Report on the Deliberation Results

June 1, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Jcovden Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Adenovirus Vector)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	May 24, 2021

Results of Deliberation

In its meeting held on May 30, 2022, the Second Committee on New Drugs concluded that the product may be approved with the dosage and administration of "A single dose of 0.5 mL should be administered intramuscularly" and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a 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. Given the current limited information, the applicant is required to promptly collect safety data including information on adverse reactions, after the market launch according to plan, submit the data to the Pharmaceuticals and Medical Devices Agency, and take necessary actions to ensure the proper use of the product.
3. Taking account of more efficacy and safety outcomes to be available in the future, the applicant is required to appropriately instruct physicians to provide vaccine recipients or their legally acceptable representatives with most updated efficacy and safety information of the product in written form, and obtain their written consent through the screening questionnaire or the like prior to the administration of the product.

Review Report

May 16, 2022
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	Jcovden Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Adenovirus Vector)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	May 24, 2021
Dosage Form/Strength	Injection, 0.5 mL per dose containing not less than 8.92 $\log_{10}$ IU of a recombinant, replication-incompetent adenovirus type 26 vector that encodes a modified spike protein of the coronavirus (SARS-CoV-2) as an active ingredient
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Items Warranting Special Mention	Priority review in accordance with "Handling of regulatory review of drugs, medical devices, *in vitro* diagnostics, and regenerative medical products in association with the emergence of COVID-19" (Administrative Notice dated April 13, 2020, by the Pharmaceutical Evaluation Division and Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

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

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

Indication

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

Dosage and Administration

A single dose of 0.5 mL should be administered intramuscularly to persons aged 18 years or older.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Given the current limited information, the applicant is required to promptly collect safety data including information on adverse reactions, after the market launch according to plan, submit the data to the Pharmaceuticals and Medical Devices Agency, and take necessary actions to ensure the proper use of the product.
3. Taking account of more efficacy and safety outcomes to be available in the future, the applicant is required to appropriately instruct physicians to provide vaccine recipients or their legally acceptable representatives with most updated efficacy and safety information of the product in written form, and obtain their written consent through the screening questionnaire or the like prior to the administration of the product.

Attachment

Review Report (1)

April 11, 2022

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	Jcovden Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Adenovirus Vector)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	May 24, 2021
Dosage Form/Strength	Injection, 0.5 mL per dose containing not less than 8.92 log10 IU of a recombinant, replication-incompetent adenovirus type 26 vector that encodes a modified spike protein of the coronavirus (SARS-CoV-2) as an active ingredient

Proposed Indication

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

Proposed Dosage and Administration

A single dose of 0.5 mL should be administered intramuscularly to adults.

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List of Abbreviations

See Appendix.

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

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a single-stranded positive-sense ribonucleic acid (RNA) virus belonging to the family *Coronaviridae* and the order *Nidovirales*. Four types of coronavirus, HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, have been known to routinely infect humans causing common cold. In recent years, two types of zoonotic coronavirus causing severe pneumonia have been identified: Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). In 2019, a new coronavirus infectious and pathogenic in humans, SARS-CoV-2, was identified (*Lancet.* 2020;395:565-74, *Nat Microbiol.* 2020;5:536-44, etc.).

On December 31, 2019, the World Health Organization (WHO) was notified of cases of pneumonia of unknown cause identified in Wuhan City, Hubei Province, China. On January 30, 2020. WHO declared that the outbreak of novel coronavirus-associated pneumonia in Wuhan City as a "Public Health Emergency of International Concern"[1)] (https://www.who.int/news/item/ 30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)- emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) [last accessed on March 13, 2022]). After that, on March 11 2020, WHO declared a global pandemic of Coronavirus disease-19 (COVID-19)[2)] (https://www.who.int/director-general/speeches/detail/ who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [last accessed on March 13, 2022]), and the global pandemic continues since. Although newly developed therapeutic agents and preventive vaccines are currently available in many countries and regions, the world still faces the threat of pandemic with resurgence associated with emerging new variants. As of March 27, 2022, a total of 479,311,589 people across the world have been infected, with a total death toll of 6,122,118 (https://www.who.int/publications/m/item/weekly-epidemiological- update-on-covid-19---29-march-2022 [last accessed on March 30, 2022]). In Japan, as of March 29, 2022, 6,410,635 people have been infected, with a death toll of 27,831 (https://www.mhlw.go.jp/stf/newpage_24876.html [last accessed on March 30, 2022]).

In Japan, as of March 30, 2022, coronavirus modified uridine RNA vaccines (SARS-CoV-2) (brand names, Comirnaty Intramuscular Injection, Comirnaty Intramuscular Injection for 5 to 11 years old, and Spikevax Intramuscular Injection [previously COVID-19 Vaccine Moderna Intramuscular Injection]) and coronavirus (SARS-CoV-2) vaccine (recombinant chimpanzee adenovirus vector) (brand name, Vaxzevria Intramuscular Injection) have been approved for marketing as vaccines for the prevention of disease caused by SARS-CoV-2 infection (COVID-19). These approved vaccines have been used for temporary vaccination under the Immunization Act nationwide. As of March 30, 2022, approximately 80% of the Japanese population have completed the primary series and approximately 40% have completed the booster dose (https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html [last accessed on March 30, 2022]). In addition, multiple therapeutic agents for COVID-19 have been approved for marketing in Japan. As seen outside the country, the COVID-19 pandemic continues in

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

2) https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (last accessed on March 13, 2022)

Japan with highly contagious new variants of SARS-CoV-2 emerged, and possible future emergence of other variants cannot be denied. COVID-19 prevention by vaccination will remain an important public health measure.

Jcovden is a virus vector vaccine containing recombinant adenovirus transfected with a gene encoding the spike protein (S protein) of SARS-CoV-2 (with mutation for stabilization) as an active ingredient. The virus vector of Jcovden is a replication-incompetent recombinant human adenovirus type 26 (Ad26) vector prepared by deleting the E1 gene and a part of the E3 gene from wild-type adenovirus serotype 26 and replacing a part of the E4 gene with the corresponding sequence in adenovirus serotype 5. The S protein of SARS-CoV-2, selected as the target antigen of Jcovden, binds to angiotensin converting enzyme (ACE) 2, the receptor of host cells, and contributes to infection. Jcovden is shown to induce humoral immunity and cellular immunity against the S protein of SARS-CoV-2 (with mutation for stabilization), which is expressed in the body after its administration.

For the development of Jcovden intended for the prevention of COVID-19, clinical studies began in the US and Belgium in July 2020. In Japan, a phase I study (Study VAC31518COV1002 [Study COV1002]) began in August 2020. Jcovden was granted the Emergency Use Authorization in the US (February 2021) and conditionally approved in Europe (March 2021). As of the end of March 2022, Jcovden has been approved or conditionally approved for emergency supply in more than 100 countries or region and WHO. The applicant, Janssen Pharmaceutical K.K., has submitted an application for marketing approval of Jcovden, based on results of clinical studies conducted in and outside Japan.

2. Quality and Outline of the Review Conducted by PMDA

Jcovden is a replication-incompetent recombinant virus vaccine produced by inserting the gene encoding the S protein of SARS-CoV-2 (with mutation for stabilization) into Ad26 vector, a replication-deficient adenovirus vector.

2.1 Active substance

2.1.1 Generation and control of cell substrate

PER.C6 cells, which are the origin of master cell bank (MCB) used for manufacturing Ad26.COV2.S, were transfected with adenovirus E1 gene when the cell line was established. Therefore, E1 gene-deficient replication-incompetent adenovirus can be replicated in the cells. PER.C6 cells were genetically modified to generate the PER.C6 tetracycline repressor (TetR) cell line, which stably expresses the TetR protein that suppresses the expression of the S protein from the Ad26 vector. This cell line was used to prepare MCB and a working cell bank (WCB) is prepared from MCB. Large volume high density cell bank (LVHD-CB) prepared from WCB is used to produce the active substance of Ad26.COV2.S.

Characterizations and purity tests were performed on MCB and WCB of PER.C6 cells as well as MCB, WCB, LVHD-CB, and end of productions cells (EOPC) of PER.C6 TetR cells in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5D. No adventitious agents were detected in the range of test items performed.

MCB, WCB, and LVHD-CB of PER.C6 TetR cells are stored in [redacted]. There is no plan to regenerate a new MCB. New WCB and LVHD-CB are prepared from MCB and WCB, respectively, as necessary.

2.1.2 Preparation and control of virus seed

The master virus seed (MVS) for manufacturing Ad26.COV2.S was prepared using LVHD-CB from the original Ad26 vector with the S protein gene introduced. From the intermediate at the [redacted]th generation obtained from MVS using LVHD-CB, working virus seed (WVS) (at the [redacted]th generation from MVS) was prepared. The virus harvest prepared from WVS using LVHD-CB is used for manufacturing the active substance of Ad26.COV2.S.

MVS and WVS are stored at ≤[redacted]°C. There is no plan to regenerate a new MVS, and new WVSs are prepared from MVS as necessary.

Characterization and purity tests shown in Table 1 were performed on MVS and WVS.

Table 1. Characterization and purity tests performed on MVS and WVS

	Test	MVS	WVS
Characterization	Whole-genome sequence	○	-
	Infectivity titer	○	○
	Transgene expression (identification)	○	○
	Genetic stability (identification)	○ ([redacted]th generation)	-
Purity	Sterility	○	○
	Mycoplasma	○	○
	[redacted]	○	○
	In vitro adventitious virus[a]	○	○
	In vivo adventitious virus[b]	○	○
	Retrovirus[c]	○	-
	Replication-competent adenovirus	○	○

○, Performed; -, Not performed,
a, Test using [redacted] cells, [redacted] cells, and [redacted] cells
b, Test using [redacted] and [redacted]
c, [redacted] method

2.1.3 Manufacturing process

The manufacturing process of the active substance consists of pre-culture, expansion culture, viral production, cell lysis, deoxyribonucleic acid (DNA) precipitation, clarification, anion-exchange chromatography, polishing and buffer exchange, active substance preparation, testing and filling, and cryopreservation. Critical steps are [redacted], [redacted], [redacted], [redacted] as well as [redacted], and [redacted].

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

2.1.4 Safety evaluation of adventitious agents

Biological materials, etc. used in the manufacturing process of active substance include PER.C6 TetR cells (production cells) and bovine milk casein hydrolysate (used in the production of benzonase that is to be added in [redacted]). Both materials have been confirmed to meet the Standards for Biological Ingredients.

Of the cell substrate, the cell banks were tested for purity on the following items: sterility, mycoplasma, [redacted], [redacted], *in vitro* adventitious virus ([redacted] cells and [redacted] cells), *in vivo* adventitious virus ([redacted], [redacted], [redacted], and [redacted]), retrovirus, human-derived virus ([redacted] virus, [redacted] virus, [redacted] virus, [redacted] virus [redacted] and [redacted], [redacted] virus [redacted] and [redacted], [redacted] virus [redacted], [redacted] and [redacted], [redacted] virus, [redacted] virus, and [redacted] virus [redacted]). The presence of adventitious agents was ruled out within the range of test items performed.

Virus seeds were tested for purity as shown in Table 1. The presence of adventitious agents was ruled out within the range of test items performed.

[redacted] prepared from WVS are tested for [redacted], [redacted], and [redacted]; [redacted] after expansion culture are tested for [redacted], [redacted], and [redacted]; and [redacted] after viral production in the manufacturing process of the active substance are tested for [redacted], [redacted], mycoplasma, and *in vitro* adventitious virus. Specifications for the active substance include microbial limit, bacterial endotoxins, and replication-competent adenovirus. In the manufacturing process of the vaccine product, tests for [redacted] and [redacted] are specified as in-process control tests. Specifications for the vaccine product include bacterial endotoxins and sterility.

2.1.5 Manufacturing process development

Table 2 shows major changes in the manufacturing process made during the development of the active substance. The active substance used in non-clinical studies and early clinical studies was manufactured by Process a. The active substance used in clinical studies was manufactured by Process a, b, or c. The active substance contained in the to-be-marketed vaccine product was manufactured by Process f. For each change in the manufacturing process, the pre-change and post-change active substance were shown to have comparable quality attributes by batch analysis and characterization.

Table 2. Major changes in manufacturing process of active substance

Manufacturing process	Changes
From Process a to Process b	• Establishment of [redacted] • Change of [redacted] (change of [redacted])
From Process b to Process c	• Change of conditions in [redacted] process
From Process c to Process d From Process c to Process e	• Change of [redacted] • Change of [redacted] • Scale-up of [redacted] process and [redacted] process • Change of conditions in [redacted] process • Change of [redacted] (change of [redacted])
From Process e to Process f	• Scale-up of [redacted] process and [redacted] process

2.1.6 Characterization

2.1.6.1 Structure, physicochemical and biological properties

The active substance was subjected to characterizations shown in Table 3.

Table 3. Outline of characterization

Item (method)	
Structure	Viral genome sequence (method and), analysis of transgene and (analysis)
Physicochemical properties	Molecular weight of virus ( ), particle size distribution of virus ( ), identity of viral proteins, and assay of degradation products (,)
Biological properties	Level of expressed protein, molecular weight, mass (, , ,)

2.1.6.2 Product-related substances/Product-related impurities

Product-related impurities identified were empty adenovirus or incomplete adenovirus, adenovirus aggregates, degradation products of adenovirus proteins or post-translated proteins, and free adenovirus protein (free hexon). Of these, classified as an important impurity is appropriately controlled by the specifications for the vaccine product ([and]), and or is appropriately controlled by the specifications for the active substance and vaccine product ( ).

2.1.6.3 Process-related impurities

Host cell proteins and host cell DNA were identified as important process-related impurities and are appropriately controlled by the active substance specifications. The other process-related impurities were evaluated for clearance and exposure risk and are all classified as non-important impurities.

2.1.7 Control of active substance

The proposed specifications for the active substance include description, virus identification (polymerase chain reaction [PCR]), viral protein fingerprint, host cell proteins, host cell DNA, transgene expression, infectivity titer, viral particle/infectivity titer ratio, microbial limit, bacterial endotoxins, absence of replication-competent adenovirus, pH, content of polysorbate 80, and assay (viral particle [vector] concentration).

2.1.8 Stability of active substance

Table 4 shows stability studies of the active substance. The long-term testing showed no changes with time throughout the period covered by the submitted test data, and the specifications were met. Results from ongoing tests are presented in the Review Report (2).

Table 4. Stability studies of active substance (as of March 2022)

	Storage condition	Manufacturing process	Number of batches	Test period	Storage form
Long-term[a]	°C ± °C	Process e	4	months	container
		Process f	3	Ongoing	

a Long-term testing (°C ± °C) is ongoing and continued until months.

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

Jcovden is a vial product containing Ad26.COV2.S at a concentration of 9.22 $\log_{10}$ IU/mL per vial. Each vial delivers 5 doses. The labeled volume is 2.5 mL, but the vial contains an overfill to allow the extraction of 5 doses. The excipients of vaccine product are sodium chloride, citric acid hydrate, sodium citrate hydrate, polysorbate 80, hydroxypropyl-β-cyclodextrin, absolute ethanol, sodium hydroxide,

hydrochloric acid, and water for injection. The primary container consists of a glass vial and a chlorobutyl rubber stopper. The secondary package is a paper box.

2.2.2 Manufacturing process

The manufacturing process of the vaccine product consists of buffer preparation, thawing of the active substance, formulation, sterile filtration and filling, labeling, packaging, and storage. The vaccine product is stored in a glass vial at −20°C ± 5°C. Critical steps are [redacted], [redacted], [redacted] and [redacted].

The manufacturing process of the vaccine product has been subjected to process validation on a commercial scale.

2.2.3 Manufacturing process development

Table 5 shows major changes in the manufacturing process made during the development of the vaccine product. The vaccine product manufactured by Process A was used in non-clinical studies. The vaccine product manufactured by Process A or B was used in clinical studies. Processes C and D differ in terms of [redacted] and [redacted] but employ the same manufacturing process. The vaccine product commercialized in Japan is manufactured by Process D. For each change in the manufacturing processes, the pre-change and post-change vaccine products have been shown to be comparable by batch analysis and characterization. Process D was added during the review period, and the currently ongoing comparability exercise is described in the Review Report (2).

Table 5. Major changes in manufacturing process of vaccine product

Manufacturing process	Changes
From Process A to Process B	• Change of [redacted] • [redacted]
From Process B to Process C From Process B to Process D	• Change of [redacted] • [redacted] • Change of [redacted] process (change of [redacted]) • Change of [redacted] (from [redacted] to [redacted])

2.2.4 Control of vaccine product

The proposed specifications for the vaccine product include description (color and turbidity), identification (virus identification and viral protein fingerprint), osmolality, pH, purity (aggregates [mean hydrodynamic radius]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, content of polysorbate 80, titer (transgene expression, infectivity titer, and viral particle/infectivity titer ratio), and assay (viral particle [vector] concentration). In addition, purity (aggregates [polydispersity]) was specified during the review process.

2.2.5 Stability of vaccine product

Table 6 shows stability studies of the vaccine product. The long-term testing showed no over-time changes throughout the period covered by the submitted test data, and the specifications were met. Results from ongoing tests are presented in the Review Report (2).

Table 6. Stability studies of vaccine product (as of March 2022)

	Storage condition	Manufacturing process of active substance	Manufacturing process of vaccine product	Number of batches	Test period	Storage form
Long-term[a]	−20 ± 5°C	Process d	Process C	3	3 months	Glass vial, chlorobutyl rubber stopper
		Process f	Process D	3	Ongoing	
	5 ± 3°C	Process d	Process C	3	3 months	
		Process f	Process D	3	Ongoing	

a, Long-term testing is ongoing and continued until [redacted] months. Of the test items in the long-term testing, [redacted] was tested by [redacted].

2.R Outline of the review conducted by PMDA

Based on the data submitted to date, PMDA concluded that there are no critical quality problems that may affect the evaluation of nonclinical or clinical study results of Jcovden. PMDA instructed the applicant to promptly submit results of the ongoing long-term testing of the active substance and vaccine product as well as study results related to the changes in the manufacturing process of the vaccine product, which was added during the review. The review results are described in the Review Report (2).

2.R.1 Novel excipients

Jcovden (vaccine product) contains hydroxypropyl-β-cyclodextrin, which has not been used for intramuscular vaccination. Based on the precedented use of this excipient for intravenous administration and the following review, PMDA concluded that there are no particular problems.

2.R.1.1 Specifications and stability

Based on the submitted data, PMDA concluded that quality of hydroxypropyl-β-cyclodextrin is appropriately controlled by the established specifications, and its stability has no problems.

2.R.1.2 Safety

Based on the submitted data, PMDA concluded that the amount of hydroxypropyl-β-cyclodextrin used in the proposed vaccine product is unlikely to raise safety issues.

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

The applicant submitted data on primary pharmacodynamics, in the form of results from immunogenicity studies in mice, rabbits, hamsters, and monkeys, and challenge studies in hamsters and monkeys. Although no safety pharmacology studies have been conducted, the effects on the central nervous, cardiovascular, and respiratory systems were evaluated in a repeated-dose toxicity study in rabbits [see Section 5.2].

3.1 Primary pharmacodynamics

3.1.1 Mouse immunogenicity study (CTD 4.2.1.1.1 to 4.2.1.1.2)

3.1.1.1 Investigation of specific immunoglobulin G (IgG) antibodies and neutralizing antibodies (CTD 4.2.1.1.1)

A single dose of Jcovden (10^8, 10^9, or 10^{10} vp/body) or non-transfected Ad26 vector (Ad26 Empty) (10^{10} vp/body), which was used as a negative control, was intramuscularly administered to BALB/c mice (10 females in the Jcovden group, 5 females in the control group), and the immunogenicity against SARS-CoV-2 was assessed. The results are as follows:

- The measurements of S-protein-specific IgG antibodies in serum specimens by enzyme-linked immunosorbent assay (ELISA) 14 and 28 days after administration of the test article revealed dose-dependent production of S-protein-specific IgG antibodies.
- The measurements of neutralizing antibodies against SARS-CoV-2[3)] in serum specimens by microneutralization assay 14 and 28 days after administration of Jcovden (10^{10} vp/body) (Days 14 and 28) revealed increases in neutralizing antibody titer on both days. The neutralizing antibody titer on Day 28 was higher than that on Day 14.

3.1.1.2 Investigation of S-protein-specific IgG subtype and T-cell response (CTD 4.2.1.1.2)

A single dose of Jcovden (10^{10} vp/body), a helper T cell (Th)2 positive control mixture of recombinant S protein[4)] (50 μg/body) and aluminum phosphate ($AlPO_4$) adjuvant (100 μg/body), or a negative control of $AlPO_4$ adjuvant (100 μg/body) was intramuscularly administered to BALB/c mice (6 females each in the Jcovden group and positive control group, 3 females in the negative control group), and the S protein specific T-cell response and S-protein-specific IgG subtype were evaluated. The results are as follows:

- An analysis of IgG subtypes (IgG1 and IgG2a) in serum specimens by ELISA on 13 days after the administration of the test article (Day 13) revealed a higher IgG2a/IgG1 ratio in the Jcovden group than in the positive control group, indicating that Jcovden would induce Th1-dominant immune responses.
- The S-protein-specific T-cell response was investigated by enzyme-linked immunospot (ELISpot), ELISA, and intracellular cytokine staining (ICS). Spleen cells were isolated from each group on Day 13, stimulated with a peptide pool of the wild-type S protein, and analyzed for cytokine responses by ELISpot and ELISA. The analysis revealed that Jcovden increased secretion of Th1-related interferon-gamma (IFN-γ) but did not increase the secretion of Th2-related interleukin (IL)-4, IL-5, or IL-10. In the Th2 positive control, in contrast, Jcovden increased secretion of IL-5 but IFN-γ secretion was undetectable or found at a low concentration. The analysis by ICS revealed that Jcovden induced IFN-γ-producing cluster of differentiation (CD)8+ T cells as well as IL-2-producing CD4+ T cells and CD8+ T cells.

3.1.2 Rabbit immunogenicity study (CTD 4.2.1.1.3)

Two doses of Jcovden (5×10^9 or 5×10^{10} vp/body) or negative control (physiological saline) were intramuscularly administered to New Zealand White (NZW) rabbits (n = 5 females/group) at an interval of 8 weeks, and immunogenicity against SARS-CoV-2 was assessed. The results are as follows:

- IgG antibodies specific to the S protein of SARS-CoV-2 (ELISA): The measurements of S-protein-specific IgG antibodies in serum specimens in each group revealed an increase in S-protein-specific IgG antibody titer over time up to 56 days after the first dose of Jcovden (as of the second dose). A further increase was observed in antibody titer 14 days after the second dose of Jcovden, and the increased titer was maintained until the last measurement point (98 days after the first dose).
- The measurements of neutralizing antibodies against SARS-CoV-2[5)] in serum specimens by microneutralization assay in each group revealed increased neutralizing antibodies against SARS-

3) Clinical isolate SARS-CoV-2/human/NLD/Leiden-0001/2020 (Leiden-0001)
4) Genetically modified S protein that has become soluble by replacement of the transmembrane domain with the foldon trimerization domain of T4 fibritin and stabilized by the same mutation as done in Jcovden
5) Clinical isolate SARS-CoV-2/human/NLD/Leiden-0008/2020 (Leiden-0008) (SARS-CoV-2 variant with glycine (G) substituted for aspartic acid at position 614 in the S protein [D614G variant] [B.1 strain])

CoV-2 over time up to 56 days after the first dose of Jcovden (as of the second dose). In addition, a further increase was observed in neutralizing antibody titer 14 days after the second dose of Jcovden, and the increased titer was kept or slightly decreased until the last measurement point (98 days after the first dose).

- The S-protein-specific T-cell response was investigated using peripheral blood mononuclear cells (PBMCs) from each group by ELISpot. PBMCs were stimulated with a peptide pool of the wild-type S protein and analyzed for cytokine responses. Jcovden increased secretion of Th1-related IFN-γ at either dose 21 days after the first dose, and the secretion further increased 14 days after the second dose. In the negative control group, the secretion of IFN-γ was not observed at any measurement timepoint.

3.1.3 Hamster challenge study (CTD 4.2.1.1.4)

A single dose or 2 doses (28 days apart) of Jcovden (10^9 or 10^{10} vp/body) or negative control (Ad26 Empty) (10^{10} vp/body) were intramuscularly administered to Syrian hamsters (n = 6 males/group), and immune responses to SARS-CoV-2 and disease prevention effect were evaluated. The results are as follows:

- S-protein-specific IgG antibodies and neutralizing antibodies against SARS-CoV-2[6)] in serum specimens 28 days after the single dose or second dose of the test article (just before exposure to SARS-CoV-2) were measured in each group by ELISA and microneutralization assay. Jcovden induced the production of antibodies at either dose.
- Animals were intranasally exposed to SARS-CoV-2[7)] (10^2 $TCID_{50}$/100 μL) 28 days after the single dose or the second dose of Jcovden, and disease prevention effect was investigated. As compared with the negative control, Jcovden at either dose decreased infectious viral loads in the lung and pharyngeal swab specimens and improved histopathological scores in the respiratory tract.[8)]

3.1.4 Monkey challenge study (CTD 4.2.1.1.6)

A single dose of Jcovden (10^{11} vp/body) or negative control (physiological saline) was intramuscularly administered to rhesus monkeys (Jcovden group, n = 6/sex; control group, n = 10/sex), and the immune responses to SARS-CoV-2 and disease prevention effect were evaluated. The results are as follows:

- S-protein-specific IgG antibodies and receptor-binding-domain(RBD)-specific IgG antibodies in serum specimens were measured 12, 27, 35, and 53 days after the administration of the test article by ELISA. Jcovden induced production of both types of IgG antibodies.
- Neutralizing antibodies against gene recombinant SARS-CoV-2[9)] and against pseudovirus[10)] in serum specimens were measured 12 and 27 days after the administration of the test article. Increased neutralizing antibody titer was observed in the Jcovden group on both days. The neutralizing antibody titer 27 days after administration was higher than that 12 days after administration.

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6) The measurement was performed using clinical isolate SARS-CoV-2/human/NLD/Leiden-0001/2020 (Leiden-0001) for the serum specimens 28 days after the single dose and clinical isolate SARS-CoV-2/human/NLD/Leiden-0008/2020 (Leiden-0008) for the serum specimens 28 days after the second dose.

7) Isolate BetaCoV/Munich/BavPat1/2020 (G614)

8) Severity of alveolitis, bronchiolitis, bronchitis, tracheitis, and rhinitis was determined by scoring infiltration of inflammatory cells (4 grades), extent of alveolitis (4 grades), thickening of alveolar wall, alveolar hemorrhage and degree of type II pneumocyte hyperplasia (3 grades), and degrees of bronchial and perivascular cuffing (4 grades) and totaling the scores.

9) Luciferase-and-GFP-expressing SARS-CoV-2 virus prepared by full-length gene recombination using gene sequence of Seattle Washington isolate (D614)

10) Pseudovirus that is based on lentivirus carrying a luciferase reporter gene and expresses the S protein of SARS-CoV-2 derived from Wuhan/WIV04/2019 strain on the membrane surface

- PBMCs from each group 4 and 8 weeks after the administration of the test article (2 weeks after exposure to SARS-CoV-2) were stimulated with a wild-type S protein peptide pool, and S-protein-specific cellular immune responses were evaluated by ELISpot. Jcovden increased the secretion of Th1-related IFN-γ, and the IFN-γ concentration after exposure to SARS-CoV-2 was lower than that before the exposure. In the negative control group, the secretion of IFN-γ was not observed at any measurement timepoint.
- Animals were intranasally or intratracheally exposed to SARS-CoV-2[11] (10^5 $TCID_{50}$) 6 weeks after the single dose of the test article, and disease prevention effect was investigated. As compared with the negative control, Jcovden decreased viral RNA loads in the alveolar lavage fluid and nasal swab fluid, and improved histopathological scores[12] in the respiratory tract, despite no differences in clinical signs.

3.2 Safety pharmacology

No independent safety pharmacology studies of Jcovden were conducted. The safety pharmacology of Jcovden was evaluated based on clinical signs in a repeated intramuscular dose toxicity study in rabbits (CTD 4.2.3.2.1) [see Section 5.2]. The applicant explained that Jcovden had no effect on physiological functions of the cardiovascular, respiratory, and central nervous systems.

3.R Outline of the review conducted by PMDA

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

3.R.1 Mechanism of action

The applicant's explanation about the action mechanism of Jcovden:
Intramuscularly injected Jcovden is considered to infect cells around the administration site, allowing S protein to express in the infected cells. *In vivo* studies of Jcovden showed the production of neutralizing antibodies against SARS-CoV-2 (mice, rabbits, hamsters, and monkeys), Th1-dominant immune responses with a high IgG2a/IgG1 ratio (mice) and increases IFN-γ-producing CD8+ T cells (mice, rabbits, and monkeys), and a certain level of disease prevention against SARS-CoV-2 (hamsters and monkeys).

Based on the above study results, Jcovden is considered to induce *in vivo* production of neutralizing antibodies against SARS-CoV-2 and Th1-dominant immune responses (humoral immunity and cellular immunity), which inhibit SARS-CoV-2 from entering host cells and eliminate SARS-CoV-2 vial particles and SARS-CoV-2-infected cells, thereby helping prevention from SARS-CoV-2 infection.

PMDA accepted the applicant's explanation.

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[11] SARS-CoV-2 USA-WA1/2020 isolate (D614)

[12] A sum of scores given on a scale of 1 to 6 to each of microscopic findings on alveolar edema and infiltration, inflammation and interstitial/wall thickening, monocyte infiltration in the bronchus and perivascular region, macrophage infiltration in the alveolar space and bronchial space, neutrophil infiltration in the alveoli, hyperplasia of bronchiolar alveoli, and hyperplasia of bronchus-associated lymphoid tissue

3.R.2 Induction of neutralizing antibodies against SARS-CoV-2 variants

PMDA asked the applicant to explain the induction of neutralizing antibodies of Jcovden against SARS-CoV-2 variants that have been reported after Jcovden was developed.

The applicant's explanation:

As of March 2, 2022, SARS-CoV-2 variants classified as Variants of Concern (VOCs) in WHO and Japan are Alpha (B.1.1.7 lineage), Beta (B.1.351 lineage), Gamma (P.1 lineage), Delta (B.1.617.2, AY.1, and AY.2 lineages), and Omicron (B.1.1.529, BA.1, and BA.2 lineages) variants. The possibility that all these SARS-CoV-2 variants may escape from the vaccine-induced neutralization antibodies is of concern.

The capability of Jcovden-induced antibodies to neutralize these SARS-CoV-2 variants was investigated using serum specimens from nonhuman primates (NHPs) which received single or 2 doses of Jcovden. Neutralizing antibody titers against the Alpha variant and Mink Cluster 5 variants as well as neutralizing antibody titers against SARS-CoV-2 variants with the S protein gene altered by not only the mutation with glycine at position 614 substituted for aspartic acid (D614G) but also N439K, Y453F, S477N, and N501Y mutations were similar to neutralizing antibody titer against the SARS-CoV-2 variant with glycine (G) substituted for aspartic acid at position 614 in the S protein (D614G variant) (*J Exp Med.* 2021;218:e20202756). The neutralizing antibody titer against the Beta variant, in contrast, was 5 to 8 times lower than that against the D614G variant (*J Exp Med.* 2021;218:e20202756). NHP vaccinated with Jcovden were exposed to the D614G variant (*Nature.* 2020;586:583-8, *J Exp Med.* 2021;218:e20202756) and Beta variant (*Nature.* 2021;596:423-7) to evaluate its prevention of infection. Jcovden prevented infection with the variants investigated.

A report is available from studies on a booster dose of Jcovden after the primary series with a single dose of Jcovden or 2 doses of Comirnaty Intramuscular Injection was given to NHP to investigate its immune response to the Omicron variant and the prevention of infection after exposure to the variant. According to the report, as compared with the negative control, the booster dose of Jcovden significantly increased neutralizing antibody titer against the Omicron variant and significantly decreased the secretion of IFN-γ and viral loads in the upper and lower respiratory tracts 4 days after the exposure to the variant (https://cdn.who.int/media/docs/default-source/blue-print/animal_dan-barouch_whoconsultation_omicron_immunity_14feb2022.pdf?sfvrsn=5540f88c_7 [[last accessed on March 8, 2022]). For Jcovden's induction of neutralizing antibodies against VOCs including the Omicron variant, an additional non-clinical study is currently underway.

Neutralizing antibody titers against the D614G, Alpha, Beta, Gamma, and Delta variants in serum specimens from subjects 71 days after the single dose of Jcovden in foreign Study COV3001 were measured [see Section 7.2.2]. The titer against the Alpha variant was similar to that against the D614G variant, but those against the Beta, Gamma, and Delta variants were 3.6, 3.4, and 1.6 times, respectively, lower than that against the D614G variant (bioRxiv posted online July 1, 2021. doi: https://doi.org/10.1101/2021.07.01.450707, preprint).

For variants that may newly emerge in the future, the applicant plans to monitor the efficacy of Jcovden against each of them by evaluating vaccine-induced neutralizing activities against VOCs in clinical specimens. Then, the applicant plans to evaluate efficacy of Jcovden against new variants by comparing serological analysis results against VOCs with new clinical efficacy data of Jcovden or by examining a correlation between data on the prevention of VOCs-induced infection and neutralizing antibody titers against these variants.

PMDA accepted the applicant's explanation. The discussion about the efficacy of Jcovden against variants continues in Section 7.R.2.5.

3.R.3 Risk of diseases enhancement

Animal studies of vaccines against SARS-CoV and MERS-CoV have revealed a risk of enhanced symptoms after infection in vaccinated animals (risk of vaccine-associated enhanced respiratory disease [VAERD]) as compared with unvaccinated animals (*J Virol.* 2015;89:2995-3007, *Hum Vaccin Immunother.* 2016;12:2351-6). PMDA asked the applicant to explain a risk of VAERD associated with Jcovden.

The applicant's explanation:
The risk of VAERD has been reported with vaccines for not only SARS-CoV and MERS-CoV but also respiratory syncytial virus (RSV) and influenza virus, which cause respiratory diseases. The vaccine-associated worsening of lung lesions in animal models are considered associated with Th2-dominant cytokine production, high CD4+/CD8+ T-cell ratio and other cell infiltration, the production of weakly neutralizing antibodies, and immune complex formation or antibody-dependent enhancement (*J Virol.* 1986;57:721-8, *J Clin Microbiol.* 1986;24:197-202). Various animal studies [see Sections 3.1.1, 3.1.2, 3.1.3, and 3.1.4] show that the administration of Jcovden led to the production of neutralizing antibodies against SARS-CoV-2 and the induction of Th1-dominant humoral immunity and cellular immunity. In Jcovden challenge studies in hamsters and monkeys [see Sections 3.1.3 and 3.1.4], Jcovden did not cause bronchial or bronchiolar inflammation or perivascular infiltration of lymphocytes (monocytes). Alveolar infiltration of eosinophils was not observed either. Accordingly, no events suggestive of lung lesions worsened by Jcovden were observed.

Based on these findings, the risk of Jcovden-induced VAERD is considered low.

PMDA accepted the applicant's explanation. The risk of disease enhancement in human receiving Jcovden is discussed in Section 7.R.3.4.

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

The applicant submitted results of biodistribution studies using Ad26 vector encoding the Clade A envelope protein of HIV type 1 (Ad26.ENVA.01) and Ad26 vector encoding the pre-fusion conformation-stabilized F protein [pre-F] of RSV A2 strain (Ad26.RSV.preF), which were prepared by inserting parts of human immunodeficiency virus (HIV) and RSV genes, respectively, into the same platform Ad26 vector as that used in Jcovden.

4.1 Biodistribution (CTD 4.2.2.3.1 to 4.2.2.3.2)

A single dose of Ad26.ENVA.01 or Ad26.RSV.preF was intramuscularly administered to rabbits to investigate the distribution in various tissues (Table 7).

Table 7. Biodistribution studies of Ad26.ENVA.01 and Ad26.RSV.preF

Test system No. of animals	Route of administration	Observation period (days)	Dose (vp/animal)	Samples	Analytical techniques
Male and female rabbits (NZW) n = 5/sex/time point	Intramuscularly	11, 61, 91	5×10^{10}	Muscle and skin at the administration site, blood, iliac lymph node, mesenteric lymph node, testis, ovary, brain, heart, lung, liver, spleen, kidney, thymus, and bone marrow	Viral genome DNA derived from Ad26.ENVA.01 was measured by quantitative PCR using DNA extracted from each tissue as a sample, and the copy number per μg of DNA sample was calculated. The lower limit of quantification was 50 copies/μg DNA, and the detection limit was 10 copies/μg DNA.
Male and female rabbits (NZW) n = 5/sex/time point	Intramuscularly	11, 90, 120,[a] 180[b]	1×10^{11}	Muscle and skin at the administration site, iliac lymph node, mesenteric lymph node, popliteal lymph node, blood, testis, ovary, brain, heart, lung, liver, spleen, kidney, thymus, and bone marrow	Viral genome DNA derived from Ad26.RSV.preF was measured by quantitative PCR using DNA extracted from each tissue as a sample. The lower limit of quantification was 28.6 copies/μg DNA, and the detection limit was 7.1 copies/μg DNA.

a, On Day 120, only the iliac lymph node, popliteal lymph node, spleen, and skin and muscle at the administration site were subjected to sample preparation.
b, On Day 180, only the iliac lymph node and spleen were subjected to sample preparation.

Ad26.ENVA.01-derived DNA fragments were detected in the muscle at the administration site, adjacent iliac lymph node, spleen, and skin at the administration site. The concentrations of DNA fragments in the muscle at the administration site were 6.1×10^1 to 1.2×10^4 copies/μg DNA (7 of 10 animals; of 10 animals, 7 provided samples containing DNA at the lower limit of quantification or higher) on Day 11 and 1.2×10^2 copies/μg DNA (1 of 10 animals) on Day 91. The concentrations of DNA fragments in the iliac lymph node were 1.2×10^2 to 8.7×10^3 copies/μg DNA (10 of 10 animals) on Day 11 and 5.0×10^1 to 1.8×10^3 copies/μg DNA (2 of 10 animals) on Day 91. The concentrations of DNA fragments in the spleen were 5.0×10^1 to 1.2×10^2 copies/μg DNA (4 of 10 animals) on Day 11, and no DNA fragments were detected on Day 61 and thereafter. In the skin at the administration site, DNA fragments were detected at a concentration of the lower limit of quantification or lower in 1 of 10 animals on Day 11, and no DNA fragments were detected on Day 61 and thereafter.

Ad26.RSV.preF-derived DNA fragments were detected in the skin at the administration site, adjacent iliac lymph node, spleen, popliteal lymph node, and muscle at the administration site. The concentrations of DNA fragments in the skin at the administration site were 3.9×10^1 to 6.3×10^3 copies/μg DNA (4 of 10 animals) on Day 11 and 2.8×10^2 copies/μg DNA (1 of 10 animals) on Day 90, and no DNA fragments were detected on Day 120 and thereafter. The concentrations of DNA fragments in the iliac lymph node were 6.3×10^1 to 3.9×10^2 copies/μg DNA (9 of 10 animals) on Day 11 and 3.8×10^1 copies/μg DNA (1 of 10 animals) on Day 180. The concentrations of DNA fragments in the spleen

were 3.7×10^1 to 1.2×10^2 copies/μg DNA (6 of 10 animals) on Day 11, and on Day 120, DNA fragments were detected in 1 of 10 animals at a concentration below the lower limit of quantification, but no DNA fragments were detected on Day 90 or 180. The concentration of DNA fragments in the popliteal lymph node was 2.9×10^1 copies/μg DNA (1 of 10 animals) on Day 11, and no DNA fragments were detected on Day 90 and thereafter. In the muscle at the administration site, DNA fragments were detected at a concentration of the lower limit of quantification or lower in 1 of 10 animals on Day 11, and no DNA fragments were detected on Day 90 and thereafter.

In either study, no DNA fragments were detected in the other sites at any time point.

4.R Outline of the review conducted by PMDA

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

4.R.1 Non-clinical pharmacokinetics of Jcovden

PMDA asked the applicant to explain reasons for their view that the biodistribution of Jcovden be explainable based on the results of biodistribution studies with Ad26.ENVA.01 and Ad26.RSV.preF prepared by the Ad26 platform technology, which has been also applied to the preparation of Jcovden.

The applicant's explanation:
The Ad26 vector virus used in Jcovden enters host cells through the binding of its viral capsid proteins (fiber and penton) to receptors on the cellular surface (CD46, etc.). Jcovden differs from Ad26.ENVA.01 and Ad26.RSV.preF in the inserted gene expression cassette (transgene and promoter sequence), but the differences would not alter the structure of viral particles, having no impact on tissue tropism. In addition, the Ad26 vector is deficient in the E1 gene region essential for viral replication, and thus once entering a cell, this vector no longer infects or enters the other cells. Actually, Ad26.ENVA.01 and Ad26.RSV.preF are demonstrated to show similar distributions.

