject (0.7%) in the Group D after the first dose; and in 2 subjects (1.6%) in the Group A, 2 subjects (1.5%) in the Group B, 8 subjects (5.8%) in the Group C, and 3 subjects (2.2%) in the Group D after the second dose.

Table 13 shows unsolicited adverse events and adverse reactions observed in ≥2% of subjects in any of the groups. Grade ≥3 unsolicited adverse events were observed in 4 subjects (2.8%) in the Group A, 6 subjects (4.2%) in the Group B, 2 subjects (1.4%) in the Group C, and 5 subjects (3.4%) in the Group D. Grade ≥3 adverse events observed in ≥2 subjects in any group were hyperkalaemia in 2 subjects (1.4%) in the Group A, blood pressure increased in 2 subjects (1.4%) in the Group B, and blood creatine phosphokinase increased in 2 subjects (1.4%) in the Group D. Grade ≥3 unsolicited adverse reactions were observed in 2 subjects (1.4%) in the Group A, 1 subject (0.7%) in the Group B, 1 subject (0.7%) in the Group C, and 1 subject (0.7%) in the Group D. There were no Grade ≥3 unsolicited adverse reactions observed in multiple subjects.

Table 13. Unsolicited adverse events and adverse reactions observed in ≥2% of subjects in any group (ITT)

MedDRA PT	Group A N = 144	Group B N = 145	Group C N = 145	Group D N = 146
	n (%)	n (%)	n (%)	n (%)
Adverse events				
All adverse events	48 (33.1)	49 (34.0)	35 (24.1)	53 (36.3)
Diarrhoea	5 (3.4)	1 (0.7)	4 (2.8)	6 (4.1)
Headache	4 (2.8)	3 (2.1)	2 (1.4)	3 (2.1)
Fatigue	3 (2.1)	2 (1.4)	1 (0.7)	3 (2.1)
Hyperkalaemia	3 (2.1)	3 (2.1)	2 (1.4)	2 (1.4)
Urticaria	3 (2.1)	0	0	1 (0.7)
Blood creatine phosphokinase increased	2 (1.4)	3 (2.1)	2 (1.4)	2 (1.4)
COVID-19	2 (1.4)	1 (0.7)	1 (0.7)	3 (2.1)
Adverse reactions				
All adverse reactions	12 (8.3)	15 (10.4)	13 (9.0)	15 (10.3)
Urticaria	3 (2.1)	0	0	1 (0.7)

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

Within 208 days after the initial dose of vaccine, serious adverse events were observed in 3 subjects in the Group B (small intestinal obstruction, atrial fibrillation, and cholecystitis in 1 subject each), 1 subject in the Group C (chronic lymphocytic leukaemia), and 5 events in 3 subjects in the Group D (ischaemic stroke, accidental overdose, drug abuse, deep vein thrombosis, and pulmonary venous thrombosis in 1 subject each). A causal relationship to the study vaccine was denied for all of these serious adverse events.

An adverse event leading to study discontinuation was observed in 1 subject in Group C (diarrhoea). The event was observed after the second dose, and its causal relationship to the study vaccine was not ruled out.

There were no adverse events that resulted in death.

7.2 Phase III study

7.2.1 Foreign phase I/II/III study (CTD 5.3.5.1-01; Study ARCT-154-01; study period, ongoing since August 2021; data cut-off on January 12, 2023)

Study ARCT-154-01 was conducted to investigate the efficacy, safety, and immunogenicity of Kostaive vaccinated as the primary series. In Parts 1, 2, and 3a, the immunogenicity and safety of Kostaive were evaluated as compared with those of the placebo control. In Part 3b, the efficacy and safety of Kostaive were evaluated against the placebo control.[26)]

7.2.1.1 Parts 1, 2, and 3a of Study ARCT-154-01

A randomized, observer-blind,[27)] placebo-controlled, parallel-group study was conducted to investigate the safety and immunogenicity of Kostaive in healthy adults aged ≥18 years[28)] (target sample size, 100 subjects in Part 1, 300 subjects in Part 2, and 600 subjects in Part 3a; Kostaive group and placebo group at a ratio of 3:1 in each Part) at 16 study sites in Vietnam.

[26)] Data of Part 3c (investigation of immunogenicity and safety, as compared with those of Vaxzevria) were not submitted in the present application.

[27)] The investigator, the study staff at study sites, subjects, the responsible persons of the study-supervising organization, and the representative of the sponsor directly monitoring the study were blinded to the study.

[28)] Subjects in Part 1 were healthy adults aged ≥18 and <60 years

In Part 1, subjects were randomized to the Kostaive 5 μg group or placebo (physiological saline) group at a 3:1 ratio, and received the study vaccine intramuscularly twice, 28 days apart, and at 2 months after the second dose (Day 92), received Kostaive (placebo group) or placebo (Kostaive group) intramuscularly twice, 28 days apart. In Part 2 and Part 3a, subjects were randomized to the Kostaive 5 μg group or placebo group at a 3:1 ratio[29)] and received the study vaccine intramuscularly twice, 28 days apart. At 2 months after the second dose (Day 92), subjects received either of the following treatments: (1) Subjects receiving Kostaive at the initial assignment were randomized to the Kostaive 5 μg group or placebo group at a 3:1 ratio and received a single dose of the study vaccine, followed by intramuscular administration of placebo after 28 days; and (2) subjects receiving the placebo at the initial allocation received Kostaive 5 μg twice, 28 days apart.

In Parts 1, 2, and 3a,[30)] of 1,002 subjects randomized, 1,001 subjects (749 in the Kostaive group, 252 in the placebo group) received the study vaccine at least once and were included in ITT, and according to the study vaccine they actually received, 1,001 subjects (748 in the Kostaive group, 253 in the placebo group) were included in the safety analysis population. Subjects who received the study vaccine and submitted the reactogenicity diary (1,001 subjects [748 in the Kostaive group, 253 in the placebo group] after the first dose, 977 subjects [732 in the Kostaive group, 245 in the placebo group] after the second dose) were included in the reactogenicity analysis population. Of the subjects in ITT, 724 subjects in the Kostaive group and 242 subjects in the placebo group who met all of the following criteria were included in the immunogenicity analysis population: (1) Subjects who received all study vaccines specified in the study protocol; (2) subjects without evidence of COVID-19 on Day 1; and (3) subjects with available data of immunogenicity test after at least 1 dose. Immunogenicity against the original strain was evaluated in 537 subjects in an exploratory manner.[31)]

The primary endpoint of immunogenicity was seroresponse rate (SRR) at 28 days after the second dose. Table 14 shows the results of immunogenicity including the secondary endpoints.

29) Stratified by age (18 to <60 years, ≥60 years) and presence/absence of risk factors for severe COVID-19 (in subjects aged <60 years).
30) The dosage regimen in Parts 1, 2, and 3a were identical up to 2 months after the second dose (Day 92, before the third dose). The safety and immunogenicity data of all parts are described as pooled data as initially planned.
31) Samples of 541 subjects (planned number, 539) were measured by the validated microneutralization titer assay. The exploratory analysis was conducted on 537 subjects in the immunogenicity population excluding 4 subjects with missing samples on Day 1 or with COVID infection at any time from Day 1 to 57.

Table 14. Serum neutralizing antibody response against the original strain (Parts 1/2/3a of Study ARCT-154-01, immunogenicity evaluation population)

		Kostaive (N = 724)	Placebo (N = 242)
Baseline	n	403	134
	GMC (IU/mL)[a)]	7.0 [6.6, 7.5]	6.5 [5.8, 7.3]
28 days after the second dose	n	392	131
	GMC (IU/mL)[a)]	145.7 [135.1, 157.2]	7.7 [6.9, 8.7]
	GMC ratio (IU/mL)[a)]	18.9 [16.3, 21.9]	
	n	391	131
	GMFR[a)]	20.9 [19.2, 22.9]	1.2 [1.1, 1.3]
SRR	N1	391	131
	n1[b)]	375	3
	SRR (%)[c)]	95.9 [93.4, 97.6]	2.3 [0.5, 6.5]

The number in the brackets indicates a two-sided 95% CI.
N = Number of subjects analyzed, n = Number of subjects without missing data at the evaluation time point, N1 = Number of subjects evaluable for SRR, n1 = Number of subjects with antibody response
If the antibody titer was below LLOQ, the value 0.5 × LLOQ was used for analysis (quantification range [LLOQ to ULOQ]: 10 to 111433 AU/mL [original strain], 1 IU/mL = 1.275 AU/mL)
a) Two-sided 95% CI was calculated based on t-distribution in the logarithmically transformed value of antibody titer or the difference in the logarithmically transformed value of the antibody titer
b) Number of subjects who met the definition of antibody response (a ≥4-fold increase in antibody titer from the level before the primary series [a half of LLOQ if the titer was below LLOQ]).
c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.

The safety observation period was as follows:

- Solicited adverse events[25)] (local [pain, erythema (redness), swelling (induration), injection site tenderness] and systemic [pyrexia, headache, fatigue, myalgia, arthralgia, nausea, chills, diarrhoea, dizziness, vomiting]) were collected from the subject diary for 7 days after the study vaccination.
- Unsolicited adverse events (adverse events other than solicited adverse events observed within 7 days after the study vaccination) were collected for 28 days after the study vaccination.
- Serious adverse events, adverse events of special interest, and adverse events leading to study discontinuation were collected between the study vaccination and Day 210 (adverse events in the Kostaive group and the placebo group were collected from the second dose up to 2 months after the vaccination [Day 92]).

Table 15 shows solicited adverse events observed in Part 1, 2, or 3a.

Table 15. Solicited adverse events observed after each vaccination (Part 1/2/3a, reactogenicity analysis population)

MedDRA PT	First dose				Second dose			
	Kostaive N = 748		Placebo N = 253		Kostaive N = 732		Placebo N = 245	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	586 (78.3)	27 (3.6)	51 (20.2)	1 (0.4)	452 (61.7)	18 (2.5)	28 (11.4)	0
Pain	485 (64.8)	6 (0.8)	34 (13.4)	1 (0.4)	359 (49.0)	4 (0.5)	16 (6.5)	0
Erythema (redness)	6 (0.8)	0	0	0	2 (0.3)	0	0	0
Swelling (induration)	25 (3.3)	0	1 (0.4)	0	13 (1.8)	0	0	0
Injection site tenderness	550 (73.5)	26 (3.5)	42 (16.6)	0	417 (57.0)	17 (2.3)	25 (10.2)	0
Systemic (all events)	557 (74.5)	21 (2.8)	120 (47.4)	2 (0.8)	506 (69.1)	36 (4.9)	93 (38.0)	1 (0.4)
Pyrexia[b)]	65 (8.7)	3 (0.4)	3 (1.2)	0	77 (10.5)	10 (1.4)	5 (2.0)	0
Headache	271 (36.2)	6 (0.8)	56 (22.1)	1 (0.4)	271 (37.0)	14 (1.9)	45 (18.4)	1 (0.4)
Fatigue	404 (54.0)	8 (1.1)	72 (28.5)	1 (0.4)	391 (53.4)	18 (2.5)	59 (24.1)	0
Myalgia	322 (43.0)	5 (0.7)	42 (16.6)	1 (0.4)	243 (33.2)	9 (1.2)	28 (11.4)	0
Arthralgia	222 (29.7)	9 (1.2)	35 (13.8)	1 (0.4)	204 (27.9)	10 (1.4)	22 (9.0)	0
Nausea	37 (4.9)	0	5 (2.0)	0	36 (4.9)	0	5 (2.0)	0
Chills	190 (25.4)	5 (0.7)	26 (10.3)	0	229 (31.3)	7 (1.0)	20 (8.2)	0
Diarrhoea	48 (6.4)	0	16 (6.3)	0	31 (4.2)	0	9 (3.7)	0
Dizziness	163 (21.8)	5 (0.7)	38 (15.0)	2 (0.8)	128 (17.5)	6 (0.8)	23 (9.4)	1 (0.4)
Vomiting	9 (1.2)	0	2 (0.8)	0	12 (1.6)	0	3 (1.2)	0

N = Number of subjects analyzed, n = Number of subjects with events
a) Number of subjects with Grade ≥1 event(s)
b) ≥38°C, ≥39°C for Grade ≥3 events

Table 16 shows unsolicited adverse events or adverse reactions observed in ≥1% of subjects in either group. A Grade ≥3 unsolicited adverse event was observed in only 1 subject (toothache) in the Kostaive group. Its causal relationship to Kostaive was denied.

Table 16. Adverse events or adverse reactions observed in ≥1% of subjects in either group (safety analysis population)

MedDRA PT	Adverse events		Adverse reactions	
	Kostaive (N = 748)	Placebo (N = 253)	Kostaive (N = 748)	Placebo (N = 253)
	n (%)	n (%)	n (%)	n (%)
All events	245 (32.8)	92 (36.4)	44 (5.9)	14 (5.5)
Headache	40 (5.3)	17 (6.7)	3 (0.4)	2 (0.8)
Application site haematoma	24 (3.2)	11 (4.3)	0	0
Hypertension	20 (2.7)	4 (1.6)	14 (1.9)	2 (0.8)
Influenza	17 (2.3)	6 (2.4)	0	0
Diarrhoea	16 (2.1)	2 (0.8)	2 (0.3)	0
Cough	13 (1.7)	3 (1.2)	0	0
Oropharyngeal pain	13 (1.7)	2 (0.8)	0	0
Arthralgia	10 (1.3)	5 (2.0)	0	1 (0.4)
Pharyngitis	9 (1.2)	5 (2.0)	0	0
Fatigue	8 (1.1)	1 (0.4)	4 (0.5)	1 (0.4)
Injection site haematoma	8 (1.1)	2 (0.8)	0	0
Rhinorrhoea	8 (1.1)	1 (0.4)	0	0
Back pain	7 (0.9)	3 (1.2)	0	0
Toothache	7 (0.9)	4 (1.6)	0	0

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

Serious adverse events were observed in 14 subjects in the Kostaive group (1.9%, COVID-19 in 11 subjects, upper respiratory tract infection, foot fracture, dermal cyst in 1 subject each) and in 16 subjects in the placebo group (6.3%, COVID-19 in 12 subjects, atrial fibrillation, urticaria, muscle injury, and vertigo positional in 1 subject each). A causal relationship to the study vaccine could not be ruled out for atrial fibrillation and urticaria in 1 subject each in the placebo group.

Adverse events leading to study discontinuation were observed in none of subjects in the Kostaive group and in 2 subjects in the placebo group (0.8%, atrial fibrillation and urticaria in 1 subject each). A causal relationship to the study vaccine could not be ruled out in either of the subjects in the placebo group.

No death occurred.

7.2.1.2 Part 3b of Study ARCT-154-01

A randomized, observer-blind, placebo-controlled, parallel-group study was conducted to investigate the efficacy and safety of Kostaive in healthy adults aged ≥18 years (target sample size, 16,000 subjects[32)] [8,000 in the Kostaive group, 8,000 in the placebo group]) at 16 study sites in Vietnam.

Subjects were randomized to the Kostaive 5 μg group or placebo (physiological saline) group at a 1:1 ratio and received the study vaccine intramuscularly twice, 28 days apart, and at 2 months after the second dose (Day 92), the subjects in the Kostaive group received placebo, and subjects in the placebo group received Kostaive, intramuscularly twice, at 28 days apart.

Subjects were stratified by age (18 to <60 years, ≥60 years) and by presence or absence of risk factors for severe COVID-19[33)] (in subjects aged <60 years).

Of 16,107 randomized subjects, 16,100 subjects (8,056 in the Kostaive group, 8,044 in the placebo group) received ≥1 dose of the study vaccine and were included in ITT. A total of 16,100 subjects (8,059 in the Kostaive group, 8041 in the placebo group) who actually received the study vaccine were included in the safety analysis population. Subjects who received the study vaccine and submitted the reactogenicity diary (15,813 after the first dose [7,927 in the Kostaive group, 7,886 in the placebo group], 15,340 after the second dose [7,702 in the Kostaive group, 7,638 in the placebo group]) were included in the reactogenicity analysis population. Of the subjects in ITT, subjects who received the study vaccine twice as stipulated in the study protocol and did not have history of SARS-CoV-2 infection from the first dose up to 7 days after the second dose (7,787 in the Kostaive group, 7,723 in the placebo group) were included in mITT and used as the primary efficacy analysis population. The number of subjects who received the third and fourth dose of the study vaccine (Kostaive or placebo) at 2 months after the second dose (Day 92) was 7,462 and 6,961, respectively, in the Kostaive-placebo group and 7,353 and 6,790, respectively, in the placebo-Kostaive group.

The primary endpoint was vaccine efficacy (VE) (VE = 1 – "Hazard ratio of the Kostaive group to the placebo group") based on the cases of confirmed COVID-19 (occurrence from 7 days to 2 months after the end of the second dose).

