Report on the Deliberation Results

June 14, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Covgoze Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Shionogi & Co., Ltd.
Date of Application	November 24, 2022

Results of Deliberation

In its meeting held on July 31, 2023, the Second Committee on New Drugs presented findings shown in Attachment 1 and concluded that the deliberation should be continued.

In the subsequent meeting held on May 24, 2024, the Second Committee on New Drugs had discussion based additional data provided in Attachment 2, and concluded that the application for marketing approval for the product may be approved after modifying the dosage and administration as shown below and that this result should be presented to the Pharmaceutical Affairs 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.

Indication

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

Dosage and Administration

The antigen preparation and the proprietary solution 0.75 mL are added and mixed.
For the primary series, 2 doses of 0.5 mL each are intramuscularly injected usually 4 weeks apart.

Approval Conditions

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

Attachment 1

Deliberation about Covgoze Intramuscular Injection at the meeting of the Second Committee on New Drugs held on July 31, 2023

June 14, 2024

In the review report dated May 17, 2023, prepared by the Pharmaceuticals and Medical Devices Agency (PMDA), the following 2 clinical studies were reviewed:

(1) The phase III study (Study U0231) that evaluated the superiority of Covgoze Intramuscular Injection (Covgoze) to Vaxzevria Intramuscular Injection (Vaxzevria) in the geometric mean titer (GMT) of neutralizing antibody after 2 doses of the study vaccine in adults aged ≥18 years who had not previously received novel coronavirus (Severe Acute Respiratory Syndrome CoronaVirus-2 [SARS-CoV-2]) vaccines with no history of SARS-CoV-2 infection

(2) The phase II/III study (Study U0223) that evaluated the non-inferiority of Covgoze to Comirnaty Intramuscular Injection (Comirnaty) in the GMT of neutralizing antibodies after a booster dose of the study vaccine in adults aged ≥20 years who had received the second dose of Comirnaty at least 6 months before

The neutralizing antibody titers in the control vaccine groups (Vaxzevria and Comirnaty groups) were lower than predicted from the results of preceding clinical studies and researches of both Vaxzevria and Comirnaty (see the tables below). In response to this, staff of the Ministry of Health, Labour and Welfare (MHLW) and PMDA conducted a for-cause inspection of (a) Testing Facility A, which performed the neutralizing antibody titer assay for the concerned clinical studies, and (b) Shionogi & Co., Ltd., the sponsor of the clinical studies (hereafter, "the applicant") before deliberation at the Second Committee on New Drugs (hereafter, "the Committee"), in accordance with the provisions in Article 80-2, Paragraph 7 and Article 80-5, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960).

Study U0231 (primary series)

Neutralizing antibody titer 28 days after the second dose of the study vaccine (original strain) (Study U0231, immunogenicity analysis population)

	Covgoze (N = 562)		Vaxzevria (N = 579)	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
Baseline (before first dose)	562	2.61 [2.54, 2.68]	579	2.59 [2.53, 2.66]
28 days after second dose	497	19.92 [18.68, 21.23]	514	3.63 [3.41, 3.87]

Antibody titers below the lower limit of quantification (LLOQ) were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects who had no missing data at any sampling point

Study U0223 (booster dose)

Neutralizing antibody titer after study vaccination (original strain) (Study U0223, immunogenicity analysis population)

	Covgoze (N = 101)		Comirnaty (N = 102)	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
Before booster dose	101	5.47 [4.81, 6.21]	102	6.65 [5.73, 7.72]
14 days post-vaccination	101	127.57 [112.03, 145.28]	101	139.48 [122.50, 158.82]
28 days post-vaccination	101	124.97 [108.33, 144.18]	101	109.70 [95.73,125.70]

Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects who had no missing data at any sampling point

1. For-cause Inspection of Testing Facility A

In the for-cause inspection of Testing Facility A, the inspectors checked standard operating procedures for the neutralizing antibody titer assay, measurement records, and validation results, and interviewed assay operators. No particular problems were identified. The following subsections show neutralizing antibody titers of other specimens (i.e., specimens not from the studies included in the application data) measured at Testing Facility A.