Accordingly, the biodistribution of intramuscularly administered Jcovden is presumed to be similar to those of Ad26.ENVA.01 and Ad26.RSV.preF, and thus it is possible to evaluate the biodistribution of Jcovden without conducting a study with Jcovden.

PMDA asked the applicant to explain (a) the elimination of administered Jcovden and of S protein expressed from Jcovden; (b) shedding of Jcovden; (c) transfer of Jcovden into milk and placenta; and (d) risk of recombination between Ad26 vector virus in Jcovden and wild-type adenovirus.

The applicant's explanation:
(a) Elimination of administered Jcovden and S protein expressed from Jcovden
In the biodistribution studies of Ad26.ENVA.01 and Ad26.RSV.preF, Ad26 vector-derived DNA was mostly eliminated from the body 90 or 91 days after the administration of each test article. In some animals (2-4 of 10), DNA fragments were detected at the administration site and adjacent iliac lymph node on Day 90 or 91 and in the iliac lymph node on Day 180. Because of their trace amounts detected, Jcovden-derived DNA, once distributed in the body, is inferred to decrease over time and be eliminated

after a certain period. Although the elimination of S protein expressed from Jcovden has not been investigated, it is considered unlikely to be expressed after the elimination of Jcovden-derived DNA.

(b) Shedding of Jcovden

In a clinical study of recombinant, replication-incompetent, Ad26 vector encoding the GP of EBOV Mayinga variant (Ad26.ZEBOV), a vaccine prepared by inserting a part of an Ebola virus gene into the same platform Ad26 vector as that used in Jcovden, shedding of this vaccine after intramuscular administration was evaluated using nasal swab and urine specimens, but no Ad26 vector-derived DNA fragments were detected. In a clinical study of tetravalent HIV vaccine which is based on recombinant replication incompetent adenovirus serotype 26 (Ad26) vectors that consist of Ad26.Mos1.Gag-Pol, Ad26.Mos2.Gag-Pol, Ad26.Mos1.Env, and Ad26.Mos2S.Env (Ad26.Mos4.HIV), a vaccine prepared by inserting a part of an HIV gene into the same platform Ad26 vector as that used in Jcovden, Ad26 vector-derived DNA fragments were detected in nasal swab and urine specimens from some of the intramuscularly vaccinated subjects, but no infectious viruses were detected in these specimens. Furthermore, in a clinical study of Ad26.RSV.preF, viral vector DNA was detected mainly in the administration site in intramuscularly vaccinated subjects at low concentrations, but its elimination was confirmed by Day 8. In specimens from sites other than the administration site (middle turbinate swabs, throat swabs, rectal swabs, urine, blood, and semen), no infectious viruses were detected. Thus, a trace amount of Ad26 vector-derived DNA was detected in a part of excreta transiently. However, no infectious viruses were detected, indicating no risk of infection through exposure to Jcovden in individuals other than the vaccine recipients.

(c) Transfer of Jcovden into milk and placenta

Transfer of Jcovden into milk was not investigated in the biodistribution studies, but Jcovden is considered unlikely to shed into milk and affect suckling infants because the results of biodistribution studies of Ad26.ENVA.01 and Ad26.RSV.preF showed their limited distribution profiles (the administration site, draining lymph nodes, and spleen). and also on the shedding evaluation in the clinical studies of Ad26.ZEBOV and Ad26.Mos4.HIV, shedding of infectious viruses was not observed. Although transfer of Jcovden into placenta was not investigated in the biodistribution studies, the above-mentioned limited distribution profiles in the biodistribution studies of Ad26.ENVA.01 and Ad26.RSV.preF indicate that Jcovden unlikely to be distributed in the placenta.

(d) Risk of recombination between Ad26 vector virus in Jcovden and wild-type adenovirus

The risk of recombination between Ad26 vector virus in Jcovden and wild-type adenovirus is considered low based on the above-mentioned limited distribution profiles in the biodistribution studies, which indicate that coinfection of a single cell by both viruses is unlikely. A risk evaluation on theoretically possible recombinants indicates that the risk of recombination, if any, would not outweigh pathogenicity of wild-type adenovirus.

PMDA accepted the applicant’s explanation.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted data on toxicity of Jcovden in a form of the results from repeated-dose toxicity and reproductive and developmental toxicity studies.

5.1 Single dose toxicity

No single dose toxicity studies of Jcovden have been conducted. However, toxicity of a single dose of Jcovden (acute toxicity) was evaluated based on results after the first dose in a repeated intramuscular dose toxicity study in rabbits (CTD 4.2.3.2.1) [see Section 5.2]. No deaths occurred after the administration of Jcovden, and erythema, edema, and increased body temperature (+0.5°C) were observed at the administration site.

5.2 Repeated-dose toxicity (CTD 4.2.3.2.1)

The repeated intramuscular dose toxicity study of Jcovden in rabbits was conducted (Table 8). The major findings were inflammatory changes at the administration site.

Table 8. Repeated-dose toxicity study

Test system	Route of administration	Treatment period	Dose (mL/body)	Major findings	NOAEL (mL/body)	Attached document CTD
Male and female rabbits (NZW)	Intramuscularly	4 weeks (every 2 weeks, 3 doses in total) + 3-week withdrawal	0,[a] 1[b,c]	1[d]: Edema and inflammation[e] at the administration site; increases in white blood cells, lymphocytes, and monocytes; and increased fibrinogen and C-reactive protein Reversible	1	4.2.3.2.1

a, 0.9% sodium chloride in water
b, 1×10^{11} vp/dose
c, Administered into 1 site of the femoral muscle at 1 mL
d, IgG specific to S protein was detected on Days 31 and 50.
e, Inflammation was observed around the sciatic nerve adjacent to the administration site, but it was inflammation extended from the administration site, and thus was considered as a rabbit-specific reaction attributable to the administration procedure.

5.3 Genotoxicity

Because the Ad26 vector used in Jcovden has no ability to integrate itself into chromosomes, no genotoxicity studies of Jcovden were conducted.

5.4 Carcinogenicity

Because Jcovden is not intended to be continuously used for ≥6 months in clinical settings, no carcinogenicity studies of Jcovden were conducted.

5.5 Reproductive and developmental toxicity (CTD 4.2.3.5.2.1)

The reproductive and developmental toxicity study was conducted in rabbits (Table 9). Jcovden did not have any effects on parental animals and the next generation.

Table 9. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Treatment period	Dose (mL/body)	Major findings	NOAEL (mL/body)	Attached document CTD
Study for embryo-fetal development as well as effects on pre- and postnatal development, including maternal function	Female rabbit (NZW)	Intramuscularly	Female: 7 days before mating to Gestation Day 20 (3 doses)	0,[a] 1[b,c]	Maternal animal 1[d]: None Embryo and fetus 1[d]: None F1 offspring 1[d]: None	Maternal animal (general toxicity, reproductive capacity): 1 Embryo and fetus: 1 F1 offspring: 1	4.2.3.5.2.1

a, ,0.9% sodium chloride in water
b, 1×10^{11} vp/dose
c, Administered into 1 site of the biceps femoris muscle at 1 mL
d, IgG specific to S protein was detected in maternal animal on Gestation Day 29 (cesarean section group) or Gestation Day 28 (spontaneous delivery group) and Post-partum Day 28 and in fetuses on Gestation Day 29 (cesarean section group) and F1 offspring on Postnatal Day 28.

5.6 Local tolerance

Local tolerance of Jcovden was evaluated based on the results of repeated intramuscular dose toxicity (CTD 4.2.3.2.1) and reproductive and developmental toxicity studies (CTD 4.2.3.5.2.1) in rabbits. Reversible mild edema and inflammation were observed at the administration site of Jcovden [see Section 5.2].

5.R Outline of the review conducted by PMDA

Based on the submitted data and the results of the following reviews, PMDA concluded that there was no particular problem in the toxicity of Jcovden.

5.R.1 Effect on reproductive cells

PMDA asked the applicant to explain a risk of the integration of Jcovden-derived DNA into chromosomes of reproductive cells.

The applicant's explanation:
In general, a risk of inadvertent integration of viral vector into reproductive cells depends on replication competence, integration capability (integration mechanism), and biodistribution of the vector (ICH Considerations "General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors" [Administrative Notice dated June 23, 2015]). The Ad26 vector used in Jcovden has neither viral replication competence nor integration capability into host cell chromosomes. Furthermore, in the biodistribution studies in which Ad26.ENVA.01 and Ad26.RSV.preF prepared by introducing a part of a non-SARS-CoV-2 gene into the same platform Ad26 vector as that used in Jcovden were intramuscularly administered to rabbits, no Ad26 vector-derived DNA was detected in the testis or ovary by quantitative PCR (detection limit; 10 copies/μg DNA for Ad26.ENVA.01, 7.1 copies/μg DNA for Ad26.RSV.preF) [see Section 4.1].

Based on the above, the applicant considers that Jcovden poses no risk of the integration of the viral vector into chromosomes of reproductive cells.

PMDA accepted the applicant's explanation.

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

No applicable studies have been conducted.

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

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

Table 10. Summary of clinical studies for efficacy and safety of Jcovden

Data category	Region	Study ID	Phase	Study population*	Number of subjects enrolled	Dosage regimen**	Objective of study
Evaluation	Japan	COV1002	I	Healthy adults aged ≥20 and ≤55 years and adults aged ≥65 years[a]	250	Two doses of Jcovden 5×10^{10} vp, Jcovden 1×10^{11} vp, or placebo intramuscularly administered 2 months apart.	Safety Immunogenicity
	Foreign	COV1001	I/IIa	Healthy adults aged ≥18 and ≤55 years and adults aged ≥65 years[a]	810	A single dose or 2 doses of Jcovden 5×10^{10} vp, Jcovden 1×10^{11} vp, or placebo intramuscularly administered, if applicable, 2 months apart.	Safety Immunogenicity
	Foreign	COV3001	III	Adults aged ≥18 years[b]	44,325	A single dose of Jcovden 5×10^{10} vp or placebo intramuscularly administered.	Safety Efficacy Immunogenicity
	Foreign	COV3009	III	Adults aged ≥18 years[b]	31,835	Two doses of Jcovden 5×10^{10} vp or placebo, intramuscularly administered 2 months apart.	Safety Efficacy Immunogenicity
Reference	Foreign	COV2001	IIa	Healthy adults aged ≥18 and ≤55 years and adults aged ≥65 years	599	<Cohort 1[c]> • Two doses of Jcovden 1.25×10^{10} vp, Jcovden 2.5×10^{10} vp, Jcovden 5×10^{10} vp, or placebo intramuscularly administered 2 months apart. • A single dose of Jcovden 5×10^{10} vp or Jcovden 1×10^{11} vp and then a single dose of placebo intramuscularly administered 2 months apart. • Two doses of Jcovden 5×10^{10} vp or placebo intramuscularly administered 1 or 3 months apart.	Safety Immunogenicity
				Adolescent aged ≥12 and ≤17 years	33	<Cohort 2[d]> A single dose or 2 doses of Jcovden 2.5×10^{10} vp, Jcovden 5×10^{10} vp, or placebo intramuscularly administered, if applicable, 2 months apart.	
	Foreign	DMID 21-0012[e]	I/II	Adults aged ≥18 years who have completed the vaccination[f] against SARS-CoV-2 ≥12 weeks ago	150	A single dose of Jcovden 5×10^{10} vp intramuscularly administered.	Safety Immunogenicity

*All studies but Study DMID 21-0012 excluded subjects vaccinated against SARS-CoV-2.
**Physiological saline was used as placebo.
a, Including elderly aged ≥65 years who had a stable underlying disease
b, Including subjects with comorbidities potentially related to a risk of severe COVID-19
c, Four months after the second dose of the study vaccine, subjects treated with ≥1 dose of Jcovden received a single dose of Jcovden 1.25×10^{10} vp intramuscularly, and subjects treated only with placebo received a single dose of placebo intramuscularly.
d, Based on reactogenicity data in the sentinel cohort aged 16 to 17 years (who received Jcovden 2.5×10^{10} vp or placebo), subsequent subject enrollment was discontinued.
e, Subjects to receive a booster dose of non-Jcovden SARS-CoV-2 vaccine constituted a study group, but only study results in the Jcovden group were submitted.
f, Comirnaty Intramuscular Injection (2 doses of 30 μg of tozinameran), Spikevax Intramuscular Injection (2 doses of 100 μg of elasomeran), and Jcovden (single dose of Jcovden 5×10^{10} vp)

7.1 Japanese clinical studies

7.1.1 Japanese phase I study (CTD 5.3.1.1.2; Japanese Study COV1002; August 2020 to March 2022; data cut-off on December 28, 2020 [Cohort 1] and February 22, 2021 [Cohort 2])

A randomized, double-blind,[13)] placebo-controlled study was conducted at 3 study centers in Japan to evaluate the safety and immunogenicity of Jcovden in Japanese subjects aged ≥20 and ≤55 years and ≥65 years (target sample size, 250 subjects [200 in the Jcovden group, 50 in the placebo group]).

13) Persons who prepared the study vaccine at study centers were unblinded.

Two doses of the study vaccine (Jcovden 5×10^{10} vp, Jcovden 1×10^{11} vp, or placebo) were intramuscularly administered 2 months apart. This study comprised 2 cohorts of different age brackets (Cohort 1 aged ≥20 and ≤55 years, Cohort 2 aged ≥65 years). Subjects in each cohort were assigned to receive Jcovden 5×10^{10} vp, Jcovden 1×10^{11} vp, or placebo at a ratio of 2:2:1.

All 250 randomized subjects received ≥1 dose of the study vaccine and were included in the full analysis set (FAS) and safety analysis population. The following are a breakdown of all subjects:

Cohort 1: 125 subjects (51 in the Jcovden 5×10^{10} vp group, 50 in the Jcovden 1×10^{11} vp group, 24 in the placebo group)

Cohort 2: 125 subjects (50 in the Jcovden 5×10^{10} vp group, 49 in the Jcovden 1×10^{11} vp group, 26 in the placebo group)

Of these, 249 subjects (125 in Cohort 1, 124 in Cohort 2 [50, 49, and 25]) were included in the per protocol immunogenicity (PPI) population and immunogenicity analysis population, except 1 subject with a protocol deviation potentially affecting immunogenicity results (use of prohibited concomitant drugs). To evaluate the safety data on serious adverse events observed in Study COV3001, which was underway overseas at that time [see Section 7.2.2], all the ongoing clinical studies of Jcovden were suspended (October 11 to 27, 2020). This suspension delayed the second dose of the study vaccine and blood collection scheduled on the same day in Cohort 1 (the second dose of the study vaccine was administered 73 to 88 days after the first dose [median, 78 days]). To minimize an impact of the study suspension, the protocol was revised (third edition, dated December 1, 2020) so that the delayed second dose of the study vaccine by the suspension would not be deemed as a critical protocol deviation potentially affecting the immunogenicity, and the affected subjects remained in the PPI population.

Neutralizing antibody titer against SARS-CoV-2 (by microneutralization assay against wild-type SARS-CoV-2 variant[14]) was evaluated as an immunogenicity endpoint.

Table 11 shows changes in neutralizing antibody titer against SARS-CoV-2 after each dose of the study vaccine.

[14] Derived from the SARS-CoV-2 Victoria/1/2020 strain, isolated from a patient who developed COVID-19 after arriving in Australia from China (Wuhan)

Table 11. GMT of neutralizing antibody titer against SARS-CoV-2 (50% inhibitory dilution) and seroconversion rate[a] (PPI population)

Cohort			Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group			Jcovden 5×10^{10} vp	Jcovden 1×10^{11} vp	Placebo	Jcovden 5×10^{10} vp	Jcovden 1×10^{11} vp	Placebo
Baseline		Subjects analyzed (n)	51	50	24	50	49	25
		GMT [two-sided 95% CI]	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
After the first dose	14 days	Subjects analyzed	50	50	24	50	49	25
		GMT [two-sided 95% CI]	277 [225, 342]	375 [277, 509]	<LLOQ	152 [120, 193]	204 [156, 267]	<LLOQ
		Subjects with seroconversion (n)	50	47	2	45	44	1
		Seroconversion rate (%) [two-sided 95% CI][b]	100 [93, 100]	94 [83, 99]	8 [1, 27]	90 [78, 97]	90 [78, 97]	4 [0, 20]
	28 days	Subjects analyzed (n)	50	49	24	50	49	25
		GMT [two-sided 95% CI]	269 [228, 318]	375 [306, 460]	<LLOQ	311 [259, 374]	405 [323, 507]	<LLOQ
		Subjects with seroconversion	49	47	0	49	49	0
		Seroconversion rate (%) [two-sided 95% CI][b]	98 [89, 100]	96 [86, 100]	0 [0, 14]	98 [89, 100]	100 [93, 100]	0 [0, 14]
After the second dose	14 days	Subjects analyzed (n)	43	31	23	48	45	23
		GMT [two-sided 95% CI]	1049 [828, 1329]	1470 [1156, 1870]	<LLOQ	504 [404, 627]	651 [501, 847]	<LLOQ
		Subjects with seroconversion (n)	43	31	1	48	45	0
		Seroconversion rate (%) [two-sided 95% CI][b]	100 [92, 100]	100 [89, 100]	4 [0, 22]	100 [93, 100]	100 [92, 100]	0 [0, 15]
	28 days	Subjects analyzed (n)	43	31	23	48	45	23
		GMT [two-sided 95% CI]	1088 [817, 1449]	1671 [1155, 2418]	<LLOQ	429 [335, 550]	478 [374, 610]	<LLOQ
		Subjects with seroconversion (n)	43	31	1	48	45	0
		Seroconversion rate (%) [two-sided 95% CI][b]	100 [92, 100]	100 [89, 100]	4 [0, 22]	100 [93, 100]	100 [92, 100]	0 [0, 15]

Lower limit of quantification (LLOQ) was 58.
a, Percentage of subjects with the titer changed from below the LLOQ to equal to or above the LLOQ or increased ≥4 times from baseline
b, Clopper-Pearson method

For the safety evaluation, the observation periods were specified as below. Severity of adverse events was assessed in accordance with a partially modified version of the severity classification (Tables 67 to 69 [see Section 11.1]) in the Food and Drug Administration (FDA) guidance for toxicity grading scale in clinical studies of preventive vaccines (Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007).[15)]

- Solicited adverse events (local [injection site pain and tenderness, erythema, induration, and swelling] and systemic [fatigue, headache, nausea, myalgia, and pyrexia (body temperature ≥38°C)]): for 7 days after each dose of the study vaccine (collected from subject diaries)
- Unsolicited adverse events (excluding solicited adverse events): for 28 days after each dose of the study vaccine
- Serious adverse events: for 1 year after the first dose of the study vaccine

Tables 12 and 13 show solicited adverse events observed within 7 days after each dose of the study vaccine.

15) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials | FDA [[last accessed on March 31, 2022]

Table 12. Solicited adverse events (localized) observed within 7 days after each dose of study vaccine (FAS)

After the first dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 51)	Jcovden 1×10^{11} vp (n = 50)	Placebo (n = 24)	Jcovden 5×10^{10} vp (n = 50)	Jcovden 1×10^{11} vp (n = 49)	Placebo (n = 26)
Injection site pain and tenderness	42 (82.4%)	43 (86.0%)	2 (8.3%)	18 (36.0%)	23 (46.9%)	1 (3.8%)
Injection site erythema	3 (5.9%)	1 (2.0%)	0	1 (2.0%)	1 (2.0%)	0
Injection site induration	0	3 (6.0%)	0	0	1 (2.0%)	0
Injection site swelling	1 (2.0%)	2 (4.0%)	0	0	2 (4.1%)	0
After the second dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 43)	Jcovden 1×10^{11} vp (n = 31)	Placebo (n = 23)	Jcovden 5×10^{10} vp (n = 48)	Jcovden 1×10^{11} vp (n = 45)	Placebo (n = 24)
Injection site pain and tenderness	36 (83.7%)	24 (77.4%)	0	16 (33.3%)	18 (40.0%)	2 (8.3%)
Injection site erythema	1 (2.3%)	1 (3.2%)	0	1 (2.1%)	1 (2.2%)	0
Injection site induration	1 (2.3%)	1 (3.2%)	0	0	2 (4.4%)	0
Injection site swelling	1 (2.3%)	1 (3.2%)	0	0	3 (6.7%)	0

Number of subjects with events (incidence)

Table 13. Solicited adverse events (systemic) observed within period of 7 days after each dose of study vaccine (FAS)

After the first dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 51)	Jcovden 1×10^{11} vp (n = 50)	Placebo (n = 24)	Jcovden 5×10^{10} vp (n = 50)	Jcovden 1×10^{11} vp (n = 49)	Placebo (n = 26)
Fatigue	37 (72.5%)	44 (88.0%)	1 (4.2%)	11 (22.0%)	17 (34.7%)	4 (15.4%)
Myalgia	34 (66.7%)	37 (74.0%)	2 (8.3%)	7 (14.0%)	13 (26.5%)	0
Headache	27 (52.9%)	37 (74.0%)	0	8 (16.0%)	12 (24.5%)	0
Pyrexia[a]	13 (25.5%)	37 (74.0%)	0	2 (4.0%)	5 (10.2%)	0
Nausea	8 (15.7%)	7 (14.0%)	0	4 (8.0%)	3 (6.1%)	0
After the second dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 43)	Jcovden 1×10^{11} vp (n = 31)	Placebo (n = 23)	Jcovden 5×10^{10} vp (n = 48)	Jcovden 1×10^{11} vp (n = 45)	Placebo (n = 24)
Fatigue	20 (46.5%)	19 (61.3%)	0	5 (10.4%)	8 (17.8%)	3 (12.5%)
Myalgia	20 (46.5%)	14 (45.2%)	0	11 (22.9%)	7 (15.6%)	3 (12.5%)
Headache	14 (32.6%)	10 (32.3%)	0	2 (4.2%)	4 (8.9%)	1 (4.2%)
Pyrexia[a]	3 (7.0%)	10 (32.3%)	0	0	0	0
Nausea	5 (11.6%)	4 (12.9%)	0	0	1 (2.2%)	0

Number of subjects with events (incidence)
a, ≥38°C (oral or axillary temperature)

The incidences of unsolicited adverse events and adverse reactions observed within 28 days after each dose of the study vaccine were 41.2% (21 of 51) and 23.5% (12 of 51) in the Jcovden 5×10^{10} vp group, 46.0% (23 of 50) and 38.0% (19 of 50) in the Jcovden 1×10^{11} vp group, and 12.5% (3 of 24) and 0% (0 of 24) of subjects in the placebo group in Cohort 1; and 34.0% (17 of 50) and 14.0% (7 of 50) in the Jcovden 5×10^{10} vp group, 30.6% (15 of 49) and 6.1% (3 of 49) of subjects in the Jcovden 1×10^{11} vp group, and 15.4% (4 of 26) and 15.4% (4 of 26) in the placebo group in Cohort 2. Tables 14 and 15 show unsolicited adverse events observed in ≥2 subjects in any group and unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out.

Table 14. Unsolicited adverse events observed in ≥2 subjects in any group within 28 days after each dose of study vaccine (FAS)

After the first dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 51)	Jcovden 1×10^{11} vp (n = 50)	Placebo (n = 24)	Jcovden 5×10^{10} vp (n = 50)	Jcovden 1×10^{11} vp (n = 49)	Placebo (n = 26)
Arthralgia	2 (3.9%)	4 (8.0%)	0	0	0	0
Diarrhoea	2 (3.9%)	3 (6.0%)	0	0	0	0
Eczema	2 (3.9%)	0	0	0	1 (2.0%)	0
Vertigo	1 (2.0%)	1 (2.0%)	0	0	2 (4.1%)	0
Headache	1 (2.0%)	2 (4.0%)	0	0	1 (2.0%)	0
Cough	0	2 (4.0%)	0	0	0	1 (3.8%)
Myalgia	0	2 (4.0%)	0	1 (2.0%)	0	0
Decreased appetite	0	2 (4.0%)	0	0	1 (2.0%)	0
Pruritus	0	2 (4.0%)	0	0	0	0
Administration site pruritus	0	1 (2.0%)	0	3 (6.0%)	1 (2.0%)	2 (7.7%)
Rhinorrhoea	0	1 (2.0%)	0	1 (2.0%)	3 (6.1%)	1 (3.8%)
Osteoarthritis	0	0	0	2 (4.0%)	0	0
Urticaria	0	0	0	2 (4.0%)	0	0
Musculoskeletal stiffness	0	0	0	0	2 (4.1%)	0
After the second dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 43)	Jcovden 1×10^{11} vp (n = 31)	Placebo (n = 23)	Jcovden 5×10^{10} vp (n = 48)	Jcovden 1×10^{11} vp (n = 45)	Placebo (n = 24)
Administration site pruritus	2 (4.7%)	1 (3.2%)	0	2 (4.2%)	0	1 (4.2%)
Diarrhoea	2 (4.7%)	0	0	0	0	0
Fatigue	2 (4.7%)	0	0	0	0	0
Headache	2 (4.7%)	0	0	0	0	0

Number of subjects with events (incidence)

Table 15. Unsolicited adverse events observed in ≥2 subjects in any group within 28 days after each dose of study vaccine for which a causal relationship to study vaccine could not be ruled out (FAS)

After the first dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 51)	Jcovden 1×10^{11} vp (n = 50)	Placebo (n = 24)	Jcovden 5×10^{10} vp (n = 50)	Jcovden 1×10^{11} vp (n = 49)	Placebo (n = 26)
Arthralgia	1 (2.0%)	4 (8.0%)	0	0	0	0
Diarrhoea	1 (2.0%)	2 (4.0%)	0	0	0	0
Cough	0	2 (4.0%)	0	0	0	1 (3.8%)
Myalgia	0	2 (4.0%)	0	0	0	0
Headache	0	2 (4.0%)	0	0	0	0
Decreased appetite	0	2 (4.0%)	0	0	0	0
Administration site pruritus	0	1 (2.0%)	0	3 (6.0%)	1 (2.0%)	2 (7.7%)
Rhinorrhoea	0	1 (2.0%)	0	0	0	1 (3.8%)
Musculoskeletal stiffness	0	0	0	0	2 (4.1%)	0
After the second dose						
Cohort	Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
Group (Subjects analyzed)	Jcovden 5×10^{10} vp (n = 43)	Jcovden 1×10^{11} vp (n = 31)	Placebo (n = 23)	Jcovden 5×10^{10} vp (n = 48)	Jcovden 1×10^{11} vp (n = 45)	Placebo (n = 24)
Administration site pruritus	2 (4.7%)	1 (3.2%)	0	2 (4.2%)	0	1 (4.2%)
Arthralgia	1 (2.3%)	3 (9.7%)	0	0	0	0

Number of subjects with events (incidence)

As of the data cut-off date, serious adverse events were observed in 1 subject (sudden hearing loss) in the Jcovden 5×10^{10} vp group in Cohort 1 and in 1 subject (intervertebral disc protrusion) in the Jcovden 1×10^{11} vp group in Cohort 2, and a causal relationship to the study vaccine was ruled out for both events. Outcomes of these events resolved and were resolving. There were neither adverse events leading to study discontinuation nor deaths.

7.2 Foreign clinical studies

7.2.1 Foreign phase I/II study (CTD 5.3.1.1.1; Foreign Study COV1001; ongoing since July 2020; data cut-off on October 30, 2020 [Cohort 1a] and December 14, 2020 [Cohort 1b and Cohort 3])

A randomized, double-blind,[16] placebo-controlled study was conducted at 12 study centers in Belgium and the US to evaluate the safety and immunogenicity of Jcovden in adults aged ≥18 and ≤55 years and ≥65 years (target sample size, 1,045 subjects [860 in the Jcovden group, 185 in the placebo group]).

A single dose or two doses of the study vaccine (Jcovden 5×10^{10} vp, Jcovden 1×10^{11} vp, or placebo) were intramuscularly administered, where applicable, 2 months apart. This study comprised multiple cohorts of different age brackets (Cohorts 1 and 2 aged ≥18 and ≤55 years, Cohort 3 aged ≥65 years). Table 16 shows dosage regimens in each group by cohort, and in Cohorts 1 and 3, subjects were assigned to group of the 5 different dosage regimens. In Cohort 2, the study was initiated after the dose had been selected based on interim analysis results in Cohort 1a. For this application, analysis results in Cohorts 1 and 3 excluding those in Cohort 2 were submitted.

Table 16. Dosage regimens by cohort in Study COV1001

Cohort	Group	First dose (Day 1)	Second dose (Day 57)	Target sample size
Cohorts 1* and 3	Jcovden 5×10^{10} vp × 2 doses	Jcovden 5×10^{10} vp	Jcovden 5×10^{10} vp	Cohort 1a: 75 per group Cohort 1b: 5 per group Cohort 3: 75 per group
	Jcovden 5×10^{10} vp × 1 dose	Jcovden 5×10^{10} vp	Placebo	
	Jcovden 1×10^{11} vp × 2 doses	Jcovden 1×10^{11} vp	Jcovden 1×10^{11} vp	
	Jcovden 1×10^{11} vp × 1 dose	Jcovden 1×10^{11} vp	Placebo	
	Placebo	Placebo	Placebo	
Cohort 2a	Jcovden 5×10^{10} vp × 1 dose (4 groups**)	Jcovden 5×10^{10} vp	-	120
	Placebo	Placebo	-	15
Cohort 2b	Jcovden 5×10^{10} vp × 2 doses (4 groups**)	Jcovden 5×10^{10} vp	Jcovden 5×10^{10} vp	120
	Placebo	Placebo	Placebo	15

*Consisting of Cohort 1a and Cohort 1b for exploratory immunogenicity evaluation (epitope mapping, characterization of induced antibodies, etc.)

**A single dose of Jcovden 5×10^{10} vp was administered 6, 12, or 24 months after the last dose (the first dose of the study vaccine in Cohort 2a or the second dose of the study vaccine in Cohort 2b) in 3 groups (placebo was administered at the time point when no dose of Jcovden was scheduled); and placebo was administered at all time points of 6, 12, and 24 months after the last dose (the first dose of the study vaccine in Cohort 2a or the second dose of the study vaccine in Cohort 2b) in 1 group.

A total of 380 subjects were randomized to Cohort 1b, 25 subjects to Cohort 1b, and 405 subjects to Cohort 3. Of these, 377 subjects in Cohort 1a (77 in the Jcovden 5×10^{10} vp × 2-dose group, 75 in the Jcovden 5×10^{10} vp × 1-dose group, 75 in the Jcovden 1×10^{11} vp × 2-dose group, 73 in the Jcovden 1×10^{11} vp × 1-dose group, 77 in the placebo group), 25 subjects in Cohort 1b (5, 5, 5, 5, 5), and 403 subjects in Cohort 3 (81, 80, 82, 79, 81) received ≥1 dose of the study vaccine and were included in the FAS and safety analysis population. Of these, 369 subjects in Cohort 1a (74, 75, 74, 71, 75) and 398 subjects in Cohort 3 (79, 80, 82, 78, 79) who had no protocol deviation potentially affecting on immunogenicity results and provided immunogenicity data were included in the PPI population and immunogenicity analysis population. Neutralizing antibody titer against SARS-CoV-2 was measured in 125 subjects (25 per group)[17] in each cohort randomly sampled by a predetermined procedure. To evaluate the safety data on serious adverse events observed in Foreign Study COV3001, which was underway at that time [see Section 7.2.2], all ongoing clinical studies of Jcovden were suspended

16) Persons who prepared the study vaccine at a study center were unblinded.
17) Because eligibility of an US testing facility for neutralizing antibody measurements was not confirmed, only subjects at the study centers in Belgium were subjected to random sampling to form the analysis subset.

(October 11 to 27, 2020). This suspension delayed the second dose of the study vaccine and blood collection scheduled on the same day in Cohort 3, except the first enrolled 15 subjects (the second dose of the study vaccine was administered 78 to 107 days after the first dose [median 87 days]). To minimize the impact of the study suspension, the protocol was revised (seventh edition, dated November 3, 2020) so that the delayed second dose of the study vaccine by the suspension would not be deemed as a critical protocol deviation potentially affecting the immunogenicity and the affected subjects remained in the PPI population.

Neutralizing antibody titer against SARS-CoV-2 in Cohorts 1a and 3 (by microneutralization assay against wild-type SARS-CoV-2 variant[18)]) was evaluated as an immunogenicity endpoint.

Tables 17 and 18 show changes in neutralizing antibody titer against SARS-CoV-2 after each dose of the study vaccine in Cohorts 1a and 3.

Table 17. GMT of neutralizing antibody titer against SARS-CoV-2 (50% inhibitory dilution) and seroconversion rate[a] (Cohort 1a, PPI population)

Group			Jcovden 5×10^{10} vp × 2 doses	Jcovden 5×10^{10} vp × 1 dose	Jcovden 1×10^{11} vp × 2 doses	Jcovden 1×10^{11} vp × 1 dose	Placebo
Study vaccine (top, first dose/bottom, second dose)			Jcovden 5×10^{10} vp Jcovden 5×10^{10} vp	Jcovden 5×10^{10} vp Placebo	Jcovden 1×10^{11} vp Jcovden 1×10^{11} vp	Jcovden 1×10^{11} vp Placebo	Placebo Placebo
Baseline		Subjects analyzed (n)	25	25	25	25	25
		GMT [two-sided 95% CI]	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
After the first dose of study vaccine	28 days	Subjects analyzed (n)	25	24	25	25	25
		GMT [two-sided 95% CI]	224 [168, 298]	224 [158, 319]	354 [220, 571]	215 [169, 273]	<LLOQ
		Subjects with seroconversion (n)	22	23	23	24	0
		Seroconversion rate (%) [two-sided 95% CI][b]	88 [69, 97]	96 [79, 100]	92 [74, 99]	96 [80, 100]	0 [0, 14]
After the second dose of study vaccine	14 days	Subjects analyzed (n)	24	24	25	24	22
		GMT [two-sided 95% CI]	827 [651, 1052]	321 [237, 434]	1266 [913, 1757]	388 [303, 497]	<LLOQ
		Subjects with seroconversion (n)	24	24	25	24	1
		Seroconversion rate (%) [two-sided 95% CI][b]	100 [86, 100]	100 [86, 100]	100 [86, 100]	100 [86, 100]	5 [0, 23]
	28 days	Subjects analyzed (n)	24	24	24	24	22
		GMT [two-sided 95% CI]	849 [664, 1086]	338 [230, 496]	1229 [886, 1706]	377 [283, 503]	<LLOQ
		Subjects with seroconversion (n)	24	24	24	24	1
		Seroconversion rate (%) [two-sided 95% CI][b]	100 [86, 100]	100 [86, 100]	100 [86, 100]	100 [86, 100]	5 [0, 23]

Lower limit of quantification (LLOQ) was 58.
a, Percentage of subjects with the titer changed from below the LLOQ to equal to or above the LLOQ or increased ≥4 times from baseline
b, Clopper-Pearson method

18) Derived from the SARS-CoV-2 Victoria/1/2020 strain, isolated from a patient who had COVID-19 after arriving in Australia from China (Wuhan)

Table 18. GMT of neutralizing antibody titer against SARS-CoV-2 (50% inhibitory dilution) and seroconversion rate[a] (Cohort 3, FAS*)

Group			Jcovden 5×10^{10} vp × 2 doses	Jcovden 5×10^{10} vp × 1 dose	Jcovden 1×10^{11} vp × 2 doses	Jcovden 1×10^{11} vp × 1 dose	Placebo
Study vaccine (top, first dose/bottom, second dose)			Jcovden 5×10^{10} vp / Jcovden 5×10^{10} vp	Jcovden 5×10^{10} vp / Placebo	Jcovden 1×10^{11} vp / Jcovden 1×10^{11} vp	Jcovden 1×10^{11} vp / Placebo	Placebo / Placebo
Baseline		Subjects analyzed (n)	25	24	25	25	25
		GMT [two-sided 95% CI]	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
After the first dose of study vaccine	14 days	Subjects analyzed (n)	12	11	14	11	12
		GMT [two-sided 95% CI]	242 [110, 532]	184 [98, 343]	209 [121, 361]	133 [71, 249]	<LLOQ
		Subjects with seroconversion (n)	10	10	13	8	0
		Seroconversion rate (%) [two-sided 95% CI][b]	83 [52, 98]	100 [69, 100]	93 [66, 100]	73 [39, 94]	0 [0, 26]
	28 days	Subjects analyzed (n)	25	25	25	25	25
		GMT [two-sided 95% CI]	298 [200, 444]	258 [163, 410]	261 [168, 406]	173 [132, 225]	<LLOQ
		Subjects with seroconversion (n)	24	23	21	23	0
		Seroconversion rate (%) [two-sided 95% CI][b]	96 [80, 100]	96 [79, 100]	84 [64, 95]	92 [74, 99]	0 [0, 14]
After the second dose of study vaccine	14 days	Subjects analyzed (n)	3	3	3	3	3
		GMT [two-sided 95% CI]	658 [<LLOQ, 23233]	349 [<LLOQ, 17219]	771 [126, 4721]	289 [81, 1029]	<LLOQ
		Subjects with seroconversion (n)	3	3	3	3	0
		Seroconversion rate (%) [two-sided 95% CI][b]	100 [29, 100]	100 [29, 100]	100 [29, 100]	100 [29, 100]	0 [0, 71]

Lower limit of quantification (LLOQ) was 58.
*In light of the second dose of the study vaccine in many subjects delayed by the suspension, the analysis was performed on the FAS (including subjects who received the second dose of the study vaccine beyond the predetermined period).
a, Percentage of subjects with the titer changed from below the LLOQ to equal to or above the LLOQ or increased ≥4 times from baseline
b, Clopper-Pearson method

The observation periods were specified as follows. Severity of adverse events was assessed in accordance with Tables 67 to 69 [see Section 11.1].

- Solicited adverse events (local [injection site pain and tenderness, erythema, and swelling] and systemic [fatigue, headache, nausea, myalgia, and pyrexia (body temperature ≥38°C)]): for 7 days after each dose of the study vaccine (collected from subject diaries)
- Unsolicited adverse events (excluding solicited adverse events): for 28 days after each dose of the study vaccine
- Serious adverse events: for 1 year after the last dose of the study vaccine

Tables 19 and 20 show solicited adverse events observed within 7 days after each dose of the study vaccine in Cohorts 1a and 3. Trends of solicited adverse events in Cohort 1b were similar to those in Cohorts 1a and 3.