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32) Assuming the anticipated VE of 50% against the placebo group for the Kostaive group, with the null hypothesis of VE set at ≤30% and a one-sided significance level of 0.025, the number of cases of confirmed COVID-19 required to reject the null hypothesis with a statistical power of ≥90% is 372. Ensuring 8,000 subjects in each group was considered to allow (a) to accrue a sufficient number of confirmed COVID-19 cases from 7 days to 2 months after the end of the second dose of study vaccine and (b) to detect ≥1 case of adverse event with the incidence of 0.1% at the probability of >99.9% for safety.

33) Higher Risk for Severe COVID-19 indicated by CDC (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html).

Confirmed COVID-19 cases were defined as subjects who met the following 2 criteria according to Food and Drug Administration (FDA) Guidance on the Development of Vaccines to Prevent COVID-19[34]:

- Subjects SARS-CoV-2 positive by nucleic acid amplification testing of nasal swab
- Occurrence or aggravation of at least one of the following symptoms:
  Pyrexia or chills, cough, shortness of breath or dyspnoea, malaise, myalgia or bodily pain, headache, new loss of taste or smell, chills, sore throat, nasal congestion or runny nose, nausea or vomiting, and diarrhoea

The criterion for the efficacy was "the lower limit of two-sided 95% confidence interval of VE is >30%," according to the FDA Guidance.[34] The VE [two-sided 95% CI] based on the incidence rate of COVID-19, the primary endpoint, was 56.6% [48.7%, 63.3%] (Table 17), with the lower limit of the two-sided 95% confidence interval exceeding the pre-defined level of 30%.

Table 17. VE against COVID-19 onset from 7 days to 2 months after the second dose (Part 3b of Study ARCT-154-01, mITT)

	N	T	n	VE [two-sided 95% CI] (%)[a]
Kostaive	7787	1131.7	200	56.6 [48.7, 63.3]
Placebo	7723	1100.6	440	

N = Number of subjects analyzed, T = Total follow-up period (person-years), n = Number of subjects with confirmed COVID-19

a) Cox proportional hazard model with covariates of age/risk factors for severe COVID-19 (18-59 years old [without risk factor], 18-59 years old [with risk factor], ≥60 years old), and region

Of 643 subjects with COVID-19-confirmed, 537 subjects (including 3 subjects who received COVID-19 vaccine outside the clinical study; they were excluded from analysis) were subjected to genetic characterization of SARS-CoV-2, which allowed collection of data on SARS-CoV-2 strains in 482 subjects. Most of the cases were infection by the Delta variant (477 subjects, 164 in the Kostaive group, 313 in the placebo group), and infection by the Alpha variant (2 subjects in the placebo group), Beta variant (1 subject in the placebo group), and the Omicron variant (2 subjects, 1 subject in each group).

The safety observation items and period were the same as those in Parts 1, 2, and 3a. Figure 18 shows the solicited adverse events observed in Part 3b.

[34] Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19)

Table 18. Solicited adverse events observed after each vaccination (Part 3b of Study ARCT-154-01, reactogenicity analysis population)

MedDRA PT	First dose				Second dose			
	Kostaive (N =7927)		Placebo (N =7886)		Kostaive (N =7702)		Placebo (N =7638)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	3474 (43.8)	40 (0.5)	858 (10.9)	0	2401 (31.2)	10 (0.1)	585 (7.7)	1 (0.0)
Pain	3029 (38.2)	29 (0.4)	676 (8.6)	0	2063 (26.8)	7 (0.1)	467 (6.1)	0
Erythema (redness)	79 (1.0)	1 (0.0)	18 (0.2)	0	37 (0.5)	0	9 (0.1)	0
Swelling (induration)	224 (2.8)	2 (0.0)	29 (0.4)	0	80 (1.0)	1 (0.0)	10 (0.1)	0
Injection site tenderness	3003 (37.9)	32 (0.4)	659 (8.4)	0	2043 (26.5)	7 (0.1)	429 (5.6)	1 (0.0)
Systemic (all events)	3816 (48.1)	115 (1.5)	2499 (31.7)	35 (0.4)	3214 (41.7)	113 (1.5)	1796 (23.5)	23 (0.3)
Pyrexia[b)]	417 (5.3)	53 (0.7)	101 (1.3)	12 (0.2)	505 (6.6)	63 (0.8)	92 (1.2)	11 (0.1)
Headache	1925 (24.3)	19 (0.2)	1235 (15.7)	7 (0.1)	1649 (21.4)	24 (0.3)	836 (10.9)	3 (0.0)
Fatigue	2344 (29.6)	27 (0.3)	1307 (16.6)	9 (0.1)	1926 (25.0)	27 (0.4)	901 (11.8)	4 (0.1)
Myalgia	1615 (20.4)	13 (0.2)	692 (8.8)	3 (0.0)	1196 (15.5)	7 (0.1)	550 (7.2)	2 (0.0)
Arthralgia	1431 (18.1)	23 (0.3)	910 (11.5)	4 (0.1)	1171 (15.2)	17 (0.2)	679 (8.9)	4 (0.1)
Nausea	247 (3.1)	0	171 (2.2)	1 (0.0)	195 (2.5)	1 (0.0)	108 (1.4)	0
Chills	1491 (18.8)	19 (0.2)	558 (7.1)	4 (0.1)	1344 (17.5)	17 (0.2)	386 (5.1)	1 (0.0)
Diarrhoea	318 (4.0)	2 (0.0)	242 (3.1)	3 (0.0)	165 (2.1)	2 (0.0)	134 (1.8)	1 (0.0)
Dizziness	1050 (13.2)	10 (0.1)	720 (9.1)	6 (0.1)	848 (11.0)	8 (0.1)	445 (5.8)	0
Vomiting	94 (1.2)	0	54 (0.7)	1 (0.0)	73 (0.9)	1 (0.0)	32 (0.4)	0

N = Number of subjects analyzed, n = Number of subjects with events
a) Number of subjects with Grade ≥1 event(s), b) ≥38°C, ≥39°C for Grade ≥3 events

Table 19 shows the unsolicited adverse events and adverse reactions observed in ≥1% of subjects in either group. Grade ≥3 unsolicited adverse events were observed in 23 subjects (0.3%) in the Kostaive group and in 35 subjects (0.4%) in the placebo group. The adverse event observed in ≥0.1% of subjects in either group was hypertension, which occurred in 5 subjects (0.1%) in the Kostaive group and in 3 subjects (<0.1%) in the placebo group. A causal relationship to the study vaccine was denied in all of them.

Table 19. Unsolicited adverse events and adverse reactions observed in ≥1% of subjects in either group (Part 3b of Study ARCT-154-01, safety analysis population)

MedDRA PT	Adverse events		Adverse reactions	
	Kostaive (N = 8059)	Placebo (N = 8041)	Kostaive (N = 8059)	Placebo (N = 8041)
	n (%)	n (%)	n (%)	n (%)
All events	1982 (24.6)	2076 (25.8)	323 (4.0)	276 (3.4)
Hypertension	333 (4.1)	314 (3.9)	141 (1.7)	132 (1.6)
Headache	241 (3.0)	264 (3.3)	23 (0.3)	16 (0.2)
Influenza	181 (2.2)	177 (2.2)	0	1 (0.0)
Cough	116 (1.4)	138 (1.7)	0	0
Arthralgia	110 (1.4)	121 (1.5)	46 (0.6)	40 (0.5)
Tachycardia	110 (1.4)	95 (1.2)	27 (0.3)	16 (0.2)
Pharyngitis	89 (1.1)	102 (1.3)	0	0
COVID-19	74 (0.9)	180 (2.2)	0	0
Oropharyngeal pain	52 (0.6)	87 (1.1)	0	0

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

From Day 92, the study vaccine (Kostaive or placebo) was administered alternately, and data were collected separately in each period (Days 1-92, Days 92-210). From Day 92 to Day 210, subjects receiving Kostaive in the first and second doses and placebo in the third and fourth doses were referred to as the "Kostaive-placebo group," and subjects receiving placebo in the first and second doses and Kostaive in the third and fourth doses were referred to as the "placebo-Kostaive group."

During the period from Day 1 to Day 92, death occurred in 5 of 8,059 subjects in the Kostaive group (0.1%, hypoglycaemia, pancreatitis, lung neoplasm malignant, pharyngeal cancer metastatic, and COVID-19 in 1 subject each) and in 16 of 8,041 subjects in the placebo group (0.2%, COVID-19 in 9

subjects, lymphadenopathy, hepatic cirrhosis, hepatic cancer, aortic dissection, pneumonia, pneumonia acinetobacter, and septic shock in 1 subject each). A causal relationship to the study vaccine was denied for all events. During the period from Day 92 to Day 210, death occurred in 9 of 7,458 subjects in the Kostaive-placebo group (0.1%, accidental death and other unspecified death in 2 subjects each, acute myocardial infarction, septic shock, injury, lip cancer/oral cancer, and malignant lung neoplasm in 1 subject each) and in 4 of 7,349 subjects in the placebo-Kostaive group (0.1%, COVID-19 in 2 subjects, and craniocerebral injury and cerebrovascular accident in 1 subject each). A causal relationship to the study vaccine was denied for all events.

During the period from Day 1 to Day 92, serious adverse events were observed in 118 of 8,059 subjects (1.5%) in the Kostaive group and in 201 of 8,041 subjects (2.5%) in the placebo group. Serious adverse events observed in ≥2 subjects were COVID-19 in 39 subjects, appendicitis and hypertensive crisis in 4 subjects each, vestibular disorder and cerebral infarction in 3 subjects each, and myocardial ischaemia, gastritis, type IV hypersensitivity reaction, pneumonia, urinary tract infection, lung neoplasm malignant, and hypertension in 2 subjects each in the Kostaive group; and COVID-19 in 127 subjects, gastritis in 6 subjects, vestibular disorder in 5 subjects, pneumonia in 4 subjects, gastric ulcer, haemorrhoids, craniocerebral injury, appendicitis, bronchitis, spinal osteoarthritis, spondylopathy traumatic, facial paresis, and hypertensive crisis in 2 subjects each in the placebo group. Serious adverse events for which a causal relationship to the study vaccine could not be ruled out were observed in 11 subjects in the Kostaive group (hypertensive crisis and type IV hypersensitivity reaction in 2 subjects, injection site reaction, dermatitis contact, hypersensitivity, urticaria, headache, deep vein thrombosis,[35)] and hypertension in 1 subject each) and in 5 subjects in the placebo group (hypertensive crisis in 2 subjects and vestibular disorder, vaccination-related reactions, and cerebrovascular disorder in 1 subject each). The outcome was “resolved” for all of them. During the period from Day 92 to Day 210, serious adverse events were observed in 88 of 7,462 subjects (1.2%) in the Kostaive-placebo group and in 91 of 7,353 subjects (1.2%) in the placebo-Kostaive group. Serious adverse events observed in ≥2 subjects were COVID-19 in 10 subjects, vestibular disorder and cerebrovascular accident in 3 subjects each, and gastritis, gastrooesophageal reflux disease, intestinal perforation, death, cholelithiasis, pneumonia, septic shock, accidental death, injury, limb injury, and breast cancer in 2 subjects each in the Kostaive-placebo group; and COVID-19 in 13 subjects, appendicitis in 6 subjects, myocardial ischaemia, pneumonia, and nephrolithiasis in 3 subjects each, vestibular disorder, cataract, haemorrhoids, pancreatitis, craniocerebral injury, osteoarthritis, sciatica, breast cancer, lipoma, ovarian cyst, chronic obstructive pulmonary disease, and cerebrovascular insufficiency in 2 subjects each in the placebo-Kostaive group. There were no serious adverse events for which a causal relationship to the study vaccine could not be ruled out.

Adverse events leading to study discontinuation from Day 1 to Day 92 occurred in 14 of 8,059 subjects (0.2%) in the Kostaive group and in 25 of 8,041 subjects (0.3%) in the placebo group. The events observed in ≥2 subjects were tachycardia and lung neoplasm malignant in 2 subjects each in the Kostaive

35) A 7[redacted]-year-old woman. The subject had past history of thrombophlebitis superficial of lower limbs (in 20[redacted]), essential hypertension (in 20[redacted]), and hyperthyroidism. After receiving 1 dose of Kostaive, she experienced embolism and thrombosis of the popliteal vein (preferred term [PT], deep vein thrombosis) on Day 15. Although the investigator determined that the causal relationship to Kostaive could not be ruled out, the sponsor determined that the events was causally unrelated to Kostaive, taking into account the patient’s age and important disease histories such as thrombophlebitis and hypertension.

group and COVID-19 in 9 subjects, upper respiratory tract infection, and hypertension in 2 subjects each in the placebo group. Adverse events leading to study discontinuation for which a causal relationship could not be ruled out occurred in 2 subjects only (type IV hypersensitivity reaction and urticaria in 1 subject each) in the Kostaive group. Adverse events leading to study discontinuation from Day 92 to Day 210 were observed in 16 of 7,462 subjects (0.2%) in the Kostaive group and in 10 of 7,353 subjects (0.1%) in the placebo group. The events observed in ≥2 subjects were hypertension in 4 subjects, death, accidental death in 2 subjects each in the Kostaive-placebo group and hypertension in 3 subjects, COVID-19 and tachycardia in 2 subjects each in the placebo-Kostaive group. Adverse events leading to study discontinuation for which a causal relationship could not be ruled out occurred in 3 subjects (hypertension in 2 subjects and tachycardia in 1 subject) in the Kostaive-placebo group and in subjects (tachycardia and anaphylactic reaction in 1 subject each) in the placebo-Kostaive group. These events resolved except for tachycardia (not resolved) in the placebo-Kostaive group.

7.2.2 Japanese phase III study (CTD 5.3.5.1-04; Study ARCT-154-J01; study period, ongoing since November 2022; data cut-off on March 27, 2023)

A randomized, observer-blind,[36)] active vaccine-controlled, parallel-group study was conducted to investigate the safety and immunogenicity of Kostaive at 11 study sites in Japan. The subjects were healthy adults aged ≥18 years[37)] who had received 2 doses of SARS-CoV-2 vaccine (Comirnaty or Spikevax, both of which are monovalent [against the original strain]) as the primary series and Comirnaty (monovalent [against the original strain]) as the booster dose ≥3 months before (target sample size, 780 subjects[38)] [390 in the Kostaive group, 390 in the Comirnaty group]).

A single dose of Kostaive 5 μg or Comirnaty 0.3 mL[39)] was administered intramuscularly.

All of the 828 randomized subjects[40)] (420 in the Kostaive group, 408 in the Comirnaty group) received ≥1 study vaccine and were included in the safety analysis population. A total of 417 subjects in the Kostaive group and 408 subjects in the Comirnaty group, excluding subjects without data of neutralizing antibody titer against SARS-CoV-2 (the original strain), were included in the full analysis set (FAS). Of the subjects in FAS, 385 subjects in the Kostaive group and 374 subjects in the Comirnaty group were included in the per protocol set (PPS)-1. Subjects positive for antibody against SARS-CoV-2 nucleocapsid before the study vaccination and subjects with serious protocol deviations were excluded from PPS-1. A total of 413 subjects in the Kostaive group and 400 subjects in the Comirnaty group, excluding subjects with serious protocol deviations, were included in PPS-2.

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36) The investigator, the study staff at study sites, subjects, the responsible persons of the study-supervising organization, and the sponsor were blinded to the study.

37) The following patients related to COVID-19 infection were excluded: (a) Patients who had acute disease or pyrexia of ≥37.5℃ from 1 day before screening; (b) patients positive for SARS-CoV-2 antigen at screening; (c) patients confirmed to have been infected with SARS-CoV-2 or patients with a history of COVID-19 with sequelae, within the past 4 months

38) The following assumptions were made: (a) The ratio of geometric mean titers (GMR) was 1.0, (b) the SD of the neutralizing antibody titer was 0.400, and (c) SRR of each vaccination group was 85%. In order to verify the non-inferiority of GMT and SRR in Kostaive against those of Comirnaty (non-inferiority margin was 0.67 for GMT and −10% for SRR at one-sided significance level of 2.5%) at ≥90% probability, 270 subjects per group are required to be analyzed. Assuming the drop-out of approximately 10% of assigned subjects and exclusion of approximately 20% subjects from the primary analysis population because of infection before vaccination, the number of subjects in this study was 780 (390 per group).

39) Comirnaty 0.3 mL contained 30 μg of tozinameran RNA.

40) Subjects were randomized using the following stratification factors: Time after the last dose (<5 months, ≥5 months), sex, age (<65 years, ≥65 years), and study site.