1.1 Neutralizing antibody titer assay results of NIBSC standard/control sera

A total of 6 standard or control sera of the National Institute for Biological Standards and Control (NIBSC), ranging from the negative control serum (WHO reference Panel, Negative) to the international standard serum (WHO international Standard), were subjected to the neutralizing antibody titer assay. The neutralizing antibody titer assay at Testing Facility A was found to have no problem in repeatability or assay sensitivity.

Neutralizing antibody titer assay results of NIBSC standard/control sera at Testing Facility A (original strain)

ID	Name of sample	Result from Run 1	Result from Run 2	Result from Run 3
A	WHO international Standard	160	80	80
B	WHO reference Panel, High	80	80	80
C	WHO reference Panel, Mid	40	20	40
D	WHO reference Panel, Low S, high N	20	10	10
E	WHO reference Panel, Low	10	10	10
F	WHO reference Panel, Negative	<5	<5	<5
Positive control (reference range, 40-160 fold)		80	80	80
Negative control (reference range, <5 fold)		<5	<5	<5
Challenge virus titer		75 $TCID_{50}$	115 $TCID_{50}$	86 $TCID_{50}$

According to international unit (IU) figures calculated from the above assay results, the applicant estimated neutralizing antibody titers measured at Testing Facility A, based on the past neutralizing antibody titers after the primary series of Vaxzevria or Comirnaty, reported in the literature or other sources. The applicant presented the following results at the problem-discussion steering committee of the Japan Agency for Medical Research and Development (AMED) on September 16, 2021.

Vaccine	IU/mL	Neutralizing antibody titer at Testing Facility A (estimate)
Vaxzevria	453	46
Comirnaty	1435	145

1.2 Neutralizing antibody titer assay results of sera from Vaxzevria or Comirnaty recipients

Human sera after the primary series of Vaxzevria or Comirnaty for research, provided by the sponsor, were subjected to the neutralizing antibody titer assay. The GMTs of neutralizing antibodies were 10 in Vaxzevria recipients and 63.5 in Comirnaty recipients.

Neutralizing antibody titer assay results of sera after the primary series of Vaxzevria at Testing Facility A (original strain)

	Testing Facility A No.	Neutralizing antibody titer
Vaxzevria recipient serum	311-4594	10
	311-4595	10
	311-4596	20
	311-4597	5
	311-4598	20
	311-4599	20
	311-4600	10
	311-4601	20
	311-4602	5
	311-4503	<5
Positive control (reference range, 20-80 fold)	(a)	40
	(b)	40
	(c)	20
Negative control (reference range, <5 fold)	(a)	<5
	(b)	<5
	(c)	<5
Challenge virus titer 87 $TCID_{50}$		

Neutralizing antibody titer assay results of sera after the Comirnaty primary series at Testing Facility A (original strain)

	Testing Facility A No.	Neutralizing antibody titer	Re-assay result
Comirnaty recipient serum	311-3594	40	
	311-3595	10	
	311-3596	40	
	311-3597	Re-assay	320
	311-3598	80	
	311-3599	80	
	311-3600	80	
	311-3601	Re-assay	320
	311-3602	10	
	311-3603	320	
	311-3604	20	
	311-3605	20	
	311-3606	20	
	311-3607	40	
	311-3608	Re-assay	320
	311-3609	40	
	311-3610	Re-assay	1280
	311-3611	20	
	311-3612	80	
	311-3613	40	
	311-3614	80	
Positive control (reference range, 20-80 fold)	(a)	40	40
	(b)	40	20
	(c)	20	40
	(d)	20	40
Negative control (reference range, <5 fold)	(a)	<5	<5
	(b)	<5	<5
	(c)	<5	<5
	(d)	<5	<5
Challenge virus titer		56 $TCID_{50}$	87 $TCID_{50}$

The National Institute of Infectious Diseases, which transferred techniques of neutralizing antibody titer assay to Testing Facility A, measured neutralizing antibody titers after the primary series and a booster dose (third dose) of Comirnaty. The results (GMTs) are as follows (*Med.* 2022 Jun 10;3(6):406-421.e4.).