Table 19. Solicited adverse events observed within 7 days after each dose of study vaccine (Cohort 1a, FAS)

First dose						
Group (Subjects analyzed)		Jcovden 5×10^{10} vp × 2 doses (n = 77)	Jcovden 5×10^{10} vp × 1 dose (n = 75)	Jcovden 1×10^{11} vp × 2 doses (n = 75)	Jcovden 1×10^{11} vp × 1 dose (n = 73)	Placebo (n = 77)
Study vaccine		Jcovden 5×10^{10} vp	Jcovden 5×10^{10} vp	Jcovden 1×10^{11} vp	Jcovden 1×10^{11} vp	Placebo
Local	Injection site pain and tenderness	48 (62.3%)	49 (65.3%)	57 (76.0%)	59 (80.8%)	7 (9.1%)
	Injection site swelling	2 (2.6%)	0	3 (4.0%)	2 (2.7%)	0
	Injection site erythema	1 (1.3%)	0	1 (1.3%)	1 (1.4%)	0
Systemic	Fatigue	36 (46.8%)	36 (48.0%)	53 (70.7%)	49 (67.1%)	11 (14.3%)
	Headache	34 (44.2%)	33 (44.0%)	45 (60.0%)	54 (74.0%)	12 (15.6%)
	Myalgia	28 (36.4%)	33 (44.0%)	43 (57.3%)	46 (63.0%)	2 (2.6%)
	Nausea	17 (22.1%)	18 (24.0%)	17 (22.7%)	26 (35.6%)	3 (3.9%)
	Pyrexia[a]	11 (14.3%)	14 (18.7%)	29 (38.7%)	29 (39.7%)	0
Second dose						
Group (Subjects analyzed)		Jcovden 5×10^{10} vp × 2 doses (n = 74)	Jcovden 5×10^{10} vp × 1 dose (n = 74)	Jcovden 1×10^{11} vp × 2 doses (n = 74)	Jcovden 1×10^{11} vp × 1 dose (n = 67)	Placebo (n = 74)
Study vaccine		Jcovden 5×10^{10} vp	Placebo	Jcovden 1×10^{11} vp	Placebo	Placebo
Local	Injection site pain and tenderness	49 (66.2%)	5 (6.8%)	54 (73.0%)	7 (10.4%)	1 (1.4%)
	Injection site swelling	2 (2.7%)	0	2 (2.7%)	0	0
	Injection site erythema	1 (1.4%)	0	3 (4.1%)	0	0
Systemic	Fatigue	36 (48.6%)	16 (21.6%)	36 (48.6%)	14 (20.9%)	10 (13.5%)
	Headache	25 (33.8%)	15 (20.3%)	34 (45.9%)	10 (14.9%)	7 (9.5%)
	Myalgia	19 (25.7%)	3 (4.1%)	33 (44.6%)	4 (6.0%)	2 (2.7%)
	Nausea	5 (6.8%)	8 (10.8%)	11 (14.9%)	5 (7.5%)	2 (2.7%)
	Pyrexia[a]	3 (4.1%)	0	14 (18.9%)	1 (1.5%)	0

Number of subjects with events (incidence)
a, ≥38°C (oral temperature)

Table 20. Solicited adverse events observed within 7 days after each dose of study vaccine (Cohort 3, FAS)

First dose						
Group (Subjects analyzed)		Jcovden 5×10^{10} vp × 2 doses (n = 81)	Jcovden 5×10^{10} vp × 1 dose (n = 80)	Jcovden 1×10^{11} vp × 2 doses (n = 82)	Jcovden 1×10^{11} vp × 1 dose (n = 79)	Placebo (n = 81)
Study vaccine		Jcovden 5×10^{10} vp	Jcovden 5×10^{10} vp	Jcovden 1×10^{11} vp	Jcovden 1×10^{11} vp	Placebo
Local	Injection site pain and tenderness	36 (44.4%)	26 (32.5%)	32 (39.0%)	31 (39.2%)	5 (6.2%)
	Injection site swelling	2 (2.5%)	1 (1.3%)	1 (1.2%)	1 (1.3%)	1 (1.2%)
	Injection site erythema	0	1 (1.3%)	1 (1.2%)	3 (3.8%)	0
Systemic	Fatigue	26 (32.1%)	25 (31.3%)	30 (36.6%)	33 (41.8%)	12 (14.8%)
	Headache	23 (28.4%)	22 (27.5%)	31 (37.8%)	25 (31.6%)	11 (13.6%)
	Myalgia	17 (21.0%)	16 (20.0%)	22 (26.8%)	23 (29.1%)	5 (6.2%)
	Nausea	4 (4.9%)	3 (3.8%)	7 (8.5%)	4 (5.1%)	5 (6.2%)
	Pyrexia[a]	4 (4.9%)	3 (3.8%)	6 (7.3%)	7 (8.9%)	0
Second dose						
Group (Subjects analyzed)		Jcovden 5×10^{10} vp × 2 doses (n = 81)	Jcovden 5×10^{10} vp × 1 dose (n = 80)	Jcovden 1×10^{11} vp × 2 doses (n = 82)	Jcovden 1×10^{11} vp × 1 dose (n = 79)	Placebo (n = 81)
Study vaccine		Jcovden 5×10^{10} vp	Placebo	Jcovden 1×10^{11} vp	Placebo	Placebo
Local	Injection site pain and tenderness	41 (53.2%)	3 (3.8%)	50 (62.5%)	11 (14.1%)	9 (11.4%)
	Injection site swelling	1 (1.3%)	0	1 (1.3%)	1 (1.3%)	0
	Injection site erythema	1 (1.3%)	1 (1.3%)	0	0	0
Systemic	Fatigue	23 (29.9%)	15 (18.8%)	29 (36.3%)	15 (19.2%)	17 (21.5%)
	Headache	20 (26.0%)	10 (12.5%)	27 (33.8%)	16 (20.5%)	16 (20.3%)
	Myalgia	17 (22.1%)	7 (8.8%)	17 (21.3%)	8 (10.3%)	8 (10.1%)
	Nausea	1 (1.3%)	4 (5.0%)	4 (5.0%)	7 (9.0%)	6 (7.6%)
	Pyrexia[a]	1 (1.3%)	0	2 (2.5%)	0	1 (1.3%)

Number of subjects with events (incidence)
a, ≥38°C (oral temperature)

Table 21 shows incidences of unsolicited adverse events and adverse reactions observed within 28 days after each dose of the study vaccine.

Table 21. Unsolicited adverse events and adverse reactions observed within 28 days after each dose of study vaccine (FAS)

Cohort		Jcovden 5×10^{10} vp × 2 doses	Jcovden 5×10^{10} vp × 1 dose	Jcovden 1×10^{11} vp × 2 doses	Jcovden 1×10^{11} vp × 1 dose	Placebo
1a	Subjects analyzed	n = 77	n = 75	n = 75	n = 73	n = 77
	Adverse events	16 (20.8%)	21 (28.0%)	29 (38.7%)	30 (41.1%)	17 (22.1%)
	Adverse reactions	9 (11.7%)	13 (17.3%)	20 (26.7%)	17 (23.3%)	5 (6.5%)
1b	Subjects analyzed	n = 5	n = 5	n = 5	n = 5	n = 5
	Adverse events	4 (80.0%)	3 (60.0%)	5 (100%)	4 (80.0%)	3 (60.0%)
	Adverse reactions	1 (20.0%)	0	5 (100%)	3 (60.0%)	0
3	Subjects analyzed	n = 81	n = 80	n = 82	n = 79	n = 81
	Adverse events	20 (24.7%)	17 (21.3%)	23 (28.0%)	32 (40.5%)	23 (28.4%)
	Adverse reactions	5 (6.2%)	8 (10.0%)	10 (12.2%)	14 (17.7%)	3 (3.7%)

Number of subjects with events (incidence)

Tables 22 to 25 show unsolicited adverse events observed in ≥2 subjects in any group and unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out in Cohorts 1a and 3. In Cohort 1b, unsolicited adverse events observed in ≥2 subjects in any group included chills in 80.0% (4 of 5) of subjects, hyperhidrosis in 60.0% (3 of 5) , and arthralgia in 20.0% (1 of 5) in the Jcovden 1×10^{11} vp × 2-dose group, and chills in 60.0% (3 of 5) subjects, hyperhidrosis in 40.0% (2 of

5), and arthralgia in 40.0% (2 of 5) in the Jcovden 1×10^{11} vp × 1-dose group. A causal relationship could not be ruled out for all events except for arthralgia in 1 subject in the Jcovden 1×10^{11} vp × 1-dose group.

Table 22. Unsolicited adverse events observed in ≥2 subjects in any group within 28 days after each dose of study vaccine (Cohort 1a, FAS)

Group (Subjects analyzed)	Jcovden 5×10^{10} vp × 2 doses (n = 77)	Jcovden 5×10^{10} vp × 1 dose (n = 75)	Jcovden 1×10^{11} vp × 2 doses (n = 75)	Jcovden 1×10^{11} vp × 1 dose (n = 73)	Placebo (n = 77)
Fatigue	0	3 (4.0%)	1 (1.3%)	1 (1.4%)	5 (6.5%)
Chills	3 (3.9%)	3 (4.0%)	6 (8.0%)	11 (15.1%)	1 (1.3%)
Pyrexia[a]	2 (2.6%)	2 (2.7%)	3 (4.0%)	1 (1.4%)	1 (1.3%)
Back pain	2 (2.6%)	2 (2.7%)	2 (2.7%)	2 (2.7%)	0
Pharyngodynia	1 (1.3%)	2 (2.7%)	0	1 (1.4%)	2 (2.6%)
Syncope	0	2 (2.7%)	0	1 (1.4%)	0
Vomiting	0	2 (2.7%)	0	0	0
Upper respiratory tract infection	4 (5.2%)	1 (1.3%)	0	1 (1.4%)	0
Nasopharyngitis	1 (1.3%)	1 (1.3%)	2 (2.7%)	0	1 (1.3%)
Decreased appetite	0	1 (1.3%)	1 (1.3%)	2 (2.7%)	1 (1.3%)
Headache	3 (3.9%)	0	1 (1.3%)	3 (4.1%)	1 (1.3%)
Diarrhoea	2 (2.6%)	0	0	1 (1.4%)	0
Flu like symptoms	0	0	2 (2.7%)	0	0
Malaise	0	0	1 (1.3%)	3 (4.1%)	0
Abdominal pain	0	0	1 (1.3%)	2 (2.7%)	1 (1.3%)
Alanine aminotransferase increased	0	0	2 (2.7%)	1 (1.4%)	0

Number of subjects with events (incidence)
a, ≥38°C (oral temperature)

Table 23. Unsolicited adverse events observed in ≥2 subjects in any group within 28 days after each dose of study vaccine for which a causal relationship could not be ruled out (Cohort 1a, FAS)

Group (Subjects analyzed)	Jcovden 5×10^{10} vp × 2 doses (n = 77)	Jcovden 5×10^{10} vp × 1 dose (n = 75)	Jcovden 1×10^{11} vp × 2 doses (n = 75)	Jcovden 1×10^{11} vp × 1 dose (n = 73)	Placebo (n = 77)
Chills	3 (3.9%)	3 (4.0%)	6 (8.0%)	11 (15.1%)	1 (1.3%)
Pyrexia[a]	2 (2.6%)	2 (2.7%)	3 (4.0%)	1 (1.4%)	1 (1.3%)
Back pain	2 (2.6%)	2 (2.7%)	1 (1.3%)	2 (2.7%)	0
Fatigue	0	2 (2.7%)	1 (1.3%)	0	2 (2.6%)
Vomiting	0	2 (2.7%)	0	0	0
Decreased appetite	0	1 (1.3%)	1 (1.3%)	2 (2.7%)	1 (1.3%)
Flu like symptoms	0	0	2 (2.7%)	0	0
Malaise	0	0	1 (1.3%)	3 (4.1%)	0

Number of subjects with events (incidence)
a, ≥38°C (oral temperature)

Table 24. Unsolicited adverse events observed in ≥2 subjects in any group within 28 days after each dose of study vaccine (Cohort 3, FAS)

Group (Subjects analyzed)	Jcovden 5×10^{10} vp × 2 doses (n = 81)	Jcovden 5×10^{10} vp × 1 dose (n = 80)	Jcovden 1×10^{11} vp × 2 doses (n = 82)	Jcovden 1×10^{11} vp × 1 dose (n = 79)	Placebo (n = 81)
Chills	1 (1.2%)	2 (2.5%)	6 (7.3%)	6 (7.6%)	1 (1.2%)
Fatigue	1 (1.2%)	2 (2.5%)	2 (2.4%)	0	1 (1.2%)
Dizziness	0	2 (2.5%)	0	1 (1.3%)	0
Cough	0	2 (2.5%)	0	0	0
Nasopharyngitis	2 (2.5%)	1 (1.3%)	0	0	0
Diarrhoea	1 (1.2%)	1 (1.3%)	2 (2.4%)	0	2 (2.5%)
Headache	0	1 (1.3%)	4 (4.9%)	2 (2.5%)	1 (1.2%)
Myalgia	0	1 (1.3%)	1 (1.2%)	0	2 (2.5%)
Injection site haemorrhage	0	1 (1.3%)	1 (1.2%)	2 (2.5%)	1 (1.2%)
Hypertension	3 (3.7%)	0	2 (2.4%)	3 (3.8%)	1 (1.2%)
Systolic hypertension	2 (2.5%)	0	0	0	0
Arthralgia	2 (2.5%)	0	3 (3.7%)	1 (1.3%)	1 (1.2%)
Bradycardia	2 (2.5%)	0	0	0	1 (1.2%)
Upper respiratory tract infection	0	0	0	3 (3.8%)	1 (1.2%)
Back pain	0	0	3 (3.7%)	0	2 (2.5%)
Hyperkalaemia	0	0	2 (2.4%)	1 (1.3%)	0
Insomnia	0	0	0	3 (3.8%)	0
Pruritus	0	0	0	2 (2.5%)	1 (1.2%)
Pyrexia[a]	0	0	0	2 (2.5%)	0

Number of subjects with events (incidence)
a, ≥38°C (oral temperature)

Table 25. Unsolicited adverse events observed in ≥2 subjects in any group within 28 days after each dose of study vaccine for which a causal relationship could not be ruled out (Cohort 3, FAS)

Group (Subjects analyzed)	Jcovden 5×10^{10} vp × 2 doses (n = 81)	Jcovden 5×10^{10} vp × 1 dose (n = 80)	Jcovden 1×10^{11} vp × 2 doses (n = 82)	Jcovden 1×10^{11} vp × 1 dose (n = 79)	Placebo (n = 81)
Chills	1 (1.2%)	2 (2.5%)	6 (7.3%)	6 (7.6%)	0
Fatigue	0	2 (2.5%)	0	0	1 (1.2%)
Injection site haemorrhage	0	1 (1.3%)	1 (1.2%)	2 (2.5%)	1 (1.2%)

Number of subjects with events (incidence)

As of the data cut-off date, serious adverse events were observed in 1 subject (pyrexia) in the Jcovden 1×10^{11} vp × 1-dose group, 1 subject (blood pressure decreased) in the Jcovden 1×10^{11} vp × 2-dose group, and 1 subject (multiple sclerosis) in the placebo group in Cohort 1a; 1 subject (nephrolithiasis) in the Jcovden 5×10^{10} vp × 2-dose group in Cohort 1b; 1 subject (pneumonia legionella) in the Jcovden 5×10^{10} vp × 1-dose group and 1 subject (aural polyp) in the placebo group in Cohort 3. A causal relationship to the study vaccine could not be ruled out for pyrexia and multiple sclerosis in 1 subject each (2 subjects) in Cohort 1a, which however resolved or were resolving. Adverse events leading to study discontinuation occurred in 3 subjects in Cohort 1a; 2 subjects who experienced serious adverse events (pyrexia and multiple sclerosis in 1 subject each) and 1 subject who experienced a non-serious adverse event (COVID-19) discontinued the study. However, a causal relationship to the study vaccine was ruled out for all events except pyrexia and multiple sclerosis. No deaths occurred in any cohort.

7.2.2 Foreign phase III study (CTD 5.3.5.1.1; Study COV3001; ongoing since September 2020; data cut-off on January 22, 2021 [primary analysis] and July 9, 2021 [analysis at the end of double-blind period])

A randomized, double-blind,[19] placebo-controlled, parallel-group study is ongoing at 210 study centers in 8 countries (US, Mexico, Colombia, Peru, Chile, Brazil, Argentine, and South Africa) to evaluate the efficacy and safety of Jcovden in subjects aged ≥18 years (target sample size, 40,000 subjects [20,000 each in the Jcovden group and placebo group[20]]). The protocol was revised after the start of study, which allowed an opportunity for subjects in the placebo groups to receive an approved SARS-CoV-2 vaccine in the countries where Jcovden had been used under emergency use authorization or conditional marketing authorization. According to the revised protocol, all study subjects were unblinded at an unblinding visit that was newly specified in the protocol or at Month 6 visit after study vaccination. Then, those who had been in the placebo groups during the double-blind period received a single dose of Jcovden, if agreed (fourth edition, dated February 22, 2021).

A single dose of the study vaccine (Jcovden 5×10^{10} vp or placebo) was intramuscularly administered.

Subjects were stratified by vaccination center, age (≥18 and <60 years, ≥60 years), and risk factors for severe COVID-19 (moderate to severe asthma, chronic lung disease, diabetes mellitus, serious heart disorder, moderate to severe hypertension, obesity [body mass index (BMI) ≥30 kg/m^2], chronic liver disease, sickle cell disease, thalassemia, cerebrovascular disorder, nervous system disorder [dementia], end stage renal disorder, organ transplant, malignant tumor, HIV infection and other immunodeficiencies, hepatitis B infection, and sleep apnea). The study included subjects aged ≥18 and <40 years and subjects aged ≥60 years, each of which was to account for approximately 20% and 30%, respectively, of the overall population.

Of 44,325 randomized subjects (22,174 in the Jcovden group, 22,151 in the placebo group), 43,783 subjects (21,895, 21,888) received the study vaccine and were included in the FAS and safety analysis population. Of these, 6,736 subjects (3,356, 3,380) provided their diaries with records of solicited adverse events and unsolicited adverse events and were included in the safety subset for analysis on these events. Of the FAS, 39,321 subjects (19,630, 19,691) excluding 4,462 subjects (4,217 [2,151 and 2,066] seropositive for anti-SARS-CoV-2 antibodies at baseline, 238 [107 and 131] PCR positive for SARS-CoV-2 at baseline, 69 [33 and 36] with critical deviation from the protocol) were included in the per protocol set (PP set) and the primary efficacy analysis population.

On October 11, 2020, after the start of this study, a serious adverse event (transverse sinus thrombosis leading to cerebral haemorrhage) occurred. Because of this event pre-determined to fall under the category that requires “the suspension of the study vaccination,” and all clinical studies of Jcovden including this study were suspended. After the unblinded safety evaluation at the Data Safety Monitoring

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[19] Persons who prepared the study vaccine at study centers were unblinded.

[20] For the evaluation of 2 primary endpoints (the occurrence of moderate to severe/critical COVID-19 ≥14 days after the study vaccination and the occurrence of moderate to severe/critical COVID-19 ≥28 days after the study vaccination) to verify the lower limit of two-sided 95% confidence interval (CI) of vaccine efficacy (VE) to be >30% and the point estimate of VE to be ≥50%, based on assumed VE of 60%, and a power of approximately 90% at a one-sided significance level of 2.5%, the total number of events required was estimated to be 154, indicating a total of 60,000 samples (30,000 each in the Jcovden group and placebo group). The actual incidence of events, however, was higher than previously expected, and the target sample size was thus changed to 40,000 in total (20,000 each in the Jcovden group and placebo group) in a blinded manner (revised third edition of the protocol, dated December 14, 2020).

Board (DSMB) ruled out a causal relationship to the study vaccine, and studies were resumed [see Section 7.R.3.2].

The primary efficacy endpoint when the study began was the first onset of confirmed moderate to severe/critical COVID-19[21)] occurring ≥14 days after study vaccination in subjects seronegative for anti-SARS-CoV-2 antibodies at baseline (before study vaccination) (revised first edition of the protocol, dated September 15, 2020). Then, the incidence of COVID-19 surged with the expansion of pandemic. For the purpose to evaluate the efficacy of Jcovden at a time point when higher antibody response was expected, an additional primary efficacy endpoint, i.e., the first onset of confirmed moderate to severe/critical COVID-19 occurring ≥28 days after study vaccination in subjects seronegative for anti-SARS-CoV-2 antibodies at baseline (before the study vaccination), was set (revised third edition of the protocol, dated December 14, 2021). With the 2 primary endpoints, the efficacy monitoring started when the number of subjects with confirmed COVID-19 reached the predetermined requirements.[22)] The evaluation was performed at least once weekly based on unblinded data analysis results compiled by the statistical support group (SSG), a statistical analysis team independent of the sponsor, and provided to the DSMB. In the efficacy monitoring, a truncated sequential probability ratio test (SPRT) was planned based on cumulative data on events relevant to these primary endpoints. Boundaries for the efficacy evaluation were specified based on the numbers of events relevant to the primary endpoints in the overall population and Jcovden group, by assuming that vaccine efficacy (VE) is 60% so that significant results could be yielded with a power of approximately 90% at a one-sided significance level of 0.025 on a null hypothesis of VE ≤30%. After the start of the efficacy monitoring, the primary analysis was performed when SSG's sequential evaluation data showed values exceeding the boundaries and were acknowledged as appropriate by DSMB or when the number of subjects with confirmed moderate to severe/critical COVID-19 reached 154 ≥28 days after study vaccination. When a requirement for the primary analysis was met at the median follow-up period of <8 weeks but fairly close to 8 weeks, the primary analysis was performed at the median follow-up period of 8 weeks. After the primary analysis, the study continued with the sponsor being unblinded, while investigators and subjects remained blinded.

Cases with confirmed moderate COVID-19 and confirmed severe/critical COVID-19 are defined as in Tables 26 and 27. Diagnosis including severity was made at the Clinical Severity Adjudication Committee (CSAC) in a blinded manner.

21) When confirmed to be positive for SARS-CoV-2 infection by molecular diagnosis using reverse-transcriptase polymerase chain reaction (RT-PCR)

22) When all of the following 3 requirements were met: (a) Moderate to severe/critical COVID-19 had been confirmed in ≥42 subjects ≥28 days after the study vaccination; (b) COVID-19 had been confirmed in ≥6 subjects aged ≥60 years ≥28 days after the study vaccination; and (c) severe/critical COVID-19 had been confirmed in ≥5 subjects ≥28 days after the study vaccination.

Table 26. Case definition of moderate COVID-19 in Study COV3001

RT-PCR or molecular test positive for SARS-CoV-2 in available airway specimens (nasal swab, sputum, pharyngeal swab, and salivary specimens) or other specimens
In addition, either of the following (a) or (b) is met at a given time point during the observation period: (a) Accompanied by new or worsening of 1 of the following signs and symptoms • Respiratory rate, ≥20/min • Saturation of percutaneous Oxygen (SpO_2), abnormal but >93% on room air under 1 atmospheric pressure[a] • Clinical or radiological finding of pneumonia • Radiological finding of deep vein thrombosis • Shortness of breath (dyspnoea) (b) Accompanied by new onset and/or worsening of 2 of the following signs and symptoms • Pyrexia (≥38.0°C) • Heart rate ≥90/min • Chillness (chills) or unmanageable tremulousness • Sore throat • Cough • Discomfort manifested by ≥1 finding of loss of appetite, overall poor health condition, and malaise or feelings of weakness • Headache • Muscle pain • Gastrointestinal symptoms (diarrhea, vomiting, nausea, and abdominal pain)[b] • New onset of olfactory or taste disorder or olfactory or taste alteration • Red or bruised looking toe

a, The criterion for saturation of percutaneous oxygen (SpO_2) should be adjusted according to the altitude in the study region.
b, When a subject presents with ≥2 symptoms within this symptom category (vomiting and diarrhea or malaise and loss of appetite), such symptoms are counted as 1 in this symptom definition. To meet this definition, subjects need to present with ≥2 different symptoms.

Table 27. Case definition of severe/critical COVID-19 in Study COV3001[a]

RT-PCR or molecular test positive for SARS-CoV-2 in available airway specimens (, nasal swab, sputum, pharyngeal swab, and salivary specimens) or other specimens
In addition to the above, any of the following conditions is met at a given time point during the observation period: • Clinical signs at rest suggestive of severe systemic illness (respiratory rate, ≥30/min; heart rate, ≥125/min; SpO_2, ≤93% on room air under 1 atmospheric pressure[b] or partial pressure of oxygen/ fraction of inspired oxygen [PaO_2/FiO_2], <300 mmHg)• Respiratory failure (defined as a condition needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]) • Evidence of shock (systolic blood pressure, <90 mmHg; diastolic blood pressure, <60 mmHg; or requiring vasopressors) • Significant acute renal, hepatic, or neurologic dysfunction • Admission to ICU • Deaths

a, The CSAC assesses whether severe/critical COVID-19 is applicable to each of the COVID-19 cases that meet the criteria for severe/critical disease and ones that meet the criteria for moderate disease and ≥3 signs and/or symptoms listed in Table 25.
b, The criterion for SpO_2 should be adjusted according to the altitude in the study region.

The primary analysis was performed upon recommendation of DSMB when the median follow-up period after study vaccination reached 2 months (8 weeks). Table 28 shows VE [adjusted two-sided 95% confidence interval (CI)] based on the incidences of confirmed moderate to severe/critical COVID-19 occurring ≥14 days after study vaccination and ≥28 days after study vaccination in the PP set for the investigation of the primary efficacy endpoints. Figure 1 shows cumulative incidence of confirmed moderate to severe/critical COVID-19 in the FAS. Point estimates of VE ≥14 days after study vaccination and ≥28 days after study vaccination both exceeded the predetermined efficacy criterion of 50%, and the lower limits of adjusted two-sided 95% CI for both endpoints exceeded the predetermined efficacy criterion of 30% (determined based on the FDA guidance [Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19 in June 2020]).

Table 28. VE against onset of moderate to severe/critical COVID-19 occurring ≥14 days after study vaccination and ≥28 days after study vaccination (PP set)

		Subjects analyzed (n)	Confirmed moderate to severe/critical COVID-19 (n)	Total follow-up period (person-years)	VE (%)[a] [adjusted two-sided 95% CI]
≥14 days after vaccination	Jcovden	19,630	116	3,116.57	66.9 [59.03, 73.40]
	Placebo	19,691	348	3,096.12	
≥28 days after vaccination	Jcovden	19,630	66	3,102.00	66.1 [55.01, 74.80]
	Placebo	19,691	193	3,070.65	

Type 1 error probability in the study overall is adjusted using SPRT boundary. The significance level in the study overall was one-sided of 2.5%.
a, VE = (1 − [incidence of COVID-19 in the Jcovden group/incidence of COVID-19 in the placebo group]) × 100 (%)

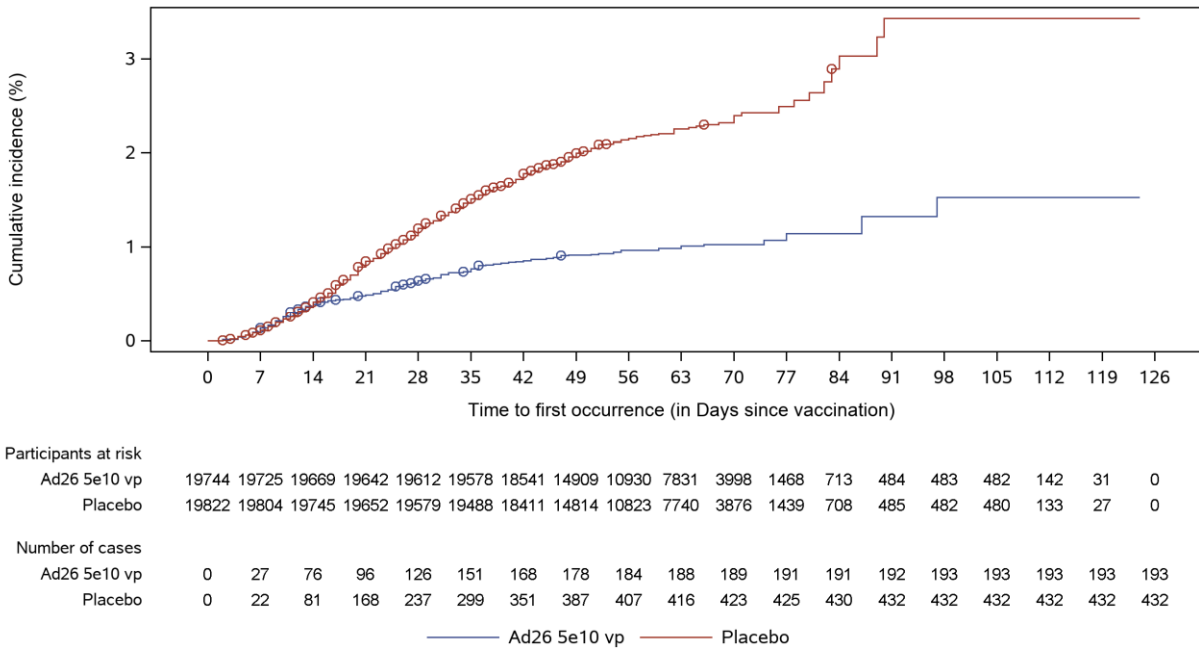

Figure 1. Cumulative incidence of confirmed moderate to severe/critical COVID-19 at the time of primary analysis (FAS)

Along with the protocol revision for unblinding of all subjects, the study plan was changed to perform an analysis at the end of the double-blind period based on data available then (revised fourth edition of the protocol, dated February 22, 2021). The analysis at the end of the double-blind period showed that VE [two-sided 95% CI] on the basis of incidence of confirmed moderate to severe/critical COVID-19 during the follow-up period of 123 days (median) was 56.3% [51.30, 60.84] ≥14 days after study vaccination and 52.9% [47.06, 58.08] ≥28 days after study vaccination.

The safety observation periods were specified as follows. Severity of adverse events was assessed in accordance with Tables 67 to 69 [see Section 11.1].

- Solicited adverse events (local [injection site pain and tenderness, erythema, and swelling] and systemic [fatigue, headache, nausea, myalgia, and pyrexia (≥38°C)]): for 7 days after study vaccination (collected from subject diaries)
- Unsolicited adverse events (excluding solicited adverse events): for 28 days after study vaccination
- Serious adverse events and adverse events leading to study discontinuation: for 1 year after the study vaccination

As of the primary analysis, the safety follow-up period is 2 months (median) after the study vaccination, and the major results are as follows.

The incidence of solicited adverse events observed within 7 days after study vaccination was 50.3% (1,687 of 3,356) in the Jcovden group and 19.5% (658 of 3,380) in the placebo group, and 55.2% (1,853 of 3,356) in the Jcovden group and 35.1% (1,188 of 3,380) in the placebo group for systemic events. Table 29 shows the incidence of each event.

Table 29. Solicited local and systemic adverse events observed within 7 days after study vaccination (safety subset)

Group (Subjects analyzed)		Jcovden (n = 3,356)	Placebo (n = 3,380)
Local	Injection site erythema	245 (7.3%)	131 (3.9%)
	Injection site pain	1,634 (48.7%)	565 (16.7%)
	Injection site swelling	178 (5.3%)	53 (1.6%)
Systemic	Fatigue	1,286 (38.3%)	729 (21.6%)
	Headache	1,308 (39.0%)	805 (23.8%)
	Myalgia	1,115 (33.2%)	432 (12.8%)
	Nausea	478 (14.2%)	329 (9.7%)
	Pyrexia[a]	302 (9.0%)	20 (0.6%)

Number of subjects with events (incidence)
a, ≥38°C (oral temperature or measured by a standard method in the region)

The incidence of unsolicited adverse events observed within 28 days after study vaccination was 13.1% (440 of 3,356) in the Jcovden group and 12.0% (407 of 3,380) in the placebo group. The incidence of adverse reactions identified among the unsolicited events was 7.2% (242 of 3,356) in the Jcovden group and 4.6% (154 of 3,380) in the placebo group. Table 30 shows unsolicited adverse events and adverse reactions observed in ≥1% of subjects in either group within 28 days after study vaccination

Table 30. Unsolicited adverse events and adverse reactions observed in ≥1% of subjects in either group within 28 days after study vaccination (safety subset)

	Adverse events		Adverse reactions	
Group (Subjects analyzed)	Jcovden (n = 3,356)	Placebo (n = 3,380)	Jcovden (n = 3,356)	Placebo (n = 3,380)
Headache	72 (2.1%)	82 (2.4%)	38 (1.1%)	33 (1.0%)
Chills	67 (2.0%)	19 (0.6%)	56 (1.7%)	8 (0.2%)
Fatigue	64 (1.9%)	77 (2.3%)	48 (1.4%)	48 (1.4%)
Myalgia	49 (1.5%)	58 (1.7%)	28 (0.8%)	31 (0.9%)
Vaccination site pain	42 (1.3%)	22 (0.7%)	41 (1.2%)	22 (0.7%)
Nasal congestion	40 (1.2%)	38 (1.1%)	10 (0.3%)	9 (0.3%)
Arthralgia	35 (1.0%)	24 (0.7%)	16 (0.5%)	10 (0.3%)
Diarrhoea	33 (1.0%)	35 (1.0%)	9 (0.3%)	8 (0.2%)
Cough	33 (1.0%)	33 (1.0%)	12 (0.4%)	4 (0.1%)
Nausea	26 (0.8%)	35 (1.0%)	14 (0.4%)	20 (0.6%)

Number of subjects with events (incidence)

As of the data cut-off for the primary analysis, 3 deaths occurred in the Jcovden group (lung abscess, pneumonia [non-COVID-19], and death in 1 subject each) and 16 subjects in the placebo group (COVID-19 in 3 subjects; death, COVID-19 pneumonia, pneumonia [nonCOVID-19] in 2 subjects each; and completed suicide, acute myocardial infarction, accidental overdose [overdose of illicit drugs], malaise [unwell possibly owing to diabetes mellitus], cardiac failure, suspected COVID-19, and sudden death in 1 subject each). A causal relationship to the study vaccine was ruled out for all deaths.

The incidence of serious adverse events was 0.4% (90 of 21,895) in the Jcovden group and 0.6% (137 of 21,888) in the placebo group. The adverse events for which a causal relationship to the study vaccine could not be ruled out occurred in 7 subjects in the Jcovden group (facial paralysis in 2 subjects; and Guillain-Barre syndrome, pericarditis, radiculitis brachial, post vaccination syndrome, and Type IV hypersensitivity reaction in 1 subject each) and 2 subjects in the placebo group (deep vein thrombosis, Epstein-Barr virus infection, and atrial fibrillation in 1 subject each [including multiple events per patient]). For outcome, as of the data cut-off for the primary analysis, all events except for Guillain-Barre syndrome and radiculitis brachial resolved or were resolving.

No adverse events led to study discontinuation in either group.

As of the data cut-off for the analysis at the end of the double-blind period, analyses were performed not only on the double-blind period data but also on these data with open-label period data combined. The following is analysis results of the double-blind period data, and adverse events observed during the open-label period are presented in Section 7.R.3. As of the data cut-off for the analysis at the end of the double-blind period, 28 deaths occurred in the Jcovden group (deaths in 7 subjects; acute respiratory failure, cardiac failure, pneumonia, COVID-19 pneumonia in 2 subjects each; and pneumonia aspiration, drowning, sudden death, accidental death, acute myocardial infarction, cardiac failure congestive, myocardial infarction, pulmonary tuberculosis, lung abscess, abdominal pain, upper gastrointestinal haemorrhage, pulmonary embolism, pulmonary oedema, multiple injuries, brain cancer metastatic, and lung neoplasm malignant in 1 subject each [including multiple events per patient]) and 55 subjects in the placebo group (COVID-19 in 13 subjects; COVID-19 pneumonia in 7 subjects; deaths in 4 subjects; sudden death and pneumonia in 3 subjects each; acute myocardial infarction, cerebrovascular accident, and completed suicide in 2 subjects each; and pulmonary embolism, respiratory distress, acute coronary syndrome, cardiac failure, malaise, multiple organ dysfunction syndrome, cardiac failure congestive, myocardial infarction, cardiac arrest, suspected COVID-19, upper respiratory tract infection, pneumothorax, pulmonary hypertension, respiratory failure, accidental overdose, injury, cancer pain, gastric cancer, metastases to liver, blood loss anaemia, pulse absent, cerebral infarction, epilepsy, uraemic encephalopathy, chronic kidney disease, physical assault, and hypertension in 1 subject each [including multiple events per patient]). A causal relationship to the study vaccine was ruled out for all deaths. The incidence of serious adverse events was 1.1% (235 of 21,898) in the Jcovden group and 1.6% (358 of 21,890) in the placebo group, and adverse events for which a causal relationship to the study vaccine could not be ruled out occurred in 10 subjects in the Jcovden group (Bell's palsy in 2 subjects and complex regional pain syndrome, Guillain-Barre syndrome, ischaemic stroke, pericarditis, retinal vein thrombosis, hypersensitivity, post vaccination syndrome, and deep vein thrombosis in 1 subject each) and 1 subject in the placebo group (atrial flutter and Epstein-Barr virus infection). All events except for complex regional pain syndrome resolved or were resolving. Complex regional pain syndrome in the Jcovden group was reported as radiculitis brachial and did not resolve as of the data cut-off for the primary analysis, but clinical symptoms and examination results did not meet either the clinical definition of radiculitis brachial or complex regional pain syndrome. Adverse events leading to study discontinuation occurred in 1 subject in the Jcovden group and 2 subjects in the placebo group, and a causal relationship to the study vaccine was ruled out for all these events.

7.2.3 Foreign phase III study (CTD 5.3.5.1.2; Study COV3009; ongoing since November 2020; data cut-off on June 25, 2021)

A randomized, double-blind,[23] placebo-controlled study is ongoing at 125 study centers in 10 countries (Belgium, Brazil, Colombia, France, Germany, Philippines, South Africa, Spain, UK, and US) to evaluate the efficacy, safety, and immunogenicity of Jcovden in subjects aged ≥18 years (target sample size, 30,000 subjects [15,000 each in the Jcovden group and placebo group[24]]). The protocol was revised after the start of study, which offered subjects randomized to the placebo groups, in the countries where Jcovden was available under emergency use authorization or conditional marketing authorization, an opportunity to receive an approved SARS-CoV-2 vaccine. According to the revised protocol, all study subjects were unblinded at an unblinding visit that was newly specified in the protocol. Then, subjects who had been in the placebo groups during the double-blind period were vaccinated with a single dose of Jcovden, if agreed, and those who were enrolled in the open-label period were assigned to receive either a single dose or 2 doses of Jcovden at a ratio of 1:1 (revised fourth edition of the protocol, dated March 12, 2021).

Two doses of the study vaccine (Jcovden 5×10^{10} vp or placebo) were intramuscularly administered 56 days (approximately 2 months) apart.

Subjects were stratified by vaccination center, age (18 to 59 years, ≥60 years), and risk factors for severe COVID-19 (moderate to severe asthma, chronic lung disease, diabetes mellitus, serious heart disorder, moderate to severe hypertension, obesity [BMI ≥30 kg/m^2], chronic liver disease, sickle cell disease, thalassemia, cerebrovascular disorder, nervous system disorder [dementia], end stage renal disorder, organ transplant, malignant tumor, HIV infection and other immunodeficiencies, hepatitis B, and sleep apnea, and stay at a nursing or long-term care center) and assigned.

Of 31,835 randomized subjects (15,976 in the Jcovden group, 15,859 in the placebo group), 31,300 subjects (15,708, 15,592) received ≥1 dose of the study vaccine[25] and were included in the FAS and primary safety analysis population. Of them, 6,067 subjects (3,015, 3,052) provided subject diaries with data on solicited adverse events and unsolicited adverse events and were included in the safety subset for analysis on these events. Of the FAS, 14,492 subjects (7,484, 7,008) were included in the PP set and the primary efficacy analysis population, excluding 16,808 subjects (14,549 [7,053 and 7,496] who received only the first dose, 3,478 [1,757 and 1,721] who were confirmed to be seropositive for anti-SARS-CoV-2 antibodies at baseline, 1,819 who were confirmed to be seropositive for anti-SARS-CoV-2 antibodies 14 days after the second dose of the study vaccine, 100 [43 and 57] who were PCR positive for SARS-CoV-2 at baseline, and 1,472 [637 and 835] who had a critical protocol deviation; including multiple events per patient).

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[23] Persons who prepared the study vaccine at study centers were unblinded.

[24] This study was intended to demonstrate the efficacy of Jcovden by evaluation on the primary endpoint (occurrence of COVID-19 occurring ≥14 days after the study vaccination), requiring the lower limit of two-sided 95% CI of VE to exceed 30%. On the assumption that VE was 65%, and the study was provided with a power of approximately 90% at a one-sided significance level of 2.5%, the total number of events required was estimated to be 104, indicating the target sample size of 30,000 in total (15,000 each in the Jcovden group and placebo group).

[25] Although 5 subjects in the Jcovden group and 55 subjects in the placebo group received the wrong study vaccine, the analysis was performed based on the actually administered the study vaccine.

The primary efficacy endpoint was "VE based on confirmed moderate to severe COVID-19 occurring ≥14 days after the second dose of the study vaccine in subjects seronegative for anti-SARS-CoV-2 antibodies at baseline (before the first dose of the study vaccine)." To evaluate the primary endpoint, the efficacy monitoring started when the number of subjects with confirmed COVID-19 reached the predetermined requirements.[26)] The evaluation was performed at least once weekly based on unblinded data analysis results compiled by SSG, independent of the sponsor, and provided to the independent Data Monitoring Committee (IDMC). In the monitoring, evaluation by truncated SPRT was planned based on cumulative data on event relevant to the primary endpoint. A boundary for the efficacy evaluation were specified based on the numbers of events relevant to the primary endpoint in the overall population and Jcovden group, by assuming that VE is 65% so that significant results could be yielded with a power of approximately 90% at a one-sided significance level of 0.025 on a null hypothesis of VE ≤30%. After the start of the efficacy monitoring, the primary analysis was performed when SSG's sequential evaluation data showed values exceeding the boundary and was acknowledged as appropriate by IDMC or when the number of subjects with confirmed moderate to severe COVID-19 reached 104 ≥14 days after study vaccination. This analysis plan was revised accompanying the revision of the protocol (fourth edition, dated March 12, 2021) due to emergency use authorization, etc., so that the primary analysis would be performed based on data in the double-blind period when the percentage of unblinded subjects reached ≥90%. On June 25, 2021 when ≥90% of subjects were unblinded and the study entered the open-label period, the primary analysis was performed as recommended by the IDMC. Confirmed COVID-19 was defined as per in Study COV3001. Confirmed diagnoses including severity in each case were made at CSAC in a blinded manner.