The primary immunogenicity endpoints were geometric mean titer (GMT) of neutralizing antibody titer against the original strain at 28 days after study vaccination in PPS-1 population and SRR (percentage of subjects showing ≥4-fold increase in neutralizing antibody titer [a half of LLOQ if the titer was below LLOQ] from the titer before the booster dose). Each of these endpoints were evaluated for non-inferiority of Kostaive over Comirnaty. The non-inferiority margin of the GMT ratio (Kostaive group/Comirnaty group) was 0.67, and the non-inferiority margin of the difference in SRR was −10%.

Table 20 shows the results of the primary immunogenicity endpoint at 28 days after the study vaccination. The lower limit of the two-sided 95% confidence interval of the difference in the ratio of geometric mean titers (GMR) of neutralizing antibody titer against the original strain and in SRR exceeded the non-inferiority limit (0.67 and −10%, respectively), fulfilling the pre-specified non-inferiority success criteria.

Table 20. Comparison of the neutralizing antibody titer against the original strain at 28 days after the study vaccination (Study ARCT-154-J01, PPS-1 population)

	Neutralizing antibody titer			Neutralizing antibody response rate			
	N	GMT[a)]	GMR[a)]	N	n	SRR (%)[b)]	Difference in SRR[c)]
Kostaive	385	5640.7 [4321.2, 7363.2]	1.43 [1.26, 1.63]	385	251	65.2 [60.2, 69.9]	13.6 [6.8, 20.5]
Comirnaty	374	3933.6 [2993.4, 5169.1]		374	193	51.6 [46.4, 56.8]	

The number in the brackets indicates two-sided 95% CI. N = Number of subjects analyzed.
n = Number of subjects with antibody response. Antibody response is defined as a ≥4-fold increase in the antibody titer from the level before the booster dose (a half of LLOQ if the titer was below LLOQ).
If the antibody titer was below LLOQ, the value 0.5 × LLOQ was used for analysis (quantification range [LLOQ to ULOQ]: 40-89947 [original strain]).
a) Log-transformed neutralizing antibody titer was calculated by analysis of covariance (ANCOVA) using treatment group as a factor and allocation factors (time from the last dose, sex, age [continuous variable]) as covariates.
b) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
c) Calculated based on the Miettinen-Nurminen method using the allocation factors (time from the last dose, sex, age) as adjustment factors.

The safety observation period was as follows:

- Solicited adverse events[41)] (local [erythema, swelling, induration, tenderness, pain] and systemic [pyrexia, arthralgia, chills, diarrhoea, dizziness, headache, malaise, nausea, vomiting, myalgia]) were collected from the subject diary for 7 days after the study vaccination.
- Unsolicited adverse events (adverse events other than solicited adverse events observed within 7 days after the study vaccination) were collected for 28 days after the study vaccination.
- Serious adverse events and adverse events of special interest were collected between the study vaccination and Day 361.

Table 21 shows solicited adverse events.

41) Severity of adverse events were evaluated according to the FDA Guidance (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007).

Table 21. Solicited adverse events (Study ARCT-154-J01, safety analysis population)

MedDRA PT	Kostaive (N = 420)		Comirnaty (N = 408)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	398 (94.8)	3 (0.7)	395 (96.8)	4 (1.0)
Erythema	52 (12.4)	0	85 (20.8)	3 (0.7)
Swelling	59 (14.0)	1 (0.2)	97 (23.8)	1 (0.2)
Induration	52 (12.4)	1 (0.2)	81 (19.9)	0
Tenderness	388 (92.4)	1 (0.2)	391 (95.8)	1 (0.2)
Pain	352 (83.8)	1 (0.2)	358 (87.7)	0
Systemic (all events)[a)]	276 (65.7)	6 (1.4)	255 (62.5)	7 (1.7)
Pyrexia[b)]	84 (20.0)	2 (0.5)	76 (18.6)	2 (0.5)
Arthralgia	112 (26.7)	1 (0.2)	113 (27.7)	2 (0.5)
Chills	126 (30.0)	2 (0.5)	103 (25.2)	4 (1.0)
Diarrhoea	28 (6.7)	0	17 (4.2)	0
Dizziness	25 (6.0)	0	13 (3.2)	1 (0.2)
Headache	165 (39.3)	3 (0.7)	125 (30.6)	3 (0.7)
Malaise	188 (44.8)	3 (0.7)	176 (43.1)	4 (1.0)
Nausea	21 (5.0)	0	16 (3.9)	0
Vomiting	2 (0.5)	0	2 (0.5)	0
Myalgia	123 (29.3)	2 (0.5)	100 (24.5)	3 (0.7)

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

a) Number of subjects with Grade ≥0 events. Grade 0 was used only for erythema, swelling, induration (<2.5 cm), and pyrexia (37.5°C-37.9°C).

b) ≥37.5°C (axillary)

Table 22 shows unsolicited adverse events and related adverse reactions observed in ≥1% of subjects in either group.

Grade ≥3 unsolicited adverse events were observed in 1 subject (0.2%) in the Kostaive group and in 6 subjects (1.5%) in the Comirnaty group. They were hepatic function abnormal in 1 subject in the Kostaive group and nasopharyngitis in 3 subjects, pyrexia, ankle fracture, and foot deformity in 1 subject each in the Comirnaty group. The adverse reaction among them was hepatic function abnormal observed in 1 subject of the Kostaive group.

Table 22. Unsolicited adverse events and adverse reactions observed in ≥1% of subjects in either group (Study ARCT-154-J01, safety analysis population)

MedDRA PT	Adverse events		Adverse reactions	
	Kostaive (N = 420)	Comirnaty (N = 408)	Kostaive (N = 420)	Comirnaty (N = 408)
	n (%)	n (%)	n (%)	n (%)
All events	81 (19.3)	111 (27.2)	55 (13.1)	68 (16.7)
Injection site pruritus	19 (4.5)	33 (8.1)	19 (4.5)	33 (8.1)
Nasopharyngitis	5 (1.2)	7 (1.7)	0	0
Rhinorrhoea	5 (1.2)	2 (0.5)	4 (1.0)	2 (0.5)
Faeces soft	4 (1.0)	1 (0.2)	4 (1.0)	0
Back pain	4 (1.0)	11 (2.7)	2 (0.5)	5 (1.2)
Hypoaesthesia	4 (1.0)	1 (0.2)	4 (1.0)	1 (0.2)
Abdominal pain upper	3 (0.7)	4 (1.0)	3 (0.7)	2 (0.5)
Blood creatine phosphokinase increased	3 (0.7)	4 (1.0)	0	0
Abdominal pain	2 (0.5)	4 (1.0)	2 (0.5)	1 (0.2)
Lymphadenopathy	0	4 (1.0)	0	4 (1.0)
Axillary pain	0	4 (1.0)	0	4 (1.0)

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

The only serious adverse event observed was foot deformity in 1 subject in the Comirnaty group. Its causal relationship to the study vaccine was denied, and its outcome was “resolved.” No death occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and review policy

The applicant's explanation about the clinical data package:

After the declaration of SARS-CoV-2 pandemic in 2020, multiple vaccines have been developed and distributed, but SARS-CoV-2 pandemic still persists as of 2023. The emergence of variants with the potential to evade immunity induced by vaccines has made disease control increasingly challenging due to the diminishing efficacy of vaccines.

The applicant has created 3 RNA vaccines ARCT-021, Kostaive (ARCT-154), and ARCT-165 as vaccines against COVID-19 [see Table 1 in Section 2.1.4]. All of them are samRNA vaccines encoding VEEV-derived replicase and S-protein of SARS-CoV-2. They are different from one another only in part of the sequence of S-protein. ARCT-021 is a vaccine candidate encoding S-protein of the original strain, whereas Kostaive and ARCT-165 contain a modification to ARCT-021 to enhance the immunogenicity (mutations in the prevalent strain at the time of development and mutations to maintain, and prevent degradation of, the antigen structure have been introduced).

Kostaive, ARCT-021, and ARCT-165 are thus LNP products composed of the identical components with the major difference in only some parts of the S-protein sequence of SARS-CoV-2. Data of ARCT-021 and ARCT-165 were also used in the clinical development of Kostaive according to the WHO Guidance[42)] and FDA Guidance.[34)]

The application for the primary series of Kostaive was submitted based on the following data obtained: (1) Efficacy, safety, and immunogenicity of Kostaive in the foreign phase I/II/III study (Study ARCT-154-01), pivotal study, and (2) the dose finding used and the safety data obtained in the clinical studies of ARCT-021 (Studies ARCT-021-04, ARCT-021-01, and ARCT-021-02). In the foreign I/II/III study (Study ARCT-154-01) in Vietnamese subjects, the subgroup analysis on race and ethnicity did not detect any clinically significant difference in the efficacy or safety between the approved RNA vaccines Comirnaty and Spikevax.[43)] Results of clinical studies on the efficacy, safety, and immunogenicity in Vietnamese subjects are thus considered to allow the prediction of the potential performance of Kostaive in diverse populations.

As for the booster dose, taking account of the situation in which the increase in anti-SARS-CoV-2-neutralizing antibody titer in blood induced by vaccination with approved SARS-CoV-2 has gradually demonstrated a clear correlation with the efficacy in preventing COVID-19 (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11), "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])" indicates that the vaccine efficacy can be evaluated using an immunogenicity bridging approach, which evaluates the efficacy based on immunogenicity by using an approved SARS-CoV-2 vaccine with proven efficacy in preventing COVID-19 as an active comparator. In Study ARCT-154-J01, non-inferiority to Comirnaty was

42) Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations (Annex 3, WHO Technical Report Series No.1039)

43) Comirnaty Intramuscular Injection: Report on Special Approval for Emergency, dated February 8, 2021, COVID-19 Vaccine Moderna Intramuscular Injection: Report on Special Approval for Emergency, dated May 17, 2021

investigated using indices based on immunogenicity in the following subjects: Japanese subjects aged ≥18 years who received the approved SARS-CoV-2 vaccine (Comirnaty or Spikevax) as the primary series and Comirnaty as the third dose at least 3 months before. Also included are the package of the data on the booster dose in Cohort B of Study ARCT-165-01 which evaluated the immunogenicity and safety of 1 booster dose of ARCT-154 in healthy adults aged 21 to 65 years who had completed the primary series with Comirnaty at least 5 months before.

PMDA's view:
The clinical data package is designed based on a series of "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" issued by PMDA and is acceptable. PMDA will evaluate the efficacy and safety of Kostaive based on the pivotal data from the foreign confirmatory study (Study ARCT-154-01) that evaluated the vaccine efficacy (VE) of the primary series with Kostaive. There are no clinical study data available on the primary series in Japanese subjects. However, given the situation that RNA vaccines (Comirnaty and Spikevax) had been approved in Japan at the start of Study ARCT-154-01, and use of these vaccines had spread to a considerable extent, development of Kostaive for the primary series in Japan would have been difficult. It is understandable that the Japanese clinical study was conducted on the booster dose. Given the situations described below, conducting a study to evaluate VE using the onset of COVID-19 as the index was unlikely to be feasible in Japan. On the basis of "Principles (Appendix 3)," the applicant's policy to evaluate the immunogenicity using approved vaccines as the controls is acceptable.

- Multiple vaccines were approved and available at the start of the Japanese phase III study (ARCT-154-J01) on the booster dose.
- Non-inferiority study of vaccine candidates against approved vaccines, using the onset of COVID-19 as the index, requires a larger number of subjects and a longer study duration than those of non-inferiority study against placebo (*Clin Trials.* 2021;18:335-42).
- There was a consensus on the need for conducting a study using immunogenicity bridging approach (International Coalition of Medicines Regulatory Authorities [ICMRA] COVID-19 Virus Variants Workshop. 24 June 2021).

The safety is assessed based not only on the results of the studies on Kostaive (Studies ARCT-154-01 and ARCT-154-J01) but also on the data of clinical studies (Studies ARCT-021-01, ARCT-021-04, and ARCT-165-01) submitted as the evaluation and reference data.

7.R.2 Efficacy

7.R.2.1 Primary endpoint

The applicant's explanation about the primary endpoint in the primary series:
As the primary efficacy endpoint in Study ARCT-154-01, the pivotal study for evaluating the efficacy of Kostaive, VE was estimated based on the number of subjects with confirmed COVID-19 from 7 days to 2 months after the end of the second dose among subjects who were serologically SARS-CoV-2-negative at baseline.

Confirmed COVID-19 cases were defined as subjects who met the following 2 criteria, based on the FDA Guidance on the development of COVID-19-preventive vaccines[34]:

- SARS-CoV-2 positive by nucleic acid amplification testing of nasal swab
- Occurrence or aggravation of at least one of the following symptoms:
  Pyrexia or chills, cough, shortness of breath or dyspnoea, malaise, myalgia or body aches, headache, new loss of taste or smell, chills, sore throat, nasal congestion or runny nose, queasy or vomiting, and diarrhoea.

VE was evaluated from 7 days to 2 months after the second dose. After the third dose planned at 2 months after the second dose (Day 92), the study vaccine was administered alternately (placebo in the Kostaive group, Kostaive in the placebo group). A 2-dose primary series is required to induce a potent immune response against COVID-19 in SARS-CoV-2-naïve individuals. Usually, antibody titer reaches the peak 14 to 28 days after the second dose, while antibody involved in the prevention of onset appears earlier, usually 1 to 2 weeks after the second dose (*Sci Rep.* 2022;12:21232, *N Engl J Med.* 2021;384:403-416). Pursuant to the approval of COVID-19 vaccine in Vietnam in the summer of 2021, a mass vaccination campaign was initiated in September 2021, allowing vaccination in approximately 80 million individuals by March 2022. In the circumstance where COVID-19 vaccine became available by the mass vaccination campaign, a long-term follow-up survey of a placebo-controlled study would be an ethical problem because subjects include elderly and those with co-morbid conditions associated with high risk of severe COVID-19. It was decided to limit the efficacy surveillance period to 2 months and to administer the study vaccine (Kostaive or placebo) alternately to all of the participating subjects.

PMDA's view:
It is acceptable to evaluate the VE of Kostaive against COVID-19 based on the 2-months efficacy evaluation, given the applicant's explanation and the observations that VE of RNA vaccines has been achieved relatively early (*N Engl J Med.* 2020;383:2603-15, *N Engl J Med.* 2021;384:403-16).

7.R.2.2 Efficacy and immunogenicity against COVID-19

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

(1) The primary series

In Part 3b of the foreign Study ARCT-154-01, VE [two-sided 95% CI] in mITT, the primary endpoint, was 56.6% [48.7%, 63.3%], with the lower limit of the two-sided 95% confidence interval exceeding 30%, the pre-defined efficacy criterion [see Table 17 in Section 7.2.1.2].

Table 23 and Figure 3 show the results of the secondary endpoints "VE against the onset of COVID-19 after the first dose of the study vaccine in subjects in ITT receiving at least 1 dose of the study vaccine" and the "cumulative incidence rate of COVID-19," respectively.

These results suggest the efficacy in preventing COVID-19 by 2 doses of Kostaive.

Table 23. VE against occurrence of COVID-19 (Part 3b of Study ARCT-154-01, ITT)

	N	T	n	VE [two-sided 95% CI] (%)[a)]
Kostaive	8056	1942.3	215	56.6 [49.0, 63.1]
Placebo	8043	1911.5	477	

N = Subjects analyzed, T = Total follow-up period (person-years), n = Number of subjects with confirmed COVID-19
a) Cox proportional hazard model with covariates of age/risk factors for severe COVID-19 (18-59 years old [without risk factor], 18-59 years old [with risk factors], ≥60 years old) and region

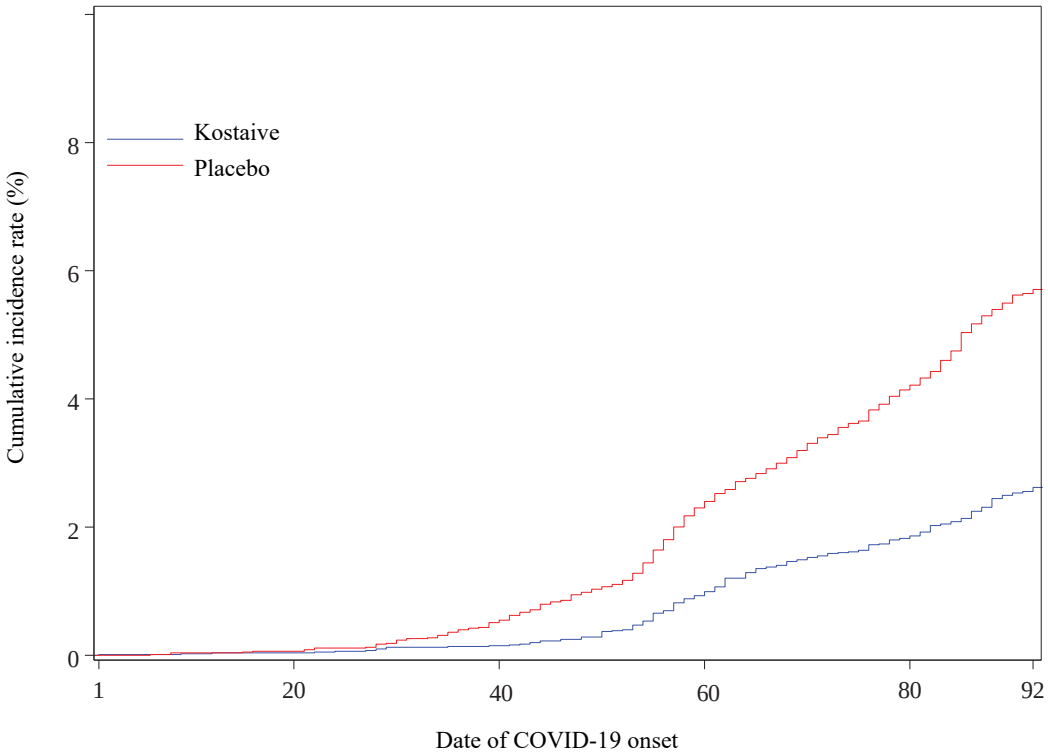


Figure 3. The primary endpoint "cumulative incidence rate of first-onset COVID-19 events" (Part 3b of Study ARCT-154-01, ITT)

Table 24 shows efficacy by subpopulations (age, risk factors, and sex) of the primary endpoint in Part 3b of foreign Study ARCT-154-01. In order to investigate the efficacy in subjects with a high risk of severe COVID-19, subjects were classified into those aged 18 to 59 years with risk, those aged 18 to 59 years without risk, and those aged ≥60 years. The analysis did not show any clear difference in the results of the primary endpoint, showing similar results among the subpopulations.