	12 days after the first dose	20 days after the second dose	3 months after the second dose	8 months after the second dose	12 days after the third dose
Neutralizing antibody titer	5	94	27	11	476

1.3 Procedures and precision control of neutralizing antibody titer assay at Testing Facility A

The standard operating procedures at Testing Facility A and records associated with the assay operations were checked to examine the handling of specimens from acceptance to neutralizing antibody titer assay. No particular problems were identified. In particular, the freeze-thaw operation of specimens, which potentially affects the potency, was found to have no problems. Randomly extracted neutralizing antibody titer assay results were checked against and shown to be the same as the corresponding data presented in the application data.

The above for-cause inspection revealed no problems in precision or sensitivity of the neutralizing antibody titer assay. Study U0231 showed low neutralizing antibody titers after the Vaxzevria primary series, and the sponsor made the following claim about this:

"The neutralizing antibody titer assay used at Testing Facility A had low sensitivity for measuring the neutralizing antibody titer after a dose of Vaxzevria. This is considered to be the reason for the low titers."

Testing Facility A stated that they did not know about the claim because they had not received any communication about this issue from the sponsor.

2. For-cause Inspection of the Applicant

2.1 Quality control and quality assurance of control vaccine

For Study U0231, the sponsor received the Vaxzevria control vaccine from the control vaccine manufacturer and then affixed the label to, packaged, and delivered the control vaccine to study sites. Temperature control during transportation was found to have no problem, according to the record. The remaining control vaccine was discarded at the study site immediately after the expiry date, according to the record. The last dose of the control vaccine was administered on March 16, 2022, and the expiry date of the control vaccine batch was March 19, 2022.

For Study U0223, the Comirnaty control vaccine given to the sponsor by the Japanese government was directly delivered to a single study site through the same scheme as that for the special temporary vaccination program. The remaining control vaccine was used for the special temporary vaccination program at this site.

The following statement is included in the guidance in Article 16, Paragraph 5 of the Ministerial Ordinance on Good Clinical Practice for Drugs (MHW Ordinance No. 28 of 1997, "GCP Ordinance") (Attachment of "Revision of the guidance in the Ministerial Ordinance on Good Clinical Practice for Drugs" [PSB/PED Notification No. 1226-4 dated December 26, 2023, by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW]):

"The sponsor should maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics."

In Studies U0231 and U0223, neither of the control vaccines underwent batch sample analysis, and no records proving that the control vaccines met the specifications (potency) throughout the study period were prepared.

2.2 Rationale for the view that the neutralizing antibody titer assay used at Testing Facility A had low sensitivity for measuring the neutralizing antibody titer after a dose of Vaxzevria

No rationale was presented for the applicant's view that the neutralizing antibody titer assay used at Testing Facility A had low sensitivity for measuring the neutralizing antibody titer after a dose of Vaxzevria. The inspectors explained that the for-cause inspection at Testing Facility A revealed no

problems in precision or sensitivity of the neutralizing antibody titer assay, and the sponsor accepted that the neutralizing antibody titer assay and its sensitivity at Testing Facility A had no problems.

The neutralizing antibody titer assay at Testing Facility B (which was additionally commissioned by the sponsor post hoc) differed in sensitivity from the assay at Testing facility A. The difference was deemed to be caused by different timing of cytopathic effect (CPE) assessment, type and number of cells seeded, etc. The seroconversion rate and neutralizing antibody titer in the Vaxzevria group in Study U0231 were lower than predicted from results of other preceding clinical studies and researches; the cause of these lower values remain unknown.