Table 31 shows results on VE [adjusted two-sided 95% CI] based on confirmed moderate to severe COVID-19 occurring ≥14 days after the second dose of the study vaccine in subjects seronegative for anti-SARS-CoV-2 antibodies at baseline (before the first dose of the study vaccine) for the evaluation of primary efficacy endpoint. Figure 2 shows cumulative incidence of confirmed moderate to severe/critical COVID-19. The lower limit of adjusted two-sided 95% CI of VE exceeded the predetermined efficacy criterion of 30%.

Table 31. VE against onset of moderate to severe/critical COVID-19 occurring ≥14 days after the second dose of study vaccine (PP set)

	Subjects analyzed (n)	Confirmed moderate to severe/critical COVID-19 (n)	Total follow-up period (person-years)	VE (%)[a] [adjusted two-sided 95% CI]
Jcovden	7,484	14	1,729.99	75.2 [54.55, 87.30]
Placebo	7,008	52	1,594.98	

a, VE = (1 − [incidence of COVID-19 in the Jcovden group/incidence of COVID-19 in the placebo group]) × 100 (%)

26) When both of the following 2 requirements were met: (a) ≥6 subjects aged ≥60 years presented with confirmed moderate to severe COVID-19 ≥14 days after the second dose of the study vaccine and (b) ≥20 subjects presented with confirmed moderate to severe COVID-19 ≥14 days after the second dose of the study vaccine

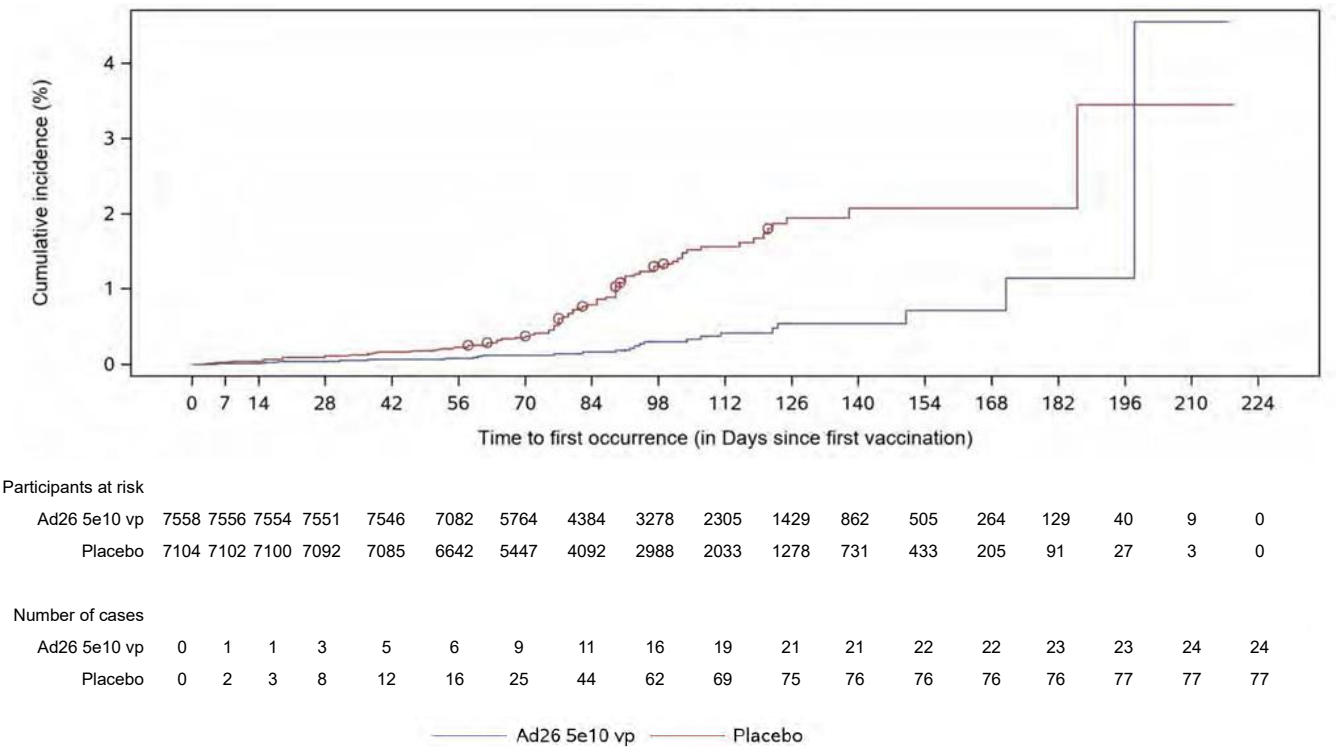

Figure 2. Cumulative incidence of confirmed moderate to severe/critical COVID-19 at the time of primary analysis (PP set)

The safety observation periods were specified as follows. Severities of adverse events were assessed in accordance with Tables 67 to 69 [see Section 11.1].

- Solicited adverse events (local [injection site pain and tenderness, erythema, and swelling] and systemic [fatigue, headache, nausea, myalgia, and pyrexia (≥38°C)]): 7 days after study vaccination (collected from subject diaries)
- Unsolicited adverse events (excluding solicited adverse events): 28 days after each dose of the study vaccine
- Serious adverse events: 2 years after the second dose of the study vaccine

Table 32 shows solicited adverse events observed within 7 days after each dose of the study vaccine.

Table 32. Solicited local and systemic adverse events observed within 7 days after study vaccination (safety subset)

		First dose		Second dose	
Group (Subjects analyzed)		Jcovden (n = 3,015)	Placebo (n = 3,052)	Jcovden (n = 1,559)	Placebo (n = 1,425)
Local	Injection site pain	1,634 (54.2%)	556 (18.2%)	877 (56.3%)	225 (15.8%)
	Injection site erythema	263 (8.7%)	142 (4.7%)	128 (8.2%)	56 (3.9%)
	Injection site swelling	167 (5.5%)	52 (1.7%)	88 (5.6%)	18 (1.3%)
Systemic	Fatigue	1,355 (44.9%)	760 (24.9%)	641 (41.1%)	293 (20.6%)
	Headache	1,291 (42.8%)	749 (24.5%)	558 (35.8%)	270 (18.9%)
	Myalgia	1,172 (38.9%)	468 (15.3%)	541 (34.7%)	186 (13.1%)
	Nausea	546 (18.1%)	316 (10.4%)	225 (14.4%)	100 (7.0%)
	Pyrexia[a]	150 (5.0%)	14 (0.5%)	38 (2.4%)	4 (0.3%)

Number of subjects with events (incidence)
a, ≥38°C (oral temperature or measured by a standard method in the region)

The incidence of unsolicited adverse events observed within 28 days after study vaccination was 18.6% (560 of 3,015) in the Jcovden group and 13.7% (418 of 3,052) in the placebo group. The incidence of adverse reactions identified among the unsolicited events was 11.0% (333 of 3,015) in the Jcovden group and 7.1% (217 of 3,052) in the placebo group. Table 33 shows adverse events and adverse reactions observed in ≥1% of subjects in either group within 28 days after study vaccination.

Table 33. Unsolicited adverse events and adverse reactions observed in ≥1% of subjects in either group within 28 days after study vaccination (safety subset)

	Adverse events		Adverse reactions	
Group (Subjects analyzed)	Jcovden (n = 3,015)	Placebo (n = 3,052)	Jcovden (n = 3,015)	Placebo (n = 3,052)
Fatigue	129 (4.3%)	119 (3.9%)	98 (3.3%)	92 (3.0%)
Vaccination site pain	73 (2.4%)	23 (0.8%)	70 (2.3%)	21 (0.7%)
Injection site pain	32 (1.1%)	10 (0.3%)	30 (1.0%)	10 (0.3%)
Vaccination site erythema	31 (1.0%)	15 (0.5%)	31 (1.0%)	15 (0.5%)
Chills	29 (1.0%)	8 (0.3%)	24 (0.8%)	3 (0.1%)
Headache	140 (4.6%)	120 (3.9%)	101 (3.3%)	82 (2.7%)
Myalgia	100 (3.3%)	86 (2.8%)	81 (2.7%)	67 (2.2%)
Nausea	42 (1.4%)	32 (1.0%)	27 (0.9%)	27 (0.9%)

Number of subjects with events (incidence)

During the double-blind period up to data cut-off, 4 deaths occurred in the Jcovden group (myocardial infarction, lung adenocarcinoma, cerebral haemorrhage, and death in 1 subject each) and 13 deaths occurred in the placebo group (COVID-19 and COVID-19 pneumonia in 3 subjects each; and sudden death, unevaluable event, respiratory distress, cardiac arrest, myocarditis, disseminated tuberculosis, and homicide in 1 subject each). A causal relationship to the study vaccine was ruled out for all deaths except for respiratory distress in 1 subject in the placebo group. The subject in whom a causal relationship between fatal respiratory distress and the study vaccine could not be ruled out had received Jcovden in an unblinded manner 36 days after study vaccination (placebo) and presented with respiratory distress on the same day. The cause of death was acute respiratory distress syndrome associated with COVID-19 pneumonia. During the open-label period, 9 deaths occurred (6 in the Jcovden group [myocardial infarction in 2; and chronic obstructive pulmonary disease (COPD), respiratory distress, COVID-19 pneumonia, and overdose (heroin overdose) in 1 each], 2 in the placebo group [COVID-19 pneumonia in 2]). In addition, 2 subjects (death and acute myocardial infarction in 1 each) who had received the other SARS-CoV-2 vaccine died after unblinding. A causal relationship to the study vaccine was ruled out for all deaths.

The incidence of serious adverse events in the double-blind period was 0.7% (104 of 15,705) in the Jcovden group and 0.9% (136 of 15,558) in the placebo group. The serious adverse events for which a causal relationship to the study vaccine could not be ruled out occurred in 8 subjects in the Jcovden group (pyrexia, pericarditis, allergy to vaccine, haemoptysis, facial paresis, pulmonary embolism, cerebrovascular accident, injection site swelling, vertigo, myocardial necrosis marker increased in 1 subject each [some subjects reported multiple events]) and 3 subjects in the placebo group (pulmonary embolism, respiratory distress, pancreatitis acute in 1 subject each). All events resolved or were resolving, except for respiratory distress in the placebo group.

During the double-blind period, adverse events led to study discontinuation in 5 subjects in the Jcovden group (cerebral haemorrhage, bipolar disorder, suicidal ideation, urticaria, benign prostatic hyperplasia,

and cervical vertebral fracture in 1 subject each [some subjects reported multiple events]) and 9 subjects in the placebo group (COVID-19 in 5 subjects; disseminated tuberculosis in 2 subjects; and ventricular extrasystoles, pulmonary embolism, constipation, delirium, diarrhoea, COVID-19 pneumonia, homicide, cardiac arrest, diabetic ketoacidosis, urinary tract infection, and HIV infection in 1 subject each [some subjects reported multiple events]). A causal relationship to the study vaccine was ruled out for all events except for urticaria in 1 subject in the Jcovden group, which was non-serious and resolved.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and data for review

In order to accelerate SARS-CoV-2 vaccine development, the International Coalition of Medicines Regulatory Authorities (ICMRA),[27)] WHO,[28)] and regulatory authorities in each country[29)] have published guidance on the development. In Japan, the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2"[30)] was published on September 2, 2020. The following concepts are mainly presented for clinical trials:

- In principle, clinical trials need to be conducted to assess the preventive effect of COVID-19 of a candidate SARS-CoV-2 vaccine for its efficacy evaluation.
- Conducting clinical studies in Japan is highly necessary for efficacy and safety investigations on a vaccine targeting Japanese subjects, even where the vaccine's disease-preventive effect is to be evaluated in a large-scale confirmatory trial overseas.
- When a large-scale confirmatory study of the candidate vaccine is conducted overseas for its disease-preventive effect as the primary endpoint, in Japan, a clinical study to confirm immunogenicity and safety in Japanese subjects will suffice, and there is no need to conduct a confirmatory clinical study to evaluate the disease-preventive effect in Japanese subjects.

In accordance with these guidance, the applicant planned and conducted a Japanese clinical study to confirm the immunogenicity and safety of Jcovden and constructed the clinical data package for the present application, including results from 2 foreign phase III studies assessing the disease-preventive effect against COVID-19 (Studies COV3001 and COV3009), foreign phase I/II (Study COV1001) and Japanese phase I (Study COV1002) studies that evaluated the safety and immunogenicity as the evaluation data.

PMDA's approach to the review on Jcovden:

In light of the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2," efficacy and safety evaluation of Jcovden is feasible based on the clinical data package constructed by the applicant. The efficacy and safety evaluation of a single dose of Jcovden will base on the results from foreign Study COV3001 as pivotal study data to investigate Jcovden's disease preventive effect, and on the results from the Japanese clinical study (Study COV1002) to further verify the immunogenicity and safety in Japanese population, for efficacy and safety evaluation of Jcovden in Japanese population. Furthermore, the efficacy and safety of 2 doses of Jcovden will be evaluated mainly

27) "Global regulatory workshop on COVID-19 vaccine development" (March 18, 2020 and June 22, 2020)
28) "Target Product Profiles for COVID-19 Vaccines, WHO R&D Blueprint, 29 April 2020" and "An international randomized trial of candidate vaccines against COVID-19, WHO R&D Blueprint, 28 May 2020"
29) FDA "Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, CBER FDA, June 2020," European Medicines Agency (EMA) "EMA considerations on COVID-19 vaccine approval"; etc.
30) https://www.pmda.go.jp/files/000236327.pdf (last accessed on April 1, 2022)

based on the results from foreign Study COV3009 investigating disease preventive effect of the 2-dose regimen of Jcovden. The safety of Jcovden will be reviewed also based on other clinical study data submitted and overseas post-marketing data.

7.R.2 Efficacy

7.R.2.1 Efficacy indicators and efficacy criteria

In foreign Study COV3001, the pivotal clinical study to evaluate the efficacy of Jcovden, the following 2 primary efficacy endpoints were specified in the revised third edition of the protocol (dated December 14, 2020):

- Confirmed moderate to severe/critical COVID-19 with the initial sign observed 14 days after study vaccination (Day 15) or later in subjects who were seronegative for anti-SARS-CoV-2 antibodies at baseline and were confirmed to be positive for SARS-CoV-2 by central PCR test
- Confirmed moderate to severe/critical COVID-19 with the initial sign observed 28 days after study vaccination (Day 29) or later in subjects who were seronegative for anti-SARS-CoV-2 antibodies at baseline and confirmed to be positive for SARS-CoV-2 by central PCR test

The definition of moderate COVID-19 cases and that of severe/critical COVID-19 in the efficacy endpoints is as per Tables 26 and 27.

The applicant's explanation about the establishment of primary endpoints:
When foreign Study COV3001 was in the planning stage, the preceding foreign Study COV1001 demonstrated Jcovden's immunogenicity, i.e., robust humoral immune responses and cellular immune responses after 14 days of the vaccination. Accordingly, in view of urgency of vaccine development amid the pandemic, it was decided that Jcovden's preventive effect on COVID-19 be investigated based on the occurrence of events 14 days after study vaccination onward, which would allow for the elucidation of relatively early-phase efficacy of single-dose vaccination, so as to provide clinically meaningful information to public health settings (revised first edition of the protocol dated September 15, 2020). Furthermore, after the start of foreign Study COV3001, the number of COVID-19 cases surged in the study regions causing the maturation of vaccine-induced immune responses, and this arose the need of further efficacy evaluation at a time point when higher antibody responses was expected. To evaluate efficacy against presumably increased immunogenicity after 14 days of Jcovden vaccination, the second primary endpoint of "COVID-19 occurring 28 days after study vaccination or later" was added (revised third edition of the protocol dated December 14, 2020). The verification of both primary endpoints would ensure strict and appropriate evaluation of the efficacy of Jcovden.

In foreign Study COV3001, case definitions of mild, moderate, and severe/critical COVID-19 were based on those recommended in the FDA guidance (Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, June 2020). Moderate COVID-19 (Table 26) was defined to cover an adequately wide range of COVID-19 cases based on epidemiological data, with the assumption that 80% to 90% of COVID-19 cases would be moderate. Mild COVID-19 in this study, on the other hand, as defined in Table 34, cases meeting the definition of mild COVID-19 were covered by the secondary endpoint, although not by the primary endpoint.

Table 34. Case definition of mild COVID-19 in foreign Study COV3001

RT-PCR or molecular test positive for SARS-CoV-2 in available airway specimens (nasal swab, sputum, pharyngeal swab, salivary specimens, etc.) or other specimens
In addition, any of the following conditions is met at a given time point during the observation period, and none of the case definitions of moderate to severe/critical COVID-19 are met. • Pyrexia (≥38.0°C) • Sore throat • Discomfort (inappetence, overall physical deconditioning, and malaise or feelings of weakness) • Headache • Muscle pain • Gastrointestinal symptoms • Cough • Chest tightness • Nasal discharge • Wheezing • Rash • Discomfort on eye or gum • Chilliness (chills) • New onset of olfactory dysfunction or taste disorder • Red or bruised looking foot or toe • Unmanageable tremulousness

The case definitions of moderate COVID-19 and severe/critical COVID-19 (Tables 26 and 27) specified based on the FDA's severity-based case definitions of COVID-19 are also consistent with the other case definitions of symptomatic COVID-19 including mild disease published by the US National Institutes of Health (NIH) and thus considered appropriate for the evaluation of Jcovden's preventive effect of against COVID-19. As of the primary analysis in foreign Study COV3001, only 4 cases were reported after 14 days of the study vaccination and were classified as mild COVID-19, demonstrating that the case definitions of moderate and severe/critical COVID-19 specified in foreign Study COV3001 covered almost all symptomatic COVID-19 cases. These results justify the primary efficacy endpoints of Jcovden in foreign Study COV3001.

PMDA's view:
In foreign Study COV3001 intended to verify the preventive effect of Jcovden against COVID-19, an additional primary endpoint was specified after the start of the study to evaluate COVID-19 cases based on at 2 different time points thereafter. The addition of the primary endpoint "14 days after study vaccination or later" is appropriate in view of WHO's recommendation[31)] that suggests to use cases occurring ≥14 days after the first vaccination as an indicator of the efficacy evaluation. The applicant's explanation about the primary endpoint of "28 days after study vaccination or later" is also understandable in view of the need of efficacy evaluation in those who have increased antibody responses with mature vaccine-induced immune responses. Patients meeting the case definition of moderate or severe/critical COVID-19, counted for the primary endpoint, are not greatly different from patients meeting case definitions set for the evaluation of the preventive effects of the approved SARS-CoV-2 vaccines against COVID-19 or US NIH's case definitions of symptomatic COVID-19. In view of the limited number of events reported after 14 days of the study vaccination in foreign Study COV3001 that did not meet the definition of moderate or severe/critical COVID-19, the study is considered to have successfully captured events necessary for the efficacy evaluation of Jcovden. Accordingly, the evaluation of the preventive effect of Jcovden against COVID-19 is feasible based on results from the primary analysis on the primary endpoints in foreign Study COV3001.

7.R.2.2 Efficacy

The applicant's explanation about efficacy results:

31) WHO R&D Blueprint, novel Coronavirus, May 2020

(a) Disease-preventive effect

Table 28 shows VE based on the 2 primary endpoints [see Section 7.R.2.1] in foreign Study COV3001, demonstrating the preventive effect of Jcovden against COVID-19.

The secondary endpoint of confirmed moderate to severe/critical COVID-19 occurring ≥14 days after study vaccination was reported by 116 subjects in the Jcovden group (total follow-up period, 3,453.14 person-years) and 349 subjects in the placebo group (3,417.14 person-years in the population irrespective of baseline serum antibody titer), and VE [two-sided 95% CI] was 67.1% [59.43, 73.35]. In the same population, 66 subjects in the Jcovden group (3,438.14 person-years) and 194 subjects in the placebo group (3,390.75 person-years) had confirmed moderate to severe/critical COVID-19 ≥28 days after study vaccination with VE [two-sided 95% CI] of 66.5% [55.72, 74.67]. The results of VE were similar to those of the primary endpoints. In a population seronegative for baseline anti-SARS-CoV-2 antibodies, confirmed symptomatic COVID-19 of any severity occurring ≥14 days after study vaccination was reported by 117 subjects in the Jcovden group (3,116.46 person-years) and 351 subjects in the placebo group (3,095.92 person-years) with VE [two-sided 95% CI] of 66.9% [59.07, 73.37]. In the same population, 66 subjects in the Jcovden group (3,102.00 person-years) and 195 subjects in the placebo group (3,070.53 person-years) had confirmed symptomatic COVID-19 of any severity ≥28 days after study vaccination with VE [two-sided 95% CI] of 66.5% [55.50, 75.05]. The results of VE were similar to those on the primary endpoints.

During foreign Study COV3001, the incidence of COVID-19 surged with rapidly increased COVID-19 cases reported. Of 1,197 subjects who were found to be positive by PCR test at local study centers by the primary analysis data cut-off, some with COVID-19 were excluded from the primary analysis in Latin America and South Africa, which require long shipping time for PCR specimens from local study centers to the central laboratory (147 subjects had not received PCR test result from the central laboratory and 215 subjects had not sent their specimens to the central laboratory). After the primary analysis, an exploratory analysis was performed including 171 subjects centrally confirmed as PCR positive. The number of subjects with COVID-19 (total follow-up period) and VE [two-sided 95% CI] was 144 subjects in the Jcovden group (3,115.00 person-years) and 438 subjects in the placebo group (3,090.73 person-years) with 67.4% [60.53, 73.17] ≥14 days after study vaccination, and 93 subjects in the Jcovden group (3,100.47 person-years) and 272 subjects in the placebo group (3,065.82 person-years) with 66.2% [57.07, 73.58] ≥28 days after study vaccination. The results were similar to those of the primary analysis.

(b) Subgroup analysis results

Tables 35 and 36 show results of the efficacy analysis in each subgroup in foreign Study COV3001. Although the evaluation had limitations depending on the number of subjects in subgroups, a certain level of the preventive effect was observed in all subgroups. However, in the subgroup of HIV infection, confirmed moderate to severe/critical COVID-19 was reported by 5 subjects each in the Jcovden group and placebo group after 14 days of the study vaccination and by 2 subjects in the Jcovden group and 4 subjects in the placebo group after 28 days of the study vaccination, although the limited numbers of subjects in the subgroup and subjects with confirmed COVID-19 evaluated should be noted. The efficacy of Jcovden thus has not been demonstrated in subjects with HIV infection at present. In the

subgroup with comorbidities (obesity, hypertension, type 2 diabetes mellitus, etc.), VE based on the number of confirmed cases of moderate to severe/critical COVID-19 ≥14 days after Jcovden vaccination was low. A possible cause for the low VE was the shorter follow-up period in subjects with comorbidities because of their delayed enrollment as compared with subjects without comorbidities. Given varied characteristics of vaccine recipients with any comorbidity that may be a high risk for severe COVID-19, potentially influential factors to the efficacy of Jcovden should be further investigated in the post-marketing setting. Meanwhile, the lower VE in South Africa than in other regions is considered attributable to the prevalent variant in the country during the study. Of subjects with confirmed COVID-19 in the country in whom a viral nucleotide sequence was available, 94.5% (86 of 91) were infected with SARS-CoV-2 Beta variant (B.1.351 lineage) [see Section 7.R.2.5].

Table 35. Efficacy analysis results by major subgroup based on confirmed moderate to severe/critical COVID-19 ≥14 days occurring after study vaccination (foreign Study COV3001 [primary analysis], PP set)

		Jcovden (n)			Placebo (n)			VE (%) [two-sided 95% CI]
		Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	umber Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	
Overall		19,514	116	3,116.57	19,544	348	3,096.12	66.9 [59.03, 73.40][c]
Age	18-64 years	15,544	107	2,530.27	15,552	297	2,511.23	64.2 [55.26, 71.61]
	≥65 years	3,970	9	586.31	3,992	51	584.89	82.4 [63.90, 92.38]
Sex	Male	10,861	59	1,740.21	10,832	180	1,719.65	67.6 [56.31, 76.28]
	Female	8,649	57	1,375.67	8,708	168	1,375.84	66.1 [53.92, 75.33]
Race[a]	White	12,123	62	1,976.98	12,133	196	1,962.31	68.6 [58.03, 76.79]
	Black or African-American	3,362	30	496.00	3,361	70	492.75	57.4 [33.82, 73.21]
	Asian	714	5	99.55	649	6	90.86	23.9 [-199.14, 81.64]
	Multiracial	1,028	4	166.97	1,080	30	171.63	86.3 [61.11, 96.49]
	American Indian or Alaska Natives	1,634	13	279.23	1,621	32	275.82	59.9 [21.39, 80.67]
Region	South America	7,922	45	1,323.72	7,962	148	1,321.45	69.6 [57.37, 78.76]
	North America (US)	9,119	32	1,414.94	9,086	135	1,394.15	76.6 [65.45, 84.63]
	South Africa	2,473	39	377.91	2,496	65	380.52	39.6 [8.77, 60.46]
Comorbidity[b]	With	7,777	47	1,139.96	7,798	126	1,133.67	62.9 [47.76, 74.05]
	Without	11,737	69	1,976.62	11,746	222	1,962.45	69.1 [59.40, 76.80]

a, Excluding native Hawaiians and others, unknown, unreported, or missing cases

b, Obesity, type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, HIV infection, serious heart disorder, asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, neurological disease, cerebrovascular disease, chronic kidney disease, malignant neoplasm, liver disease, hematopoietic cell transplant recipient in an immunosuppressed condition, organ transplant recipient in an immunosuppressed condition, thalassaemia, sickle cell disease, and cystic fibrosis

c, Adjusted two-sided 95% CI

Table 36. Efficacy analysis results by major subgroup based on the data on confirmed moderate to severe/critical COVID-19 occurring ≥28 days after study vaccination (foreign Study COV3001 [primary analysis], PP set)

		Jcovden (n)			Placebo (n)			VE (%) [two-sided 95% CI]
		Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	
Overall		19,306	66	3,102.00	19,178	193	3,070.65	66.1 [55.01, 74.80][c]
Age	18-64 years	15,378	60	2,518.73	15,253	170	2,490.11	65.1 [52.91, 74.45]
	≥65 years	3,928	6	583.27	3,925	23	580.54	74.0 [34.40, 91.35]
Sex	Male	10,764	33	1,733.12	10,649	103	1,706.86	68.4 [52.88, 79.36]
	Female	8,538	33	1,368.18	8,525	90	1,363.17	63.5 [45.01, 76.26]
Race[a]	White	11,994	37	1,968.07	11,912	106	1,947.53	65.5 [49.35, 76.91]
	Black or African-American	3,330	15	493.85	3,300	45	487.98	67.1 [39.80, 82.95]
	Asian	689	2	97.93	626	3	89.22	-
	Multiracial	1,018	1	166.05	1,055	14	169.69	92.7 [52.02, 99.83]
	American Indian or Alaska Natives	1,628	10	278.59	1,604	19	274.66	48.1 [-17.29, 78.45]
Region	South America	7,899	27	1,321.95	7,880	79	1,315.64	66.0 [46.75, 78.88]
	North America	8,958	19	1,403.79	8,835	67	1,377.40	72.2 [53.12, 84.22]
	South Africa	2,449	20	376.26	2,463	47	377.61	57.3 [26.51, 76.03]
Comorbidity[b]	With	7,684	27	1,133.60	7,626	52	1,121.67	48.6 [16.69, 68.98]
	Without	11,622	39	1,968.40	11,552	141	1,948.98	72.6 [60.71, 81.30]

- When the number of subjects with confirmed COVID-19 was <6, VE was not calculated.

a, Excluding native Hawaiians and others, unknown, unreported, or missing cases

b, Obesity, type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, HIV infection, serious heart disorder, asthma, COPD, pulmonary fibrosis, neurological disease, cerebrovascular disease, chronic kidney disease, malignant neoplasm, liver disease, hematopoietic cell transplant recipient in an immunosuppressed condition, organ transplant recipient in an immunosuppressed condition, thalassaemia, sickle cell disease, and cystic fibrosis

c, Adjusted two-sided 95% CI

(c) Efficacy against severe/critical COVID-19

In foreign Study COV3001, VE based on the incidence of confirmed severe/critical COVID-19 was evaluated as the secondary endpoint. Confirmed severe/critical COVID-19 occurring ≥14 days after study vaccination was reported by 14 subjects in the Jcovden group and 60 subjects in the placebo group, and VE [adjusted two-sided 95% CI] was 76.7% [54.56, 89.09]. Confirmed severe/critical COVID-19 occurring ≥28 days after study vaccination was reported by 5 subjects in the Jcovden group and 34 subjects in the placebo group with VE [adjusted two-sided 95% CI] of 85.4% [54.15, 96.90].

A total of 2 subjects in the Jcovden group and 8 subjects in the placebo group presented with confirmed COVID-19 requiring medical intervention (hospitalization, admission to intensive care unit [ICU], mechanical ventilation, and extracorporeal membrane oxygenation [ECMO]) ≥14 days after study vaccination, and VE [two-sided 95% CI] was 75.0% [−25.28, 97.41] in these subjects. Such confirmed cases occurred ≥28 days after study vaccination in none of subjects in the Jcovden group and 5 subjects in the placebo group, and VE was not calculated owing to the <6 relevant subjects.

(d) Immunogenicity

Tables 17 and 18 show neutralizing antibody titers 28 days after a single dose of Jcovden 5×10^{10} vp in subjects aged ≥18 and ≤55 years (Cohort 1a) and subjects aged ≥65 years (Cohort 3) in foreign Study COV1001. In both age brackets, Jcovden induced the production of neutralizing antibodies. The neutralizing antibody titer [two-sided 95% CI] after a single dose of Jcovden 5×10^{10} vp in Cohort 3 increased from 14 days to 28 days after vaccination.

In foreign Study COV3001, 380 subjects (252 in the Jcovden group, 128 in the placebo group) were randomly selected from study centers in South Africa, Brazil, and the US. These subjects underwent ELISA for concentrations of antibodies binding to SARS-CoV-2 S protein in specimens at baseline and after 28 days of the study vaccination.[32)] As shown in Table 37, concentrations of antibodies binding to S protein at 28 days after study vaccination did not largely differ among the countries. The geometric mean concentration (GMC) [two-sided 95% CI] of antibodies binding to SARS-CoV-2 S protein measured by ELISA after a single dose of Jcovden 5×10^{10} vp in foreign Study COV1001 was 478 EU/mL [379, 603], and 586 EU/mL [445, 771] 28 days after the first dose of the study vaccine in the Jcovden 5×10^{10} vp × 1-dose group and the 5×10^{10} vp × 2-dose group, respectively, which were not largely different from the results in foreign Study COV3001 (Table 37). In foreign Study COV1001, the correlation between neutralizing antibody titers against SARS-CoV-2 and the concentrations of antibodies binding to S protein 28 days after the first dose of Jcovden was analyzed. Spearman's correlation coefficient was 0.84 and 0.72, respectively, in Cohorts 1a and 3.

Table 37. GMC of antibodies binding to SARS-CoV-2 S protein (ELISA)
(foreign Study COV3001 [primary analysis], immunogenicity evaluation population)

Group (Sample size of immunogenicity evaluation population)		South Africa		Brazil		US	
		Jcovden (n = 88)	Placebo (n = 30)	Jcovden (n = 114)	Placebo (n = 74)	Jcovden (n = 50)	Placebo (n = 24)
Baseline	Subjects analyzed (n)	84	30	114	74	50	24
	GMC (EU/mL) [two-sided 95% CI]	<LLOQ [<LLOQ, <LLOQ]	<LLOQ [<LLOQ, <LLOQ]	<LLOQ [<LLOQ, <LLOQ]	<LLOQ [<LLOQ, <LLOQ]	<LLOQ [<LLOQ, <LLOQ]	<LLOQ [<LLOQ, <LLOQ]
28 days after a single dose of vaccine	Subjects analyzed (n)	80	28	86	49	48	23
	GMC(EU/mL) [two-sided 95% CI]	388 [297, 506]	<LLOQ [<LLOQ, <LLOQ]	402 [321, 505]	<LLOQ [<LLOQ, <LLOQ]	412 [306, 554]	<LLOQ [<LLOQ, <LLOQ]

The lower limit of quantification of concentration of binding antibodies was 50.3.

(e) Efficacy in Japanese population

The correlation between neutralizing antibody titers against SARS-CoV-2 and the concentrations of antibodies binding to S protein was confirmed in foreign Study COV1001, and the concentrations of antibodies binding to S protein were similar in foreign Studies COV3001 and COV1001. Accordingly, results in foreign Study COV1001 and Japanese Study 1002 were compared mainly using the neutralizing antibody titer as an indicator to investigate differences in immune response between Japanese and non-Japanese subjects. Table 11 shows neutralizing antibody titers (microneutralization assay) against SARS-CoV-2 after a single dose of Jcovden 5×10^{10} vp in Japanese Study COV1002. In

32) In foreign Study COV3001, immunogenicity evaluation on was not initially planned. After the start of the study, in response to increasing SARS-CoV-2 infection rate at some study centers in Brazil, its impact on the efficacy evaluation was verified through the investigation of the impact of Jcovden-induced immune responses to SARS-CoV-2. The immunogenicity evaluation population consisted of subjects randomly selected from those enrolled at study centers in 3 countries including those in Brazil where the infection rate increased.

both cohorts (Cohort 1, aged ≥20 and ≤55 years; Cohort 2, aged ≥65 years), the titers increased from baseline as observed after a single dose of Jcovden 5×10^{10} vp in foreign Study COV1001 (Tables 17 and 18). In terms of the concentrations of antibodies binding to SARS-CoV-2 S protein (ELISA), GMC [two-sided 95% CI] of antibodies binding to S protein 28 days after the first dose of Jcovden 5×10^{10} vp in Japanese Study COV1002 was 488 EU/mL [382, 623] in Cohort 1 and 321 EU/mL [242, 424] in Cohort 2, which were similar to the results (Table 37) yielded 28 days after a single dose of Jcovden 5×10^{10} vp in foreign Study COV3001 and foreign Study COV1001 (described earlier).

Accordingly, although neutralizing antibody titers were not measured in foreign Study COV3001, immunogenicity results in Japanese Study COV1002 and foreign Study COV1001 support similar immune responses to SARS-CoV-2 in Japanese subjects, and thus preventive effect of Jcovden against COVID-19 demonstrated in foreign Study COV3001 can be expected in Japanese population as well.

PMDA's view on the efficacy of Jcovden:
Foreign Study COV3001 showed that a single dose of Jcovden 5×10^{10} vp prevented COVID-19. In addition, Japanese Study COV1002 demonstrated that a single dose of Jcovden 5×10^{10} vp increased neutralizing antibody titers against SARS-CoV-2 in serum as compared with baseline and in the placebo group. The comparison of results on immunogenicity between clinical studies in and outside Japan revealed similarity in neutralizing antibody induction between Japanese Study COV1002 and foreign Study COV1001 in terms of both geometric mean titer (GMT) of neutralizing antibodies and seroconversion rate. The induction of antibodies binding to S protein in Japanese subjects after a single dose of Jcovden 5×10^{10} vp in Japanese Study COV1002 did not largely differ from that in non-Japanese subjects in foreign Studies COV1001 and COV3001. These efficacy and immunogenicity outcomes show similarity in antibody response to Jcovden between Japanese and non-Japanese population, indicating promising preventive effect of Jcovden against COVID-19 in Japanese population as well.

SARS-CoV-2 vaccines are also expected to prevent not only the onset of COVID-19 but also severe COVID-19. However, the evaluation of Jcovden's preventive effect against severe COVID-19 because foreign Study COV3001 was not designed for such verification. Nevertheless, the results of VE based on the incidence of confirmed severe/critical COVID-19, the secondary endpoint in foreign Study COV3001, do not raise particular doubt about the effect of Jcovden to prevent severe COVID-19.

In the prolonged COVID-19 pandemic, approved SARS-CoV-2 vaccines are used as a booster dose to those who had been vaccinated with primary series a certain time ago. The efficacy of a booster dose of Jcovden is discussed in Section 7.R.2.4.

7.R.2.3 Durability of efficacy

The applicant's explanation about durability of Jcovden's efficacy:
(a) After a single dose of Jcovden
Tables 38 and 39 show efficacy results based on the primary endpoint analysis performed at the end of the double-blind period (data cut-off on July 9, 2021) in foreign Study COV3001 yielded after the primary analysis results (data cut-off on January 22, 2021) had been available. The VE in this analysis

was lower than that in the primary analysis. The VE against severe/critical COVID-19 remained high as observed in the primary analysis.

Table 38. Results from final analysis on VE based on confirmed moderate to severe/critical COVID-19 occurring ≥14 days after study vaccination (foreign Study COV3001 [analysis at the end of the double-blind period], PP set)

		Jcovden (n)			Placebo (n)			VE (%)[a] [two-sided 95% CI]
		Subjects analyzed (n)	Confirmed COVID-19	Total follow-up period (person-years)	Subjects analyzed (n)	Confirmed COVID-19	Total follow-up period (person-years)	
Moderate to severe/critical COVID-19		19,577	484	6,685.60	19,608	1,067	6,440.18	56.3 [51.30, 60.84]
Age	18-64 years	15,441	438	5,571.99	15,437	944	5,363.61	55.3 [49.92, 60.21]
	≥65 years	3,959	46	1,113.61	3,961	123	1,076.57	63.8 [48.88, 74.81]
COVID-19 of any severity		19,577	495	6,683.78	19,608	1,082	6,437.40	55.9 [50.95, 60.46]
Severity	Severe/critical	-	56	6,774.58	-	205	6,625.15	73.3 [63.94, 80.49]
	Moderate	-	429	6,685.60	-	862	6,440.18	52.1 [46.11, 57.40]
	Mild	-	11	6,683.78	-	15	6,437.40	29.4 [-64.57, 70.66]

a, VE = (1 − [incidence of COVID-19 in the Jcovden group/incidence of COVID-19 in the placebo group]) × 100 (%)

Table 39. Results from final analysis on VE based on confirmed moderate to severe/critical COVID-19 occurring ≥28 days after study vaccination (foreign Study COV3001 [analysis at the end of the double-blind period], PP set)

		Jcovden (n)			Placebo (n)			VE (%)[a] [two-sided 95% CI]
		Subjects analyzed (n)	Confirmed COVID-19	Total follow-up period (person-years)	Subjects analyzed (n)	Confirmed COVID-19	Total follow-up period (person-years)	
Moderate to severe/critical COVID-19		19,577	433	6,658.36	19,608	883	6,400.36	52.9 [47.06, 58.08]
Age	18-64 years	15,222	393	5,549.90	15,053	790	5,330.47	52.2 [46.01, 57.77]
	≥65 years	3,891	40	1,108.46	3,871	93	1,069.89	58.5 [39.25, 72.09]
COVID-19 of any severity		19,577	443	6,656.82	19,608	895	6,398.29	52.4 [46.63, 57.64]
Severity	Severe/critical	-	46	6,733.82	-	176	6,542.13	74.6 [64.70, 82.06]
	Moderate	-	388	6,658.36	-	707	6,400.36	47.2 [40.21, 53.51]
	Mild	-	10	6,656.82	-	12	6,398.29	19.9 [-102.28, 69.00]

a, VE = (1 − [incidence of COVID-19 in the Jcovden group/incidence of COVID-19 in the placebo group]) × 100 (%)

As of the primary analysis in foreign Study COV3001, the dominant SARS-CoV-2 variant was Wuhan B.1 (D614G) variant in the US, Beta variant in South Africa, and Zeta variant in Brazil. During the follow-up period of the study, however, a massive fall in the prevalence of these variants occurred with the emergence and spread of new variant lineages. In the US, the Alpha variant emerged 4 months after the study vaccination. In South Africa, the Delta variant was identified during the open-label/cross-over period ≥5.5 months after the study vaccination. In Brazil, the Zeta variant was replaced by the Gamma variant. In Peru, Argentine, and Colombia, the Gamma variant also emerged at various timings after the primary analysis. Concurrently, the Lambda and Mu variants emerged in Peru and Colombia, respectively. The variants are known to attenuate the efficacy of SARS-CoV-2 vaccines (*Nature Med.* 2021;27:1205-11, *Nature.* 2021;593:130-5). The over-time changes in prevalent SARS-CoV-2 variants in study countries may have been related to the differences in the analysis results on Jcovden's efficacy against moderate to severe/critical COVID-19 between the primary analysis and analysis at the end of the double-blind period. In foreign Study COV3001, at the same time, the VE analysis based on moderate to severe/critical COVID-19 in subjects vaccinated with Jcovden by post-vaccination period showed a decrease in VE over time after Jcovden vaccination (Table 40). It cannot be denied that the inconsistency in analysis results among different post-vaccination time points may be indicative of decreased Jcovden's preventive effect over time.