Table 24. Efficacy of the vaccine against the occurrence of COVID-19 from 7 days to 2 months after the second dose of the study vaccine, subpopulation analysis (Part 3b of Study ARCT-154-01, mITT)

	Kostaive			Placebo			VE
	N (%)	T	n	N (%)	T	n	[two-sided 95% CI (%)][a)]
All subjects	7787 (100)	1131.7	200	7723 (100)	1100.6	440	56.6 [48.7, 63.3]
Age/risk[b)]							
18-59 years old, without risk	3704 (47.6)	535.4	119	3701 (47.9)	526.4	235	50.8 [38.7, 60.6]
18-59 years old, with risk	2719 (34.9)	396.4	53	2690 (34.8)	383.6	148	66.5 [54.2, 75.5]
≥60 years old	1364 (17.5)	199.8	28	1332 (17.2)	190.5	57	54.3 [28.2, 70.9]
Sex							
Male	3817 (49.0)	560.4	85	3793 (49.1)	543.6	206	61.1 [49.9, 69.8]
Female	3970 (51.0)	571.2	115	3930 (50.9)	557.0	234	53.3 [41.6, 62.6]

N = Number of subjects analyzed, T = Total follow-up period (person/years), n = Number of subjects with confirmed COVID-19
a) Cox-proportional hazard model
b) Higher Risk for Severe COVID-19 indicated by CDC (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)

Immunogenicity was investigated in Part 1/2/3a of the foreign Study ARCT-154-01. Results demonstrated higher SRR and GMT in the Kostaive group than in the placebo group [see Section 7.2.1.1]. The exploratory study of efficacy in Part 1/2/3a of Study ARCT-154-01, albeit at a limited scale, showed that VE [two-sided 95% CI] against the onset of COVID-19 from 7 days to 2 months after the second

dose was 56.3% [18.3%, 76.7%], suggesting the efficacy of Kostaive as in Part 3b of Study ARCT-154-01.

(2) Booster dose

In Study ARCT-154-J01, a booster dose with Kostaive or the control vaccine (Comirnaty) was administered to healthy adults who had received RNA vaccine (Comirnaty or Spikevax), and immunogenicity against SARS-CoV-2 (the original strain) was compared at 28 days after the booster dose. Results confirmed the non-inferiority of GMT of SARS-CoV-2 (the original strain)-neutralizing antibody titer and SRR in blood at 28 days after the vaccination in subjects receiving Kostaive to those in subjects receiving the control vaccine [see Section 7.2.2].

Table 25 shows the results of immunogenicity in subjects in different age groups. No clear difference was observed among age groups, despite the limitations to the interpretation of the results due to the extremely limited number of subjects aged ≥65 years.

Table 25. GMT, GMFR, and SRR in SARS-CoV-2-neutralizing antibody titer by age group (Study ARCT-154-J01, PPS-1 population)

	All subjects		<65 years of age		≥65 years of age	
	Kostaive N = 385	Comirnaty N = 374	Kostaive N = 374	Comirnaty N = 366	Kostaive N = 11	Comirnaty N = 8
Baseline						
GMT[a)]	813.1 [715.6, 924.0]	865.6 [754.8, 992.7]	822.5 [722.9, 935.9]	866.6 [754.1, 995.8]	550.7 [207.5, 1461.1]	821.3 [300.3, 2246.3]
28 days after study vaccination						
GMT[b)]	5640.7 [4321.2, 7363.2]	3933.6 [2993.4, 5169.1]	5628.2 [4310.3, 7349.1]	3953.0 [3006.8, 5197.0]	6818.2 [4054.9, 11464.4]	3218.2 [1684.4, 6148.7]
GMFR[a)]	6.70 [5.97, 7.53]	4.37 [3.98, 4.80]	6.59 [5.86, 7.41]	4.36 [3.97, 4.80]	11.65 [5.26, 25.78]	4.85 [2.62, 8.96]
GMR[b)]	1.43 [1.26, 1.63]		1.42 [1.25, 1.62]		2.12 [0.92, 4.87]	
Antibody response rate						
No. of subjects (n)	251	193	244	188	7	5
SRR (%)[c)]	65.2 [60.2, 69.9]	51.6 [46.4, 56.8]	65.2 [60.2, 70.1]	51.4 [46.1, 56.6]	63.6 [30.8, 89.1]	62.5 [24.5, 91.5]
Difference in SRR[d)]	13.6 [6.8, 20.5]		13.9 [6.8, 20.8]		1.1 [−39.7, 43.3]	

N = Number of subjects analyzed. The number in the brackets indicates two-sided 95% CI. PPS-1 population excludes subjects with a history of SARS-CoV-2 infection (anti-N antibody-positive) [see Section 7.2.2].

n = Number of subjects with antibody response. Subjects with antibody response are defined as those who showed a ≥4-fold increase in the neutralizing antibody titer from the level before the booster dose (a half of LLOQ if the titer was below LLOQ). If the antibody titer was below LLOQ, the value 0.5 × LLOQ was used for analysis. The quantification range (LLOQ to ULOQ) was 40 to 89947 (original strain).

a) Two-sided 95% CI was calculated based on the assumption of t-distribution in the difference of the logarithmically transformed value of antibody titer or the logarithmically transformed value of the rate of antibody titer increase.

b) ANCOVA of log-transformed neutralizing antibody titer using treatment group as a factor and allocation factors (time from the last dose, sex, age [continuous variable]) as covariates. Age was excluded from covariate in the subpopulations classified by age group.

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

d) Calculated based on the Miettinen-Nurminen method using the allocation factors (time from the last dose, sex, age) as adjustment factors. Age was excluded from adjustment factors in the subpopulations classified by age group.

Table 26 shows the results of immunogenicity in subjects classified by the presence/absence of a history of SARS-CoV-2 infection. Despite the difficulty due to the extremely limited number of subjects with a history of SARS-CoV-2 infection, a similar increase in the antibody titer was observed in both groups of subjects although the antibody titer was higher in subjects with a history of SARS-CoV-2 infection, indicating a similar response as in the entire population.

Table 26. GMT, GMFR, and SRR of SARS-CoV-2-neutralizing antibody titer, classified by presence/absence of history of SARS-CoV-2 infection (Study ARCT-154-J01, PPS-2 population)

	Entire population		Subjects without history of SARS-CoV-2 infection		Subjects with history of SARS-CoV-2 infection	
	Kostaive N = 413	Comirnaty N = 400	Kostaive N = 385	Comirnaty N = 374	Kostaive N = 28	Comirnaty N = 26
Baseline						
GMT[a)]	919.5 [808.8, 1045.4]	950.9 [830.9, 1088.2]	813.1 [715.6, 924.0]	865.6 [754.8, 992.7]	4988.0 [3745.2, 6643.2]	3675.0 [2496.9, 5408.9]
28 days after study vaccination						
GMT[b)]	5898.9 [4654.9, 7475.4]	4148.1 [3245.1, 5302.5]	5640.7 [4321.2, 7363.2]	3933.6 [2993.4, 5169.1]	9073.4 [5777.1, 14250.4]	6928.9 [4097.8, 11716.0]
GMFR[a)]	6.15 [5.49, 6.89]	4.15 [3.79, 4.55]	6.70 [5.97, 7.53]	4.37 [3.98, 4.80]	1.88 [1.46, 2.42]	1.95 [1.55, 2.45]
GMR[b)]	1.42 [1.26, 1.61]		1.43 [1.26, 1.63]		1.31 [0.87, 1.96]	
Antibody response rate						
No. of subjects with response (n)	254	195	251	193	3	2
SRR (%)[c)]	61.5 [56.6, 66.2]	48.8 [43.8, 53.8]	65.2 [60.2, 69.9]	51.6 [46.4, 56.8]	10.7 [2.3, 28.2]	7.7 [0.9, 25.1]
Difference in SRR[d)]	13.0 [6.3, 19.7]		13.6 [6.6, 20.5]		3.0 [−15.3, 21.1]	

N = Number of subjects analyzed. The number in the brackets indicates two-sided 95% CI. n = Number of subjects meeting the definition of antibody response (≥4-fold increase in antibody titer from the level before the booster dose [a half of LLOQ if the titer was below LLOQ]). If the antibody titer was below LLOQ, the value 0.5 × LLOQ was used for analysis. The quantification range (LLOQ to ULOQ) was 40 to 89947 (original strain).

a) Two-sided 95% CI was calculated based on the assumption of t-distribution in the difference of the logarithmically transformed value of antibody titer or the logarithmically transformed value of the rate of antibody titer increase.
b) ANCOVA of the log-transformed neutralizing antibody titer using treatment group as a factor and allocation factors (time from the last dose, sex, age [continuous variable]) as covariates.
c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
d) Calculated based on the Miettinen-Nurminen method using the allocation factors (time from the last dose, sex, age) as adjustment factors.

PMDA evaluated the efficacy of Kostaive based on the results of the foreign confirmatory study (Part 3b of Study ARCT-154-01) as described in Section 7.R.1, and also evaluated the efficacy in Japanese people based on the confirmation of the immunogenicity from the results of the Japanese clinical study (Study ARCT-154-J01).

On the basis of the documents submitted in the present application, PMDA confirmed the following and concluded that Kostaive is expected to have efficacy in Japanese people for the primary series as well:

- In Part 3b of Study ARCT-154-01, VE [two-sided 95% CI] based on the onset of COVID-19 was 56.6% [48.7%, 63.3%], with the lower limit of the two-sided 95% confidence interval exceeding pre-defined level of 30%, demonstrating the efficacy of Kostaive in preventing COVID-19 [see Table 17 in Section 7.2.1.2].
- In Part 3b of Study ARCT-154-01, no clear difference in efficacy was observed among subjects in different age and risk groups suggesting that Kostaive is expected to have efficacy regardless of risk factors or age.
- In the investigation of immunogenicity in Parts 1, 2, and 3a of Study ARCT-154-01 in the control population who were treated in the same manner as those in Part 3b, geometric mean concentration (GMC) [two-sided 95% CI] against SARS-CoV-2 (the original strain) at Day 28 after the second dose was 145.7 [135.1, 157.2] IU/mL in the Kostaive group and 7.7 [6.9, 8.7] IU/mL in the placebo group, and SRR [two-sided 95% CI] was 95.9% [93.4%, 97.6%] in the Kostaive group and 2.3% [0.5%, 6.5%] in the placebo group, demonstrating the immune response in the Kostaive group compared with the placebo group [see Table 14 in Section 7.2.1.1].
- Study ARCT-154-J01 investigating the booster dose in Japanese subjects confirmed the non-inferiority of Kostaive to the active control Comirnaty in the primary endpoints (GMT and SRR) [see Table 20 in Section 7.2.2].

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

The applicant's explanation about the efficacy of Kostaive in preventing severe COVID-19:

In order to evaluate the efficacy of Kostaive in preventing severe COVID-19, the incidence of severe COVID-19 was evaluated as the secondary endpoint among those with COVID-19 confirmed from 7 days to 2 months after the second dose in Part 3b of the foreign Study ARCT-154-01. Severe COVID-19 was defined as ≥1 of the following conditions according to the criteria of FDA Guidance[34]:

- Clinical signs at rest suggesting severe systemic disease (respiratory rate ≥30 breaths/min, heart rate ≥125 beats/min, saturation of percutaneous oxygen (SpO2) ≤93%, or partial pressure of arterial oxygen/Fraction of inspiratory oxygen (PaO2/FiO2) <300 mmHg)
- Respiratory failure (requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
- Shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit
- Death

Table 27 shows the VE in subjects with severe COVID-19 in mITT, suggesting the efficacy of Kostaive in preventing severe COVID-19 while caution is required for the interpretation because of the limited number of patients with severe COVID-19.

Table 27. VE against severe COVID-19 from 7 days to 2 months after the second dose (Part 3b of Study ARCT-154-01, mITT)

	N	T	n	VE [two-sided 95% CI] (%)[a)]
Kostaive	7787	1148.2	2	95.3 [80.5, 98.9]
Placebo	7723	1134.8	41	

N = Number of subjects analyzed, T = Total follow-up period (person-years), n = Number of subjects with severe COVID-19

a) Cox proportional hazard model with covariates of age/risk factors for severe COVID-19 (18-59 years old [without risk factor], 18-59 years old [with risk factors], ≥60 years old) and region

PMDA's view:

The study results suggest clinically significant VE in preventing severe COVID-19. Given the rapid evolution of the prevalent strains of SARS-CoV-2, it is essential to take appropriate measures such as considering the necessity of disseminating information when new information becomes available on the efficacy of Kostaive or approved vaccines (including vaccines against variants) in preventing severe COVID-19.

7.R.2.4 Immunogenicity against SARS-CoV-2 variants

The applicant's explanation about the immunogenicity against SARS-CoV-2 variants:

Table 28 shows the results of the immunogenicity test against the Omicron variant (exploratory evaluation against BA.1 lineage) in Study ARCT-154-01 administering the primary series.

Table 28. Neutralizing antibody titer against the Omicron variant (BA.1 lineage) after the primary series (Parts 1/2/3a of Study ARCT-154-01, immunogenicity analysis population)

	Neutralizing antibody titer			Neutralizing antibody response rate			
	N	GMC[a)]	GMR[a)]	N	n	SRR (%)[b)]	Difference in SRR[c)]
Kostaive	216	7.7 [7.3, 8.3]	1.0 [0.9, 1.2]	215	5	2.3 [0.8, 5.3]	2.3 [−3.3, 5.5]
Placebo	73	7.8 [6.6, 9.2]		73	0	0.0 [0.0, 4.9]	

The number in the brackets indicates two-sided 95% CI.
N = Number of subjects analyzed, n = Number of subjects with antibody response. Antibody response was defined as a ≥4-fold increase in the antibody titer from the level before the primary series (LLOQ if the titer was below LLOQ). If the antibody titer was below LLOQ, the value 0.5 × LLOQ was used for analysis.
a) Two-sided 95% CI was calculated based on t-distribution in the logarithmically transformed value of antibody titer or the difference in the logarithmically transformed value of the antibody titer.
b) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
c) Fisher's exact confidence interval was calculated.

Table 29 shows the results of immunogenicity against the Omicron variant (secondary evaluation, BA.4-5 lineage; exploratory evaluation, XBB.1.5.6 lineage) in Study ARCT-154-J01 administering the booster dose.