Table 40. VE on the basis of data on moderate to severe/critical COVID-19 by post-vaccination period (foreign Study COV3001 [analysis at the end of the double-blind period], PP set)

Post-vaccination period	Jcovden (n = 19,577)			Placebo (n = 19,608)			VE (%) [two-sided 95% CI]
	Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	
2-14 days	19,577	82	748.66	19,608	88	749.83	6.7 [-27.54, 31.77]
15-28 days	19,400	51	1,483.44	19,398	184	1,480.09	72.3 [62.10, 80.13]
29-56 days	19,113	119	2,877.42	18,924	306	2,837.44	61.7 [52.46, 69.23]
57 days to the end of double-blind	17,586	314	6,460.98	17,090	573	6,158.91	47.8 [39.95; 54.62]
57-112 days	17,586	157	5,040.02	17,090	308	4,860.10	50.8 [40.24; 59.70]
113 days to the end of double-blind	11,379	157	4,900.35	10,572	265	4,529.34	45.2 [33.04; 55.34]

An observational research (foreign Study COV4002) is currently underway to evaluate the efficacy of Jcovden in clinical use including long-term prevention of COVID-19, utilizing medical claim data in the US.[33)] An interim efficacy analysis was performed after the follow-up period up to 183 days after Jcovden vaccination based on the occurrence of COVID-19 in a group of 422,034 subjects aged ≥18 years who were vaccinated with a single dose of Jcovden between March 1 and August 17, 2021 (Jcovden group) and in 1,645,397 unvaccinated subjects (control group).[34)] In subjects who provided records of self-examination or examination at a visit or PCR test positive (including presumed positive), VE [two-sided 95% CI] of Jcovden was 76% [75, 77], and VE [two-sided 95% CI] against hospitalization due to COVID-19 was 81% [78, 82], which were considered consistent with the final analysis results of the double-blind period in foreign Study COV3001 in the US (VE [two-sided 95% CI] against moderate to severe/critical COVID-19 occurring ≥14 days after study vaccination was 72.9% [65.74, 78.70], 69.0% [37.31, 85.82] against severe/critical COVID-19, and 73.8% [0.94, 95.31] against COVID-19 requiring medical intervention including hospitalization based on objective findings). The efficacy results of a single dose of Jcovden shown in foreign Study COV4002 were considered consistent with those from researches (*MMWR.* 2021;70:1088-93, *MMWR.* 2021;70:1291-3, etc.), although different study designs and characteristics of the study population should be taken into account.

(b) Durability of immunogenicity of a single dose of Jcovden

To investigate the durability of immunogenicity of a single dose of Jcovden 5×10^{10} vp, neutralizing antibody titers against SARS-CoV-2 (microneutralization assay against SARS-CoV-2 [35)]) and concentrations of antibodies binding to SARS-CoV-2 S protein (ELISA) were measured until 8 to 9 months after vaccination in Cohorts 1a and 3 in foreign Study COV1001, and until 6 months after vaccination in foreign Study COV2001 (Tables 41 and 42). In foreign Study COV1001, neutralizing antibody titers against SARS-CoV-2 and concentrations of antibodies binding to S protein after a single dose of Jcovden continued to increase until approximately 3 months after the first dose in subjects aged ≥18 and ≤55 years (Cohort 1a), then slightly decreased 8 months after vaccination as compared to the peak values 2 or 3 months after vaccination. In subjects aged ≥65 years (Cohort 3), decreased neutralizing antibody titers and slightly decreased concentrations of binding antibodies were observed 9 months after vaccination as compared to those 1 month after vaccination. In foreign COV2001, neutralizing antibody titers against SARS-CoV-2 and the concentrations of antibodies binding to S

33) Health Verity tabulated data on inpatients, outpatients, pharmacies, and open-source medical claim data presented by testing service providers in the US.
34) Region, age, sex, and comorbidities were matched to those of subjects in the Jcovden group.
35) Variant derived from SARS-CoV-2/ Victoria/1/2020

protein increased from 1 to 2 months after vaccination and then slightly decreased. The neutralizing antibody titers decreased 5 or 6 months after vaccination as compared to those 1 month after vaccination, while concentrations of antibodies binding to S protein remain unchanged.

Table 41. Immunogenicity of a single dose of Jcovden 5×10^{10} vp (foreign Study COV1001,[a] Cohort 1a [PPI population] and Jcovden 5×10^{10} vp × 1-dose group in Cohort 3 [FAS])

Neutralizing antibodies against SARS-CoV-2					
		5×10^{10} vp × 1 dose in Cohort 1a (PPI population)		5×10^{10} vp × 1 dose in Cohort 3 (FAS*)	
		Subjects analyzed (n)	GMT [two-sided 95% CI]	Subjects analyzed (n)	GMT [two-sided 95% CI]
Baseline		25	<LLOQ	24	<LLOQ
After study vaccination	14 days	-	-	11	184 [98, 343]
	28 days	24	224 [158, 319]	25	258 [163, 410]
	56 days	25	310 [228, 422]	24	180 [120, 270]
	70 days	24	321 [237, 434]	25	183 [117, 289]
	84 days	24	338 [230, 496]	25	185 [111, 309]
	238 days	22	226 [154, 331]	22	126 [72, 222]
Antibodies binding to S protein					
		5×10^{10} vp × 1 dose in Cohort 1a (PPI population)		5×10^{10} vp × 1 dose in Cohort 3 (FAS)	
		Subjects analyzed (n)	GMC [two-sided 95% CI]	Subjects analyzed (n)	GMC [two-sided 95% CI]
Baseline		75	<LLOQ [<LLOQ, <LLOQ]	79	<LLOQ [<LLOQ, <LLOQ]
After study vaccination	14 days	-	-	63	108 [81, 145]
	28 days	69	478 [379, 603]	80	294 [238, 364]
	56 days	73	662 [518, 844]	75	366 [289, 462]
	70 days	67	612 [471, 795]	79	367 [290, 466]
	84 days	70	658 [502, 862]	78	348 [272, 444]
	238 days	68	471 [345, 642]	70	385 [245, 605]

The lower limits of quantification of neutralizing antibody titer and concentration of binding antibodies were 58 and 50.3, respectively.
a, Data cut-off on July 21, 2021

Table 42. Immunogenicity of a single dose of Jcovden 5×10^{10} vp (foreign Study COV2001, [a] PPI population)

		Jcovden 5×10^{10} vp × 1 dose (n = 80)			
		Neutralizing antibodies against SARS-CoV-2		Antibodies binding to S protein	
		Subjects analyzed	GMT [two-sided 95% CI]	Subjects analyzed	GMC [two-sided 95% CI]
Baseline		38	<LLOQ [<LLOQ, <LLOQ]	79	<LLOQ [<LLOQ, <LLOQ]
After study vaccination	14 days	38	184 [129, 262]	77	131 [99, 173]
	28 days	38	262 [215, 318]	75	353 [275, 455]
	56 days	35	281 [192, 413]	72	476 [369, 615]
	63 days	37	200 [140, 286]	76	488 [379, 628]
	70 days	37	206 [154, 274]	75	442 [341, 573]
	84 days	36	220 [153, 317]	74	455 [352, 589]
	168 days	33	171 [109, 268]	73	331 [245, 446]

The lower limits of quantification of neutralizing antibody titer and concentration of binding antibodies were 58 and 50.3, respectively.
a, Data cut-off on May 11, 2021

Accordingly, the results from the epidemiological study in clinical use of Jcovden suggest that a single dose of Jcovden maintained its efficacy for a certain period, but foreign Study COV3001 suggested decreased preventive effect against COVID-19 over time after a single dose of Jcovden, and foreign Study COV1001 showed an over-time decrease in immunogenicity.

PMDA's view:

In foreign Study COV3001, VE based on the development of moderate to severe/critical COVID-19 in the analysis at the end of the double-blind period after a single dose of Jcovden was lower than that in the primary analysis. In addition, foreign Study COV1001 showed that the immunogenicity of a single dose of Jcovden remained unchanged or increased from 1 to 3 months after vaccination but decreased 8

months after vaccination. According to reports from foreign Study COV4002 and researches, however, a single dose of Jcovden achieved favorable VE against severe/critical COVID-19. Thus, a certain level of the efficacy is expected to be maintained within the range studied. The over-time decrease in VE of Jcovden could have been due to changes in prevalent variants during the study or the emergence of new variants [see Section 7.R.2.5]. Yet, in view of findings of approved SARS-CoV-2 vaccines, possible over-time decreases in neutralizing antibody titer and VE of Jcovden cannot be denied as well. The discussion about the necessity of a booster dose is continued in the next section.

7.R.2.4 Booster dose

In foreign Study COV3001, the efficacy of a single dose of Jcovden was evaluated. Meanwhile, the development of other Ad26 vector-based vaccine product revealed a gradual decrease in antibody titer over 1-year post-vaccination. In response, the efficacy and safety of 2-dose regimen with Jcovden were evaluated in foreign Study COV3009, with the expectation that 2 doses could extend immune responses or prolong the efficacy of Jcovden.

The applicant's explanation about the efficacy of 2 doses of Jcovden:

(a) Efficacy of 2 doses of Jcovden

In foreign Study COV3009, the first and second doses of Jcovden 5×10^{10} vp or placebo were administered 2 months apart. The primary analysis on the efficacy showed that VE [adjusted two-sided 95% CI] against moderate to severe/critical COVID-19 developing ≥14 days after the second dose, the primary endpoint, was 75.2% [54.55, 87.30] (Tables 31 and 43). VE against severe/critical COVID-19 was 100% [32.62, 100]. The window of an interval between the first and second doses specified in the protocol was 37 to 75 days. In the FAS, 8,594 of 8,653 subjects (99.3%) in the Jcovden group and 8,037 of 8,075 subjects (99.5%) in the placebo group received the doses within the window, and in the PP set, all the subjects received the doses within the window.

Table 43. Efficacy of 2 doses of Jcovden (foreign Study COV3009, PP set)

		Jcovden (n)			Placebo (n)			VE (%)[a] [two-sided 95% CI[b]]
		Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	Subjects analyzed (n)	Confirmed COVID-19 (n)	Total follow-up period (person-years)	
Moderate and severe/critical COVID-19		7,484	14	1,729.99	7,008	52	1,594.98	75.2 [54.55, 87.30]
Age	18-64 years	5,358	11	1,556.34.	5,008	45	1,442.03	77.4 [54.52, 89.44]
	≥65 years	666	3	173.65	607	7	152.94	62.3 [-65.34, 93.70]
COVID-19 of any severity		7,484	60	1,729.35	7,008	113	1,593.37	51.1 [29.50, 66.45]
Severity	Severe/critical	-	0	1,730.72	-	8	1,598.87	100.0 [32.62, 100.00]
	Moderate	-	14	1,729.99	-	44	1,594.98	70.7 [45.46, 85.15]
	Mild	-	0	1,729.99	-	1	1,594.92	-

When the number of subjects with confirmed COVID-19 was <6, VE was not calculated.
a, VE = (1 − [incidence of COVID-19 in the Jcovden group/incidence of COVID-19 in the placebo group]) × 100 (%)
b, Adjusted two-sided 95% CI for moderate to severe/critical COVID-19, COVID-19 of any severity, and severe/critical COVID-19

Table 44 shows VE by subgroup. The results were consistent irrespective of age, sex, and comorbidity status. The efficacy of Jcovden is considered to have been demonstrated in all races, despite the low accuracy in VE values with a wider CI owing to the limited number of subjects in some races.

Among subgroups by region, in contrast, VE differed. VE was low in regions other than the US. During the study period, the occurrence of SARS-CoV-2 infection varied substantially by time and region, and variants of new lineage became dominant in most of the study countries. As of the primary analysis, of 469 subjects with COVID-19 confirmed during the double-blind period, 319 subjects (68.0%) provided viral sequence data, and 6.0% (19 of 319 subjects) of these subjects were infected with the reference strain,[36] and in the US, 22.9% (19 of 83 subjects) of subjects who provided sequence data were infected with the reference strain. Dominant variants were Alpha (38.2%, mainly in the US, Colombia, Spain, UK, and Philippines) and Mu (14.2%, mainly in Colombia), and the proportions of the other variants such as Beta, Delta, Gamma, and Zeta were low. Based on these results, regional differences in VE were considered potentially attributable to regional differences in dominant variants.

Table 44. Efficacy based on confirmed moderate to severe/critical COVID-19 occurring ≥14 days after the second dose of study vaccine (foreign Study COV3009, PP set)

		Jcovden			Placebo			VE (%) [two-sided 95% CI]
		Subjects analyzed (n)	Confirmed COVID-19	Total follow-up period (person-years)	Subjects analyzed (n)	Confirmed COVID-19	Total follow-up period (person-years)	
Overall		7,484	14	1,729.99	7,008	52	1,594.98	75.2 [54.55, 87.30][c]
Age	18-64 years	5,358	11	1,556.34	5,008	45	1,442.03	77.4 [55.53, 89.44]
	≥65 years	666	3	173.65	607	7	152.94	62.3 [-65.34, 93.70]
Sex	Male	3,320	9	958.29	3,139	29	900.45	70.8 [36.72, 87.86]
	Female	2,702	5	771.24	2,474	23	693.91	80.4 [47.40, 94.19]
Race[a]	White	5,014	5	1,407.78	4,608	32	1,277.23	85.8 [63.35, 95.69]
	Black or African-American	352	1	122.40	383	2	133.46	-
	Asian	327	0	96.42	301	5	88.82	-
	American Indian or Alaska Natives	151	6	48.47	158	12	48.91	49.6 [-45.24, 84.46]
Region	EU	2,966	5	833.34	2,813	15	779.24	68.8 [9.78, 91.14]
	US	2,232	1	632.40	1,999	14	559.74	93.7 [58.45, 99.85]
	South Africa	407	2	140.98	400	5	141.10	60.0 [-144.53, 96.19]
	South America	280	6	84.97	269	16	78.83	65.2 [6.40, 88.85]
	Philippines	139	0	38.30	134	2	36.07	-
Comorbidities[b]	With	2,116	5	592.77	2,008	21	550.31	77.9 [39.77, 93.49]
	Without	3,908	9	1,137.23	3,607	31	1,044.67	73.3 [42.61, 88.83]

a, Excluding native Hawaiians and those in other, multiracial, unknown, not reported, or missing status
b, Asthma, cancer, cerebrovascular disease, cystic fibrosis, chronic kidney disease, COPD, serious heart disorder, hypertension, hematopoietic cell transplant recipient in an immunosuppressed condition, organ transplant recipient in an immunosuppressed condition, liver disease, neurological disease, obesity, pulmonary fibrosis, sickle cell disease, type 1 diabetes mellitus, type 2 diabetes mellitus, and thalassaemia
c, Adjusted two-sided 95% CI

[36] The variant derived from SARS-CoV-2 Wuhan-Hu1 with a mutation causing amino acid substitution of D614G

(b) Immunogenicity of 2 doses of Jcovden and its duration

At the end of the double-blind period in foreign Study COV3009, the immunogenicity with 2 doses of the study vaccine administered 2 months apart was evaluated by measuring concentrations of antibodies binding to S protein (ELISA). The neutralizing antibody titer was not measured. The GMC [two-sided 95% CI] of the measured values in the Jcovden group was 367 EU/mL [295, 456] 28 days after the first dose, 518 EU/mL [422, 635] before the second dose, and 2220 EU/mL [1794, 2748] 14 days after the second dose.

Table 45 shows neutralizing antibody titers in subjects who received 2 doses of Jcovden 5×10^{10} vp in Cohort 1a (aged ≥18 and ≤55 years) and Cohort 3 (aged ≥65 years) in foreign Study COV1001. In both age brackets, the second dose further increased the neutralizing antibody titers. A geometric mean fold rise (GMFR) of the titer 14 days after the second dose of Jcovden to that before the second dose was 2.9 [2.3, 3.8] in Cohort 1a and 4.1 [3.1, 5.4] in Cohort 3. The greater rise of the neutralizing antibody titer in Cohort 3 than in Cohort 1a is potentially attributable to the longer interval between the doses.

Table 45. Neutralizing antibody titers in subjects who received 2 doses of Jcovden 5×10^{10} vp (foreign Study COV1001,[b] Cohort 1a [PPI population] and Jcovden group in Cohort 3 [FAS])

		Cohort 1a (aged ≥18 and ≤55 years)			Cohort 3 (aged ≥65 years)		
		Subjects analyzed (n)	GMT [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]	Subjects analyzed (n)	GMT [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]
Baseline		25	<LLOQ [<LLOQ, <LLOQ]	-	25	<LLOQ [<LLOQ, <LLOQ]	-
28 days after the first dose		25	224 [168, 298]	3.8 [2.8, 5.0]	25	298 [200, 444]	4.8 [3.3, 6.9]
Before the second dose[a]		25	288 [221, 376]	4.9 [3.7, 6.3]	24	223 [139, 359]	3.8 [2.6, 5.6]
After the second dose	14 days	24	827 [651, 1052]	13.9 [10.9, 17.7]	24	903 [567, 1438]	14.5 [9.4, 22.5]
	28 days	24	849 [664, 1086]	14.3 [11.2, 18.3]	24	973 [587, 1611]	15.6 [9.7, 25.0]
	6 months	24	465 [348, 620]	7.8 [5.9, 10.4]	0	<LLOQ (-;-)	-

a ,The interval between doses in Cohort 1a was 2 months (53-63 days after the first dose), but in Cohort 3, the interval was extended to 78 to 107 days (median 87 days) due to the suspension of the study.
b, Data cut-off on July 21, 2021

In Japanese Study COV1002, 2 doses of Jcovden 5×10^{10} vp were administered 2 months apart in Cohort 1 (aged ≥20 and ≤55 years) and Cohort 2 (aged ≥65 years). In both cohorts, neutralizing antibody titers increased after the second dose. GMFR [two-sided 95% CI] of the titer 14 days after the second dose of the study vaccine to that before the second dose was 2.2 [1.8, 2.8] in Cohort 1 and 1.7 [1.3, 2.4] in Cohort 2. The immune responses to the second dose of Jcovden were also demonstrated in Japanese subjects as with immunogenicity results in foreign clinical studies (Table 46).

Table 46. Neutralizing antibody titers in subjects who received 2 doses of Jcovden 5 × 10^{10} vp 2 months apart (Japanese Study COV1002, PPI population)

		Cohort 1 (aged ≥20 and ≤55 years)			Cohort 2 (aged ≥65 years)		
		Subjects analyzed (n)	GMT [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]	Subjects analyzed (n)	GMT [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]
Baseline		51	<LLOQ [<LLOQ, <LLOQ]	-	50	<LLOQ [NE, NE]	-
After the first dose	14 days	50	277 [225, 342]	4.7 [3.9, 5.8]	50	152 [120, 193]	2.8 [2.3, 3.4]
	28 days	50	269 [228, 318]	4.6 [3.9, 5.4]	50	311 [259, 374]	5.4 [4.6, 6.5]
Before the second dose		45	456 [373, 559]	7.8 [6.4, 9.5]	49	281 [204, 386]	4.9 [3.6, 6.7]
After the second dose	14 days	43	1049 [828, 1329]	17.9 [14.2, 22.7]	48	504 [404, 627]	8.7 [7.0, 10.8]
	28 days	43	1088 [817, 1449]	18.6 [14.0, 24.7]	48	429 [335, 550]	7.4 [5.8, 9.5]

Accordingly, the single-dose vaccination regimen of Jcovden 5 × 10^{10} vp remains useful, but a booster dose of Jcovden administered ≥2 months after the first dose is expected to increase the immune response and thereby enhance the preventive effect against COVID-19 including diseases caused by new SARS-CoV-2 variants.

PMDA's view:
Based on the experience in the development of the other Ad26 vector platform vaccines as with Jcovden, foreign Study COV3009 was conducted in parallel with foreign Study COV3001 to evaluate the efficacy of 2 doses of Jcovden administered 2 months apart, and demonstrated the preventive effect of the 2-dose regimen against COVID-19. Furthermore, immunogenicity evaluation in foreign Study COV1001, etc. in subjects who received 2 doses of Jcovden showed that the 2-dose regimen of Jcovden increased neutralizing antibody titers against SARS-CoV-2 and maintained immune responses for a certain period. At present, no surrogate indicator has been established for immunogenicity against SARS-CoV-2 required for the prevention of COVID-19, but a correlation between prevention and neutralizing antibody titer is suggested (*Nature Med.* 2021;27:1205-11). In view of findings with approved SARS-CoV-2 vaccines (*N Engl J Med.* 2021;385:1393-1400), maintenance of high neutralizing antibody titers is meaningful for long-term prevention of COVID-19 and as measures against the resurgence of COVID-19 pandemic with emerging variants. The single-dose regimen of Jcovden is suggested to maintain VE against severe/critical COVID-19 but reduced VE over time [see Section 7.R.2.3] In this prolonged COVID-19 pandemic, long-term retention of immunogenicity against SARS-CoV-2 is essential, the use of a booster dose given at a certain interval after a single dose of Jcovden, as practiced with the other SARS-CoV-2 vaccines, deserves consideration to prevent COVID-19 for an extended period.

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

7.R.2.5 Efficacy against variants

The applicant's explanation about the efficacy of Jcovden against variants:
(a) VE of single dose of Jcovden against variants
To investigate an impact of SARS-CoV-2 gene mutation on the efficacy of Jcovden, a SARS-CoV-2 whole-genome sequence analysis was performed in subjects with confirmed COVID-19 occurring ≥14 and ≥28 days after a single dose of the study vaccine at the primary analysis in foreign Study COV3001.

SARS-CoV-2 genome sequence was analyzed in 512 of 714 subjects with confirmed COVID-19. In the US, the reference strain[37)] was found in 96.4% (190 of 197) of the subjects, and in South Africa, the Beta variant (B.1.351 lineage) was found in 94.5% (86 of 91) of the subjects. In Brazil, the Zeta variant (P.2 lineage) and the reference strain were found in 69.4% (86 of 124) and 30.6% (38 of 124) of the subjects, respectively. According to VE by region (Tables 35 and 36), a certain level of the efficacy was observed ≥28 days after Jcovden vaccination in South Africa (Beta variant dominant), and VE in South America including Brazil (Zeta variant partially dominant) was similar to that in the US (reference strain dominant). The efficacy of Jcovden against variants shown during foreign Study COV3001 is therefore considered unaffected or hardly affected by mutations of the virus prevalent during the study.

In foreign Study COV3001, an impact of mutations in prevalent virus strains on the efficacy of Jcovden was evaluated in response to changing prevalent virus strains in the study regions after the primary analysis. Table 47 shows VE against variants (designated during the study as VOC and Variants of Interest [VOI] by WHO) in the analysis at the end of the double-blind period. Although the data of the variants causing COVID-19 in limited number of subjects warrant careful interpretation, VE against Alpha variant was comparable to or higher than that against the reference strain; VE against the Beta variant after 14 day of vaccination was lower than that against the reference strain, but the VE after 29 days of vaccination was almost comparable to that against the reference strain; and VE against the Gamma, Lambda, and Mu variants was low. Because the Delta variant emerged in the late phase of foreign Study COV3001 (≥5.5 months after the study vaccination), the data of the Delta variant are limited, resulting in a wider two-sided 95% CI of VE, and thus an appropriate conclusion could not be drawn.

37) The variant derived from SARS-CoV-2 Wuhan-Hu1 with a mutation causing amino acid substitution of D614G

Table 47. VE based on confirmed moderate to severe/critical COVID-19 occurring ≥14 and ≥28 days after a single dose of study vaccine by variant[a] (foreign Study COV3001, analysis at the end of the double-blind period, PP set)

	≥14 days after the study vaccine			≥28 days after the study vaccine		
	Jcovden	Placebo	VE (%) [two-sided 95% CI]	Jcovden	Placebo	VE (%) [two-sided 95% CI]
Subjects analyzed (n)	19,577	19,608		19,577	19,608	
Total follow-up period	6685.6 person-years	6440.2 person-years		6658.4 person-years	6400.4 person-years	
	Confirmed COVID-19	Confirmed COVID-19		Confirmed COVID-19	Confirmed COVID-19	
All subjects	484	1,067	56.3 [51.30, 60.84]	433	883	52.9 [47.08, 58.08]
Reference strain[b]	32	108	71.5 [57.31, 81.39]	30	69	58.2 [34.96, 73.72]
Other than reference strain	265	454	43.8 [34.43, 51.86]	239	413	44.4 [34.61, 52.76]
VOCs						
Alpha[c]	9	29	70.1 [35.13, 87.55]	9	29	70.2 [35.27, 87.58]
Beta[c]	36	56	38.1 [4.20, 60.43]	23	46	51.9 [19.06, 72.19]
Gamma[c]	74	112	36.4 [13.87, 53.20]	74	112	36.5 [14.05, 53.30]
Delta	11	10	-6.0 [-178.30, 59.15]	11	10	-5.7 [-177.71, 59.23]
VOIs[d]						
Zeta	34	93	64.8 [47.32, 76.95]	25	67	64.1 [42.45, 78.30]
Mu	38	57	35.8 [1.49, 58.56]	38	57	35.9 [1.69, 58.65]
Lambda	43	46	10.0 [-39.53, 41.98]	43	46	10.1 [-39.23, 42.11]
Epsilon	8	17	54.7 [-10.83, 83.07]	5	14	65.7 [-0.86, 90.32]
Iota	0	4	-	0	4	-
Eta	0	0	-	0	0	-
Kappa	0	0	-	0	0	-
Theta	0	0	-	0	0	-

a, SARS-CoV-2 variants designated during Study COV3001 as VOC or VOI by WHO
b, Wuhan-Hu1 reference sequence + D614G
c, The position was changed to "previously circulating VOCs" (changed on March 9, 2022)
d, All variants were re-designated as "previously circulating VOIs" (changed on July 6, 2021 for Epsilon, Zeta, and Theta; on September 21, 2021 for Eta, Iota and Kappa; and on March 9, 2022 for Lambda and Mu).

In foreign Study COV3009, of subjects with confirmed COVID-19 who were subjected to the primary endpoint evaluation, 42 subjects (7 in the Jcovden group, 35 in the placebo group) provided analysis results on SARS-CoV-2 genome sequence. The efficacy against each variant (limited to the variants affecting ≥6 subjects) was analyzed. VE [two-sided 95% CI] based on moderate to severe/critical COVID-19 occurring ≥14 days after the second dose of Jcovden 5×10^{10} vp was 94.2% [62.91, 99.86] against the Alpha variant and 63.1% [−27.86, 91.56] against the Mu variant. COVID-19 caused by the Delta variant occurred ≥14 days after the second dose of the study vaccine in 3 subjects (2 in the Jcovden group, 1 in the placebo group), precluding efficacy evaluation of Jcovden.

In the implementation research (foreign Study COV3012) in healthcare professionals aged ≥18 years is currently underway in South Africa by the South Africa Medical Research Council (SAMRC). In the research, the efficacy of a single dose of Jcovden is evaluated in clinical settings based on the incidence of COVID-19 occurring ≥28 days after Jcovden vaccination. VE [two-sided 95% CI] of a single dose of Jcovden was 86% [57, 100] and 62% [42, 76] respectively, against death and hospitalization due to COVID-19 caused by the Beta variant and 82% [74, 89] and 67% [62, 71] respectively, against those caused by the Delta variant (*Lancet.* 2022;399:1141-53). The efficacy of Jcovden against the Omicron variant, which emerged after results on the efficacy of Jcovden were yielded from foreign Studies COV3001 and COV3009, was evaluated in an extension study from foreign Study COV3012 (Study COV3021). In the study, the second dose of Jcovden was administered to healthcare providers aged ≥18 years 6 to 9 months after the first dose. The enrollment began just before the prevalence of Omicron variant first reported in South Africa early November 2021. VE [two-sided 95% CI] against hospitalization due to COVID-19 occurring between November 15 and December 20, 2021 was 63%

[31, 81], 84% [67, 92], and 85% [54, 95] against hospitalization occurring 0 to 13 days, 14 to 27 days, and 1 to 2 months, respectively, after the second dose of Jcovden (medRxiv published online Dec 29, 2021. doi: https://doi.org/10.1101/2021.12.28.21268436, preprint).

(b) Immunogenicity of Jcovden against variants

Neutralizing antibody titers against SARS-CoV-2 Alpha, Beta, and Delta variants were measured using serum specimens from some of the subjects in the Jcovden 5×10^{10} vp × 1-dose group in Cohort 1a in foreign Study COV1001 (Table 48). Neutralizing antibody titers against Alpha, Beta, and Delta variants in serum specimens 28 days after Jcovden vaccination were <1/8, <1/40, and <1/37, respectively, of the neutralizing antibody titer against the reference strain (wild-type strain[38)]), but GMTs against all the variants increased 70 days after vaccination. Neutralizing antibody titers against Delta variant only were measured 8 months after vaccination. The resultant GMT was lower than that against the reference strain.

Table 48. GMT [two-sided 95% CI] of neutralizing antibodies against major variants after a single dose of Jcovden 5×10^{10} vp (foreign Study COV1001,[a] Cohort 1a)

Time after a single dose of Jcovden	Subjects measured (n)	Reference strain	Variant		
			Alpha	Beta	Delta
28 days	6	573.09 [267.88, 1226.08]	64.78 [29.82, 140.71]	14.02 [7.78, 25.28]	15.21 [7.65, 30.25]
70 days	6	403.32 [170.26, 955.37]	119.37 [54.71, 260.46]	40.78 [23.52, 70.69]	27.59 [11.24, 67.74]
	14[b]	374.84 [270.54, 519.35]	112.72 [82.19, 154.59]	26.88 [17.58, 41.09]	-
8 months	6	224.17 [125.17, 401.45]	-	-	21.58 [8.76, 53.16]

a, Data cut-off on July 21, 2021
b, Including 6 subjects to be measured 28 days after a single dose of Jcovden

To evaluate immunogenicity against variants in subjects who received 2 doses of Jcovden 5×10^{10} vp 2 months apart, neutralizing antibody titers against the Alpha and Beta variants 14 days after the second dose (Day 71) were measured using serum specimens collected from some of the subjects in Jcovden 5×10^{10} vp × 2-dose group in Cohort 1a in foreign Study COV1001. GMT [two-sided 95% CI] of neutralizing antibodies was 397.96 [282.06, 561.50] and 108.52 [80.72, 145.90] against the Alpha and Beta variants, respectively, which were lower than GMT (1656.06 [1046.03, 2621.87]) of neutralizing antibodies against the reference strain but 3.5 and 4 times higher than that in specimens collected from 14 subjects 70 days after a single dose of Jcovden 5×10^{10} vp (Day 71) including 6 subjects with a specimen measured 28 days after the single dose (Table 48).

The immunogenicity of Jcovden against the Omicron variant was investigated based on neutralizing antibody titers and concentrations of antibodies binding to S protein in serum specimens collected 1 and 8 months after a single dose of Jcovden in foreign Study COV3001, which were both lower than that against the reference strain (*Nature.* 2022;603:493-6). A single dose of Comirnaty Intramuscular Injection or Jcovden was administered ≥6 months after the completion of the primary series with 2 doses of Comirnaty Intramuscular Injection. After the injection of a booster dose of Jcovden, the neutralizing antibody titers against the Omicron variant were lower than those against the reference strain but increased over the period from 2 to 4 weeks after vaccination, and the neutralizing antibody titer

38) Derived from the SARS-CoV-2 Victoria/1/2020 strain, isolated from a patient who had COVID-19 after arriving at Australia from China (Wuhan)

(median) 4 weeks after-vaccination was 41 times higher than that before the booster injection. In contrast, the booster dose of Comirnaty Intramuscular Injection increased the neutralizing antibody titer against Omicron variant to a higher level than that after the booster injection of Jcovden in 2 weeks after vaccination, but decreased in Week 4 after vaccination (medRxiv published online Dec 29, 2021. doi: https://doi.org/10.1101/2021.12.02.21267198, preprint).

PMDA's view:
A single dose of Jcovden 5×10^{10} vp has promising efficacy against the Alpha variant, which was prevalent during foreign Study COV3001, as is the case with the reference strain. However, the efficacy of Jcovden tended to be inferior against the Beta variant, a non-Alpha variant, to that against the reference strain in foreign Study COV3001 with low neutralizing antibody titers against the variant. Therefore, the decreased efficacy of a single dose of Jcovden cannot be denied. However, given the limited number of COVID-19 events caused by these variants and the study design that was not intended to evaluate efficacy against each variant, it is difficult to conclude how Jcovden is effective against each variant, more specifically, to what extent non-Alpha variant-induced COVID-19 will be prevented or to what extent such effect will be attenuated, only based on results in foreign Study COV3001. It is also difficult to determine the efficacy of the 2-dose regimen with Jcovden 5×10^{10} vp against non-Alpha variants, i.e., differences in efficacy among variants, only based on results in foreign Study COV3009.

Meanwhile, the highly contagious Omicron and other variants were identified in many countries including Japan after the periods of these studies. The efficacy of Jcovden against these variants has not been evaluated in clinical studies. However, the Omicron variant, which has a variety of mutations in the gene coding S protein, may reduce the efficacy of the other SARS-CoV-2 vaccines, and a significant decrease in neutralization activity has been reported with Jcovden as well (*Nature.* 2022;602:664-70, *Nature.* 2022;603:493-6).

As described above, limited information is available from the clinical studies about the preventive effect of Jcovden against COVID-19 caused by variants. Thus the possibility cannot be denied that the results from the major clinical studies and findings from literature on hand may be inconsistent with the efficacy of Jcovden against variant-associated COVID-19 shown in foreign Study COV3001. At the same time, foreign Studies COV3012 and COV3021, which evaluated the efficacy in clinical use, reported decreases in COVID-19-asssociated hospitalization and deaths caused by prevalent non-Alpha variants. These results do not completely deny the clinical significance of Jcovden, including a certain level of the efficacy against the currently prevalent Omicron variant. The applicant should continue to closely monitor the emergence and prevalence of variants and collect data on the immunogenicity of Jcovden such as the induction of neutralization against variants, including those from non-clinical studies, and the clinical efficacy. New findings should be provided to healthcare professionals as necessary, and any appropriate actions should be taken accordingly.

7.R.2.6 Impact of existing immunity against adenovirus on the efficacy

For being a human adenoviral vector-based vaccine product, the efficacy and safety of Jcovden may be affected by the recipient's existing immune responses to adenoviruses.

The applicant's explanation about the impact of existing immunity against adenovirus:
The Ad26 vector was selected as a platform of vaccine development because historical data available in the US and Europe indicate low prevalence of Ad26 in humans. In Japan, however, there are no historical data on the positive rate of serum neutralizing antibodies against Ad26, which is reported to largely differ depending on the location, ranging from 10% to 80% (*Vaccine.* 2011;29:5203-59, *J Virol.* 2010;84:10522-32, etc.).

To determine the positive rate of serum antibodies against Ad26, anti-Ad26 neutralizing antibody titers (luciferase reporter assay) were measured in serum specimens from subjects in Cohort 1a and Cohort 3 in foreign Study COV1001 and subjects in Japanese Study COV1002, as well as some of the subjects in Brazil and the US in foreign Study COV3001. Anti-Ad26 neutralizing antibodies were detected at baseline in serum specimens from 2.0% (2 of 100) of subjects in Cohort 1a and 16.3% (16 of 98) of subjects in Cohort 3 in foreign Study COV1001; 3.2% (4 of 125) of subjects in Cohort 1 (aged ≥20 and ≤55 years) and 29.0% (36 of 124) of subjects in Cohort 2 (aged ≥65 years) in Japanese Study COV1002; and 2.0% (1 of 50) of subjects in the Jcovden group and 4.2% (1 of 24) of subjects in the placebo group in the US and 32.5% (37 of 114) of subjects in the Jcovden group and 28.4% (21 of 74) of subjects in the placebo group in Brazil in foreign Study COV3001.

Table 49 shows neutralizing antibody titers against SARS-CoV-2 (wild-type strain) 28 days after vaccination in Cohort 2 in Japanese Study COV1002 by baseline anti-Ad26 neutralizing antibody. Anti-SARS-CoV-2 neutralizing antibody titers increased irrespective of baseline anti-Ad26 neutralizing antibodies, and the presence of anti-Ad26 neutralizing antibodies at baseline is thus considered to have no impact on Jcovden's induction of neutralizing antibodies against SARS-CoV-2 (wild-type strain).

Table 49. Neutralizing antibody titer against SARS-CoV-2 (wild-type strain) (GMT) by baseline anti-Ad26 neutralizing antibodies (Japanese Study COV1002, Cohort 2)

	Negative for anti- Ad26 neutralizing antibodies at baseline			Positive for anti-Ad26 neutralizing antibodies at baseline		
	5×10^{10} vp	1×10^{11} vp	Placebo	5×10^{10} vp	1×10^{11} vp	Placebo
Number of subjects	35	38	15	15	11	10
Baseline [two-sided 95% CI]	<LLOQ [NE, NE]	<LLOQ [NE, NE]	<LLOQ [NE, NE]	<LLOQ [NE, NE]	<LLOQ [NE, NE]	<LLOQ [NE, NE]
28 days post-vaccination [two-sided 95% CI]	278 [222, 348]	423 [321, 559]	<LLOQ [NE, NE]	406 [296, 556]	347 [244, 494]	<LLOQ [NE, NE]

In foreign Study COV1001, immunity against Ad26 was also evaluated after a single dose or 2 doses of Jcovden 5×10^{10} vp or 1×10^{11} vp, 2 months apart where applicable. Anti-Ad26 neutralizing antibody titers at baseline and after a single dose were shown to have no impact on Jcovden's induction of anti-SARS-CoV-2 neutralizing antibodies 28 or 70 days after the first dose or 28 days after the second dose (*N Engl J Med.* 2021;384:1824-35).

In the clinical studies using the other Ad26 vector vaccines developed by the applicant, existing anti-Ad26 neutralizing antibodies have not been shown to have any clear impact on immune responses induced by single dose or multiple doses (*Lancet HIV.* 2020;7:e688-98, *Lancet.* 2018;392:232-43, etc.).

Based on the above, the applicant considers that anti-Ad26 neutralizing antibodies at baseline have no impact on a rise in neutralizing antibodies against SARS-CoV-2 (wild-type strain). Of note, in Japanese Study COV1002, foreign Study COV3001, etc., adverse events did not differ by baseline anti-Ad26 neutralizing antibodies.

PMDA's view:
In Japanese and foreign clinical studies of Jcovden, neutralizing antibodies against SARS-CoV-2 (wild-type strain) increased in subjects tested positive for anti-Ad26 neutralizing antibodies at baseline as well, suggesting no concerns about evident impact of such antibodies at baseline on immune responses to Jcovden. At present, no special attention is required for the use of Jcovden in anti-Ad26 neutralizing antibody-positive recipients. The applicant, however, should continue collecting relevant information and take appropriate measures based on new findings, because it is unclear whether the positive rate of ant-Ad26 neutralizing antibody in Japanese population in Japanese Study COV1002 represents the positive rate in the overall Japanese population and to what extent the baseline anti-Ad26 neutralizing antibody status would affect the preventive effect of Jcovden.

7.R.3 Safety

The main focus of safety evaluation is the population of subjects who received the proposed dose of Jcovden 5×10^{10} vp in foreign Study COV3001, Japanese Study COV1002, and foreign Study COV3009. The evaluation of deaths, serious adverse events other than deaths, and adverse events of special interest includes the population of subjects who received a dose other than the proposed dose in the studies submitted.

7.R.3.1 Safety in clinical studies

The applicant explained the safety of Jcovden in clinical studies as follows.

7.R.3.1.1 Adverse events

(a) Foreign Study COV3001

Table 50 shows a summary of adverse events observed after a single dose of the study vaccine in foreign Study COV3001. In all clinical studies of Jcovden, solicited local adverse events were all deemed to be related to the study vaccine as specified in the protocol. For adverse events other than solicited local adverse events, a relationship to the study vaccine was judged by investigators.

Table 50. Summary of incidences of adverse events (foreign Study COV3001 [primary analysis], safety subset or FAS)

	Adverse events		Causally related	
Safety subset				
Group (Subjects analyzed)	Jcovden (3,356)	Placebo (3,380)	Jcovden (3,356)	Placebo (3,380)
Solicited local adverse events	1,687 (50.3%)	658 (19.5%)	1,687 (50.3%)	658 (19.5%)
Grade 3	23 (0.7%)	6 (0.2%)	23 (0.7%)	6 (0.2%)
Grade 4	0	0	0	0
Solicited systemic adverse events	1,853 (55.2%)	1,188 (35.1%)	1,819 (54.2%)	1,131 (33.5%)
Grade 3	61 (1.8%)	21 (0.6%)	60 (1.8%)	20 (0.6%)
Grade 4	0	0	0	0
Unsolicited adverse events	440 (13.1%)	407 (12.0%)	242 (7.2%)	154 (4.6%)
Grade 3	16 (0.5%)	16 (0.5%)	5 (0.1%)	1 (<0.1%)
Grade 4	3 (0.1%)	2 (0.1%)	0	0
FAS				
Group (Subjects analyzed)	Jcovden (21,895)	Placebo (21,888)	Jcovden (21,895)	Placebo (21,888)
Serious adverse events	90 (0.4%)	137 (0.6%)	7 (0.03%)	2 (0.01%)
Deaths	3 (0.01%)	16 (0.07%)	0	0

Number of subjects with events (incidence)
For definitions of Grades 3 and 4, see Tables 67 to 69.

The incidences of solicited local and systemic adverse events are shown Table 29. Table 51 shows Grade ≥3 solicited local and systemic adverse events. Incidences of both Grade ≥3 solicited local and systemic adverse events were low, and no Grade 4 events occurred.

Table 51. Grade ≥3 solicited local and systemic adverse events (foreign Study COV3001 [primary analysis], safety subset)

		Adverse events		Causally related	
Group (Subjects analyzed)		Jcovden (3,356)	Placebo (3,380)	Jcovden (3,356)	Placebo (3,380)
Local	Injection site pain	11 (0.3%)	2 (0.1%)	11 (0.3%)	2 (0.1%)
	Injection site erythema	7 (0.2%)	2 (0.1%)	7 (0.2%)	2 (0.1%)
	Injection site swelling	7 (0.2%)	2 (0.1%)	7 (0.2%)	2 (0.1%)
Systemic	Fatigue	35 (1.0%)	9 (0.3%)	35 (1.0%)	9 (0.3%)
	Headache	23 (0.7%)	9 (0.3%)	22 (0.7%)	9 (0.3%)
	Myalgia	32 (1.0%)	6 (0.2%)	32 (1.0%)	5 (0.1%)
	Nausea	6 (0.2%)	6 (0.2%)	6 (0.2%)	6 (0.2%)
	Pyrexia	8 (0.2%)	0	8 (0.2%)	0

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.

The median time to onset of solicited local adverse events was 2 days after vaccination in the Jcovden group and 1 to 2 days after vaccination in the placebo group with the median duration of within 3 days in both groups. The median time to onset of solicited systemic adverse events was 2 days after vaccination in the Jcovden group and 2 to 3 days after vaccination in the placebo group with the median duration of within 1 to 2 days in both groups.

Table 30 shows the incidences of unsolicited adverse events. Grade ≥3 events occurred in 0.6% (19 of 3,356) of subjects in the Jcovden group and 0.5% (18 of 3,380) of subjects in the placebo group. Events in 5 subjects in the Jcovden group (chills, fatigue, malaise, diarrhoea, pain in extremity, and headache in 1 subject each [some subjects reported multiple events]) and 1 subject in the placebo group (arthralgia, dizziness, nasal congestion, sneezing, and wheezing in 1 subject each [the subject experienced multiple events]) were considered causally related to the study vaccination, but all the events were confirmed to have resolved. No Grade 4 events occurred.

(b) Foreign Study COV3009

Table 52 shows the incidences of adverse events occurring after each dose of the study vaccine in the Jcovden group and placebo group in foreign Study COV3009.

Table 52. Summary of adverse events (foreign Study COV3009, safety subset or FAS)

	After the first dose		After the second dose	
Safety subset				
Group (Subjects analyzed)	Jcovden (3,015)	Placebo (3,052)	Jcovden (1,559)	Placebo (1,425)
Solicited local adverse events	1,676 (55.6%)	653 (21.4%)	896 (57.5%)	252 (17.7%)
Grade ≥3	9 (0.3%)	6 (0.2%)	10 (0.6%)	3 (0.2%)
Solicited systemic adverse events	1,764 (58.5%)	1,138 (37.3%)	821 (52.7%)	442 (31.0%)
Grade ≥3	55 (1.8%)	14 (0.5%)	25 (1.6%)	5 (0.4%)
Solicited systemic adverse events considered causally related to study vaccine	1,715 (56.9%)	1,081 (35.4%)	810 (52.0%)	423 (29.7%)
Grade ≥3	53 (1.8%)	14 (0.5%)	25 (1.6%)	5 (0.4%)
Unsolicited adverse events	454 (15.1%)	332 (10.9%)	159 (10.2%)	120 (8.4%)
Grade ≥3	21 (0.7%)	16 (0.5%)	12 (0.8%)	7 (0.5%)
Unsolicited adverse events considered causally related to study vaccine	283 (9.4%)	179 (5.9%)	79 (5.1%)	49 (3.4%)
Grade ≥3	9 (0.3%)	5 (0.2%)	5 (0.3%)	1 (0.1%)
FAS				
Group (Subjects analyzed)	Jcovden (15,708)		Placebo (15,592)	
Serious adverse events	104 (0.7%)		136 (0.9%)	
Deaths	4 (<0.1%)		13 (<0.1%)	

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.

Table 32 shows the incidences of solicited local and systemic adverse events. Table 53 shows Grade ≥3 solicited local and systemic adverse events. No Grade 4 events occurred.

Table 53. Grade ≥3 solicited local and systemic adverse events after each dose of study vaccine (foreign Study COV3009, safety subset)

		After the first dose				After the second dose			
		Adverse events		Causally related		Adverse events		Causally related	
Group (Subjects analyzed)		Jcovden (3,015)	Placebo (3,052)	Jcovden (3,015)	Placebo (3,052)	Jcovden (1,559)	Placebo (1,425)	Jcovden (1,559)	Placebo (1,425)
Local	Injection site erythema	2 (0.1%)	1 (<0.1%)	2 (0.1%)	1 (<0.1%)	7 (0.4%)	2 (0.1%)	7 (0.4%)	2 (0.1%)
	Injection site pain	3 (0.1%)	4 (0.1%)	3 (0.1%)	4 (0.1%)	3 (0.2%)	1 (0.1%)	3 (0.2%)	1 (0.1%)
	Injection site swelling	4 (0.1%)	1 (<0.1%)	4 (0.1%)	1 (<0.1%)	2 (0.1%)	0	2 (0.1%)	0
Systemic	Fatigue	26 (0.9%)	7 (0.2%)	25 (0.8%)	7 (0.2%)	14 (0.9%)	2 (0.1%)	14 (0.9%)	2 (0.1%)
	Headache	23 (0.8%)	5 (0.2%)	21 (0.7%)	5 (0.2%)	10 (0.6%)	3 (0.2%)	10 (0.6%)	3 (0.2%)
	Myalgia	23 (0.8%)	4 (0.1%)	22 (0.7%)	4 (0.1%)	9 (0.6%)	1 (0.1%)	9 (0.6%)	1 (0.1%)
	Nausea	9 (0.3%)	5 (0.2%)	8 (0.3%)	5 (0.2%)	3 (0.2%)	0	3 (0.2%)	0
	Pyrexia	2 (0.1%)	0	1 (<0.1%)	0	1 (0.1%)	0	1 (0.1%)	0

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.

For solicited adverse events, the median time to onset of local adverse events was 1 to 2 days after vaccination in the Jcovden group and 1 day after that in the placebo group, with the median duration of 2 to 3 days in the Jcovden group and 1 to 2 days in the placebo group. The time to onset and duration did not largely differ between events after the first and second doses. For solicited systemic adverse events, the median time to onset was 2 days after vaccination in the Jcovden group and 2 to 5 days after

vaccination in the placebo group, with the median duration of 1 to 2 days in both Jcovden group and placebo group. In the Jcovden group, the time to onset and duration did not largely differ between events after the first and second doses.

Table 33 shows the incidences of unsolicited adverse events. Grade ≥3 events occurred in 0.7% (21 of 3,015) of subjects in the Jcovden group and 0.5% (16 of 3,052) of subjects in the placebo group after the first dose and 0.8% (12 of 1,559) of subjects in the Jcovden group and 0.5% (7 of 1,425) of subjects in the placebo group after the second dose. Table 54 shows Grade ≥3 unsolicited adverse events considered causally related to the study vaccine.

Table 54. Grade ≥3 unsolicited adverse events considered causally related to study vaccine (foreign Study COV3009, safety subset)

After the first dose		
	Jcovden (3,015)	Placebo (3,052)
Grade ≥3 events considered causally related to study vaccine	9 (0.3%)	5 (0.2%)
Headache	5 (0.2%)	2 (0.1%)
Fatigue	1 (<0.1%)	2 (0.1%)
Injection site pain	1 (<0.1%)	0
Injection site erythema	0	1 (<0.1%)
Tenderness	0	1 (<0.1%)
Vaccination site erythema	0	1 (<0.1%)
Pericarditis	1 (<0.1%)	0
Diarrhoea	1 (<0.1%)	0
Nausea	0	2 (0.1%)
Myalgia	1 (<0.1%)	1 (<0.1%)
Urticaria	1 (<0.1%)	0
After the second dose		
	Jcovden (1,559)	Placebo (1,425)
Grade ≥3 events considered causally related to study vaccine	5 (0.3%)	1 (0.1%)
Fatigue	1 (0.1%)	1 (0.1%)
Vaccination site erythema	1 (0.1%)	0
Nausea	1 (0.1%)	0
Myalgia	1 (0.1%)	0
Rash	1 (0.1%)	0

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.

For both solicited and unsolicited adverse events, safety profiles after the first and second doses were similar without an increase of incidence after the second dose.

(c) Japanese Study COV1002

Table 55 is a summary of adverse events in the Jcovden 5×10^{10} vp group and placebo group in Japanese Study COV1002.

Table 55. Summary of adverse events (Japanese Study COV1002, FAS)

First dose	Cohort 1				Cohort 2			
	Adverse events		Causally related		Adverse events		Causally related	
Group (Subjects analyzed)	Jcovden 5 × 10^{10} vp (51)	Placebo (24)	Jcovden 5 × 10^{10} vp (51)	Placebo (24)	Jcovden 5 × 10^{10} vp (50)	Placebo (26)	Jcovden 5 × 10^{10} vp (50)	Placebo (26)
Solicited local adverse events	42 (82.4%)	2 (8.3%)	42 (82.4%)	2 (8.3%)	18 (36.0%)	1 (3.8%)	18 (36.0%)	1 (3.8%)
Grade ≥3	1 (2.0%)	0	1 (2.0%)	0	0	0	0	0
Solicited systemic adverse events	45 (88.2%)	2 (8.3%)	45 (88.2%)	2 (8.3%)	13 (26.0%)	4 (15.4%)	13 (26.0%)	4 (15.4%)
Grade ≥3	4 (7.8%)	0	4 (7.8%)	0	1 (2.0%)	0	1 (2.0%)	0
Unsolicited adverse events	15 (29.4%)	2 (8.3%)	7 (13.7%)	0	15 (30.0%)	4 (15.4%)	6 (12.0%)	4 (15.4%)
Grade ≥3	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0
Serious adverse events other than deaths	1 (2.0%)	0	0	0	0	0	0	0
Second dose	Cohort 1				Cohort 2			
	Adverse events		Causally related		Adverse events		Causally related	
Group (Subjects analyzed)	Jcovden 5 × 10^{10} vp (43)	Placebo (23)	Jcovden 5 × 10^{10} vp (43)	Placebo (23)	Jcovden 5 × 10^{10} vp (48)	Placebo (24)	Jcovden 5 × 10^{10} vp (48)	Placebo (24)
Solicited local adverse events	36 (83.7%)	0	36 (83.7%)	0	16 (33.3%)	2 (8.3%)	16 (33.3%)	2 (8.3%)
Grade ≥3	0	0	0	0	0	0	0	0
Solicited systemic adverse events	28 (65.1%)	0	27 (62.8%)	0	13 (27.1%)	5 (20.8%)	13 (27.1%)	4 (16.7%)
Grade ≥3	1 (2.3%)	0	1 (2.3%)	0	0	0	0	0
Unsolicited adverse events	12 (27.9%)	1 (4.3%)	6 (14.0%)	0	6 (12.5%)	3 (12.5%)	2 (4.2%)	1 (4.2%)
Grade ≥3	0	0	0	0	1 (2.1%)	0	0	0
Serious adverse events	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.

Tables 12 and 13 show the incidences of solicited local and systemic adverse events in Japanese Study COV1002. Table 56 lists Grade ≥3 events. These events including systemic adverse events were considered causally related to the study vaccination. The occurrence of solicited adverse events and Grade ≥3 solicited adverse events tended to be lower in the elderly group (Cohort 2) than in the non-elderly group (Cohort 1). Solicited adverse events was similar after the first and second doses. The incidences of solicited adverse events and Grade ≥3 solicited adverse events after the second dose were lower than those after the first dose.

Table 56. Grade ≥3 solicited adverse events after each dose of study vaccine (Japanese Study COV1002, FAS)

After the first dose		Cohort 1		Cohort 2	
		Jcovden 5 × 10^{10} vp (51)	Placebo (24)	Jcovden 5 × 10^{10} vp (50)	Placebo (26)
Local	Injection site pain and tenderness	1 (2.0%)	0	0	0
	Injection site erythema	0	0	0	0
	Injection site swelling	0	0	0	0
	Injection site induration	0	0	0	0
Systemic	Fatigue	3 (5.9%)	0	0	0
	Myalgia	2 (3.9%)	0	0	0
	Headache	4 (7.8%)	0	1 (2.0%)	0
	Pyrexia[a]	0	0	1 (2.0%)	0
	Nausea	1 (2.0%)	0	0	0
After the second dose		Cohort 1		Cohort 2	
		Jcovden 5 × 10^{10} vp (43)	Placebo (23)	Jcovden 5 × 10^{10} vp (48)	Placebo (24)
Local	Injection site pain and tenderness	0	0	0	0
	Injection site erythema	0	0	0	0
	Injection site induration	0	0	0	0
	Injection site swelling	0	0	0	0
Systemic	Fatigue	1 (2.3%)	0	0	0
	Myalgia	1 (2.3%)	0	0	0
	Headache	1 (2.3%)	0	0	0
	Pyrexia[a]	0	0	0	0
	Nausea	0	0	0	0

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.
a, ≥38°C (oral or axillary temperature)

For solicited adverse events, the median time to onset of pain or tenderness at the vaccination site was 1 day after vaccination in the Jcovden 5 × 10^{10} vp group and 1 to 2 days after vaccination in the placebo group, with the median duration of 2 to 3 days in the Jcovden 5 × 10^{10} vp group and 1 day in the placebo group. The median time to onset of solicited systemic adverse events was 1 to 3.5 days after vaccination in both Jcovden 5 × 10^{10} vp group and placebo group, with the median duration of 1 to 2 days in the Jcovden 5 × 10^{10} vp group and 1 to 6 days in the placebo group.

Grade 3 hypertension, an unsolicited adverse event, occurred in 1 subject in the Jcovden 5 × 10^{10} vp group in Cohort 2 after the second dose, but a causal relationship to Jcovden was ruled out for the event.

Accordingly, in the Japanese population, incidences of adverse events were higher, particularly in subjects aged 20 to 55 years than in foreign Studies COV3001 and COV3009. However, the higher incidences were considered attributable to the injection volume of 1.0 mL in Japanese Study COV1002 as well as to carefulness and commitment of the investigators and subjects to the adverse event reporting, in light of the nature of the phase I study. In addition, although the small number of subjects in Japanese Study COV1002 allows only limited comparison with foreign Studies COV3001 and COV3009, the profile of adverse events in the Japanese study was similar to that in the foreign clinical studies; and most events were Grade 1 or 2, and neither deaths nor serious adverse events other than deaths occurred, indicating no Japanese-specific safety concerns.

7.R.3.1.2 Adverse events by age bracket

Table 57 is a summary of adverse events in foreign Study COV3001 by age group, and Table 58 shows the incidences of solicited adverse events. The incidences of adverse events and Grade ≥3 events tended to be low in the subgroup aged ≥65 years as compared to that aged 18 to 64 years in the Jcovden group in foreign Study COV3001.

Table 57. Summary of adverse events by age subgroup (foreign Study COV3001 [primary analysis], safety subset or FAS)

	18-64 years		≥65 years	
Safety subset				
Group (Subjects analyzed)	Jcovden (2,593)	Placebo (2,594)	Jcovden (763)	Placebo (786)
Solicited local adverse events	1,444 (55.7%)	505 (19.5%)	243 (31.8%)	153 (19.5%)
Grade ≥3	19 (0.7%)	4 (0.2%)	4 (0.5%)	2 (0.3%)
Solicited systemic adverse events	1,546 (59.6%)	941 (36.3%)	307 (40.2%)	247 (31.4%)
Grade ≥3	52 (2.0%)	12 (0.5%)	9 (1.2%)	9 (1.1%)
Solicited systemic adverse events considered causally related to study vaccine	1,523 (58.7%)	895 (34.5%)	296 (38.8%)	236 (30.0%)
Grade ≥3	51 (2.0%)	12 (0.5%)	9 (1.2%)	8 (1.0%)
Unsolicited adverse events	361 (13.9%)	327 (12.6%)	79 (10.4%)	80 (10.2%)
Grade 3	10 (0.4%)	13 (0.5%)	6 (0.8%)	3 (0.4%)
Grade 4	2 (0.1%)	2 (0.1%)	1 (0.1%)	0
Unsolicited adverse events considered causally related to study vaccine	202 (7.8%)	118 (4.5%)	40 (5.2%)	36 (4.6%)
FAS				
Group (Subjects analyzed)	Jcovden (17,636)	Placebo (17,586)	Jcovden (4,259)	Placebo (4,302)
Serious adverse events	60 (0.3%)	90 (0.5%)	30 (0.7%)	47 (1.1%)
Deaths	2 (<0.1%)	10 (0.1%)	1 (<0.1%)	6 (0.8%)

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.

Table 58. Summary of solicited local and systemic adverse events by age subgroup (foreign Study COV3001 [primary analysis], safety subset)

		18-64 years		≥65 years	
		Jcovden (2,593)	Placebo (2,594)	Jcovden (763)	Placebo (786)
Local	Injection site erythema	210 (8.1%)	103 (4.0%)	35 (4.6%)	28 (3.6%)
	Grade 3	6 (0.2%)	2 (0.1%)	1 (0.1%)	0
	Injection site pain	1,408 (54.3%)	439 (16.9%)	226 (29.6%)	126 (16.0%)
	Grade 3	8 (0.3%)	0	3 (0.4%)	2 (0.3%)
	Injection site swelling	160 (6.2%)	39 (1.5%)	18 (2.4%)	14 (1.8%)
	Grade 3	6 (0.2%)	2 (0.1%)	1 (0.1%)	0
Systemic	Fatigue	1,069 (41.2%)	574 (22.1%)	217 (28.4%)	155 (19.7%)
	Grade 3	28 (1.1%)	4 (0.2%)	7 (0.9%)	5 (0.6%)
	Headache	1,121 (43.2%)	649 (25.0%)	187 (24.5%)	156 (19.8%)
	Grade 3	20 (0.8%)	5 (0.2%)	3 (0.4%)	4 (0.5%)
	Myalgia	955 (36.8%)	331 (12.8%)	160 (21.0%)	101 (12.8%)
	Grade 3	29 (1.1%)	1 (<0.1%)	3 (0.4%)	5 (0.6%)
	Nausea	398 (15.3%)	248 (9.6%)	80 (10.5%)	81 (10.3%)
	Grade 3	3 (0.1%)	3 (0.1%)	3 (0.4%)	3 (0.4%)
	Pyrexia	284 (11.0%)	16 (0.6%)	18 (2.4%)	4 (0.5%)
	Grade ≥3	7 (0.3%)	0	1 (0.1%)	0

Number of subjects with events (incidence)
For a definition of Grade 3, see Tables 67 to 69.

Table 59 is a summary of adverse events after each dose in foreign Study COV3009 by age subgroup, and Table 60 shows the incidences of solicited adverse events. Incidences of adverse events and Grade

≥3 events tended to be low after each dose in the subgroup aged ≥65 years as compared to that aged 18 to 64 years in the Jcovden group.

Table 59. Summary of adverse events after each dose by age subgroup (foreign Study COV3009, safety subset or FAS)

	18-64 years				≥65 years			
	After the first dose		After the second dose		After the first dose		After the second dose	
Safety subset								
Group (Subjects analyzed)	Jcovden (2,402)	Placebo (2,408)	Jcovden (1,370)	Placebo (1,245)	Jcovden (613)	Placebo (644)	Jcovden (89)	Placebo (180)
Solicited local adverse events	1,465 (61.0%)	545 (22.6%)	820 (59.9%)	233 (18.7%)	211 (34.4%)	108 (16.8%)	76 (40.2%)	19 (10.6%)
Grade ≥3	7 (0.3%)	5 (0.2%)	9 (0.7%)	2 (0.2%)	2 (0.3%)	1 (0.2%)	1 (0.5%)	1 (0.6%)
Solicited systemic adverse events	1,511 (62.9%)	955 (39.7%)	742 (54.2%)	392 (31.5%)	253 (41.3%)	183 (28.4%)	79 (41.8%)	50 (27.8%)
Grade ≥3	48 (2.0%)	11 (0.5%)	24 (1.8%)	4 (0.3%)	7 (1.1%)	3 (0.5%)	1 (0.5%)	1 (0.6%)
Solicited systemic adverse events considered causally related to study vaccine	1,478 (61.5%)	909 (37.7%)	733 (53.5%)	376 (30.2%)	237 (38.7%)	172 (26.7%)	77 (40.7%)	47 (26.1%)
Grade ≥3	47 (2.0%)	11 (0.5%)	24 (1.8%)	4 (0.3%)	6 (1.0%)	3 (0.5%)	1 (0.5%)	1 (0.6%)
Unsolicited adverse events	362 (15.1%)	278 (11.5%)	137 (10.0%)	104 (8.4%)	92 (15.0%)	54 (8.4%)	22 (11.6%)	16 (8.9%)
Grade ≥3	15 (0.6%)	13 (0.5%)	8 (0.6%)	7 (0.6%)	6 (1.0%)	3 (0.5%)	4 (2.1%)	0
Unsolicited adverse events considered causally related to study vaccine	231 (9.6%)	153 (6.4%)	69 (5.0%)	45 (3.6%)	52 (8.5%)	26 (4.0%)	10 (5.3%)	4 (2.2%)
Grade ≥3	6 (0.2%)	5 (0.2%)	4 (0.3%)	1 (0.1%)	3 (0.5%)	0	1 (0.5%)	0
FAS								
Group (Subjects analyzed)	Jcovden (12,883)		Placebo (12,725)		Jcovden (2,821)		Placebo (2,863)	
Serious adverse events	69 (0.5%)		94 (0.7%)		35 (1.2%)		42 (1.5%)	
Deaths	2 (<0.1%)		8 (<0.1%)		2 (0.1%)		8 (0.3%)	

For a definition of Grade 3, see Tables 67 to 69.

Table 60. Solicited adverse events after each dose by age subgroup (foreign Study COV3009, safety subset)

		18-64 years				≥65 years			
		After the first dose		After the second dose		After the first dose		After the second dose	
		Jcovden (2,402)	Placebo (2,408)	Jcovden (1,370)	Placebo (1,245)	Jcovden (613)	Placebo (644)	Jcovden (189)	Placebo (180)
Local	Injection site erythema	234 (9.7%)	118 (4.9%)	121 (8.8%)	53 (4.3%)	29 (4.7%)	24 (3.7%)	7 (3.7%)	3 (1.7%)
	Grade ≥3	2 (0.1%)	1 (<0.1%)	6 (0.4%)	1 (0.1%)	0	0	1 (0.5%)	1 (0.6%)
	Injection site pain	1,432 (59.6%)	464 (19.3%)	806 (58.8%)	207 (16.6%)	202 (33.0%)	92 (14.3%)	71 (37.6%)	18 (10.0%)
	Grade ≥3	3 (0.1%)	3 (0.1%)	3 (0.2%)	1 (0.1%)	0	1 (0.2%)	0	0
	Injection site swelling	148 (6.2%)	48 (2.0%)	85 (6.2%)	15 (1.2%)	19 (3.1%)	4 (0.6%)	3 (1.6%)	3 (1.7%)
	Grade ≥3	2 (0.1%)	1 (<0.1%)	2 (0.1%)	0	2 (0.3%)	0	0	0
Systemic	Fatigue	1,181 (49.2%)	639 (26.5%)	587 (42.8%)	266 (21.4%)	174 (28.4%)	121 (18.8%)	54 (28.6%)	27 (15.0%)
	Grade ≥3	23 (1.0%)	7 (0.3%)	14 (1.0%)	2 (0.2%)	3 (0.5%)	0	0	0
	Headache	1,128 (47.0%)	632 (26.2%)	510 (37.2%)	246 (19.8%)	163 (26.6%)	117 (18.2%)	48 (25.4%)	24 (13.3%)
	Grade ≥3	20 (0.8%)	4 (0.2%)	10 (0.7%)	2 (0.2%)	3 (0.5%)	1 (0.2%)	0	1 (0.6%)
	Myalgia	1,030 (42.9%)	398 (16.5%)	497 (36.3%)	166 (13.3%)	142 (23.2%)	70 (10.9%)	44 (23.3%)	20 (11.1%)
	Grade ≥3	21 (0.9%)	4 (0.2%)	9 (0.7%)	1 (0.1%)	2 (0.3%)	0	0	0
	Nausea	474 (19.7%)	255 (10.6%)	204 (14.9%)	83 (6.7%)	72 (11.7%)	61 (9.5%)	21 (11.1%)	17 (9.4%)
	Grade ≥3	8 (0.3%)	3 (0.1%)	2 (0.1%)	0	1 (0.2%)	2 (0.3%)	1 (0.5%)	0
	Pyrexia	137 (5.7%)	11 (0.5%)	36 (2.6%)	4 (0.3%)	13 (2.1%)	3 (0.5%)	2 (1.1%)	0
	Grade ≥3	2 (0.1%)	0	1 (0.1%)	0	0	0	0	0

For a definition of Grade 3, see Tables 67 to 69.

Tables 55 and 56 show the events by age group in Japanese Study COV1002. The incidences of adverse events and Grade ≥3 events tended to be low in the elderly group (Cohort 2, aged ≥65 years) as compared to the non-elderly group (Cohort 1, aged 20-55 years) [see Section 7.R.3.1.1].

The incidences of solicited adverse events in Cohort 2 (aged ≥65 years) were not largely different from those in subjects aged ≥65 years in foreign Studies COV3001 and COV3009 (Tables 57 to 60), but the incidences tended to be high in Cohort 1 (aged 20-55 years) as compared to the counterpart age groups in these foreign clinical studies. The incidences of unsolicited adverse events tended to be high in Japanese Study COV1002 as compared to foreign Studies COV3001 and COV3009 (Tables 55, 57, and 59).

7.R.3.1.3 Serious adverse events

As of the data cut-off date (July 21, 2021) in ongoing foreign Study COV1001, serious adverse events occurred in 12 subjects (in addition to adverse events presented in Section 7.2.1, uterine prolapse in 2 subjects; and hip fracture, atrial fibrillation, coronary artery disease, breast cancer stage II, breast disorder, asphyxia, and anaphylactic shock in 1 subject each [some subjects reported multiple events]) after Jcovden vaccination (all regimens), and a causal relationship to Jcovden was ruled out for all events except for pyrexia in 1 subject (Cohort 1a, 1×10^{11} vp × 1-dose group). A death of 1 subject was reported after Jcovden vaccination (in Cohort 2a, 5×10^{10} vp group, asphyxia [due to strangulation]), but a causal relationship to Jcovden was ruled out for the event.

In Japanese Study COV1002, 2 subjects experienced serious adverse events after Jcovden vaccination (all regimens) [see Section 7.1.1] as of the data cut-off date (December 28, 2020 in Cohort 1, February 22, 2021 in Cohort 2), and a causal relationship to Jcovden was ruled out for both events. No deaths occurred.

In foreign Study COV2001, as of the data cut-off date (May 11, 2021 in Cohort 1, April 23, 2021 in Cohort 2), 6 subjects experienced serious adverse events after Jcovden vaccination (all regimens) (hepatic cyst, osteoarthritis, cerebrospinal fluid leakage, pyrexia, pancytopenia, acute myeloid leukaemia, pneumonia, systemic candida infection, lung adenocarcinoma, and bacteraemia in 1 subject each [some subjects reported multiple events], all in Cohort 1), and a causal relationship to Jcovden was ruled out for all events. A death of 1 subject was reported in the 2.5×10^{10} vp × 2-dose group (death [unknown cause of death]), for which a causal relationship to Jcovden was ruled out.

In foreign Study COV3001, as of the analysis at the end of the double-blind period (data cut-off on July 9, 2021), deaths of 28 subjects were reported [see Section 7.2.2] in the Jcovden group during the double-blind period and additional 12 subjects (COVID-19 in 4 subjects; pulmonary embolism and deaths in 2 subjects each; and sepsis, completed suicide, cardio-respiratory arrest, and cardiac arrest in 1 subject each) died during the open-label period. A causal relationship to Jcovden could not be ruled out by an investigator for the death from pulmonary embolism in 1 subject. The subject experienced pulmonary embolism 57 days after Jcovden vaccination, based on a history of [redacted] and [redacted], the applicant judged that the death was not causally related to Jcovden. Postmortem test revealed that the subject tested marginally positive for anti-platelet factor 4 (PF4) antibodies. Serious

adverse events including events during the open-label period occurred in 1.2% (436 of 35,618) of subjects in the Jcovden group, and a causal relationship to Jcovden could not be ruled out for the events in 18 subjects (ischaemic stroke in 3 subjects, Bell's palsy, pulmonary embolism, and deep vein thrombosis in 2 subjects each; Guillain-Barre syndrome, venous thrombosis limb, retinal vein thrombosis, atrial fibrillation, pericarditis, complex regional pain syndrome, post vaccination syndrome, hypersensitivity, headache, and asthma in 1 subject each [some subjects reported multiple events]). All events except for deep vein thrombosis, pulmonary embolism, complex regional pain syndrome [see Section 7.2.2], venous thrombosis limb, and fatal pulmonary embolism were confirmed to have resolved or be resolving [for thromboembolism after Jcovden vaccination in this study, see Section 7.R.3.2].

In foreign Study COV3009, deaths of 4 subjects in the Jcovden group were reported during the double-blind period and 6 subjects (myocardial infarction in 2 subjects; and COPD, COVID-19 pneumonia, heroin overdose, and respiratory distress in 1 subject each) died during the open-label period, as of the data cut-off date (June 25, 2021). A causal relationship to Jcovden was ruled out for all deaths. Serious adverse events including during the open-label period occurred in 0.8% (191 of 23,755) of subjects in the Jcovden group, and a causal relationship to Jcovden could not be ruled out for the events in 12 subjects (pyrexia, pericarditis, allergy to vaccine, haemoptysis, facial paresis, pulmonary embolism, and cerebrovascular accident in 2 subjects each; and injection site swelling, vertigo, myocardial necrosis marker increased, deep vein thrombosis, leukopenia, thrombocytopenia, venous thrombosis limb, and thrombosis in 1 subject each [some subjects reported multiple events]). All events except for deep vein thrombosis were confirmed to have resolved or be resolving.

As shown in Sections 7.R.3.1.1 to 7.R.3.1.3, Japanese and foreign clinical studies revealed low incidences of Grade ≥3 adverse events and low incidences of deaths and serious adverse events, most of which had no causal relationship to Jcovden. In view of these results rise no critical concerns in the safety profile of a single dose or 2 doses of Jcovden, and Jcovden is well tolerated.

PMDA's view:
Most of solicited local and systemic adverse events in the submitted data of Japanese and foreign clinical studies were at Grade 1 or 2 and resolved. Tendencies in adverse events did not differ clearly after the first and second doses. At present, the occurrence of unsolicited adverse events and serious adverse events or the age bracket-based occurrence of adverse events rose no critical concerns potentially influential to decision making on the approval of Jcovden. Nevertheless, the occurrence of Grade ≥3 solicited adverse events that would interfere with activities of daily living, although at low incidences, is important information for vaccine recipients and thus should be appropriately provided to healthcare professionals and vaccine recipients. Adverse events of special interest are discussed in Section 7.R.3.2.

Limited data on the long-term safety post-vaccination with Jcovden are available. The applicant should continue collecting the relevant information in post-marketing settings.

7.R.3.2 Adverse events of special interest

The applicant's explanation about adverse events of special interest:

In the clinical studies of Jcovden, no particular adverse events of special interest were specified at the start. However, in response to reported thrombosis with thrombocytopenia syndrome following vaccination with Jcovden in foreign post-marketing settings, all clinical studies of Jcovden were suspended to evaluate a risk of the event (April 2021).Upon the study suspension, protocols of all clinical studies were revised to specify thrombosis with thrombocytopenia syndrome as an adverse event of special interest (revision of protocols, May to June 2021). All thrombotic events and thrombocytopenia (platelet count, <150,000/μL) were regarded as suspected adverse events of special interest and were documented throughout a period from the study vaccination to the end or early discontinuation of the study.

At the same time, injectable vaccines are known to have a risk of severe allergic reactions including anaphylaxis, which are thus events of special interest, thus the review covers these events. In addition, thrombotic or thromboembolic events and immune-mediated or inflammatory events were also subjected to evaluation. These are adverse events of special interest subjected to regular evaluation based on clinical study and post-marketing data of Jcovden, and were found to show disproportionally higher incidences after vaccination with Jcovden particularly in comparison with historical data.

(a) Severe allergic reactions including anaphylaxis

As of the primary analysis in foreign Study COV3001, there were no adverse events meeting the Brighton Collaboration case definition of anaphylaxis (*Vaccine.* 2007;25:5675-84). Allergic reactions observed in ≥6 subjects in the Jcovden group were rash (24 subjects in the Jcovden group, 16 in the placebo group), urticaria (8, 3), and hypersensitivity (6, 4). Type IV hypersensitivity reaction occurred in 1 subject as a severe allergic reaction. A causal relationship to Jcovden could not be ruled out for the event, but the event did not meet the Brighton Collaboration case definition of anaphylaxis.

In foreign Study COV3012, an uncontrolled study ongoing in South Africa, severe allergic reactions including anaphylaxis occurred in 6 subjects (flushing and shortness of breath [chest tightness]; headache and back pain; giddiness and paraesthesia lower limb; pyrexia, swollen tongue, and mild dyspnoea; anaphylaxis; and hypersensitivity in 1 subject each) as of [redacted], 20[redacted]. All events except for giddiness and paraesthesia lower limb were considered causally related to Jcovden vaccination. All events were resolving or resolved. One subject with pyrexia, swollen tongue, and mild dyspnoea was judged to have anaphylaxis (level 2) according to the Brighton Collaboration case definition of anaphylaxis.

According to the latest Periodic Benefit Risk Evaluation Report (PBRER) (from [redacted], 20[redacted] [international birthdate] to [redacted], 20[redacted][39)]), 180 cases of severe allergic reactions including anaphylaxis and related events (in Medical Dictionary for Regulatory Activities Japanese version [MedDRA] Standardised MedDRA Queries [SMQ] "Anaphylactic reaction") were reported from 178 recipients (median age [range] of 40 [19-80] years) in foreign post-marketing settings, and all were

[39)] According to reports, as the cumulative count, 62,358 individuals received Jcovden in clinical studies (up to [redacted], 20[redacted]), and 33,584,049 doses were administered in post-marketing settings (from [redacted], 20[redacted] to [redacted], 20[redacted]).

serious. They included 102 cases of anaphylactic reaction, 29 case of anaphylactic shock, 19 cases of shock, 18 cases of anaphylactoid reaction, and 12 cases of circulatory collapse. A total of 66 cases resolved; 19 cases were resolving; 15 cases did not resolve; 14 cases resulted in deaths; and 66 cases remain unreported.

These major clinical studies and foreign post-marketing evaluation revealed cases with anaphylaxis or anaphylactic shock which was most likely causally related to Jcovden, and thus these events were determined as important identified risks. Therefore persons with severe hypersensitivity to any ingredient of Jcovden are ineligible for the vaccination, and such caution should be given in the package insert, etc.

(b) Thrombotic or thromboembolic events

Recipients vaccinated with Jcovden or Vaxzevria Intramuscular Injection developed thrombosis with thrombocytopenia syndrome, although rare (*N Engl J Med.* 2021;384:2092-101, *N Engl J Med.* 2021;384:2124-30). Thrombosis with thrombocytopenia syndrome is pathologically similar to heparin-induced thrombocytopenia (HIT), and is induced by antibodies recognizing PF4-heparin complexes that activate platelets through the Fc receptor and thereby promote coagulation (*N Engl J Med.* 2021;384:2092-2101, *N Engl J Med.* 2021;384:2124-30). The antibodies potentially bind to PF4 without heparin, thereby activating platelets (*Blood Adv.* 2021;5:4256-64). Of 16 recipients who experienced thrombosis with thrombocytopenia syndrome after Vaxzevria Intramuscular Injection, many presented with the increased titer of antibodies recognizing PF4-heparin complexes (*Ann Intern Med.* 2021;174:1480-2). The following details the occurrence of thrombotic and thromboembolic events including thrombosis with thrombocytopenia syndrome.

- Thrombotic or thromboembolic events in clinical studies

As of the data cut-off date (January 22, 2021) for the primary analysis in foreign Study COV3001, thrombotic or thromboembolic events (arteries and veins) occurred in 14 subjects (0.1%) in the Jcovden group and 10 subjects (<0.1%) in the placebo group (Table 61). Many subjects with a relevant event had comorbidities (obesity, hypothyroidism, diabetes mellitus, etc.) potentially causing the event. The number of subjects with deep venous thrombosis was disproportionate between the Jcovden group and placebo group, but the event was assessed as related to the study vaccination by investigators for 2 subjects (1 each in the Jcovden group and placebo group). Of those with the event related to the study vaccination, 1 subject in the Jcovden group who experienced non-serious deep vein thrombosis 27 days after Jcovden vaccination had a history of [redacted] and [redacted].

Table 61. Incidences of thrombotic and thromboembolic events (foreign Study COV3001, FAS)

	Jcovden		Placebo	
	Serious	Non-serious	Serious	Non-serious
Deep vein thrombosis	4	5	2	1
Deep vein thrombosis[a]	1	4	1	1
Pulmonary embolism	3	1	1	0
Cerebrovascular event[b]	4[c]	0	2	1
Cardiovascular event	2	0	3	0
Gastrointestinal event	0	0	0	1
Total	9	5	7	3

a, Including lower limb venous thrombosis (non-serious) in 1 subject
b, Including transverse sinus thrombosis in 1 subject meeting the criteria for suspension of the study
c, Two events were reported in the same subject.

For thromboembolic events with thrombocytopenia syndrome observed before the analysis data cut-off (July 9, 2021) at the end of the double-blind period in foreign Study COV3001, applicability to the following case definitions was assessed at the internal assessment committee of adverse events of special interest.

- Tentative Brighton Collaboration case definition (Brighton Collaboration. Interim case definition of thrombosis with thrombocytopenia syndrome [TTS]. v 10.16.3, May 8, 2021. https://brightoncollaboration.us/wp-content/uploads/2021/05/TTS-Interim-Case-Definition-v10.16.3-May-23-2021.pdf [last accessed on April 3, 2022])
- Centers for Disease Control and Prevention (CDC) Tier1 or Tier2 case definition (ACIP. Update: Thrombosis with thrombocytopenia syndrome [TTS] following COVID-19 vaccination, May 12, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf [last accessed on April 3, 2022])

Of 17 events reported in the study, 13 events met levels 1 to 3 of the Brighton Collaboration case definition criteria. A serious thromboembolic event with thrombocytopenia syndrome (transverse sinus thrombosis leading to cerebral haemorrhage) in 1 subject vaccinated with Jcovden was classified as thrombosis with thrombocytopenia syndrome that met both level 1 of Brighton Collaboration case definition criteria for and the case definition criteria specified by CDC. The event was assessed as causally related to the study vaccination under a blinded condition and met the provision for suspension of the study vaccination in the protocol (a case where a serious adverse event for which a causal relationship to Jcovden could not be ruled out has occurred in ≥1 subject). Then, in all ongoing clinical studies of Jcovden, the study vaccination was suspended (October 2020) to evaluate the safety of Jcovden. The case evaluation by an independent external DSMB concluded that the clinical studies could be continued because of the lack of clear evidence showing that the study vaccination caused the event. The additional investigation revealed that a serum specimen from the subject with the event tested positive for anti-PF4 antibodies, and this serious adverse event was considered causally related to the study vaccination.