Table 29. Comparison of neutralizing antibody titer against the Omicron variant after booster dose (Study ARCT-154-J01, PPS-1 population)

	Neutralizing antibody titer			Neutralizing antibody response rate		
	N	GMT[a)]	GMR[b)]	n	SRR (%)[c)]	Difference in SRR[d)]
BA.4-5 lineage (Day 29)[e)]						
Kostaive	385	2193.3 [1901.1, 2530.5]	1.30 [1.07, 1.58]	269	69.9 [65.0, 74.4]	11.6 [4.9, 18.3]
Comirnaty	374	1654.6 [1447.0, 1891.9]		217	58.0 [52.8, 63.1]	
BA.4-5 lineage (Day 91)[e)]						
Kostaive	379	1958.2 [1705.4, 2248.5]	—	243	64.1 [59.1, 69.0]	—
Comirnaty	366	921.2 [794.3, 1068.5]		147	40.2 [35.1, 45.4]	
XBB.1.5.6 lineage (Day 29)[f)]						
Kostaive	359	145.8 [128.0, 166.1]	1.17 [0.98, 1.41]	213	59.3 [54.1, 64.5]	9.1 [1.9, 16.3]
Comirnaty	349	121.7 [106.3, 139.2]		174	49.9 [44.5, 55.2]	

The number in the brackets indicates two-sided 95% CI; —, Not calculated.
N = Number of subjects analyzed, n = Number of subjects with antibody response.
Antibody response was defined as a ≥4-fold increase in the antibody titer from before the booster dose (a half of LLOQ if the titer was below LLOQ). If the antibody titer was below LLOQ, the value 0.5 × LLOQ was used for analysis.
a) Two-sided 95% CI was calculated by assuming t-distribution of the log-transformed values.
b) ANCOVA
c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
d) Calculated based on the Miettinen-Nurminen method.
e) Pseudovirus-neutralizing antibody assay
f) Microneutralizing antibody assay

The booster dose with Kostaive was shown to induce neutralizing antibodies against a variety of variant strains such as the Omicron subvariant (BA.4-5 and XBB.1.5 lineages). GMT and SRR against BA.4-5 lineage on Day 91 were lower than those on Day 29 in the Comirnaty group, whereas they remained at comparable levels in the Kostaive group.

PMDA's view:
GMC and SRR of the neutralizing antibody against the Omicron variant after the primary series were low (Table 28), suggesting that the primary series alone does not show sufficient efficacy against the variants. The booster dose (Table 29) induced neutralizing antibody to the same extent as did the approved control RNA vaccine (Comirnaty against the original strain), suggesting that Kostaive is expected to have a certain level of efficacy against the Omicron variant. Since the neutralizing antibody titer against XBB.1.5.6 lineage of the Omicron variant is lower than the titer against BA.4-5 lineage, development of a vaccine against XBB.1 lineages will be necessary [see Section 7.R.4].

In Study ARCT-154-J01, immunogenicity was investigated only until Day 91, precluding between-group comparison with this limited information. Whether the tendency of higher neutralizing antibody titer in the Kostaive group than in the Comirnaty group on Day 91 predicts the persistence of the efficacy of Kostaive (efficacy in preventing COVID-19, etc.) is currently unclear.

7.R.2.5 Cellular immunity

The applicant investigated cellular immunity in an exploratory manner before and after the booster dose in Study ARCT-154-J01. In both Kostaive and Comirnaty groups, Th-1-dominant cellular immunity was observed. No marked changes were observed in responses of IFN-γ^+, $CD4^+$, reactive T cells or IFN-γ^+, $CD8^+$, reactive T cells against S-protein of the original strain between before and after vaccination. Cell-mediated immune reaction was investigated in an exploratory manner in Study ARCT-165-01 as well. Fragment crystallizable region (Fc) effector function measured by luciferase assay of NK cell-activating spike-specific antibody increased on Day 29 against many variants (Beta variant, Delta variant, Omicron variant B.1.1.529 lineage) in the Kostaive group. The cell-mediated immune reaction was Th-1 dominant.

PMDA's view:

Only limited information is available on the cellular immune response, precluding the accurate evaluation of the relationship between the response and efficacy. The applicant should continue to collect information and provide new findings affecting public health to healthcare professionals.

7.R.3 Safety

7.R.3.1 Safety profiles

PMDA reviewed, as pivotal studies, Part 3b of Study ARCT-154-01 for the primary series and Study ARCT-154-J01 for booster dose. Table 30 summarizes the incidences of adverse events in Part 3b of Study ARCT-154-01 and Study ARCT-154-J01.

Table 30. Summary of incidences of adverse events in Part 3b of Studies ARCT-154-01 and ARCT-154-J01 (safety analysis population)

	Study ARCT-154-01				Study ARCT-154-J01	
	First dose of primary series		Second dose of primary series		First booster dose	
	Kostaive N = 8059	Placebo N = 8041	Kostaive N = 8059	Placebo N = 8041	Kostaive N = 420	Comirnaty N = 408
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Solicited local adverse events[a)]	3474 (43.8)	858 (10.9)	2401 (31.2)	585 (7.7)	398 (94.8)	395 (96.8)
Grade ≥3	40 (0.5)	0	10 (0.1)	1 (0.0)	3 (0.7)	4 (1.0)
Solicited systemic adverse events[b)]	3816 (48.1)	2499 (31.7)	3214 (41.7)	1796 (23.5)	276 (65.7)	255 (62.5)
Grade ≥3	115 (1.5)	35 (0.4)	113 (1.5)	23 (0.3)	6 (1.4)	7 (1.7)
Unsolicited adverse events	1125 (14.0)	1001 (13.7)	1096 (13.9)	1241 (15.9)	81 (19.3)	111 (27.2)
Grade ≥3	10 (0.1)	18 (0.2)	13 (0.2)	17 (0.2)	1 (0.2)	6 (1.5)
Adverse events leading to death	2 (0.0)	5 (0.1)	4 (0.1)	0	0	0
Serious adverse events	38 (0.5)	48 (0.6)	40 (0.5)	61 (0.8)	0	1 (0.2)
Adverse events leading to treatment discontinuation	3 (0.0)	5 (0.1)	4 (0.1)	0	—	—

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

a) Number of subjects with Grade ≥1 events in Study ARCT-154-01, number of subjects with Grade ≥0 events in Study ARCT-154-J01. Grade 0 was used only for erythema, swelling, and induration (<2.5 cm).

b) ≥38°C (site of measurement not specified) in Study ARCT-154-01, ≥37.5°C (axillary) in Study ARCT-154-J01

(1) Primary series

1) Solicited adverse events

Table 18 shows the incidence of solicited adverse events (observed within 7 days after vaccination) [see Section 7.2.1.2]. Most of them were mild or moderate in severity.

The time-to-onset and duration of solicited adverse events in Part 3b of Study ARCT-154-01 were evaluated. The median time-to-onset of solicited localized adverse events was 1 day both in the Kostaive group and in the placebo group. The median duration was 1 to 2 days in the Kostaive group and 1 to 3 days in the placebo group. The time-to-onset and the duration did not significantly differ between after the first dose and the second dose. The median time-to-onset of solicited systemic adverse events was 1 to 2 days both in the Kostaive group and in the placebo group. The median duration was 1 to 2 days in the Kostaive group and 1 to 3 days in the placebo group. The range [min, max] of the time-to-onset after vaccination and the duration were both [1, 7] days. The time-to-onset and the duration after the first dose were not significantly different from those after the second dose in the Kostaive group. The solicited adverse events that lasted even after Day 7[44)] were observed in 58 subjects (0.8%) after the first dose and in 72 subjects (0.9%) after the second dose in the Kostaive group and in 66 subjects (0.8%) after the first dose and in 72 subjects (0.9%) after the second dose in the placebo group, showing extremely low incidences and no significant difference between the Kostaive group and the placebo group.

2) Unsolicited adverse events and serious adverse events

Table 19 shows the incidences of unsolicited adverse events [see Section 7.2.1.2]. Most of them were mild or moderate in severity. As described in Section 7.2.1.2, there were several serious adverse events for which a causal relationship to the study vaccine could not be ruled out, but all of them resolved. Thus, vaccination with Kostaive did not cause any conditions requiring particular concerns.

3) Adverse events by age group

Table 31 shows solicited adverse events (all and Grade ≥3 events) by age groups. The incidence of solicited adverse events tended to be lower in the elderly subjects than in non-elderly subjects both after the first and the second dose.

44) Duration of solicited adverse events (defined as those observed within 7 days after the study vaccination) was investigated up to Day 7, and those observed thereafter were classified into unsolicited adverse events. For unsolicited local and systemic adverse events, their incidences were investigated.

Table 31. Solicited adverse events after each dose of vaccination in subpopulations classified by age group (Part 3b of Study ARCT-154-01, reactogenicity analysis population)

MedDRA PT	First dose				Second dose			
	Kostaive		Placebo		Kostaive		Placebo	
	18-59 years	≥60 years	18-59 years	≥60 years	18-59 years	≥60 years	18-59 years	≥60 years
	N = 6547	N = 1380	N = 6522	N = 1364	N = 6351	N = 1351	N = 6312	N = 1326
Local (all events)[a)]	3076 (47.0)	398 (28.8)	750 (11.5)	108 (7.9)	2099 (33.0)	302 (22.4)	510 (8.1)	75 (5.7)
Grade ≥3	38 (0.6)	2 (0.1)	0	0	10 (0.2)	0	1 (0.0)	0
Pain	2687 (41.0)	342 (24.8)	586 (9.0)	90 (6.6)	1806 (28.4)	257 (19.0)	405 (6.4)	62 (4.7)
Grade ≥3	28 (0.4)	1 (0.1)	0	0	7 (0.1)	0	0	0
Erythema (redness)	67 (1.0)	12 (0.9)	17 (0.3)	1 (0.1)	32 (0.5)	5 (0.4)	8 (0.1)	1 (0.1)
Grade ≥3	0	1 (0.1)	0	0	0	0	0	0
Swelling (Induration)	197 (3.0)	27 (2.0)	28 (0.4)	1 (0.1)	76 (1.2)	4 (0.3)	9 (0.1)	1 (0.1)
Grade ≥3	2 (0.0)	0	0	0	1 (0.0)	0	0	0
Injection site tenderness	2671 (40.8)	332 (24.1)	585 (9.0)	74 (5.4)	1809 (28.5)	234 (17.3)	378 (6.0)	51 (3.8)
Grade ≥3	31 (0.5)	1 (0.1)	0	0	7 (0.1)	0	1 (0.0)	0
Systemic (all events)	3354 (51.2)	462 (33.5)	2124 (32.6)	375 (27.5)	2762 (43.5)	452 (33.5)	1514 (24.0)	282 (21.3)
Grade ≥3	106 (1.6)	9 (0.7)	27 (0.4)	8 (0.6)	106 (1.7)	7 (0.5)	21 (0.3)	2 (0.2)
Pyrexia[b)]	377 (5.8)	40 (2.9)	84 (1.3)	17 (1.2)	454 (7.1)	51 (3.8)	79 (1.3)	13 (1.0)
Grade ≥3	4 (0.7)	4 (0.3)	10 (0.2)	2 (0.1)	60 (0.9)	3 (0.2)	10 (0.2)	1 (0.1)
Headache	1737 (26.5)	188 (13.6)	1074 (16.5)	161 (11.8)	1451 (22.8)	198 (14.7)	718 (11.4)	118 (8.9)
Grade ≥3	18 (0.3)	1 (0.1)	5 (0.1)	2 (0.1)	23 (0.4)	1 (0.1)	3 (0.0)	0
Fatigue	2079 (31.8)	265 (19.2)	1132 (17.4)	175 (12.8)	1684 (26.5)	242 (17.9)	770 (12.2)	131 (9.9)
Grade ≥3	25 (0.4)	2 (0.1)	7 (0.1)	2 (0.1)	26 (0.4)	1 (0.1)	3 (0.0)	1 (0.1)
Myalgia	1460 (22.3)	155 (11.2)	597 (9.2)	95 (7.0)	1043 (16.4)	153 (11.3)	475 (7.5)	75 (5.7)
Grade ≥3	12 (0.2)	1 (0.1)	2 (0.0)	1 (0.1)	7 (0.1)	0	1 (0.0)	1 (0.1)
Arthralgia	1230 (18.8)	201 (14.6)	759 (11.6)	151 (11.1)	988 (15.6)	183 (13.5)	569 (9.0)	110 (8.3)
Grade ≥3	22 (0.3)	1 (0.1)	4 (0.1)	0	16 (0.3)	1 (0.1)	4 (0.1)	0
Nausea	227 (3.5)	20 (1.4)	152 (2.3)	19 (1.4)	174 (2.7)	21 (1.6)	98 (1.6)	10 (0.8)
Grade ≥3	0	0	1 (0.0)	0	1 (0.0)	0	0	0
Chills	1373 (21.0)	118 (8.6)	503 (7.7)	55 (4.0)	1229 (19.4)	115 (8.5)	340 (5.4)	46 (3.5)
Grade ≥3	16 (0.2)	3 (0.2)	2 (0.0)	2 (0.1)	17 (0.3)	0	1 (0.0)	0
Diarrhoea	277 (4.2)	41 (3.0)	221 (3.4)	21 (1.5)	147 (2.3)	18 (1.3)	116 (1.8)	18 (1.4)
Grade ≥3	2 (0.0)	0	2 (0.0)	1 (0.1)	0	2 (0.1)	1 (0.0)	0
Dizziness	917 (14.0)	133 (9.6)	622 (9.5)	98 (7.2)	738 (11.6)	110 (8.1)	388 (6.1)	57 (4.3)
Grade ≥3	9 (0.1)	1 (0.1)	5 (0.1)	1 (0.1)	8 (0.1)	0	0	0
Vomiting	86 (1.3)	8 (0.6)	48 (0.7)	6 (0.4)	64 (1.0)	9 (0.7)	29 (0.5)	3 (0.2)
Grade ≥3	0	0	0	1 (0.1)	1 (0.0)	0	0	0

N = Number of subjects analyzed, n = Number of subjects with events
a) Number of subjects with Grade ≥1 events
b) ≥38°C, ≥39°C for Grade ≥3 events

(2) Booster dose

1) Solicited adverse events

Table 21 shows the incidence of solicited adverse events [see Section 7.2.2]. Most of them were mild or moderate in severity.

The time-to-onset and duration of solicited adverse events in Study ARCT-154-J01 were evaluated. The median time-to-onset [range] of solicited local adverse events was 1 [1, 4] day(s) in the Kostaive group and 1 [1, 3] day(s) in the Comirnaty group. The median duration [range] was 4 [1, 29] days[45)] in the Kostaive group and 4 [2, 15] day(s) in the Comirnaty group. For solicited systemic adverse events, the median time-to-onset [range] was 2 [1, 7] days in the Kostaive group and 2 [1, 5] days in the Comirnaty group, and the median duration [range] was 3 [1, 9] days in the Kostaive group and 2 [2, 12] days in the Comirnaty group.

[45)] Of the solicited adverse events in the Kostaive group, only tenderness lasted 29 days at the maximum, while the maximum duration of other events was 17 days for erythema, 6 days for swelling, 8 days for induration, and 10 days for pain, which were similar to those observed in the Comirnaty group.

2) Unsolicited adverse events and serious adverse events

No significant difference was observed in the safety profile regarding the unsolicited adverse events [see Table 22 in Section 7.2.2] between the Kostaive group and the Comirnaty group. No serious adverse events were observed in the Kostaive group as described in Section 7.2.2. Thus, vaccination with Kostaive did not raise any significant concerns.

3) Adverse events by age group

Table 32 shows solicited adverse events by age group (all and Grade ≥3 events). There was no clear difference in the incidence of solicited adverse events among age groups, although comparison is difficult due to the extremely limited number of elderly subjects investigated.

Table 32. Solicited adverse events by age group (Study ARCT-154-J01, safety analysis population)

MedDRA PT	All Grades				Grade ≥3			
	Kostaive		Comirnaty		Kostaive		Comirnaty	
	<65 years N = 408	≥65 years N = 12	<65 years N = 400	≥65 years N = 8	<65 years N = 408	≥65 years N = 12	<65 years N = 400	≥65 years N = 8
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	389 (95.3)	9 (75.0)	387 (96.8)	8 (100.0)	3 (0.7)	0	4 (1.0)	0
Erythema	52 (12.7)	0	84 (21.0)	1 (12.5)	0	0	3 (0.8)	0
Swelling	59 (14.5)	0	95 (23.8)	2 (25.0)	1 (0.2)	0	1 (0.3)	0
Induration	52 (12.7)	0	79 (19.8)	2 (25.0)	1 (0.2)	0	0	0
Tenderness	380 (93.1)	8 (66.7)	383 (95.8)	8 (100.0)	1 (0.2)	0	1 (0.3)	0
Pain	346 (84.8)	6 (50.0)	351 (87.8)	7 (87.5)	1 (0.2)	0	0	0
Systemic (all events)[a)]	274 (67.2)	2 (16.7)	250 (62.5)	5 (62.5)	6 (1.5)	0	7 (1.8)	0
Pyrexia[b)]	83 (20.3)	1 (8.3)	76 (19.0)	0	2 (0.5)	0	2 (0.5)	0
Arthralgia	111 (27.2)	1 (8.3)	111 (27.8)	2 (25.0)	1 (0.2)	0	2 (0.5)	0
Chills	126 (30.9)	0	102 (25.5)	1 (12.5)	2 (0.5)	0	4 (1.0)	0
Diarrhoea	27 (6.6)	1 (8.3)	17 (4.3)	0	0	0	0	0
Dizziness	25 (6.1)	0	13 (3.3)	0	0	0	1 (0.3)	0
Headache	164 (40.2)	1 (8.3)	124 (31.0)	1 (12.5)	3 (0.7)	0	3 (0.8)	0
Malaise	187 (45.8)	1 (8.3)	172 (43.0)	4 (50.0)	3 (0.7)	0	4 (1.0)	0
Nausea	21 (5.1)	0	16 (4.0)	0	0	0	0	0
Vomiting	2 (0.5)	0	2 (0.5)	0	0	0	0	0
Myalgia	122 (29.9)	1 (8.3)	97 (24.3)	3 (37.5)	2 (0.5)	0	3 (0.8)	0

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

a) Number of subjects with Grade ≥0 events. Grade 0 was used only for erythema, swelling, induration (<2.5 cm), and pyrexia (37.5°C-37.9°C).

b) ≥37.5°C (axillary)

7.R.3.2 Adverse events of special interest

PMDA reviewed the incidence, in the submitted clinical study data, of the following adverse events/adverse reactions of special interest observed after administration of other RNA vaccines: Shock/anaphylaxis, myocarditis/pericarditis, vaccine-associated enhanced disease (VAED)/vaccine-associated enhanced respiratory disease (VAERD), and Guillain-Barre syndrome.