In foreign Study COV3009, arterial thromboembolism occurred in 6 subjects in the Jcovden group and 9 subjects in the placebo group, and venous thromboembolism in 2 subjects in the Jcovden group and 6 subjects in the placebo group. Deep vein thrombosis with thrombocytopenia syndrome occurred in 1 subject in the Jcovden group, and deep vein thrombosis and pulmonary embolism in 1 subject in the placebo group. According to the Brighton Collaboration case definition criteria, these events were assessed as level 3, level 1 (deep vein thrombosis), and level 3 (pulmonary embolism), respectively, but

none of them met the CDC case definition criteria. During the safety follow-up period after the data cut-off date (data locked on August 23, 2021), 1 subject in the Jcovden group died from myocardial infarction. The case was assessed as level 5 (classified as TTS) according to the Brighton Collaboration case definition criteria but did not meet the CDC criteria.

Thrombotic or thromboembolic events were suspected in 5 subjects in Cohort 3 in foreign Study COV1001, specifically, deep vein thrombosis in 2 subjects, and transient ischaemic attack, thrombocytopenia, and myocardial infarction in 1 subject each. All events resolved or were resolving except for deep vein thrombosis in 1 subject in the Jcovden 1×10^{11} vp × 1-dose group (did not resolve as of the data cut-off date [July 21, 2021]). All events were assessed as causally unrelated to the study vaccination, and none of the events were classified as thrombosis with thrombocytopenia syndrome.

In foreign Study COV2001, thrombotic events occurred in 2 subjects, specifically, thrombophlebitis and ischaemic stroke in 1 subject each. Both were assessed as causally unrelated to the study vaccination.

- Case-control study

Thrombosis with thrombocytopenia syndrome developing after vaccination with Jcovden or Vaxzevria Intramuscular Injection is suggested to be related to anti-PF4 antibodies. To investigate a relationship of thromboembolic events[40] observed after Jcovden vaccination to anti-PF4 antibodies, a case-control study was conducted based on data in foreign Study COV3001. The study included 58 subjects who experienced thromboembolic events irrespective of the platelet count as of [redacted], 20[redacted] (32 in the Jcovden group, 26 in the placebo group) and 58 control subjects[41] (32 in the Jcovden group, 26 in the placebo group), and anti-PF4 antibodies in these subjects before and after the study vaccination were measured (anti-PF4 IgG ELISA[42]). The measurements results were used to investigate the association with the occurrence of thromboembolic events. Of 58 subjects who experienced thromboembolic events, 7 subjects (6 of 32 subjects [19%] in the Jcovden group, 1 of 26 subjects [4%] in the placebo group) tested positive for anti-PF4 antibodies at any measurement time point. None of the control subjects who did not have the events tested positive for anti-PF4 antibodies. Of the 6 anti-PF4 antibody-positive subjects in the Jcovden group, 3 subjects (hemiparesis, myocardial infarction, and cerebrovascular accident in 1 subject each) had anti-PF4 antibodies at baseline but did not show increased anti-PF4 antibody titer after Jcovden vaccination. The remaining 3 subjects tested negative for anti-PF4 antibodies at baseline and had increased anti-PF4 antibody titer after Jcovden vaccination. The time point with a positive result for anti-PF4 antibodies obtained and time to onset of thromboembolism in these 3 subjects are as follows:

- A specimen collected 10 days after study vaccination tested positive for anti-PF4 antibodies (optical density [OD] value, 2.626). Transverse sinus thrombosis occurred 20 days after vaccination. The event was determined as thrombosis with thrombocytopenia syndrome (CDC Titer 1/2, Brighton Collaboration level 1).
- Deep vein thrombosis occurred 39 days after study vaccination, and a specimen collected 85 days after that tested positive for anti-PF4 antibodies (OD value, 0.849).

[40] Identified based on MedDRA SMQ "Embolic and thrombotic events" (irrespective of platelet count)
[41] Subjects with matched age, sex, and country were selected from subjects who did not experience thromboembolic events.
[42] Validated measurement method approved by US FDA (cut-off absorbance was 0.4)

- Embolism venous occurred 35 days after study vaccination, and a specimen collected 69 days after that tested positive for anti-PF4 antibodies (OD value, 0.612). The subject experienced the thromboembolic event 13 days after SARS-CoV-2 infection.

The thromboembolic event in 1 subject in the placebo group, who tested positive for anti-PF4 antibodies after the study vaccination, was paraparesis. In all anti-PF4 antibody-positive subjects were negative for platelet activation measured by serotonin release assay.

In summary, subjects who had thromboembolic events after the study vaccination in the either placebo or Jcovden group were found to be positive for anti-PF4 antibodies before or after study vaccination. In contrast, one of the control subjects who did not have thromboembolic events tested positive for anti-PF4 antibodies before or after study vaccination. In this investigation, anti-PF4 antibodies were detected in a larger proportion of the subjects who experienced thromboembolic events after Jcovden vaccination than in the control subjects. Because of the limited number of subjects investigated, the investigation should be continued.

● Thrombotic or thromboembolic events in foreign post-marketing settings

According to the latest PBRER (covering from [redacted], 20[redacted] to [redacted], 20[redacted]), 454 cases of thrombosis with thrombocytopenia syndrome (MedDRA SMQ "Embolic and thrombotic events" or "Haematopoietic thrombocytopenia" or MedDRA high level term [HLT] "Thrombocytopenia") were reported in 206 vaccine recipients (107 women, 93 men, and 6 recipients with unknown sex; 40 recipients aged 18-35 years, 63 recipients aged 36-50 years, 60 recipients aged 51-64 years, 34 recipients aged ≥65 years, and 9 recipients with unknown age [including 1 adult]), and 451 cases in 205 recipients were serious. Events reported ≥5 times were pulmonary embolism (65 cases), thrombosis (47 cases), deep vein thrombosis (38 cases), cerebral venous sinus thrombosis (32 cases), portal vein thrombosis (15 cases), ultrasound doppler abnormal and cerebrovascular accident (12 cases each), venogram abnormal (11 cases), cerebral venous thrombosis, disseminated intravascular coagulation and jugular vein thrombosis (10 cases each), cerebral thrombosis and superior sagittal sinus thrombosis (8 cases each), transverse sinus thrombosis, thrombotic thrombocytopenic purpura and angiogram cerebral abnormal (7 cases each), haemorrhagic stroke, hemiparesis, venous thrombosis, mesenteric vein thrombosis and thrombectomy (6 cases each), and thrombophlebitis superficial, myocardial infarction, portosplenomesenteric venous thrombosis, splenic vein thrombosis, transient ischaemic attack, and pulmonary thrombosis (5 cases each). A total of 179 cases remained unresolved, 68 cases resulted in deaths, 61 cases were resolving, 32 cases resolved, 3 cases resolved with sequelae, and there were 111 cases with unreported outcomes.

During the same period, 3,726 cases with venous thrombosis (MedDRA SMQ "Embolic and thrombotic events, venous," and "Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous") were reported in 2,709 individuals (1,477 women, 1,146 men, and 86 recipients with unknown sex; 1 recipient aged 17 years, 325 recipients aged 18-35 years, 677 recipients aged 36-50 years, 832 recipients aged 51-64 years, 641 recipients aged ≥65 years, 18 adults, 3 elderly, and 212 recipients with unknown age), and 3,611 cases in 2,645 individuals were serious. Of these, events reported ≥50 times were thrombosis (826 cases), pulmonary embolism (601 cases), deep vein thrombosis (517 cases),

cerebrovascular accident (370 cases), ultrasound doppler abnormal (169 cases), hemiparesis (113 cases), pulmonary thrombosis (102 cases), cerebral venous sinus thrombosis (80 cases), thrombophlebitis superficial (63 cases), angiogram cerebral abnormal (55 cases), and cerebral thrombosis (52 cases). A total of 1,688 cases remained unresolved, 493 cases resolved, 287 cases were resolving, 217 cases resulted in deaths; 14 cases resolved with sequelae, and there were 1,027 cases with unreported outcomes.

The latest safety summary report (covering from [redacted], 20[redacted] to [redacted], 20[redacted]) reviewed thrombotic or thromboembolic events in 978 recipients (cumulative number of the recipients with events, 4,398). A total of 50 cases occurred after booster dose(s) (including 40 cases occurring after 2 doses of Jcovden [homologous booster dose] and 10 case after a booster dose of Jcovden following the primary series of a different SARS-CoV-2 vaccine [heterologous booster dose]). Of 928 cases occurring after a single dose of Jcovden, 911 cases were serious. The most common event was thrombosis (271 cases) followed by pulmonary embolism (149 cases) and cerebrovascular accident (126 cases) in this order. Of the 928 cases, 61 cases were thrombotic or thromboembolic events with thrombocytopenia syndrome (<150,000/μL), and 33 cases with unknown details.

All 834 cases with thrombotic and thromboembolic events without thrombocytopenia syndrome, except for 163 cases, occurred within 28 days after vaccination. All 61 thrombotic or thromboembolic events with thrombocytopenia syndrome occurred within 28 days after vaccination. Table 62 shows events occurring within 28 days after vaccination that were reported ≥3 times. Of 834 thrombotic or thromboembolic events without thrombocytopenia syndrome, 106 cases resulted in deaths. In 3 of these death cases, the recipients had no other risk factors of thrombotic or thromboembolic events, suggesting a relationship to Jcovden vaccination.

Table 62. Thrombotic or thromboembolic events counted ≥3 times in safety summary report (covering from [redacted], 20[redacted] to [redacted], 20[redacted])

	Thrombotic and thromboembolic events without thrombocytopenia syndrome (671 events)	Thrombotic and thromboembolic events with thrombocytopenia syndrome (61 events)
Mixed	Thrombosis (194), cerebrovascular accident (96), hemiparesis (27), ultrasound doppler abnormal (20), hemiplegia (16), cerebral infarction (12), cerebral thrombosis (12), intracardiac thrombus (9), monoplegia (9), monoparesis (6), thrombectomy (5), angiogram abnormal (4), disseminated intravascular coagulation (4), embolic stroke (4), infarction (4), paraplegia (4), quadriparesis (4), diplegia (3), embolism (3), haemorrhagic stroke (3), haemorrhoids thrombosed (3), paraparesis (3), and renal infarct (3)	Thrombosis (23), thrombosis with thrombocytopenia syndrome (11), cerebral thrombosis (3), and disseminated intravascular coagulation (3)
Venous	Pulmonary embolism (93), deep vein thrombosis (65), pulmonary thrombosis (29), cerebral venous sinus thrombosis (8), thrombophlebitis (8), venous thrombosis limb (8), superficial vein thrombosis (6), venous thrombosis (5), portal vein thrombosis (4), mesenteric vein thrombosis (3), and retinal vein occlusion (3)	Cerebral venous sinus thrombosis (14), pulmonary embolism (13), deep vein thrombosis (8), cerebral venous thrombosis (4), portal vein thrombosis (4), jugular vein thrombosis (3), superior sagittal sinus thrombosis (3), transverse sinus thrombosis (3), and venous thrombosis (3)
Arterial	Myocardial infarction (61), transient ischaemic attack (18), ischaemic stroke (16), acute myocardial infarction (13), blindness transient (6), peripheral artery thrombosis (5), amaurosis fugax (4), arterial thrombosis (3), coronary arterial stent insertion (3), and retinal artery occlusion (3)	Thrombotic thrombocytopenic purpura (3)

Figures in parentheses indicate numbers of cases.

Of 61 cases with thrombotic or thromboembolic events with thrombocytopenia syndrome (<150,000/μL), 51 cases occurred in recipients aged 18 to 64 years. Mainly among women aged ≤50 years, events were reported from recipients in a wide age range from 18 to 90 years. A total of 19 cases resulted in deaths. A relationship to Jcovden was suggested for 4 cases, of which 2 resulted in deaths.

A total of 50 cases occurred after a booster dose of Jcovden, and 1 case with cerebral venous sinus thrombosis with thrombocytopenia syndrome occurred after a heterologous booster dose. The recipient with the event was presented with symptoms such as headache and weakness of hands 12 days after a booster dose of Jcovden, and was diagnosed as having cerebral venous sinus thrombosis with thrombocytopenia syndrome, which resulted in death. In addition, 40 cases with thrombotic or thromboembolic events without thrombocytopenia syndrome occurred after a homologous booster dose (5 resulted in deaths), and 9 cases occurred after a heterologous booster dose (3 resulted in deaths). Many of these events were mixed or venous thrombosis.

Based on these outcomes from clinical studies and foreign post-marketing settings, a causal relationship of thrombosis with thrombocytopenia syndrome to Jcovden cannot be ruled out, and it is classified as an important identified risk. Accordingly, caution should be given against potential rare cases with thrombosis such as cerebral venous sinus thrombosis, visceral venous thrombosis (portal vein thrombosis, etc.), or arterial thrombosis after Jcovden vaccination, which may be accompanied by thrombocytopenia syndrome and possibly result in a fatal outcome, with the fact that many of these events occurred within 3 weeks after Jcovden vaccination. In patients with suspected thrombosis with thrombocytopenia syndrome, the use of heparin could be rather harmful, and alternative treatment may be needed. Thrombotic or thromboembolic events, if occurring after Jcovden vaccination, should be diagnosed and treated in consultation with appropriate Japanese and foreign guidelines as well as experts of thrombosis and embolism. In view of these points, healthcare professionals and vaccine recipients will be advised to pay attention to signs and symptoms of thromboembolism and/or thrombocytopenia after Jcovden vaccination. Based on available safety information of Jcovden, venous thromboembolism is also considered as an important potential risk. The incidence of arterial thromboembolism, in contrast, is consistent with historical incidences, and thus it is not considered as a safety concern of Jcovden.

(c) Immune-mediated and neuroinflammatory events

In foreign Study COV3001, immune-mediated and neuroinflammatory events of demyelinating diseases occurred in 4 subjects in the Jcovden group (neuropathy peripheral in 2 subjects, and hypergammaglobulinaemia benign monoclonal and Guillain-Barre syndrome in 1 subject each) and 5 subjects in the placebo group (neuropathy peripheral and sensory loss in 2 subjects each and Guillain-Barre syndrome in 1 subject). In view of the above result, immune-mediated and neuroinflammatory events are subjected to pharmacovigilance activities as events of special interest. The following is foreign post-marketing safety information related to immune-mediated and neuroinflammatory events according to the latest PBRER (period from [redacted], 20[redacted] to [redacted], 20[redacted]):

- Guillain-Barre syndrome (GBS)

During a period from [redacted], 20[redacted] to [redacted], 20[redacted], 263 cases with GBS and related events (MedDRA SMQ “Guillain-Barre syndrome”) were reported in 255 individuals (aged 55 years [median] [range, 22-

87 years]), and all were serious. Of these, events reported ≥2 times were Guillain-Barre syndrome (239 cases), chronic inflammatory demyelinating polyradiculoneuropathy (7 cases), demyelinating polyneuropathy (6 cases), Miller Fisher syndrome (6 cases), and subacute inflammatory demyelinating polyneuropathy (4 cases). A total of 133 cases remained unresolved; 41 cases were resolving; 15 cases resolved; 5 cases resolved with sequelae; 1 case resulted in death; and 68 cases had an unreported outcome. Many of these cases reported from foreign post-marketing settings provide limited information for the evaluation of a causal relationship of GBS to Jcovden. However, in view of the inconsistency between the incidence after Jcovden vaccination and historical data, the disease is regarded as an important identified risk of Jcovden. GBS will be warned in the package insert as a clinically significant adverse reaction.

● Encephalitis (including acute disseminated encephalomyelitis [ADEM] and meningoencephalitis)
During the period from [redacted], 20[redacted] to [redacted], 20[redacted], 165 cases with encephalitis-related events (MedDRA SMQ "Noninfectious meningitis," "Noninfectious encephalopathy/delirium," and "Noninfectious encephalitis") were reported in 159 Jcovden recipients (aged 41 years [median] [range, 18-101 years]), and 114 of the 165 cases were serious. Of these, events reported ≥2 times were photophobia (67 cases), encephalitis (26 cases), delirium (22 cases), encephalopathy (8 cases), ADEM, meningitis and noninfective encephalitis (7 cases each), metabolic encephalopathy (4 cases), encephalomyelitis (3 cases), delirium febrile, meningitis aseptic, and posterior reversible encephalopathy syndrome (2 cases each). A total of 54 cases remained resolved, 42 cases resolved, 19 cases were resolving, 6 cases resulted in deaths, 2 cases resolved with sequelae; and the outcomes of 42 cases were unreported. Comparison between incidences of ADEM after Jcovden vaccination and historical incidences revealed inconsistency. The review on encephalitis (including ADEM and meningoencephalitis) at the time of preparation of the latest summary safety report (period from [redacted], 20[redacted] to [redacted], 20[redacted]) indicates an incidences of encephalitis except for photophobia (including ADEM) and ADEM after Jcovden vaccination inconsistent with historical data.

As described, many encephalitis-related events (including acute disseminated encephalomyelitis [ADEM] and meningoencephalitis) were reported, and comparison between the incidences after Jcovden vaccination were inconsistent with historical data. However, a relationship of these events to Jcovden is unclear at present due to limited information. Inflammatory symptoms involving the central nervous system remain adverse events of special interest and thus will be closely monitored ongoingly.

● Transverse myelitis
During the period from [redacted], 20[redacted] to [redacted], 20[redacted], 51 transverse-myelitis -related events (MedDRA preferred terms [PTs] "Myelitis transverse," "Immune-mediated neurological disorder," and "Noninfectious myelitis," etc.) were reported in 41 Jcovden recipients (aged 42.5 years [median] [range, 18-75 years]), and all were serious. The reported events were myelitis transverse (29 cases), demyelination (9 cases), myelitis (7 cases), neuromyelitis optica spectrum disorder (4 cases), and autoimmune demyelinating disease (2 cases). A total of 35 cases remained unresolved, 8 cases were resolving, 2 cases resolved, and the outcomes of 6 cases remained unreported. The incidences after Jcovden vaccination were inconsistent with historical data. The review on transverse myelitis at the time

of the preparation of the latest summary safety report (period from [redacted], 20[redacted] to [redacted], 20[redacted]) also indicates an inconsistency between the incidences after Jcovden vaccination and historical data.

Despite the inconsistency between the incidences after Jcovden vaccination and historical data, published literature and the causality assessment of Jcovden in the observed cases, etc. indicate uncertainty in the association between these events and Jcovden. Transverse myelitis will remain an adverse event of special interest and be subjected to further vigilance.

PMDA's view:
The applicant's planned safety measures, i.e., monitoring allergic reactions including shock and anaphylaxis in the clinical studies and foreign post-marketing settings, listing "shock and anaphylaxis" as important identified risks in the risk management plan, and providing cautionary advice in the package insert, etc., are appropriate. Eligibility for Jcovden, as with other vaccines, should be confirmed based on medical history, and vaccine recipients should be monitored for abnormality for a certain period of time after vaccination. Healthcare professionals should be advised to take appropriate measures in case of any abnormality.

The applicant explained their planned preventive measures against thrombosis with thrombocytopenia syndrome, which include listing the event as an important identified risk of Jcovden, advising caution against its risk in the package insert, and providing information to healthcare professionals and vaccine recipients, including points to remember for early detection of initial symptoms and treatment to minimize the risk, which are acceptable. However, the applicant mentioned only venous thromboembolism as an important potential risk of Jcovden, while the data provided by the applicant show the occurrence of both arterial and venous thrombosis without thrombocytopenia syndrome after Jcovden vaccination. Taking this into account, the applicant should specify "thrombosis" as an important potential risk of Jcovden and continue collecting post-marketing data to take appropriate actions. Thrombotic and thromboembolic events were also reported from recipients of a Jcovden booster dose. Although limited current information, the booster vaccine recipients should be subjected to vigilance as practiced after the primary dose of Jcovden. The applicant should provide healthcare professionals and vaccine recipients with information about prior occurrence of thrombotic and thromboembolic events after Jcovden vaccination including time to onset and initial symptoms.

The applicant explained that caution will be given against the risk of "Guillain-Barre syndrome," immune-mediated and neuroinflammatory events, as an important identified risk of Jcovden in the package insert, etc., which is acceptable. The package insert, however, should also advise that vaccine recipients be explained of this possible event developing as a clinically significant adverse reaction and measures to be taken in case of an initial symptom or symptom of this illness. Serious immune-mediated and neuroinflammatory events other than Guillain-Barre syndrome were reported from Jcovden recipients in the clinical studies and foreign post-marketing settings, and comparison between their incidences in the Jcovden group and historical data showed inconsistency. Given these, these events should be specified as important potential risks of Jcovden, and the package insert should inform that ADEM and transverse myelitis were reported from the foreign post-marketing settings and advise that vaccine recipients should be explained about symptoms suspected of these events. Caution should be

advised against facial paralysis because it is an immune-mediated or neuroinflammatory event occurring in the clinical studies, for which a causal relationship could not be ruled out, albeit no consistency seen between its incidence in the studies and historical data. In Japan, the applicant should also continue collecting post-marketing data and take appropriate measures.

7.R.3.3 Safety in special populations

7.R.3.3.1 Vaccine recipients with underlying diseases

Tables 63 and 64 summarize adverse events in subjects with and without underlying diseases at baseline in foreign Studies COV3001 and COV3009. After either single dose or 2 doses of Jcovden, incidences of solicited local and systemic adverse events were lower in subjects with underlying diseases than in subjects without underlying diseases. The incidences of unsolicited adverse events including serious events in the Jcovden group and placebo group did not tend to greatly differ between subjects with and without underlying diseases.

Table 63. Summary of adverse events in subjects with and without underlying diseases* at baseline (foreign Study COV3001 [primary analysis], safety subset)

	With underlying diseases		Without underlying diseases	
	Jcovden (1,135)	Placebo (1,164)	Jcovden (2,221)	Placebo (2,216)
Solicited local adverse events	487 (42.9%)	226 (19.4%)	1,200 (54.0%)	432 (19.5%)
Grade ≥3	7 (0.6%)	2 (0.2%)	16 (0.7%)	4 (0.2%)
Solicited systemic adverse events	563 (49.6%)	423 (36.3%)	1,290 (58.1%)	765 (34.5%)
Grade ≥3	15 (1.3%)	10 (0.9%)	46 (2.1%)	11 (0.5%)
Solicited systemic adverse events considered causally related to study vaccine	547 (48.2%)	411 (35.3%)	1,272 (57.3%)	720 (32.5%)
Grade ≥3	15 (1.3%)	10 (0.9%)	45 (2.0%)	10 (0.5%)
Unsolicited adverse events	147 (13.0%)	144 (12.4%)	293 (13.2%)	263 (11.9%)
Grade 3	4 (0.4%)	7 (0.6%)	12 (0.5%)	9 (0.4%)
Grade 4	0	1 (0.1%)	3 (0.1%)	1 (<0.1%)
Unsolicited adverse events considered causally related to study vaccine	64 (5.6%)	52 (4.5%)	178 (8.0%)	102 (4.6%)

* Obesity, type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, serious heart disorder, asthma, COPD, pulmonary fibrosis, neurological disease, cerebrovascular disease, chronic kidney disease, cancer, liver disease, hematopoietic cell transplant recipient in an immunosuppressed condition, thalassaemia, and sickle cell disease

For definitions of Grades 3 and 4, see Tables 67 to 69.

Table 64. Summary of adverse events after each dose in subjects with and without underlying diseases* at baseline (foreign Study COV3009, safety subset)

	With underlying diseases				Without underlying diseases			
	After the first dose		After the second dose		After the first dose		After the second dose	
	Jcovden (1,257)	Placebo (1,297)	Jcovden (599)	Placebo (550)	Jcovden (1,758)	Placebo (1,755)	Jcovden (960)	Placebo (875)
Solicited local adverse events	637 (50.7%)	275 (21.2%)	290 (48.4%)	97 (17.6%)	1,039 (59.1%)	378 (21.5%)	606 (63.1%)	155 (17.7%)
Grade ≥3	5 (0.4%)	2 (0.2%)	6 (1.0%)	0	4 (0.2%)	4 (0.2%)	4 (0.4%)	3 (0.3%)
Solicited systemic adverse events	685 (54.5%)	467 (36.0%)	273 (45.6%)	174 (31.6%)	1,079 (61.4%)	671 (38.2%)	548 (57.1%)	268 (30.6%)
Grade ≥3	16 (1.3%)	9 (0.7%)	10 (1.7%)	5 (0.9%)	39 (2.2%)	5 (0.3%)	15 (1.6%)	0
Solicited systemic adverse events considered causally related to study vaccine	659 (52.4%)	443 (34.2%)	268 (44.7%)	164 (29.8%)	1,056 (60.1%)	638 (36.4%)	542 (56.5%)	259 (29.6%)
Grade ≥3	15 (1.2%)	9 (0.7%)	10 (1.7%)	5 (0.9%)	38 (2.2%)	5 (0.3%)	15 (1.6%)	0
Unsolicited adverse events	202 (16.1%)	149 (11.5%)	62 (10.4%)	48 (8.7%)	252 (14.3%)	183 (10.4%)	97 (10.1%)	72 (8.2%)
Grade ≥3	9 (0.7%)	10 (0.8%)	7 (1.2%)	4 (0.7%)	12 (0.7%)	6 (0.3%)	5 (0.5%)	3 (0.3%)
Unsolicited adverse events considered causally related to study vaccine	126 (10.0%)	85 (6.6%)	28 (4.7%)	19 (3.5%)	157 (8.9%)	94 (5.4%)	51 (5.3%)	30 (3.4%)
Grade ≥3	5 (0.4%)	1 (0.1%)	3 (0.5%)	1 (0.2%)	4 (0.2%)	4 (0.2%)	2 (0.2%)	0

* Obesity, type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, serious heart disorder, asthma, COPD, pulmonary fibrosis, neurological disease, cerebrovascular disease, chronic kidney disease, cancer, liver disease, hematopoietic cell transplant recipient in an immunosuppressed condition, thalassaemia, sickle cell disease, other lung diseases, and sleep apnea

For definitions of Grades 3 and 4, see Tables 67 to 69.

PMDA confirmed, based on the clinical study results, that the safety profile in subjects with underlying diseases raised no safety concerns warranting special attention as compared with the overall population or subjects without underlying diseases. Although limited underlying diseases in subjects enrolled in the clinical studies, in post-marketing settings, Jcovden will presumably be administered to those with various underlying diseases including frailty, immunodeficient or immunosuppressed condition. The applicant should collect safety information from vaccine recipients with diverse characteristics and take appropriate measures.

7.R.3.3.2 Pregnant or breastfeeding women

The applicant's explanation about the use of Jcovden in pregnant or breastfeeding women:

Pregnancy was observed in 49 women (36 received Jcovden) as of the data cut-off date (July 9, 2021) for the primary analysis in foreign Study COV3001. The outcomes of pregnancy in most of these women are unknown, but in 22 women who presumably received Jcovden within 3 months before becoming pregnant, abortion incomplete and abortion missed were reported from 1 woman each, and in 14 women who received Jcovden during pregnancy, abortion spontaneous, ectopic pregnancy, and abortion incomplete were reported from 1 woman each. In 11 women who received placebo within 3 months before becoming pregnant, abortion incomplete, abortion missed, and fetal growth abnormality were reported in 1 woman each. All events were reported as serious, but a causal relationship to the study vaccine was ruled out. In foreign Study COV3009, pregnancy was reported in 30 women as of data lock for safety evaluation (August 23, 2021). Of these, 21 women received Jcovden within 3 months before becoming pregnant or during pregnancy, and the remaining 9 women received placebo. Most of the reported pregnancy had unknown outcome, but in 12 women who possibly received Jcovden within 3 months before becoming pregnant, abortion spontaneous and abortion were reported by 1 woman each,

and in 9 women who received Jcovden during pregnancy, congenital anomaly was reported by 1 woman. In 4 women who received placebo within 3 months before becoming pregnant, abortion spontaneous was reported by 1 woman, while 5 women who received placebo during pregnancy reported ectopic pregnancy. These were reported as serious events, but a causal relationship to the study vaccine was ruled out for all events.

The use of Jcovden in pregnant or breastfeeding women was comprehensively evaluated based on safety data of Jcovden obtained from the clinical studies and foreign post-marketing settings during a certain time period. In the safety database of Jcovden as of [redacted], 20[redacted], Jcovden were used in 691 cases of pregnant women or breastfeeding women (146 cases in clinical studies, 545 cases in foreign post-marketing settings). Of these, gestational exposure to Jcovden occurred in 569 cases, lactational exposure in 90 cases , and exposure during both pregnancy and breastfeeding occurred in 1 case. A total of 31 cases revealed exposure through their partners who participated in the clinical studies. In 601 pregnancy-related cases, 549 were identified as pregnancy cases. Of 118 cases of pregnancy with known outcome, 45 resulted in abortion (including abortion incomplete and abortion missed), the majority of which occurred in women vaccinated with Jcovden during a periconceptional period or early pregnancy. When more pregnancy outcomes from women continuing pregnancy are available through the further follow-up survey, the consistency between the abortion rate in the follow-up population and the spontaneous abortion rate will be assessed. A serious adverse event in pregnant women and/or their infant was reported by only 1 recipient, other than common post-vaccination reactogenicity, and no events with an evident causal relationship to Jcovden vaccination were reported. Of note, there were no reports on rare serious adverse events related to Jcovden including thrombosis with thrombocytopenia syndrome, venous thrombosis, immune thrombocytopenia, and Guillain-Barre syndrome. Nevertheless, limited information precludes the conclusion on the consistency in the incidences of these events between pregnant and non-pregnant vaccine recipients. Meanwhile, in terms of exposure in pregnant women, adequate relevant information is available with other Ad26 vector vaccines including ones under development (Ebola vaccine approved in Europe in July 2020 [brand name, Zabdeno], RSV vaccines], etc.), and the use of these Ad26 vectors in this population has raised no safety concerns.

Phase III studies of Jcovden (foreign Studies COV3001 and COV3009) accepted the participation of breastfeeding women, and approximately 200 breastfeeding women received Jcovden. In these vaccine recipients, no Jcovden-related serious adverse events occurred. While a total of 1,042 breastfeeding women received Ad26 vector-platform Ebola vaccine until now, the excretion of ingredients of Jcovden or antibodies induced by Jcovden into milk in humans remains unclear. No human data on effects of Jcovden on lactation or breastfed infants are available. The excretion of Ad26 vector into milk has not been evaluated in clinical or non-clinical biodistribution or virus shedding studies. Jcovden, however, is considered unlikely to be excreted into milk based on the results of non-clinical studies that showed limited biodistribution of the other Ad26 vector-based vaccine and clinical studies of the vaccine that showed limited excretion pathways. Even if a small amount of Jcovden is transiently excreted into milk, it will not pose a risk to breastfed infants, because Jcovden is a vaccine with a replication-incompetent virus vector that does not encode complete SARS-CoV-2 virus information.

As described, the use of Jcovden in pregnant or breastfeeding women raises no specific safety concerns and has shown positive overall benefit-risk profile. When its benefits of vaccination outweigh its possible risks, the use of Jcovden is reasonable in this population to prevent SARS-CoV-2 infection. At present, however, limited safety information of Jcovden is available from pregnant or breastfeeding women, and thus the evaluation will be further continued based on safety information from overseas, along with additional vigilance activities in Japan based on data from post-marketing surveillance and spontaneous reports .

PMDA accepted the applicant's view.

7.R.3.4 Risk of disease enhancement

A potential theoretical risk of SARS-CoV-2 vaccines is a vaccine-associated enhanced disease (VAED) including VAERD (*Vaccine.* 2020;38:4783-91, *Science.* 2020;368:945-6).

The applicant's explanation about VAED of Jcovden including VAERD:
Clinical symptoms of COVID-19 are not limited to respiratory symptoms, and vigilance activities of Jcovden have been underway, taking into account of not only VAERD but also a wider range of VAED. The results of non-clinical studies of Jcovden suggested that Jcovden would unlikely cause VAERD or VAED [see Section 3.R.3]. The immunogenicity evaluation in foreign Study COV1001 showed that Jcovden induced cellular immunity with Th1-dominant CD4 immune responses, suggesting a low risk of VAERD or VAED.

In foreign Study COV3001, the risk of VAED/VAERD was investigated by examining whether the incidences of severe/critical diseases or deaths from events diagnosed as COVID-19 were higher in the Jcovden group than those in the placebo group. Severe/critical COVID-19 occurred in 5 subjects in the Jcovden group and 34 subjects 28 days after study vaccination, and 14 subjects in the Jcovden group and 60 subjects in the placebo group 14 days after vaccination. Furthermore, throughout the study, COVID-19 was reported as a serious adverse event from 8 subjects in the Jcovden group and 44 subjects in the placebo group, indicating higher frequency in the placebo group. Accordingly, the results of clinical studies are not considered indicative of no potential risk of VAED including VAERD.

Cumulative safety data presented in the latest PBRER (from [redacted], 20[redacted] to [redacted], 20[redacted]) and latest summary safety report (from [redacted], 20[redacted] to [redacted], 20[redacted]) do not suggest a risk of Jcovden-associated VAED including VAERD.

The lack of long-term safety and efficacy data, however, has failed to provide adequate evidence to completely rule out the risk. The risk of VAED in recipients of Jcovden will be further investigated based on the updated information from the clinical studies and ongoing post-marketing surveillance in and outside Japan. Appropriate measures will be taken when newly obtained data are indicative of potential impact on the risk-benefit balance of Jcovden.

PMDA accepted the applicant's explanation. The applicant should continue collecting data on the risk of Jcovden-associated enhanced disease in post-marketing settings. When any new finding is available,

the applicant should discuss actions to take immediately, take appropriate measures, and provide information, etc.

7.R.3.5 Safety information from overseas after use authorization or marketing approval

The applicant's explanation about major events reviewed based on post-marketing foreign safety information other than events reviewed in Section 7.R.3.2:

(a) Immune thrombocytopenia (ITP)

Based on the results of clinical studies of Jcovden and foreign post-marketing data, cases related to immune thrombocytopenia falling under the MedDRA SMQ of "Haematopoietic thrombocytopenia" or the HLT of "Thrombocytopenia," were extracted (data locked on [redacted], 20[redacted]), and ITP events were identified according to the case definition of ITP published in 2018 by the American Society of Hematology (*Hematology.* 2018;v2018:561-7). No ITP events were reported after Jcovden vaccination in Japanese and foreign clinical studies. In foreign Study COV3012 (open-label, non-company sponsored), 2 ITP events ("confirmed" and "likely" for 1 event each) were reported. In foreign post-marketing settings, 217 ITP events were reported, including 151 "suspected" events, 63 "likely" events, and 3 "confirmed" events. A total of 4 events resulted in death (3 "suspected" events, 1 "likely" event). Of the ITP events, 9 likely events, 2 suspected events, and 3 confirmed events occurred in recipients with a history of ITP, which worsened within 34 days (median, 7 days) after Jcovden vaccination. Half of these case reports were from the US. Many of spontaneous case reports lacked details, which limited the evaluation, but comparisons between the incidences of Jcovden-associated events and those in historical data revealed inconsistency in both all thrombocytopenic and ITP cases. Although ITP occurred extremely rarely after Jcovden vaccination, the event was reported from the clinical studies and foreign post-marketing settings with some cases resulting in deaths. Therefore, recognizing ITP as an important potential risk, healthcare professionals and vaccine recipients will be advised via the package insert, etc. of the importance of platelet count testing to be performed according to the risk of ITP or as necessary, and information collection and vigilance activities should be continued through the post-marketing surveillance, etc.

(b) Capillary leak syndrome (CLS)

In foreign post-marketing settings as of [redacted], 20[redacted], CLS occurred in 3 Jcovden recipients. In response, a risk of CLS after Jcovden vaccination was evaluated. In the clinical studies, CLS was not reported after Jcovden vaccination. In the safety database of Jcovden covering the period from [redacted], 20[redacted] to [redacted], 20[redacted], CLS was identified in 7 vaccine recipients (3 men and 4 women median age [range], 62.1 years [50-92 years]). The median time to onset after Jcovden vaccination was 1 day. All 7 events were serious. A total of 4 vaccine recipients died of the events, 1 recipient remained unresolved, and 1 recipient had an unreported outcome.

Because the temporal association between vaccination and the onset of CLS, etc. suggested a causal relationship to Jcovden, the applicant considered it necessary to advise caution about the risk in the package insert, etc. Some of the vaccine recipients who developed fatal CLS had had a history of CLS, and the possibility cannot be ruled out that Jcovden may promote the onset or worsening of CLS in those with a history of CLS. The package insert will advise that those who have a history of CLS are ineligible for Jcovden.

The applicant's approaches including specifying ITP as an important potential risk of Jcovden and information provision about the risk, as well as advising risk minimization measures such as a platelet count test, etc., are appropriate. Ineligibility for Jcovden of those who have a history of CLS, which would be advised via the package insert, is acceptable. The safety evaluation of Jcovden is continued in the ongoing clinical studies and has also been conducted periodically based on safety information collected in foreign post-marketing settings, and safety measures are taken as necessary. PMDA considers it important to continue collecting safety information of Jcovden in and outside Japan appropriately and take safety measures as necessary.

7.R.4 Clinical positioning and indication

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

The applicant's explanation about clinical positioning of Jcovden:
Foreign Study COV3001 has demonstrated the efficacy of Jcovden vaccination in preventing moderate or severe COVID-19 at a single dose. Jcovden is also expected to prevent severe/critical COVID-19, with confirmed safety and tolerability. In foreign Study COV3009, 2 doses of Jcovden administered 2 months apart for further enhancement and extended prevention of COVID-19 also demonstrated its efficacy in preventing moderate or severe COVID-19, without particular safety problems. Jcovden's prevention of COVID-19 at a single dose demonstrated in foreign Study COV3001 is considered beneficial for the global pandemic. In the prolonged COVID-19 pandemic, a booster dose of Jcovden ≥2 months after the first dose is expected to not only enhance and maintain its preventive effect against COVID-19 but also show a certain extent of efficacy against new variants.

Thawed Jcovden can be stored at 2°C to 8°C and is easy to handle at medical facilities. Its single-dose regimen also allows for relatively smooth implementation of vaccination programs. Jcovden will reduce burdens on medical facilities and personnel involved in vaccination.

In Japan, most people have completed the primary series of a SARS-CoV-2 vaccine, and booster vaccination programs are in progress. However, the primary series of approved SARS-CoV-2 vaccines are designed with 2 doses, and there are people, although limited in number, who remain unvaccinated or have not completed the primary series for various reasons, such as work schedule and concerns about adverse reactions. With Jcovden, only a single dose can achieve the preventive effect as a primary series, which can reduce burdens associated with vaccination and contribute to the promotion of the COVID-19 vaccination program. Jcovden will offer an option to people who are reluctant to receive a SARS-CoV-2 vaccine over a concern about possible adverse reactions reported with mRNA-platform vaccines or those who are ineligible for the booster dose of an mRNA-platform vaccine owing to a history of adverse reactions such as allergic reaction to the first dose.

Jcovden has been approved for conditional marketing or emergency supply in ≥100 countries or region and by WHO. Jcovden also was granted Emergency Use Authorization for booster dose in the US in October 2021. In Europe, partial change application of Jcovden was approved in December 2021, which allows for its use as booster doses. Accordingly, for being used as a booster dose vaccine in the US and

Europe, Jcovden may also be used extensively in Japan for those who have previously vaccinated with Jcovden overseas and wish to receive Jcovden as booster dose in Japan. Outside Japan, an open-label study (NIH/National Institute of Allergy and Infectious Diseases [NIAID]-sponsored phase I/II study [Study DMID21-0012], CTD 5.3.5.1.4) was conducted to evaluate the safety and immunogenicity of a booster dose of Jcovden 5×10^{10} vp or the other SARS-CoV-2 vaccines (Spikevax Intramuscular Injection or Comirnaty Intramuscular Injection) in adults aged ≥18 years who had received the last dose in the primary series of Jcovden, Spikevax, or Comirnaty Intramuscular Injection ≥12 weeks before the study vaccination. Subjects who had received Jcovden, Spikevax, or Comirnaty Intramuscular Injection for the primary series (50 subjects in the primary Jcovden group, 49 subjects in the primary Spikevax group, 51 subjects in the primary Comirnaty group) received Jcovden, and all 150 subjects were included in the safety and immunogenicity analysis populations. GMFR representative of a ratio of the neutralizing antibody titer (luciferase reporter assay using pseudovirus) 14 days after the booster dose of Jcovden to that before the booster dose was 4.1, 6.2, and 12.5 in the primary Jcovden group, primary Spikevax group, and primary Comirnaty group, respectively, showing that the booster dose of Jcovden strengthened humoral immune responses irrespective of the vaccine used for the primary series. For the safety, of the solicited adverse events (local events including pain/tenderness, erythema/redness, and induration/swelling; and systemic events including headache, malaise and fatigue, myalgia, arthralgia, nausea, chills, and pyrexia [≥38°C]) observed within 7 days after the booster dose of Jcovden, a major solicited local adverse event was pain/tenderness, and major solicited systemic adverse events were malaise/fatigue, myalgia, and headache. The incidences of unsolicited adverse events and adverse reactions observed within 28 days after the booster dose of Jcovden (unsolicited adverse events for which a causal relationship to Jcovden could not be ruled out) were 36.0% (18 of 50) and 6.0% (3 of 50) in the primary Jcovden group, 30.6% (15 of 49) and 14.3% (7 of 49) in the primary Spikevax group, and 39.2% (20 of 51) and 15.7% (8 of 51) in the primary Comirnaty group. As of the data cut-off date (September 24, 2021), a serious adverse event (cholecystitis acute) occurred in 1 subject in the primary Spikevax group, but a causal relationship to Jcovden was ruled out. There were no deaths or adverse events leading to study discontinuation .

In currently ongoing foreign Study COV2008, the immunogenicity and safety of Jcovden administered after the primary series of Comirnaty Intramuscular Injection are evaluated. When the results are available, appropriate measures such as the revision of the package insert will be taken. In view of the progress in public vaccination programs with approved SARS-CoV-2 vaccines in Japan, Jcovden can serve as a new option for a booster dose (heterologous booster dose) in those who have received a SARS-CoV-2 vaccine other than Jcovden.

PMDA's view:
In Japan, as of March 31, 2022, several therapeutic agents for SARS-CoV-2 infection are available, and approved vaccines for the prevention of COVID-19 as with Jcovden include Comirnaty Intramuscular Injection (Pfizer Japan Inc.), Vaxzevria Intramuscular Injection (AstraZeneca K.K.), and Spikevax Intramuscular Injection (previously COVID-19 Vaccine Moderna Intramuscular Injection, Takeda Pharmaceutical Co., Ltd.). Unlike these preceding 3 vaccine products, the efficacy of Jcovden was demonstrated at a single dose [see Sections 7.2.2 and 7.R.2.2], and the efficacy of the booster dose administered ≥2 months apart was also confirmed [see Sections 7.2.3 and 7.R.2.4].From a safety point

of view, thrombosis with thrombocytopenia syndrome, etc. occurred in the clinical studies of Jcovden and foreign post-marketing settings, and these are the events of special interest for Vaxzevria Intramuscular Injection, a vaccine using a platform similar to that of Jcovden. These events warrant attention in the use of Jcovden as in the use of Vaxzevria Intramuscular Injection, but such risks are manageable with appropriate cautionary advice given and adherence to proper use. In view of benefits of the efficacy in prevention of COVID-19 and expected efficacy against SARS-CoV-2 variants observed with Jcovden, the safety of Jcovden is considered tolerable. Furthermore, Jcovden was developed as a vaccine product to be stored at 2°C to 8°C after thawing and thus can be stored in a refrigerator basically as with vaccines to for the prevention of infection with seasonal influenza, etc. used in Japan. No special measures are required for distribution, delivery, or storage. While the approved vaccines for the prevention of COVID-19 are intended for 2-dose regimen primary series, Jcovden has been demonstrated to have efficacy in the single-dose regimen. Accordingly, Jcovden is expected to offer a new option of vaccine for prevention against SARS-CoV-2 infection, which is in demand in this prolonged pandemic. In Japan, approximately 80% of people have completed the primary series of the approved SARS-CoV-2 vaccines, and mRNA vaccine recipients account for 99.9%. However, a certain proportion of people have not completed the primary series, including those who experienced adverse reactions of an mRNA vaccine and others reluctant to receive mRNA vaccines for various reasons. Because Jcovden is one of the effective SARS-CoV-2 vaccines widely used overseas and is a vaccine with a platform different from
major mRNA vaccines in Japan, the approval of Jcovden as an additional option for COVID-19 prevention is of significance.

Based on the above consideration, PMDA has concluded that the indication of Jcovden should be "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" as proposed.

7.R.5 Dosage and administration

The applicant explained the dosage regimen of Jcovden as follows.

7.R.5.1 Dosage and number of doses

The applicant's explanation about the dosage and number of doses of Jcovden:
In foreign Study COV1001, the first clinical study of Jcovden, 2 dosages of 5×10^{10} vp and 1×10^{11} vp were selected for evaluation based on the results of clinical studies of the other Ad26 vector vaccines in adults.

In foreign Study COV1001, an interim analysis was performed on the immunogenicity and safety results from 375 subjects aged ≥18 and ≤55 years 28 days after the first dose and available results in subjects aged ≥65 years. The analysis showed that a single dose of Jcovden either 5×10^{10} vp or 1×10^{11} vp induced humoral immune responses and Th1-dominant cellular immune responses. These results showed high percentages of responders to humoral immunity and cellular immunity with the single dose. A single-dose regimen, if effective in prevention, would have considerable advantages in vaccine supply and vaccination promotion under the COVID-19 pandemic. Accordingly, In foreign Study COV3001, a confirmatory study for the efficacy of Jcovden, the single-dose regimen of Jcovden 5×10^{10} vp was selected.

Foreign Study COV3001 demonstrated the efficacy of single dose of Jcovden 5×10^{10} vp [see Section 7.R.2] with acceptable safety and tolerability [see Section 7.R.3]. Therefore, it is appropriate to specify the single-dose regimen of Jcovden 5×10^{10} vp as the primary series regimen for the prevention of COVID-19.

Foreign Study COV3001 and other studies, on the other hand, suggested over-time decreases in efficacy and immunogenicity. The use of a booster dose should be considered when the prevention of symptomatic COVID-19 and severe or critical COVID-19 is the immediate priority or when there is a concern about a newly emerging VOC.

The applicant's view on the interval between the primary series and booster dose:
Table 65 shows neutralizing antibody titers in cohorts in which subjects received the second dose of Jcovden 5×10^{10} vp 2 or 3 months after the first dose in foreign Study COV2001. GMTs 14 and 28 days after the second dose of Jcovden and GMFRs to the titer at baseline were higher in the 3-month-interval cohort than in the 2-month-interval cohort.

Table 65. Neutralizing antibody titers in subjects who received 2 doses of Jcovden 5×10^{10} vp 2 or 3 months apart (foreign Study COV2001, PPI population)

		2-month interval			3-month interval		
		Subjects analyzed (n)	GMT [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]	Subjects analyzed (n)	GMT [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]
Baseline		38	<LLOQ [<LLOQ, <LLOQ]	-	37	<LLOQ	-
After the first dose	14 days	39	154 [113, 211]	2.9 [2.2, 3.7]	-	-	-
	28 days	39	260 [196, 346]	4.4 [3.3, 5.7]	-	-	-
Before the second dose		39	212 [142, 314]	3.7 [2.6, 5.2]	35	236 [169, 328]	4.1 [3.0, 5.7]
After the second dose	7 days	39	313 [219, 446]	5.6 [4.0, 7.7]	19	376 [290, 488]	6.5 [5.0, 8.4]
	14 days	39	518 [354, 758]	8.8 [6.1, 12.8]	34	904 [691, 1184]	15.6 [11.9, 20.4]
	28 days	38	424 [301, 597]	7.4 [5.4, 10.2]	37	694 [473, 1018]	12.2 [8.4, 17.6]

Table 66 shows changes in neutralizing antibody titer (luciferase reporter assay using pseudovirus[43)]) and concentration of antibodies binding to S protein (ELISA) in subjects who received the second dose of Jcovden 5×10^{10} vp 6 months after the first dose in Cohort 2a (healthy adults aged ≥18 and ≤55 years) in foreign Study COV1001. GMFR [two-sided 95% CI] representative of a ratio of the neutralizing antibody titer after the second dose to that before the second dose was 5.6 [2.5, 12.6] 28 days after the second dose, showing a rapid and remarkable rise in neutralizing antibody titer.

43) Human immunodeficiency virus Type 1 (HIV-1) vector-based pseudovirus expressing S protein derived from SARS-CoV-2 (D614G variant and Beta variants)

Table 66. GMT of neutralizing antibodies and GMC of antibodies binding to S protein after 2 doses of Jcovden 5 × 10^{10} vp 6 months apart (foreign Study COV1001, Cohort 2a [PPI population])

		Neutralizing antibodies			Antibodies binding to S protein (ELISA)		
		Subjects analyzed (n)	GMT [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]	Subjects analyzed (n)	GMC (EU/mL) [two-sided 95% CI]	GMFR from baseline [two-sided 95% CI]
Baseline		17	<LLOQ	-	27	<LLOQ (-;-)	-
28 days after the first dose		17	150 [77, 294]	4.0 [2.3, 7.2]	27	420 [322, 549]	8.4 [6.4, 10.9]
Before the second dose		17	319 [131, 779]	8.6 [3.9, 19.0]	20	798 [441, 1443]	15.9 [8.8, 28.7]
After the second dose	7 days	17	1136 [703, 1835]	27.0 [16.7, 43.7]	17	3779 [2583, 5529]	75.1 [51.3, 109.9]
	28 days	15	2127 [1426, 3171]	50.6 [30.4, 75.5]	15	5108 [3402, 7669]	101.6 [67.6, 152.5]

These results showed that 2 doses of Jcovden 5 × 10^{10} vp administered ≥2 months apart increased the neutralizing antibody titer and suggested that the titer increased with an extending period from the first dose. Foreign Study COV3009 demonstrated the efficacy of 2 doses of Jcovden 5 × 10^{10} vp administered 2 months apart and indicated no safety concerns for the second dose of Jcovden in comparison with the first dose.

Accordingly, the dosage and administration will be defined as "A single dose of 0.5 mL should be administered intramuscularly," and the "Precautions for use" section will advise that a booster dose of Jcovden may be administered ≥2 months after the first dose and inform that immune responses presumably increase with increasing interval between the first and booster doses. Although, in foreign studies such as Study COV1001, a certain level of immune response lasted for 6 months after 2 doses of Jcovden administered 2 or 3 months apart, the duration of the efficacy of 2 dose regimen will be further monitored, and the need of additional booster doses will be investigated to deal with future SARS-CoV-2 variants.

7.R.5.2 Target age group for vaccination

Clinical studies in the clinical data package submitted for this application mainly targeted subjects ≥18 years. Foreign Study COV2001, which included participants aged <18 years, was initially planned to evaluate 2 dosages of Jcovden 2.5 × 10^{10} vp and 5 × 10^{10} vp in the cohort of subjects aged ≥12 and ≤17 years, but based on the immunogenicity data of Jcovden 2.5 × 10^{10} vp obtained in the sentinel cohort of subjects aged 16 to 17 years, the evaluation of Jcovden 5 × 10^{10} vp in subjects aged 12 to 17 years was cancelled. Accordingly, the applicant considers that eligible population for Jcovden 5 × 10^{10} vp should be adults aged ≥18 years who have undergone efficacy, safety, and immunogenicity the evaluation. [redacted], the applicant plans to discuss the development in Japan as well based on results in foreign clinical studies.

PMDA's view:

The single-dose regimen of Jcovden 5 × 10^{10} vp was demonstrated to prevent COVID-19 and shown to be tolerable in foreign Study COV3001, and thus the regimen may be employed. Based on the results

on immunogenicity in Japanese Study COV1002 and foreign Studies COV1001 and COV3001, the regimen is also expected to be effective in Japanese as well [see Section 7.R.2.2].

Foreign Study COV3009 conducted in parallel with foreign Study COV3001 also demonstrated the prevention of COVID-19 by 2 doses of Jcovden administered 2 months apart. The safety of the 2-dose regimen was also shown with its tolerability in other clinical studies including Japanese Study COV1002. Results of an analysis on the efficacy at the end of the double-blind period after the primary analysis in foreign Study COV3001 and decreased immunogenicity over time after the single dose of Jcovden observed in foreign Study COV1001, etc., are indicative of attenuated preventive effect of Jcovden against COVID-19 as with approved vaccines. Therefore, as mentioned in Section 7.R.2.3, a regimen allowing for the second dose of Jcovden, which was evaluated in foreign Study COV3009, is necessary in this prolonged pandemic that requires long-lasting immunity against SARS-CoV-2. The use of second dose of Jcovden should be carefully determined for each vaccine recipient based on benefits expected from the 2 doses and safety information in view of the prevalence of SARS-CoV-2 and the characteristics of the recipient, this advice provided with relevant information. Furthermore, the applicant should also provide the updated, adequate benefit-risk information to help appropriate judgment on the need of a booster dose. Of note, how long Jcovden can sustain its efficacy after a booster dose has not been evaluated until now, and a further booster dose may be considered as necessary. However, healthcare professionals should be informed that the efficacy and safety of a 3-dose regimen of Jcovden have not been evaluated based on the currently available data.

Timing of the Jcovden booster dose after the first dose should be “at least 2 months after the first dose of Jcovden” according to the regimen in foreign Study COV3009 that is the primary basis of the efficacy and safety of the Jcovden booster dose, and the relevant information should be provided in the package insert. The second dose, administered as a booster dose even ≥2 months apart from the first dose in an inevitable situation, may be acceptable from the safety viewpoint based on the safety and immunogenicity data from foreign Study COV1001, etc. The applicant should provide healthcare professionals and vaccine recipients with information about timing of the second dose of Jcovden which was demonstrated to be tolerable in clinical studies separately. Meanwhile, the applicant’s intention to provide information about immune responses expected to increase with increasing dosing interval based on results in foreign Study COV1001, etc., is inappropriate. There is no established threshold of the immunogenicity, such as the neutralizing antibody titer, necessary for prevention of COVID-19, and clinical significance of the increase in immune response by dose interval remains unclear. Furthermore, the upper limit of acceptable dose interval has not been specified.

For the use of Jcovden as a booster dose in recipients vaccinated with any approved SARS-CoV-2 vaccines, it is difficult to evaluate efficacy and safety only based on the information currently available. At present, the applicant should communicate that the efficacy and safety of Jcovden in recipients of a different SARS-CoV-2 vaccine have not been evaluated. In view of the clinical positioning of Jcovden in Japan where the public vaccination programs with approved SARS-CoV-2 vaccines are taking place, the applicant should evaluate the efficacy and safety of Jcovden administered as a heterologous booster dose based on results that will be obtained from clinical studies including currently ongoing foreign

Study COV2008, and discuss what information to provide to healthcare professionals and vaccine recipients.

Based on the above points and applicant's explanation about eligible age range, PMDA concluded that the dosage and administration should be defined as follows.

Dosage and Administration
A single dose of 0.5 mL should be administered intramuscularly to persons aged 18 years or older.

7.R.6 Post-marketing investigations

The applicant's explanation about measures for post-marketing investigations of Jcovden:
In the risk management plan (RMP) of Jcovden, safety specification will include shock, anaphylaxis, and thrombosis with thrombocytopenia syndrome. In view of the limited safety information in Japanese population, a use-results survey (planned sample size of 3,000 individuals, observation period of 28 days) is planned to be conducted in individuals vaccinated with Jcovden to investigate the safety of Jcovden in clinical use including items specified in the RMP. When a COVID-19 case is reported in this survey, detailed information about VAED including VAERD will be collected. Considering that the risk of VAED also need to be evaluated for long-term safety, it will be comprehensively evaluated based not only on this post-marketing survey in Japan, but also on data from ongoing clinical studies, in the safety findings of Jcovden evaluated once every 2 months (issuance of safety summary report), and information from routine pharmacovigilance activities such as semiannual risk-benefit evaluation (issuance of PBRER) and spontaneous reports.

Appropriate information provision will be exercised for thrombosis with thrombocytopenia syndrome that was identified overseas as a risk of adenoviral vector-platform SARS-CoV-2 vaccines including Jcovden so that healthcare professionals and vaccine recipients are well aware of main symptoms and findings of the event as well as points to consider at diagnosis and treatment, and this will lead to early detection, diagnosis, and treatment. Diagnosis and treatment guidelines for thrombosis with thrombocytopenia syndrome have been published by related academic societies after the approval of Vaxzevria Intramuscular Injection in Japan. For cautionary advice to be given for post-marketing use of Jcovden, as with Vaxzevria Intramuscular Injection, the revision of the diagnosis and treatment guidelines based on the updated information will be discussed with the related academic societies and experts as a part of the safety measures of Jcovden.

PMDA's view on the post-marketing surveillance plan:
The applicant plans to implement the post-marketing use-results survey of Jcovden to evaluate the safety in clinical use, which is acceptable in view of the limited safety data of Jcovden in Japanese population. The use-results survey planned by the applicant, however, has an observation period of 28 days, which is not long enough to evaluate the risks specified as important identified risks including thrombosis with thrombocytopenia syndrome or important potential risks such as ITP. Depending on the prevalence of SARS-CoV-2, it may not be possible to collect data on a booster dose of Jcovden or another SARS-CoV-2 vaccine from those who have previously received Jcovden (intervals between the booster dose and preceding doses, etc.). Therefore, the survey should be designed to allow for long-term collection

of clinical data. The addition of a follow-up period may be considered after the observation period of 28 days.

The applicant's planned approach to reduce the risk of thrombosis with thrombocytopenia syndrome, including information provision to healthcare professionals and vaccine recipients and collaboration with the related academic societies or experts, is appropriate. The applicant should continue collecting information about the other identified risks, potential risks such as immune-mediated and neuroinflammatory events and ITP, as well as the safety of Jcovden in pregnant women. Foreign post-marketing data should also be evaluated. Cautionary advice and relevant information should be provided as necessary.

A final decision on the post-marketing investigation will be made, taking account of comments from the Expert Discussion.

8. Response to the Regulations on the Type 1 Use of Living Modified Organisms under Article 4 of the Cartagena Act

This issue is currently under review, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

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

Inspections is currently ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

Inspections is currently ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that Jcovden has efficacy in the prevention of COVID-19 and acceptable safety in view of its benefits. For Jcovden, development was initiated soon after COVID-19 began spreading, and foreign Study COV3001 demonstrated that Jcovden had prevented COVID-19. Jcovden is now available across the world including Europe and the US. Of note, in Japan, Jcovden is designated as one of the vaccine products valid for vaccination certificates against novel coronavirus infection under the "New Border Measures (27)" dated February 24, 2022. Under such circumstances and in view of expected clinical positioning of Jcovden, PMDA considers it clinically meaningful to make Jcovden available as a new option for prevention of COVID-19.

Although the dosage and administration and post-marketing investigation should be further discussed, PMDA has concluded that Jcovden may be approved if Jcovden is not considered to have any particular problems based on comments from the Expert Discussion.

11. Others

11.1 Severity grading scale for adverse events

In the clinical studies of Jcovden, severity of adverse events was assessed in accordance with a modified version of the FDA guidance for toxicity grading scale in clinical studies of preventive vaccines (Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007) presented in Tables 67 to 69.

Table 67. Severity classification of local reactions (including solicited local adverse events)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Pain/tenderness	Perceptible but readily tolerable symptoms. Does not interfere with activity. Mild discomfort to touch.	Remarkable symptoms. Change of activities or use of drugs is needed. Discomfort with movement.	Intolerable symptoms. Interfere with work, school, or daily activity. Use of narcotic pain reliever.	Hospitalization Pain/tenderness interferes with basic self-control
Erythema[a]	25-50 mm	51-100 mm	>100 mm	Hospitalization. Necrosis or exfoliative dermatitis.
Swelling[a]	25-50 mm	51-100 mm	>100 mm	Hospitalization. Necrosis.
Induration[a,b]	25-50 mm	51-100 mm	>100 mm	Hospitalization. Necrosis.

a, Graded based on the diameter.
b, Applied only to Japanese Study COV1002

Table 68. Severity classification of vital signs*

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Fever (°C)**	38.0-38.4	38.5-38.9	39.0-40.0	>40
Tachycardia (beats/minute)	101-115	116-130	>130	Hospitalization for arrhythmia
Bradycardia (beats/minute)***	50-54	45-49	<45	Hospitalization for arrhythmia
Hypertension; Systolic (mm Hg)	141-150	151-155	>155	Hospitalization for malignant hypertension
Hypertension; Diastolic (mm Hg)	91-95	96-100	>100	Hospitalization for malignant hypertension
Hypotension; Systolic (mm Hg)	85-89	80-84	<80	Hospitalization for hypotensive shock
Respiratory rate (breaths/minute)	17-20	21-25	>25	Intubation

* Participants should be at rest for all vital sign measurements.
** It is not allowed to drink hot or cold beverages or smoke shortly before the measurement.
*** When resting heart rate is between 60 and 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Table 69. Severity classification of systemic reactions (including solicited systemic adverse events) and systemic illness

Systemic reaction				
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Vomiting	No interference with activity or 1-2 episodes of vomiting/24 hours	Some interference with activity or >2 episodes of vomiting/24 hours	Prevents daily activity, requires outpatient IV hydration	Hospitalization Hypotensive shock
Nausea	Minimal symptoms Symptoms slightly or never interfere with work, school, or self-control activity	Remarkable symptoms Change of activities or use of drugs is needed No absence from work, school, or social activity	Intolerable symptoms Requiring rest and/or causing absence from work, school, or social activity	Hospitalization Interferes with basic self-control
Diarrhoea	2-3 loose stools or <400 g/24 hours	4-5 stools or 400-800 g/24 hours	6 or more watery stools or >800 g/24 hours or requires oral hydration	Hospitalization Hypotensive shock or IV hydration indicated
Headache	Minimal symptoms Symptoms slightly or never interfere with work, school, or self-control activity	Remarkable symptoms Change of activities or use of drugs is needed No absence from work, school, or social activity	Intolerable symptoms Requiring rest and/or causing absence from work, school, or social activity Use of narcotic pain reliever	Hospitalization Interferes with basic self-control
Fatigue	Minimal symptoms Symptoms slightly or never interfere with work, school, or self-control activity	Remarkable symptoms Change of activities or use of drugs is needed No absence from work, school, or social activity	Intolerable symptoms Requiring rest and/or causing absence from work, school, or social activity Use of narcotic pain reliever	Hospitalization Interferes with basic self-control
Myalgia	Minimal symptoms Symptoms slightly or never interfere with work, school, or self-control activity	Remarkable symptoms Change of activities or use of drugs is needed No absence from work, school, or social activity	Intolerable symptoms Requiring rest and/or causing absence from work, school, or social activity Use of narcotic pain reliever	Hospitalization Interferes with basic self-control
Systemic illness				
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Illness or clinical adverse event	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization

Review Report (2)

May 16, 2022

Product Submitted for Approval

Brand Name	Jcovden Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Adenovirus Vector)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	May 24, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Clinical data package and data for review

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.1 Clinical data package and data for review" of the Review Report (1).

1.2 Efficacy

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

- How to determine Jcovden' efficacy against variants based on the immunogenicity, including neutralizing antibody titers, remains unclear, which raise a concern. The approach for the evaluation the efficacy of Jcovden and its duration in clinical use is a challenging issue. Although the use of overseas efficacy data of approved SARS-CoV-2 vaccines will be inevitable, the applicant should continue to investigate the efficacy of Jcovden against new variants and provide outcomes to healthcare professionals and vaccine recipients appropriately.
- In Japanese Study COV1002, neutralizing antibody titers after the second dose of Jcovden were lower in subjects aged ≥65 years (Cohort 2) than in subjects aged ≥20 and <55 years (Cohort 1). In Japan, the elderly have already undergone the other SARS-CoV-2 vaccination, and Jcovden, if used for this population, will be administered as a heterologous booster dose. The applicant is therefore requested to provide healthcare professionals with as much information about immune responses induced by a heterologous booster dose of Jcovden and its efficacy, including impacts of age and other characteristics of recipients.

- The efficacy results varying by region or race that were yielded by the subgroup analysis in foreign Study COV3001 allow limited interpretation owing to the limited number of confirmed COVID-19 cases investigated and because of the impacts of variants. The applicant, however, should continue to evaluate characteristics of recipients potentially affecting the efficacy of Jcovden and to communicate the results.

PMDA asked the applicant to provide healthcare professionals and vaccine recipients with updated information appropriately about the efficacy against variants including the Omicron variant currently prevalent in Japan, the characteristics of recipients potentially affecting the efficacy and immunogenicity, and others. The applicant replied that they would take actions appropriately.

1.3 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.3 Safety" of the Review Report (1).

In view of widespread use of the approved SARS-CoV-2 vaccines in Japan, limited number of doses of Jcovden will be administered, yielding limited safety data. PMDA requested the applicant to provide healthcare professionals and vaccine recipients in Japan with necessary information without delay based on foreign safety data available earlier. The applicant responded that they would take actions appropriately. Of note, the applicant also mentioned that they would continue to update the cautionary statements in the package insert appropriately according to the latest advice given outside Japan.

1.4 Clinical positioning and indication

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.4 Clinical positioning and indication" of the Review Report (1) and made the following comments:

- Providing more vaccine options is important for the promotion of vaccination against SARS-CoV-2 in Japan. Jcovden is therefore a clinically significant vaccine as a new option for those who are not eligible for the approved SARS-CoV-2 vaccines.
- The documented efficacy of a single dose of Jcovden can be a key point in vaccine selection. However, the efficacy of Jcovden, including that against SARS-CoV-2 variants, should be further evaluated. It is also important to consider the use of other vaccines to address specific variants as necessary.
- One of the advantages Jcovden is that thawed Jcovden can be stored under refrigeration for a certain period, requiring no special measures such as use of deep freezers for distribution, delivery, or storage.

PMDA conveyed the expert advisers' comments to the applicant. The applicant responded that they would continue to evaluate the efficacy of Jcovden against known variants and discuss the development of vaccines to address variants as necessary.

1.5 Dosage and administration

At the Expert Discussion, The expert advisors supported PMDA's conclusion described in Section "7.R.5 Dosage and administration" of the Review Report (1) and made the following comments:

- The “Dosage and Administration” section may also provide information related to the booster dose of Jcovden, referring to the relevant descriptions for the approved SARS-CoV-2 vaccines as examples. Healthcare professionals may face difficulties in decision making on the use of the second dose
- In view of widespread use of the approved SARS-CoV-2 vaccines in Japan, the evaluation of Jcovden as a heterologous booster dose is important, and information including results of the clinical study (foreign Study COV2008) should be appropriately communicated.

PMDA explained the dosage and administration of Jcovden as follows, and the expert advisors supported PMDA’s conclusion.

A single dose of Jcovden has been demonstrated to have efficacy as the primary series, and unlike the other SARS-CoV-2 vaccines, the primary series and booster dose with Jcovden employ the same regimen. Given the conclusion in Section 7.R.5 of the Review Report (1), the volume per dose and vaccination route should be specified in the “Dosage and Administration” section. The “Precautions Concerning Dosage and Administration” section should advise that the second dose can be administered a booster dose 2 months apart, for which the descriptions of dosage regimens of vaccines other than SARS-CoV-2 vaccines may be used as a reference.

The decision on the use of the second dose should be based on the risk-benefit balance of Jcovden vaccination, according to the prevalence of COVID-19 (including SARS-CoV-2 variants) at the time, availability of information about the efficacy of Jcovden against the relevant variants, and conditions of vaccine recipients. The information materials for healthcare professionals and for vaccine recipients should appropriately provide necessary information for a judgment on the need of the second dose.

Until now, the efficacy and safety of Jcovden administered as a heterologous booster dose have not been evaluated, and this should be mentioned in the package insert and other materials. When results of foreign Study COV2008 are available, information related to the heterologous booster dosing should be promptly provided to healthcare professionals.

PMDA conveyed the expert advisers’ comments to applicant, and the applicant responded that they would take actions appropriately.

1.6 Post-marketing investigations

At the Expert Discussion, the expert advisors supported PMDA’s conclusion in Section “7.R.6 Post-marketing investigations” of the Review Report (1), and PMDA’s views that the risk management plan (draft) for Jcovden should include the safety specification presented in Table 70, in response to the discussion about the booster dose, etc. The applicant should implement additional pharmacovigilance activities and risk minimization activities presented in Tables 71 and 72.

Table 70. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Thrombosis with thrombocytopenia syndrome • Guillain-Barre syndrome	• Vaccine-associated enhanced disease (VAED) (including vaccine-associated enhanced respiratory disease [VAERD]) • Thrombosis • Immune thrombocytopenia • Immune-mediated and neuroinflammatory events	• Safety in pregnant women or breastfeeding women • Safety of Jcovden administered as a booster dose after the primary series of the other novel coronavirus vaccines
Efficacy specification		
Not applicable		

Table 71. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey • Foreign phase III study (Study COV3001) • Foreign phase III study (Study COV3009) • Foreign phase I/IIa study (Study COV1001) • Foreign phase II study (Study COV2008)	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information for healthcare professionals (proper use guide) • Organize and disseminate information for vaccine recipients (for people who receive Jcovden Intramuscular Injection) • Periodical publication of adverse reactions reported

Table 72. Outline of general use-results survey (draft)

Objective	To evaluate the safety of Jcovden in clinical use
Survey method	Central registry system
Population	Jcovden vaccine recipients
Observation period	90 days after the first dose of Jcovden
Planned sample size	3,000 (to be included in the safety analysis)
Main survey items	Characteristics of vaccine recipients, status of Jcovden vaccination, concomitant medications, adverse events and their details, information on COVID-19, and local adverse events (pain/tenderness, erythema, swelling, and induration at the injection site) and systemic adverse events (fatigue, headache, nausea, myalgia, and pyrexia) within 7 days after Jcovden vaccination gathered through the recipients' diary.

1.7 Quality

1.7.1 Shelf life of active substance

The applicant submitted data from the stability study of the active substance (Process e and Process f of the active substance to be used in the to-be-marketed vaccine product), which is mentioned as ongoing in the Review Report (1), conducted during the periods shown in Table 73, and explained as below. Of note, no significant changes occurred in the quality of active substance during the test period, and results met the specifications.

Table 73. Stability study of the active substance

	Storage condition	Manufacturing process	Number of batches	Test period	Storage form
Long-term[a]	[redacted]°C ± [redacted]°C	Process e	4	[redacted] months	[redacted] container
		Process f	3	[redacted] months	

a Long-term testing ([redacted]°C ± [redacted]°C) is ongoing and continued until [redacted] months.

Process e and Process f differ only by [redacted], and the analysis and characterization of active substances manufactured by these processes show comparability. The shelf life of [redacted] months may be

proposed for the active substance when stored at ≤[redacted]°C based on results of the long-term testing of the active substance manufactured through Process e. The active substance manufactured by Process f indicated no concerns about its stable at [redacted] months. The long-term testing of 3 batches of active substance manufactured by Process f is underway, and stability will be evaluated at up to [redacted] months, which covers the shelf life of the active substance.

Based on the applicant's explanation, PMDA has concluded that the shelf life of [redacted] months stored at ≤[redacted]°C for the active substance is acceptable. The applicant, however, should promptly submit the results of long-term testing of the active substance manufactured by Process f as soon as available.

1.7.2 Changes to manufacturing process of vaccine product

The applicant additionally submitted results of the comparability exercise between the vaccine products manufactured by Processes A to C and the vaccine products manufactured by Process D, which is mentioned as an ongoing in the Review Report (1). The results demonstrated the comparability of the vaccine products manufactured by these processes. Just before the finalization of the Review Report (1), the applicant examined a further change to the manufacturing process of the to-be-marketed vaccine product and proposed Process E as the post-change process. In the pre-change process, Process D, [redacted] is performed after [redacted] in [redacted] process, while in the post-change process, Process E, [redacted], [redacted], and [redacted] are performed in [redacted] after [redacted].

The applicant's explanation about impacts of the change from Process D to Process E on the quality of the vaccine product:

Table 74 shows major changes to the manufacturing process of the vaccine product, including the content in Table 5 of the Review Report (1). Although Process D and Process E differ by presence or absence of [redacted] and [redacted] in [redacted] step, the processes up to [redacted] step of [redacted] are the same. For the change from Process D to Process E, no results of the comparability exercise between vaccine products manufactured by Process E and vaccine products manufactured by existing processes are available.

Process F including [redacted] and [redacted] step as with Process E has been developed and employed at [redacted] of the to-be-marketed vaccine product in Japan. The vaccine products manufactured by Process F are demonstrated to be comparable to the vaccine products manufactured by Process D that does not include [redacted] and [redacted] step. Although Process F and Process D differs by [redacted], etc., the results of comparability exercise indicate that the presence or absence of [redacted] and [redacted] step for the vaccine product has no impact on the quality of Jcovden. The change of the manufacturing process for the to-be-marketed vaccine product from Process D to Process E and the addition of [redacted] and [redacted] step after [redacted] to the manufacturing process are considered to have no impact on the quality of the vaccine product. Of note, the applicant will assess the comparability of commercial vaccine products in Japan manufactured by Process E with the vaccine products manufactured by the existing processes.

Table 74. Major changes in manufacturing process of vaccine product

Manufacturing process	Changes
From Process A to Process B	• Change of [redacted] • [redacted]
From Process B to Process C From Process B to Process D	• Change of [redacted] • [redacted] • Change of [redacted] process (change of [redacted] and [redacted] of [redacted]) • Change of [redacted] (from [redacted] to [redacted])
From Process D to Process E	• Addition of [redacted] and [redacted] process after [redacted]
From Process B to Process F	• Change of [redacted] • [redacted] • Change to [redacted] process (changes to [redacted] and [redacted] in [redacted]), • Addition of [redacted] and [redacted] process after [redacted] • Change of [redacted] (from [redacted] to [redacted])

PMDA has concluded that the manufacturing process for the to-be-marketed vaccine product in Japan may be changed from Process D to Process E because the results of comparability exercise with the vaccine products manufactured by Process D and the vaccine products manufactured by Process F have demonstrated that the addition of [redacted] and [redacted] process of [redacted] after [redacted] has no impact on the quality of the vaccine product, and thus the change from Process D to Process E is considered to have no impact on the quality of the vaccine product. The applicant, however, should submit the results of comparability exercise between the to-be-marketed vaccine products in Japan manufactured by Process E and those manufactured by the existing processes as soon as available.

1.7.3 Shelf life of vaccine product

Table 75 shows long-term testing used in the primary stability evaluation of the vaccine product, including the content in Table 6 of the Review Report (1). The applicant additionally submitted results of the long-term testing up to 9 months of the vaccine product manufactured by Process C, which is mentioned as ongoing in the Review Report (1). The results conformed to the specifications, showing no significant changes in the quality of the vaccine product throughout the period covered. In response to the change of the manufacturing process for the to-be-marketed vaccine product in Japan from Process D to Process E, the applicant presented a long-term testing plan of the vaccine product manufactured by Process E. Furthermore, to explain the stability of the vaccine product manufactured by Process E, the applicant presented results of the long-term testing of the vaccine product manufactured by Process F, which is similar to Process E.

Table 75. Stability studies of vaccine product

	Storage condition	Manufacturing process of active substance	Manufacturing process of vaccine product	Number of batches	Test period	Storage form
Long-term storage[a]	−20 ± 5°C	Process d	Process C	3	9 months	Glass vial, chlorobutyl rubber stopper
		Process f	Process E	3	Planned	
		Process c	Process F	3	12 months	
	5 ± 3°C	Process d	Process C	3	9 months	
		Process f	Process E	3	Planned	
		Process c	Process F	3	12 months	

a Long-term testing is ongoing and continued until [redacted] month. Of measurement items in the long-term testing, [redacted] in the vaccine products manufactured by Process C was measured by [redacted] method, while that in the vaccine products manufactured by Process E is planned to be measured by [redacted]. In the vaccine products manufactured by Process F, [redacted] is not measured.

The applicant's explanation about shelf life of the vaccine product:

The long-term testing of the vaccine products manufactured by Process C, which included [redacted] testing as with the long-term testing of the vaccine products manufactured by Process E, demonstrated the stability up to 9 months of the vaccine product, although Process C did not include [redacted] and [redacted] step. Although [redacted] was not measured as a measurement item in the long-term testing, the comparison of results of the long-term testing between the vaccine products manufactured by Process F, which includes [redacted] and [redacted] step as in Process E, and the vaccine products manufactured by Process C showed no definite differences in quantitative measurement items such as infectivity titer, viral particle concentration, aggregates (mean hydrodynamic radius and polydispersity), and pH up to 9 months, and the addition of [redacted] and [redacted] step is demonstrated to have no impact on the stability of the vaccine product. Based on results of the long-term testing of the vaccine products manufactured by Process C and Process F, the shelf life of 9 months was specified for the vaccine product stored at −20°C ± 5°C. The results of the long-term testing of the vaccine products manufactured by Process E will be submitted to PMDA promptly as soon as available.

In view of the applicant's explanation, PMDA has concluded that the shelf life of 9 months stored at −20°C ± 5°C for the vaccine product is acceptable. The applicant, however, should promptly submit the results of the long-term testing of the vaccine products manufactured by Process E as soon as available.

2. Response to the Regulations on the Type 1 Use of Living Modified Organisms under Article 4 of the Cartagena Act

The use of Jcovden falls under the Type 1 Use of Living Modified Organisms under Article 4 of the Cartagena Act and has been approved for the regulations on Type 1 Use of Living Modified Organisms under the same article of the Act (approval number: 21-36V-0003).

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

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

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

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

The new drug application data (CTD 5.3.1.1.2-7) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

4. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product. The vaccine product and its active substance are both classified as powerful drugs.

Indication

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

Dosage and Administration

A single dose of 0.5 mL should be administered intramuscularly to persons aged 18 years or older.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Given the current limited information, the applicant is required to promptly collect safety data including information on adverse reactions, after the market launch according to plan, submit the data to the Pharmaceuticals and Medical Devices Agency, and take necessary actions to ensure the proper use of the product.
3. Taking account of more efficacy and safety outcomes to be available in the future, the applicant is required to appropriately instruct physicians to provide vaccine recipients or their legally acceptable representatives with most updated efficacy and safety information of the product in written form, and obtain their written consent through the screening questionnaire or the like prior to the administration of the product.

Appendix

List of Abbreviations

Ad26	adenovirus type 26
Ad26.COV2.S	Ad26.COV2.S
Ad26.ENVA.01	Ad26 vector encoding the Clade A envelope protein of HIV type 1
Ad26.Mos4.HIV	Tetravalent HIV vaccine which is based on recombinant replication incompetent adenovirus serotype 26 (Ad26) vectors that consist of Ad26.Mos1.Gag-Pol, Ad26.Mos2.Gag-Pol, Ad26.Mos1.Env, and Ad26.Mos2S.Env.
Ad26.RSV.preF	Ad26 vector encoding the pre-fusion conformation-stabilized F protein [pre-F] of RSV A2 strain
Ad26.ZEBOV	recombinant, replication-incompetent, adenovirus type 26 (Ad26) vector encoding the GP of EBOV Mayinga variant
ADEM	Acute disseminated encephalomyelitis
$AlPO_4$	aluminum phosphate
BMI	Body mass index
CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CLS	Capillary leak syndrome
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease-19
COVxxxx	Study VAC31518COVxxxx
CSAC	Clinical Severity Adjudication Committee
CTD	Common Technical Document
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
D614G variant	SARS-CoV-2 variant with glycine (G) substituted at position 614 in the S protein
ECMO	extracorporeal membrane oxygenation
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
EMA	European Medicines Agency
EOPC	End of productions cells
EU	ELISA units
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus Type 1
HLT	High level term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
ICS	intracellular cytokine staining
ICU	intensive care unit
IDMC	independent Data Monitoring Committee
IFN- γ	Interferon-gamma
IgG	Immunoglobulin G
IL	Interleukin

ITP	Immune thrombocytopenia
Jcovden	Jcovden Intramuscular Injection, coronavirus (SARS-CoV-2) vaccine (replication-incompetent gene recombinant adenovirus type 26 vector)
LLOQ	lower limit of quantification
LVHD-CB	large volume high density cell bank
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
MERS-CoV	Middle East respiratory syndrome coronavirus
MCB	Master cell bank
mRNA	Messenger ribonucleic acid
MVS	Master Virus Seed
NE	Not estimable
NHP	nonhuman primate(s)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NZW	New Zealand White
OD	Optical density
PaO_2	partial pressure of oxygen
PBMC	peripheral blood mononuclear cells
PBRER	Periodic Benefit Risk Evaluation Report
PCR	Polymerase chain reaction
PF4	Platelet factor 4
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	Per Protocol Immunogenicity
PP set	Per Protocol Set
RBD	Receptor binding domain
RMP	Risk management plan
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RT-PCR	reverse-transcriptase polymerase chain reaction
SAMRC	South Africa Medical Research Council
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SMQ	Standard MedDRA query
SpO_2	Saturation of percutaneous Oxygen
SPRT	Sequential Probability Ratio Test
SSG	Statistical Support Group
S protein	Spike protein
$TCID_{50}$	50% tissue culture infective dose
TetR	Tetracycline Repressor
Th	helper T cell
vp	Virus particles
VAERD	vaccine-associated enhanced respiratory disease
VE	Vaccine Efficacy
VOC	Variants of Concern
VOI	Variants of Interest
WCB	Working cell bank
WHO	World Health Organization
WVS	Working Virus Seed