The applicant's explanation:

(1) Shock/anaphylaxis

In Study ARCT-154-01, anaphylactic reactions in 2 subjects were reported as serious adverse events, but neither of them met the definition of anaphylaxis according to Brighton Collaboration. One of the subjects was a 4[redacted]-years-old woman in the placebo-Kostaive group. One day after vaccination with Kostaive, she had fatigue, systemic redness, urticaria, erythema, as well as pruritus and papule in the bilateral thighs and upper arms, in addition to pyrexia and diarrhoea. Subsequently, the subject was diagnosed with COVID-19. The clinical course of the symptoms was consistent with hypersensitivity reaction rather than anaphylaxis, and is possibly related to COVID-19 infection. The other subject was

a 4[redacted]-year-old woman in the placebo-Kostaive group who was diagnosed with post-vaccination anaphylaxis 190 days after the second dose of vaccination with Kostaive. She received Vaxzevria on the same day as diagnosis of anaphylaxis, suggesting that the event was caused by Vaxzevria.

There were no reports of shock/anaphylaxis either in Study ARCT-154-J01 or ARCT-021-related studies.

(2) Myocarditis/Pericarditis, Guillain-Barre syndrome, VAED/VAERD

Adverse events related to myocarditis/pericarditis, Guillain-Barre syndrome, or VAED/VAERD were not observed in any of the study data submitted.

The applicant's explanation about the safety of vaccination with Kostaive, based on the findings described in Sections 7.R.3.1 and 7.R.3.2:

The safety profile of Kostaive after the primary series and after the booster dose did not show any clear difference regardless of the age group (adults and elderly people). The safety profile of Kostaive after the booster dose was well-tolerated, showing no significant difference from the safety profile of Comirnaty after the booster dose. Most of the adverse events observed were mild or moderate and transient. Most of Grade ≥3 events were transient, resolving with or without medical intervention. For RNA vaccine, attention should be paid to shock/anaphylaxis, myocarditis/pericarditis, Guillain-Barre syndrome, and VAED/VAERD, but these events have not been observed in the clinical studies of Kostaive, except for adverse events related to shock/anaphylaxis. Since Kostaive is considered to share a similar modality with RNA vaccines, vaccine in the same class, cautions against the risk of these adverse events are still required as are the cases with vaccines in the same class.

Thus, the primary series and the booster dose of Kostaive are well-tolerated in individuals aged ≥18 years, while appropriate cautions are required given the incidences of adverse events observed in clinical studies and those observed with other vaccines in the same class.

PMDA's view:

Adverse events observed after the primary series in the Kostaive group of clinical studies were generally similar to those observed with approved RNA vaccines. No significant difference was observed in the types or incidence of adverse events between the Kostaive group and the control vaccine Comirnaty group in the clinical study on booster dose. In addition, most of the adverse events were mild to moderate in severity, and the safety profile was not different among age groups. Based on these findings, the safety of Kostaive is well tolerated in individuals aged ≥18 years.

Among adverse events of special interest, shock/anaphylaxis-related adverse events observed after vaccination with Kostaive were mild to moderate hypersensitivity and Kostaive is tolerable. Kostaive is an RNA vaccine containing a replicon, but shows no clear difference from the control vaccine in the time-to-onset or duration of adverse events, such as longer duration of adverse events than with the control. As for other adverse events of special interest with approved RNA vaccines, i.e., myocarditis/pericarditis, Guillain-Barre syndrome, and VAED/VAERD, cautions are required because occurrence of these events cannot be excluded given the following: (a) Due to the low incidences of these adverse events, definite risk evaluation from clinical study results only is difficult; and (b) taking

into account that Kostaive is an RNA vaccine, similar to approved RNA vaccines, Kostaive may cause these events after the market launch. Thus, caution should be raised about these events, as proposed by the applicant.

7.R.3.3 Safety in the special populations

The applicant's explanation about the safety of Kostaive in population with risk factors for severe COVID-19, pregnant women, and lactating women:

(1) Individuals with risk factors for severe COVID-19

In Studies ARCT-154-01 and ARCT-154-J01, safety of Kostaive was investigated in subjects with underlying medical conditions prone to develop severe COVID-19 presented at the 44th subcommittee meeting on basic vaccination policy of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (March 18, 2021) and subjects with diseases presented as risk factors for severe COVID-19 in the Guidelines for Diagnosis and Treatment of COVID-19, ver. 9.0 (dated February 10, 2023).

1) Study ARCT-154-01 (pooled data from Parts 1, 2, 3a, and 3b before cross over)

Of the subjects in the safety analysis population, 4,056 of 17,101 subjects (23.7%) (2,103 of 8,807 [23.9%] in the Kostaive group, 1,953 of 8,294 [23.5%] in the placebo group) had underlying medical conditions. The underlying medical conditions were respiratory disease (88 subjects in the Kostaive group, 88 subjects in the placebo group), cardiac disease (890 subjects, 813 subjects), renal disease (190 subjects, 168 subjects), hepatic disease (308 subjects, 274 subjects), diabetes mellitus (229 subjects, 233 subjects), blood disease (except for iron deficiency anaemia) (3 subjects, 2 subjects), malignant tumor (75 subjects, 59 subjects), nerve or neuromuscular disease (12 subjects, 5 subjects), severe psychiatric disorder, physical disability, or intellectual disability (1 subject, 6 subjects), and obesity of body mass index (BMI) ≥30 (216 subjects, 179 subjects).

Table 33. Solicited adverse events after each vaccination (Study ARCT-154-01, Subjects with underlying medical conditions in the reactogenicity analysis population)

MedDRA PT	First dose				Second dose			
	Kostaive (N = 2072)		Placebo (N = 1911)		Kostaive (N = 2034)		Placebo (N = 1863)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	889 (42.9)	15 (0.7)	186 (9.7)	0	642 (31.6)	6 (0.3)	149 (8.0)	0
Pain	774 (37.4)	8 (0.4)	148 (7.7)	0	537 (26.4)	4 (0.2)	117 (6.3)	0
Erythema (redness)	17 (0.8)	0	4 (0.2)	0	11 (0.5)	0	2 (0.1)	0
Swelling (induration)	59 (2.8)	1 (0.0)	5 (0.3)	0	23 (1.1)	0	2 (0.1)	0
Injection site tenderness	755 (36.4)	14 (0.7)	138 (7.2)	0	524 (25.8)	6 (0.3)	103 (5.5)	0
Systemic (all events)	990 (47.8)	34 (1.6)	603 (31.6)	12 (0.6)	887 (43.6)	27 (1.3)	480 (25.8)	4 (0.2)
Pyrexia[b)]	90 (4.3)	9 (0.4)	26 (1.4)	4 (0.2)	104 (5.1)	8 (0.4)	22 (1.2)	2 (0.1)
Headache	470 (22.7)	8 (0.4)	288 (15.1)	3 (0.2)	425 (20.9)	9 (0.4)	214 (11.5)	0
Fatigue	617 (29.8)	10 (0.5)	305 (16.0)	4 (0.2)	544 (26.7)	11 (0.5)	240 (12.9)	1 (0.1)
Myalgia	408 (19.7)	6 (0.3)	172 (9.0)	1 (0.1)	338 (16.6)	6 (0.3)	158 (8.5)	1 (0.1)
Arthralgia	419 (20.2)	12 (0.6)	223 (11.7)	2 (0.1)	338 (16.6)	8 (0.4)	187 (10.0)	1 (0.1)
Nausea	56 (2.7)	0	37 (1.9)	0	47 (2.3)	1 (0.0)	25 (1.3)	0
Chills	367 (17.7)	8 (0.4)	132 (6.9)	3 (0.2)	346 (17.0)	2 (0.1)	106 (5.7)	0
Diarrhoea	88 (4.2)	0	61 (3.2)	1 (0.1)	49 (2.4)	2 (0.1)	39 (2.1)	0
Dizziness	278 (13.4)	7 (0.3)	187 (9.8)	3 (0.2)	220 (10.8)	1 (0.0)	122 (6.5)	0
Vomiting	24 (1.2)	0	10 (0.5)	1 (0.1)	27 (1.3)	1 (0.0)	9 (0.5)	0

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

a) Number of subjects with Grade ≥1 adverse events

b) ≥38°C, ≥39°C for Grade ≥3 events

In subjects with underlying medical conditions, unsolicited adverse events occurred in 729 of 2,103 subjects (37.7%) in the Kostaive group and 783 of 1,953 subjects (40.1%) in the placebo group, and unsolicited adverse reactions occurred in 109 of 2,103 subjects (5.2%) in the Kostaive group and 85 of 1,953 subjects (4.4%) in the placebo group. Adverse events leading to discontinuation of the study vaccine occurred in 3 of 2,103 subjects (0.1%) in the Kostaive group and in 18 of 1,953 subjects (0.9%) in the placebo group. Serious adverse events occurred in 58 of 2,103 subjects (2.8%) in the Kostaive group and in 92 of 1,953 subjects (4.7%) in the placebo group. Adverse events leading to death occurred in 2 of 2,103 subjects (0.1%) in the Kostaive group and in 14 of 1,953 subjects (0.7%) in the placebo group. A causal relationship to the study vaccine could not be ruled out in 1 of 1,953 subjects (0.1%) in the placebo group who resulted in early discontinuation of the study vaccination, 5 of 2,103 subjects (0.2%) in the Kostaive group, and 3 of 1,953 subjects (0.2%) in the placebo group with serious adverse events.

2) Study ARCT-154-J01

Underlying medical conditions were found in 111 of 828 subjects (13.4%) in the safety analysis population (63 of 420 [15.0%] in the Kostaive group, 48 of 408 [11.8%] in the Comirnaty group). The breakdown of the underlying medical conditions was respiratory disease (14 subjects in the Kostaive group, 8 subjects in the Comirnaty group), cardiac disease (23 subjects, 21 subjects), renal disease (2 subjects, 0 subjects), hepatic disease (19 subjects, 6 subjects), diabetes mellitus (9 subjects, 12 subjects), blood disease (except for iron deficiency anaemia) (2 subjects, 1 subject), malignant tumor (2 subjects, 4 subjects), nerve or neuromuscular disease (1 subject, 0 subjects), sleep apnoea syndrome (1 subject, 3 subjects), severe psychiatric disorder or intellectual disability (1 subject, 3 subjects), and obesity with BMI ≥30 (1 subject, 1 subject).

Table 34. Solicited adverse events (Study ARCT-154-J01, subjects with underlying medical conditions in safety analysis population)

MedDRA PT	Kostaive (N = 63)		Comirnaty (N = 48)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)
Local (all events)[a)]	59 (93.7)	0	48 (100.0)	1 (2.1)
Erythema	7 (11.1)	0	12 (25.0)	1 (2.1)
Swelling	3 (4.8)	0	13 (27.1)	1 (2.1)
Induration	2 (3.2)	0	13 (27.1)	0
Tenderness	57 (90.5)	0	48 (100.0)	0
Pain	52 (82.5)	0	44 (91.7)	0
Systemic (all events)[a)]	40 (63.5)	1 (1.6)	32 (66.7)	2 (4.2)
Pyrexia[b)]	7 (11.1)	1 (1.6)	9 (18.8)	1 (2.1)
Arthralgia	22 (34.9)	0	12 (25.0)	0
Chills	15 (23.8)	0	12 (25.0)	0
Diarrhoea	6 (9.5)	0	2 (4.2)	0
Dizziness	2 (3.2)	0	1 (2.1)	0
Headache	21 (33.3)	0	10 (20.8)	0
Malaise	27 (42.9)	0	18 (37.5)	0
Nausea	6 (9.5)	0	2 (4.2)	0
Vomiting	2 (3.2)	0	0	0
Myalgia	23 (36.5)	0	10 (20.8)	1 (2.1)

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

a) Number of subjects with Grade ≥0 events. Grade 0 was used only for erythema, swelling, induration (<2.5 cm), and pyrexia (37.5°C-37.9°C).

b) ≥37.5°C (axillary)

In subjects with underlying medical conditions, unsolicited adverse events occurred in 11 of 63 subjects (17.5%) in the Kostaive group and 13 of 48 subjects (27.1%) in the Comirnaty group, and unsolicited adverse reactions occurred in 9 of 63 subjects (14.3%) in the Kostaive group and 8 of 48 subjects (16.7%) in the Comirnaty group. There were no serious adverse events or adverse events leading to death.

The incidences of solicited adverse events and all adverse events in Studies ARCT-154-01 and ARCT-154-J01 indicated that the safety profile was not significantly different regardless of underlying medical conditions, even in view of incidences of individual adverse events. These results suggest that vaccination with Kostaive in individuals with underlying medical conditions is unlikely to increase the incidence or severity of adverse events. Nevertheless, given that Kostaive has been vaccinated to only a limited number of individuals with underlying medical conditions and that they are classified as those requiring caution in vaccination in the "Interim guidelines for vaccination against COVID-19 (in Japanese)" (issued by Ministry of Health, Labour and Welfare on August 1, 2022), precautions similar to those for vaccines in the same class are required.

(2) Pregnant/lactating women

Taking account of the following, the package insert should include the precautionary statement regarding vaccination with Kostaive in pregnant and lactating women.

- Pregnant women

In Study ARCT-154-01, the following numbers of pregnant subjects were observed: 19 in the Kostaive group and 22 in the placebo group from the first dose of the study vaccination to cross-over (Day 1 to Day 92), and 11 in the placebo-Kostaive group and 14 in the Kostaive-placebo group after cross-over (after Day 92). Spontaneous abortion was observed in 1 subject in the Kostaive group, 2 subjects in the placebo group, and 1 subject in the placebo-Kostaive group. A causal relationship to Kostaive was denied for spontaneous abortion in 2 subjects after vaccination with Kostaive. In the animal study conducted using ARCT-021, a vaccine manufactured based on the same platform as Kostaive, no direct or indirect adverse effect was observed on the fertility, embryofetal development, delivery, or postnatal development. Still, given the limited data available on the safety of using Kostaive during pregnancy, safety for pregnant women has not been established. The use of Kostaive during pregnancy should be considered only when potential benefits outweigh the potential risks for the mother and the fetus.

- Lactating women

Lactating women were not included in clinical studies of Kostaive. Whether Kostaive is excreted into breast milk is unknown. The clinical necessity of Kostaive and its potential influences on breastfeeding should be considered when vaccinating lactating women with Kostaive.

PMDA's view:

Studies ARCT-154-01 and ARCT-154-J01 confirmed that there are no safety concerns requiring particular caution in subjects with underlying medical conditions compared with the entire population. No particular cautions are required in individuals with underlying medical conditions in the present circumstances. Nevertheless, given the limited experience of vaccination with Kostaive in individuals

with underlying medical conditions and the necessity of more attention to their vaccination, the same precautions as those for vaccines in the same class should be provided.

In non-clinical studies, vaccination with Kostaive did not pose any safety concerns for the parental animals or for the off-spring [see Section 5.5], but the applicant's explanation is understandable because there is no experience of vaccination with Kostaive in pregnant or lactating women and excretion of Kostaive in milk has yet to be investigated and unknown. The same precautions as those for approved RNA vaccines should be raised for pregnant and lactating women.

After the market launch, Kostaive is expected to be used in individuals with various conditions, including special populations who were excluded from the clinical studies. The applicant should collect safety information on Kostaive from a wide variety of vaccine recipients including individuals mentioned above and should consider providing additional safety measures in a timely fashion, based on the information thus obtained.

7.R.4 Clinical positioning and indication

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

The applicant's explanation about the positioning of Kostaive:
In Study ARCT-154-01 evaluating the efficacy, immunogenicity, and safety of the primary series, Kostaive demonstrated the efficacy in preventing COVID-19 and severe COVID-19, confirming the immune response against the original strain of SARS-CoV-2 and the favorable safety profile [see Section 7.2.1]. In Study ARCT-154-J01 evaluating the immunogenicity and safety of the booster dose, Kostaive induced potent immune response against the original strain of SARS-CoV-2 [see Section 7.2.2], and neutralizing antibody against SARS-CoV-2 variants including the Omicron lineage [see Section 7.R.2.4].

The results suggest that (a) Kostaive can be a novel option of vaccine for the primary series to prevent severe COVID-19, particularly in young Japanese adults who have not completed the primary series; and (b) Kostaive is considered useful as a monovalent vaccine for booster dose in order to prevent COVID-19 caused by a wide range of SARS-CoV-2 variants including Omicron, the recently predominant variant. Approval of Kostaive in Japan for the indication of the primary series and the booster dose allows prompt development and supply of vaccines in Japan for the primary series or booster dose against new variants by means of the mRNA platform of Kostaive in case of pandemic with new SARS-CoV-2 variants, and hence Kostaive is clinically useful. Clinical studies of vaccines against variants are ongoing and the application is planned to be submitted for approval in the future. Also planned are clinical studies on Kostaive in infants and children.

PMDA's view:
WHO declared the end of the "Public Health Emergency of International Concern" regarding COVID-19.[46)] In Japan, the category of COVID-19 according to the Infectious Diseases Control Act was reclassified from pandemic influenza (novel influenza or re-emerging influenza) to Class 5 infectious

[46)] 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

diseases on May 8, 2023, while SARS-CoV-2 vaccination is still ongoing as a special temporary vaccination based on the Preventative Vaccination Act. Multiple vaccines have been put into practical use, and the vaccinated population is expanding globally. Yet, the waning effect of existing vaccines has been pointed out, and booster doses of vaccine are considered necessary to maintain preventive effect (*Lancet.* 2021;398:1377-80).

The following possibility was discussed at ICMRA[47]: The composition of vaccines needs to be updated to match SARS-CoV-2 variants, and from the fall of 2023 onwards, a monovalent XBB-containing vaccine is considered a rational choice of vaccination. WHO has expressed concerns that the approved vaccines against Omicron have lower vaccine effectiveness against the XBB lineage, and issued a statement recommending the vaccination against the XBB lineage.[48] Taking into account the above discussions and the epidemic status in Japan, a monovalent vaccine against Omicron subvariant XBB.1.5 is basically used as the vaccine for the fall and winter of 2023 in Japan[49]. Given the situation above, the clinical positioning of Kostaive against the original strain, is inevitably unclear. Rather, obtaining regulatory approval for marketing of Kostaive will be significant for the rapid development of vaccines against new variants in the future.

On the basis of the above, PMDA concluded that Kostaive should be indicated for "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as proposed, similar to the approved SARS-CoV-2 vaccines.

7.R.5 Dosage and administration

The proposed dosage regimen was as follows.

Dosage and Administration (proposed)
Kostaive is suspended in 10 mL of physiological saline (Japanese Pharmacopoeia grade).
Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 4 weeks apart.
Booster dose: A single dose of 0.5 mL is injected intramuscularly.

The Precautions Concerning Dosage and Administration include the following statements:

- Vaccine recipients: Individuals aged ≥18 years
- The primary series should be given twice with caution not to mix-up with other anti-SARS-CoV-2 vaccines. If more than 4 weeks have passed since the first dose, the second dose should be administered as promptly as possible.
- The booster dose should be administered at least 3 months after the previous dose.
- The efficacy and safety of Kostaive have not been established when given as a booster dose to individuals who have received SARS-CoV-2 vaccine other than Coronavirus Modified Uridine RNA Vaccine.

47) ICMRA COVID-19 Omicron variant workshop (https://icmra.info/drupal/en/covid-19/8may2023)
48) Statement on the antigen composition of COVID-19 vaccines (https://www.who.int/news/item/18-05-2023-statement-on-the-antigen-composition-of-covid-19-vaccines)
49) The 51st meeting of the Subcommittee on Immunization and Vaccines of the Health Sciences Council (held on September 19, 2023, Material 1)

PMDA's view:
On the basis of the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety," the clinical positioning of Kostaive, and the dosage regimens of approved SARS-CoV-2 vaccines and other preventive vaccines, the dosage and administration should be modified as shown below and that precautions for the age limit for vaccination and the timing of the booster dose should be described in the "Precautions Concerning Dosage and Administration," as proposed by the applicant.

Dosage and Administration (Underline denotes changes.)
Kostaive is dissolved in 10 mL of physiological saline(Japanese Pharmacopoeia grade).
As the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 4 weeks apart.
As the booster dose, a single dose of 0.5 mL is injected intramuscularly.

7.R.5.1 Dosage and administration in the primary series and the booster dose

The applicant's explanation about the dosage regimen of Kostaive:
Study ARCT-021-01 using ARCT-021, the prototype of Kostaive, demonstrated a favorable safety profile up to the dose of 7.5 μg, but systemic adverse events including Grade 3 events were reported at a dose of 10 μg. Kostaive was therefore used at lower doses. Study ARCT-021-04 also using ARCT-021 demonstrated the following: (1) A higher immunogenicity was observed after the second dose than after the first dose in the primary series; and (2) the immunogenicity after 2 doses of the primary series was comparable between the 5 μg group and the 7.5 μg group; whereas (3) the incidence of Grade ≥2 solicited adverse events tended to be higher in the 7.5 μg group than in the 5 μg group. On the basis of the above, Study ARCT-154-01 was conducted with two 5 μg doses in the primary series. In Study ARCT-154-01, 5 μg (0.5 mL) each of Kostaive was administered intramuscularly twice, 28 days apart, as the primary series to healthy adults aged ≥18 years. Results confirmed the efficacy against COVID-19 and safety.

In Study ARCT-154-J01, as the booster dose, 5 μg (0.5 mL) of Kostaive was administered intramuscularly once to healthy adults aged ≥18 years who had received 3 doses of approved mRNA SARS-CoV-2 vaccines, and received Comirnaty as the third dose at least 3 months before. Results verified the non-inferiority in immunogenicity of the booster dose with Kostaive to Comirnaty, and confirmed the safety.

On the basis of the above, the dosage regimen for Kostaive was the dose of 0.5 mL (5 μg RNA) twice (4 weeks apart) for the primary series and once for the booster dose.

7.R.5.2 Vaccine recipients

The applicant's explanation about the vaccine recipients of Kostaive:

(1) Age limit for vaccination

Taking account of the subject age in Studies ARCT-154-01 and ARCT-154-J01, the primary series and the booster dose of Kostaive should be administered to individuals aged ≥18 years, and the age is included in Precautions Concerning Dosage and Administration.

(2) Vaccination history before vaccination with Kostaive

Efficacy (immunogenicity) and safety of Kostaive were investigated in the following Studies ARCT-154-J01 and ARCT-165-01:

Study ARCT-154-J01: The second booster dose (hereinafter referred to as "the fourth dose") in subjects who had completed the primary series (2 doses) and a booster dose (1 dose).

Study ARCT-165-01: The first booster dose (hereinafter referred to as "the third dose") in subjects who had completed the primary series (2 doses).

GMR and SRR against the original strain at 28 days after the study vaccination were similar between Studies ARCT-154-J01 and ARCT-165-01. There was no significant difference in the safety profile of Kostaive between these studies, as determined from the safety data up to 1 month after vaccination. Taking account of the observations that the immunogenicity and safety in these clinical studies were similar regardless of the number of times of SARS-CoV-2 vaccination before the study, together with the findings on approved RNA vaccines in the same class (*JAMA.* 2023;6:e232598, *MMWR*. 2022;71:971-76), it is acceptable to provide booster doses of Kostaive without any specific limitations to the number of prior SARS-CoV-2 vaccinations. Data are currently unavailable on vaccination with Kostaive in individuals who had received SARS-CoV-2 vaccines other than RNA vaccine (Comirnaty or Spikevax). A large-scale investigation in the UK reported that Comirnaty and Spikevax induced neutralizing antibody response and cellular immune response against SARS-CoV-2, regardless of the type of the vaccine used in the past (*Lancet.* 2021;398:2258-76). These data on approved vaccines suggest the efficacy and safety of the booster dose with Kostaive regardless of the type of the vaccine administered in the past. Nevertheless, the fact that Kostaive has never been administered to individuals with the history of receiving SARS-CoV-2 vaccines other than RNA vaccine will be included in the package insert to raise caution.

PMDA's view:

All of the explanations of the applicant are acceptable. The current situation in Japan shows that the number of completed vaccination varies depending on age, occupation, etc. and is not uniform. It is of clinical significance to make the booster dose with Kostaive available in individuals who have completed the primary series of SARS-CoV-2 vaccines regardless of the number of the booster dose(s).

7.R.5.3 Interval of booster dose

In Study ARCT-154-J01, the applicant investigated the immunogenicity and safety in subjects classified by the interval between the last dose and the booster dose. The subjects of this study were individuals who had received the third dose of Comirnaty, the approved vaccine, ≥3 months before. The median interval [range] between the vaccinations (time from the third dose to the administration of the study vaccine) in the primary analysis population (PPS-1) was 9.7 [4.2, 14.0] months. Table 35 shows the results of immunogenicity in PPS-1, classified by the interval of vaccinations.

Table 35. SARS-CoV-2 neutralizing antibody titer by vaccination interval (Study ARCT-154-J01, PPS-1 population)

	<10 months		≥10 months	
	Kostaive (N = 228)	Comirnaty (N = 200)	Kostaive (N = 157)	Comirnaty (N = 174)
Baseline				
GMT[a)]	901.1 [776.8, 1045.4]	869.4 [722.5, 1046.2]	700.4 [558.0, 879.2]	861.2 [701.1, 1057.7]
28 days after study vaccination				
GMT[b)]	5870.1 [4484.2, 7684.4]	3677.2 [2772.8, 4876.6]	5195.9 [4511.6, 5984.1]	4139.3 [3625.1, 4726.5]
GMFR[a)]	6.36 [5.50, 7.36]	4.08 [3.59, 4.63]	7.23 [5.96, 8.76]	4.74 [4.12, 5.45]
GMR[b)]	1.60 [1.35, 1.89]		1.26 [1.04, 1.52]	
SRR				
n	147	101	104	92
SRR (%)[c)]	64.5 [57.9, 70.7]	50.5 [43.4, 57.6]	66.2 [58.3, 73.6]	52.9 [45.2, 60.5]
Difference in SRR[d)]	14.0 [4.6, 23.1]		13.4 [2.8, 23.6]	

N = Number of subjects analyzed, the number in the brackets indicates two-sided 95% CI.
n = Number of subjects with antibody response. Subjects with antibody response are defined as those who showed a ≥4-fold increase in the neutralizing antibody titer from the level before the booster dose (a half of LLOQ if the titer was below LLOQ).
a) Two-sided 95% CI was calculated based on the assumption of t-distribution in the difference of the logarithmically transformed value of antibody titer or the logarithmically transformed value of the rate of antibody titer increase.
b) ANCOVA with age as the covariate and sex and time from the third dose (<5 months, ≥5 months) as factors
c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
d) Two-sided 95% CI was calculated based on the Miettinen-Nurminen method.

Adverse events were reported in 236 of 245 subjects (96.3%) in the Kostaive group and in 209 of 215 subjects (97.2%) in the Comirnaty group at the interval of <10 months, and in 166 of 175 subjects (94.9%) in the Kostaive group and in 190 of 193 subjects (98.4%) in the Comirnaty group at the interval of ≥10 months.

Solicited local adverse events were reported in 232 of 245 subjects (94.7%) in the Kostaive group and in 206 of 215 subjects (95.8%) in the Comirnaty group at the interval of <10 months, and in 166 of 175 subjects (94.9%) in the Kostaive group and in 189 of 193 subjects (97.9%) in the Comirnaty group at the interval of ≥10 months. Grade ≥3 solicited local adverse events were reported in 1 of 245 subjects (0.4%) in the Kostaive group and in 2 of 215 subjects (0.9%) in the Comirnaty group at the interval of <10 months, and in 2 of 175 subjects (1.1%) in the Kostaive group and in 2 of 193 subjects (1.0%) in the Comirnaty group at the interval of ≥after 10 months.

Solicited systemic adverse events were reported in 160 of 245 subjects (65.3%) in the Kostaive group and in 130 of 215 subjects (60.5%) in the Comirnaty group at the interval of <10 months, and in 116 of 175 subjects (66.3%) in the Kostaive group and in 125 of 193 subjects (64.8%) in the Comirnaty group at the interval of ≥10 months. Grade ≥3 solicited systemic adverse events were reported in 3 of 245 subjects (1.2%) in the Kostaive group and in 3 of 215 subjects (1.4%) in the Comirnaty group at the interval of <10 months, and in 3 of 175 subjects (1.7%) in the Kostaive group and in 4 of 193 subjects (2.1%) in the Comirnaty group at the interval of ≥10 months.

Neutralizing antibody titer in subjects receiving the booster dose at the interval of <5 months or ≥5 months was analyzed (Table 36). The neutralizing antibody (GMT and SRR) was comparable between the groups, although caution is warranted in interpreting the results because of the limited number of the subpopulation receiving the booster dose at the interval of <5 months.

Table 36. SARS-CoV-2-neutralizing antibody titer by vaccination interval (Study ARCT-154-J01, PPS-1 population)

	<5 months		≥5 months	
	Kostaive (N = 8)	Comirnaty (N = 3)	Kostaive (N = 377)	Comirnaty (N = 371)
28 days after study vaccination				
GMT[b)]	5499.9 [2150.0, 14069.4]	5303.8 [1143.5, 24600.1]	5485.4 [5016.2, 5998.4]	3801.0 [3474.5, 4158.0]
GMR[b)]	1.04 [0.16, 6.64]		1.44 [1.27, 1.64]	
SRR				
n	3	0	248	193
SRR (%)[c)]	37.5 [8.5, 75.5]	0.0 [0.0, 70.8]	65.8 [60.8, 70.6]	52.0 [46.8, 57.2]
Difference in SRR[d)]	37.5 [−29.3, 70.6]		13.8 [6.7, 20.7]	

N = Number of subjects analyzed, the number in the brackets indicates two-sided 95% CI.
n = Number of subjects with antibody response. Subjects with antibody response are defined as those who showed a ≥4-fold increase in the neutralizing antibody titer from the level before the booster dose (a half of LLOQ if the titer was below LLOQ).
a) Two-sided 95% CI was calculated based on the assumption of t-distribution in the difference of the logarithmically transformed value of antibody titer or the logarithmically transformed value of the rate of antibody titer increase.
b) ANCOVA with age as the covariate and sex and time from the third dose (<5 months, ≥5 months) as factors
c) Two-sided 95% CI was calculated based on the Clopper-Pearson method.
d) Two-sided 95% CI was calculated based on the Miettinen-Nurminen method.

In some populations (Part 2 and Part 3a) of Study ARCT-154-01, the third dose of Kostaive was administered at 2 months after the second dose of Kostaive (Day 92) [see Section 7.2.1.1]. Neutralizing antibody titer was measured 28 days after the third dose (Day 120). Comparison of data with those before the third dose (Day 92) showed that SRR [two-sided 95% CI] was 76.2% [69.0%, 82.5%] and geometric mean fold rise (GMFR) was 6.4 [5.5, 7.5].

These results suggest that the difference in the interval from the last dose does not lead to any significant difference in the immunogenicity or safety.

PMDA's view:
SARS-CoV-2 infection status in Japan[50)] does not necessitate vaccination every 3 months, and individuals vaccinated ≥3 months before were enrolled in Study ARCT-154-J01, and results did not show any clear difference in the immunogenicity or safety between groups with different vaccination intervals. Also, given that approved RNA vaccines can be administered at ≥3 month intervals, it is acceptable to establish the interval of vaccination with Kostaive at ≥3 months, as proposed by the applicant.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance for Kostaive:
In order to confirm the vaccination safety of Kostaive as the primary series and the booster dose in clinical practice, the applicant plans to conduct a use-result survey (planned sample size 1,250, observation period up to 12 weeks after the last dose). The planned sample size was determined to allow the detection of events (incidence 0.24% [1 of 420 subjects]) observed in the Japanese phase III study (Study ARCT-154-J01) on booster dose. Since the safety profile was similar between after the primary series and after the booster dose, the survey will allow collection of events occurring after the primary series. Given the situation in Japan where approximately 80% of people have already received the primary series, the number of individuals receiving the primary series collected in this survey will be limited.

50) Evaluation of the Latest Infection Status of SARS-CoV-2 Infection (National Institute of Infectious Diseases, http://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/covid-19.html, last accessed on August 4, 2023)

Since the policy of the Japanese government is to use SARS-CoV-2 vaccines against the Omicron subvariant XBB.1.5 lineage from Autumn in 2023, there is no plan to supply Kostaive against the original strain. The applicant plans to conduct the surveillance when the vaccine against the Omicron variant under development using Kostaive as the parent vaccine becomes available for supply.

PMDA's view on the plan of the post-marketing surveillance, etc.
In the clinical studies on Kostaive, the primary series of vaccination was investigated at a certain scale, but only limited data are available on the safety and immunogenicity of the booster dose. After marketing, Kostaive is expected to be used to a broader range of individuals not enrolled in clinical studies [see Section 7.R.3]. The applicant's plan to investigate the safety in clinical practice after the market launch is appropriate.

There are limitations to investigating adverse events with low incidence such as shock, anaphylaxis, and myocarditis/pericarditis in the planned number of vaccine recipients in the surveillance. Nevertheless, the surveillance will allow the evaluation of the incidence of related symptoms and background factors affecting the safety profile. There is thus a certain significance in the surveillance planned as a post-marketing pharmacovigilance activity.

Since Kostaive (against the original strain) is not expected to be used clinically [see Section 7.R.4], the use-result survey will be conducted after the start of the supply for the vaccine product against the prevailing variant, as proposed by the applicant. Given the expected changes in the epidemic situation of COVID-19, variants, and background of vaccine recipients (history of SARS-CoV-2 vaccination, percentage of individuals with or without history of COVID-19), the appropriateness of the surveillance plan, including the planned sample size and observation period should be reconsidered based on the latest information.

In addition to the post-marketing surveillance, the usual pharmacovigilance activities including the collection of Kostaive-related information in Japan and overseas and evaluation based on the collected information are important. The plan for the post-marketing investigation, surveillance, etc., will be finalized also based on the comments from the Expert Discussion.

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 assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

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

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Kostaive has efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that Kostaive has acceptable safety in view of its benefits. Kostaive is thus considered to provide an option for the prevention of disease caused by SARS-CoV-2 infection (COVID-19) as are the cases with approved RNA vaccines against SARS-CoV-2. Separately from the present application, the clinical significance of Kostaive should be evaluated with clinical study results on vaccines against variants to be newly developed on the basis of the marketing approval of Kostaive against the original strain.

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

Review Report (2)

November 8, 2023

Product Submitted for Approval

Brand Name	Kostaive Intramuscular Injection
Non-proprietary Name	Coronavirus (SARS-CoV-2) RNA Vaccine
Applicant	Meiji Seika Pharma Co., Ltd.
Date of Application	April 28, 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 conclusion on issues described in Review Report (1) (Sections "7.R.2 Efficacy," "7.R.4 Clinical positioning and indication," and "7.R.5 Dosage and administration").

PMDA also discussed the following points and took actions as necessary.

1.1 Safety

The PMDA's conclusion in Section "7.R.3 Safety" of the Review Report (1) was supported by the expert advisors. The following comments were raised by the expert advisors:

- Kostaive is the first product to be put into practical use as a pharmaceutical product with replicon-containing RNA as the active ingredient. It is recommended to provide detailed information on the mechanism of action, the possibility of remaining in the body, etc., to vaccine recipients and healthcare professionals
- It is necessary to explain whether the replicon contained in the product exhibits clinical characteristics different from those of approved products such as influence on the long-term safety and duration of efficacy.

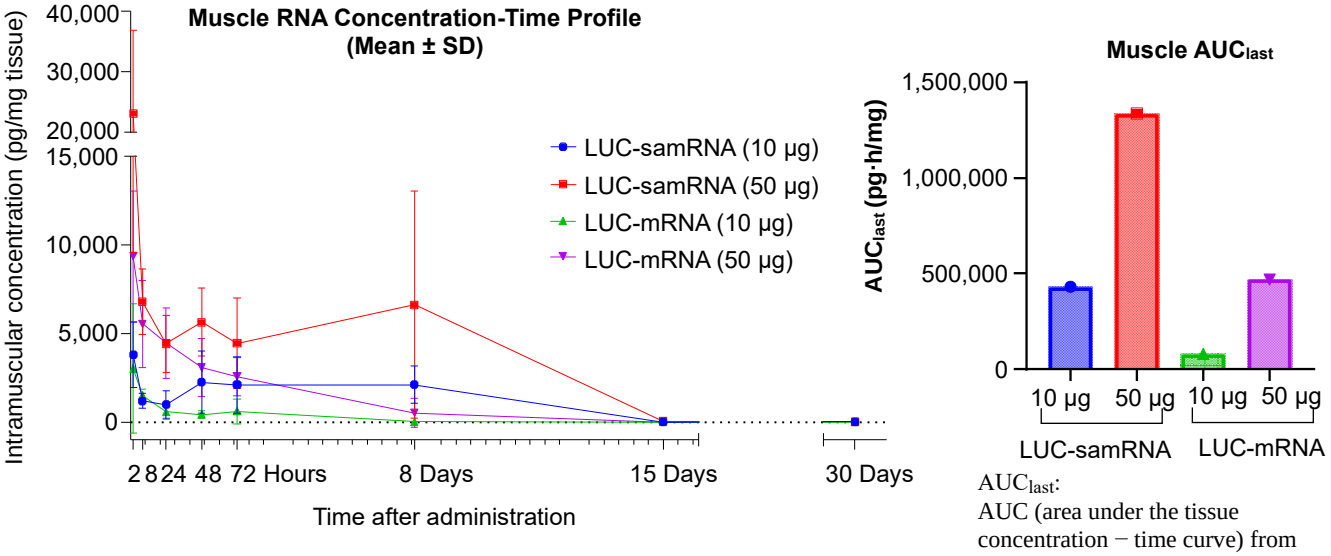
PMDA requested the applicant to include the mechanism of action of Kostaive and basic explanation on replicon in information materials, to which the applicant agreed.

PMDA confirmed the mechanism of action of replicon and its *in vivo* persistence as shown below, from the documents submitted.

As the reference data for pharmacokinetics, the applicant submitted the data of the non-clinical pharmacokinetic study in which mRNA encoding both replicase and luciferase (LUC-samRNA) and mRNA encoding luciferase alone (LUC-mRNA), encapsulated in LNP,[51)] were administered to mice and their *in vivo* persistence was investigated (CTD 4.2.2.3-03).

After the intramuscular administration, the concentration of both RNAs at the injection site decreased over time (Figure 4). Both at 10 µg and 50 µg, LUC-samRNA maintained higher concentrations than LUC-mRNA up to Day 8. Intramuscular concentration of both RNAs decreased after Day 8, and was barely detectable by Day 15 to Day 30 (concentration at Day 30 after 50 µg administration was 19.54 ± 16.64 pg/mg [LUC-mRNA] and 18.83 ± 18.24 [LUC-mRNA], respectively; BLOQ in several animals).

Figure 4. LUC-samRNA and LUC-mRNA concentrations and AUC_{last} in the muscle at the administration site in female BALB/c mice



AUC_{last}:
AUC (area under the tissue concentration − time curve) from time 0 to time of the last measurable concentration

PMDA's view on the basis of Figure 4 and the data of the pharmacokinetic study results on Kostaive (biodistribution following a single intramuscular administration in mice, Figures 1 and 2 in Section 4.2.1 in the Review Report [1]):

The replicon-containing samRNA is maintained at a higher intramuscular concentration compared with the replicon-non-containing samRNA. On the other hand, the intramuscular concentrations of both replicon-containing and non-containing RNAs become extremely low 2 weeks to 1 month after administration, suggesting that the residual time of the replicon-containing RNA in the body is unlikely to be extremely longer than that of the replicon-non-containing RNA.

[51)] The LNP used was the same as that used in vaccines ARCT-021 and ARCT-154.

The active-control vaccine (Comirnaty) used in the Japanese phase III study (Study ARCT-154-J01) is a replicon-non-containing RNA vaccine. Table 37 shows the duration of solicited adverse events. The data do not allow strict comparison of the effect of replicon, as was done for the non-clinical studies, because the amount of RNA per dose is different (5 μg in Kostaive, 30 μg in Comirnaty).

Table 37. Duration of solicited adverse events in the Japanese phase III study (Study ARCT-154-J01) (safety analysis population)

		Kostaive N = 420			Comirnaty N = 408		
		n	Median	[Range]	n	Median	[Range]
Local	Erythema	52	5.0	[2, 17]	85	3.0	[2, 14]
	Swelling	59	3.0	[2, 6]	97	3.0	[2, 14]
	Induration	52	3.0	[2, 8]	81	3.0	[2, 15]
	Tenderness	388	4.0	[1, 29]	391	4.0	[2, 15]
	Pain	352	3.0	[2, 10]	358	3.0	[2, 9]
Systemic	Pyrexia	84	2.0	[1, 3]	76	2.0	[1, 4]
	Arthralgia	112	2.0	[2, 9]	113	2.0	[2, 12]
	Chills	126	2.0	[2, 7]	103	2.0	[1, 4]
	Diarrhoea	28	2.0	[2, 6]	17	2.0	[2, 11]
	Dizziness	25	2.0	[2, 6]	13	2.0	[2, 6]
	Headache	165	2.0	[1, 9]	125	2.0	[2, 9]
	Malaise	188	2.0	[2, 9]	176	2.0	[2, 12]
	Nausea	21	2.0	[2, 5]	16	2.0	[1, 10]
	Vomiting	2	2.0	[2, 2]	2	2.0	[2, 2]
	Myalgia	123	2.0	[2, 9]	100	3.0	[2, 12]

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

No significant difference was observed in the duration of solicited adverse events between the Kostaive group and the Comirnaty group in the clinical study. On the basis of the above results, PMDA considers that the replicon in Kostaive is unlikely to cause extreme persistence or prolongation of the symptoms of adverse reactions compared with approved RNA vaccines.

The incidence of some solicited local adverse events such as erythema, swelling, and induration was lower in the Kostaive group than in the Comirnaty group [see Table 21 in Section 7.2.2 of the Review Report (1)]. However, a marked difference was not observed in the incidence of severe events (Grade ≥3), suggesting that the difference is not to the point of clinical significance. Although the amount of RNA in a single dose of Kostaive is lower than that of the approved vaccines, the submitted study data do not support an improved safety of Kostaive as compared with the approved RNA vaccines.

Immunogenicity data on Day 91 in Study ARCT-154-J01 [see Table 29 in Section 7.R.2.4 of the Review Report (1)] showed a tendency of higher neutralizing antibody titer in the Kostaive group than in the Comirnaty group. The applicant plans to evaluate immunogenicity by conducting the ongoing Japanese and foreign phase III studies (Studies ARCT-154-01 and ARCT-154-J01) up to approximately 12 months. Since the threshold titer of neutralizing antibody necessary for disease prevention remains unclear so far, PMDA considers it difficult to estimate the extent of an increase in VE from the difference in antibody titer. It should be noted that there are limitations to the interpretation of the results even if between-treatment difference is observed in the antibody titer in the clinical study data to be obtained.

1.2 Risk management plan (draft)

The PMDA's conclusion described in Section "7.R.6 Post-marketing investigations" was supported by the expert advisors.

PMDA has concluded that the risk management plan (draft) for Kostaive should include the safety specifications presented in Table 38, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 39 and 40.

Table 38. Safety specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis	• Myocarditis/pericarditis • Vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease(VAERD) • Guillain-Barre syndrome	• Safety in pregnant and lactating women receiving the vaccination

Table 39. 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 • General use-results survey • Post-marketing clinical study (Study ARCT-154-J01)	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for vaccine recipients • Periodical publication of the occurrence of adverse reactions

Table 40. Outline of general use-results survey (draft)

Objective	To evaluate the safety of Kostaive administered as the primary series (the first or second dose) or as the booster dose in clinical practice of the post-marketing setting
Survey method	Central registry system
Population	Individuals aged ≥18 years who receive Kostaive (primary series, booster dose)
Observation period	12 weeks
Planned sample size	1,250 (safety analysis population)
Main survey items	Patient background of vaccine recipients, status of vaccination with Kostaive, concomitant drugs, incidence of adverse events and adverse reactions, development of COVID-19

1.3 Shelf-life of active substance

The applicant submitted the 5'-end capping rate and the stability of poly A chain at 23-months' time point in the long-term testing of the active substance. The applicant detected no significant changes in any of the test parameters including 5'-end capping rate and poly A chain stability up to the time point of 23 months, confirming that the active substance conformed to the specifications. On the basis of the above results, the applicant explained that the shelf life of the active substance should be 23 months when stored at ≤−60°C in [redacted] container with [redacted] cap.

PMDA accepted the applicant's explanation.

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

2.1 PMDA's conclusion on 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 regulatory review based on the submitted product application documents.

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

The new drug application data (CTD 5.3.5.1-01, CTD 5.3.5.1-04) were subjected to a GCP on-site inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its regulatory review based on the submitted product application documents.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration as shown below, 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 (Underline denotes changes.)

The product is dissolved in 10 mL of physiological saline(Japanese Pharmacopoeia grade).
As the primary series, 2 doses (0.5 mL each) are injected intramuscularly, usually 4 weeks apart.
As the booster dose, a single dose of 0.5 mL is injected intramuscularly.

Approval Conditions

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

Appendix

List of Abbreviations

[redacted]	[redacted]
ARCT-021	Vaccine product containing mRNA-2002 as the active substance
ARCT-154	Vaccine product containing mRNA-2105 (active ingredient name, zapomeran) as the active substance (Kostaive)
ARCT-165	Vaccine product containing mRNA-2106 as the active substance
ATX-126	di(pentadecan-8-yl)4,4'-((((3-(dimethylamino)propyl)thio)carbonyl)azanediyl)dibutyrate
BLOQ	Below limit of quantification
BMI	Body mass index
CI	Confidence interval
Comirnaty	Comirnaty Intramuscular Injection, etc. (non-proprietary name, coronavirus [SARS-CoV-2] RNA vaccine) Pfizer Japan Inc.
COVID-19	Coronavirus disease
CQA	Critical quality attribute
CRP	C-reactive protein
CTD	Common technical document
[redacted]	[redacted]
Daichirona	Daichirona for Intramuscular Injection (non-proprietary name, coronavirus [SARS-CoV-2] RNA vaccine) Daiichi Sankyo Company, Ltd.
DNA	Deoxyribonucleic acid
[redacted]	[redacted]
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECMO	Extracorporeal membrane oxygenation
[redacted]	[redacted]
ELISpot	Enzyme-linked immunospot assay
EMA	European Medicines Agency
FAS	Full analysis set
Fc	Fragment crystallizable region
FDA	Food and Drug Administration
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMR	Ratio of Geometric mean titers
GMT	Geometric mean titer
[redacted]	[redacted]
ICMRA	International Coalition of Medicines Regulatory Authorities
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IL-6	Interleukin-6
[redacted]-HPLC	[redacted]
IP-10	Interferon gamma-induced protein 10
ITT	Intention-to-treat
Kostaive	Kostaive Intramuscular Injection (Investigational ingredient code: ARCT-154)
[redacted]	[redacted]
LC-MS/MS	Liquid chromatography-tandem mass spectrometry

LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
MCB	Master cell bank
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
mRNA	Messenger RNA
mRNA-2002	RNA encoding the sequences of VEEV non-structural protein and S-protein of the original strain
mRNA-2105	RNA encoding the sequences of VEEV non-structural protein and S-protein of the original strain with D614G mutation-
mRNA-2106	RNA encoding the sequences of VEEV non-structural protein and S-protein of the Beta variant with D614G mutation
NE	Not evaluable
nsP	Non-structural protein
Nuvaxovid	Nuvaxovid Intramuscular Injection (non-proprietary name, recombinant coronavirus [SARS-CoV-2] vaccine) Takeda Pharmaceutical Company Limited
NZW	New Zealand White
PaO2/ FiO2	Partial pressure of arterial oxygen/Fraction of inspiratory oxygen
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
PT	Preferred term
[redacted]	[redacted]
RNA	Ribonucleic acid
[redacted]-HPLC	[redacted]
[redacted]	[redacted]
samRNA	Self-amplifying mRNA
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus-2
siRNA	Small interfering RNA
Spikevax	Spikevax Intramuscular Injection (non-proprietary name, coronavirus [SARS-CoV-2] RNA vaccine) Moderna Japan Co., Ltd.
SpO2	Saturation of percutaneous oxygen
S-protein	Spike protein
SRR	Seroresponse rate
$TCID_{50}$	Median tissue culture infectious dose
Th1/Th2	T helper type 1/T helper type 2
ULOQ	Upper limit of quantification
[redacted]	[redacted]
UTR	Untranslated region
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease

Vaxzevria	Vaxzevria Intramuscular Injection (non-proprietary name, coronavirus [SARS-CoV-2] vaccine [recombinant chimpanzee adenovirus vector]) AstraZeneca K.K.
VE	Vaccine efficacy
VEEV	Venezuelan equine encephalitis virus
WHO	World Health Organization