2.3 Other items warranting special mention

The applicant replied to inquiries regarding quality control and quality assurance of the control vaccines (i.e., the process from receipt to delivery of the control vaccines as well as their control at study sites) and stated that the study vaccine control was confirmed to have no defects. In addition, concerning the lower neutralizing antibody titer in the control vaccine group in Studies U0231 and U0223 than predicted from results of the other preceding clinical studies and researches, the applicant presented their view that "the concerned values fell within the predicted variation range and were not particularly low."

3. Discussion at the Meeting of the Second Committee on New Drugs Held on July 31, 2023

The Committee made the following discussion based on the review report dated May 17, 2023 prepared by PMDA and on results of the above for-cause inspection.

- In the following 2 clinical studies, the GMT of neutralizing antibodies in the control vaccine group, either Vaxzevria or Comirnaty group, was lower than predicted from results of the other preceding clinical studies. In particular, the GMT in the Vaxzevria group was extremely low.
  (1) Study U0231, which evaluated the superiority of Covgoze to Vaxzevria in the GMT of neutralizing antibodies after 2 doses of the study vaccine in adults aged ≥18 years who had not previously received SARS-CoV-2 vaccines with no history of SARS-CoV-2 infection
  (2) Study U0223, which evaluated the non-inferiority of Covgoze to Comirnaty in the GMT of neutralizing antibodies after a booster dose of the study vaccine in adults aged ≥20 years who had received the second dose of Comirnaty at least 6 months before
- The applicant explained that the reason for the extremely low GMT of neutralizing antibodies in the Vaxzevria group was that the neutralizing antibody titer assay used at Testing Facility A (which performed the neutralizing antibody titer assay for the concerned clinical studies) had low sensitivity for measuring the SARS-CoV-2 neutralizing antibody titer after a dose of Vaxzevria. MHLW conducted a for-cause inspection of Testing Facility A in accordance with the provisions in Article 80-2, Paragraph 7 and Article 80-5, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, and confirmed that the neutralizing antibody titer assay performed by Testing Facility A had no problems in precision or sensitivity. MHLW also conducted a for-cause inspection of the applicant according to the above provisions. In the inspection, the applicant replied to inquiries regarding quality control and quality

assurance of the control vaccines (i.e., the process from receipt to delivery of the control vaccine and their control at study sites), stating that the study vaccine control was confirmed to have no defects. However, in Studies U0231 and U0223, neither of the control vaccines underwent batch sample analysis, and no records proving that the control vaccines met the specifications (potency) throughout the study period were kept.

The Committee reached the following conclusion:
Based on the above discussion, the clinical study results initially submitted for the application alone were considered unlikely to explain the efficacy of Covgoze clearly. Results from a large-scale disease-preventive study in Vietnam (Study U0232) submitted as reference data after the application should be also evaluated. Therefore, the results from Study U0232 should be evaluated for data integrity. Based on the results of the data integrity evaluation, whether Covgoze should be approved should be deliberated at the next and subsequent meetings of the Committee.

Attachment 2

Results from additional investigation on large-scale disease-preventive study of Covgoze in Vietnam (Study U0232)

June 14, 2024

At the meeting of the Second Committee on New Drugs held on July 31, 2023, whether Covgoze Intramuscular Injection (Covgoze) should be approved was deliberated, and the clinical study results alone that had been evaluated to the date of the meeting were considered unlikely to clearly explain the efficacy of Covgoze. The Committee concluded that they would evaluate new clinical study results such as results from a "randomized double-blind placebo-controlled study in Vietnam to verify the disease-preventive effect of Covgoze (Study U0232)," submitted as reference data during the review, and thereby determine whether Covgoze should be approved. In response to this conclusion, staff of the Ministry of Health, Labour and Welfare (MHLW) and PMDA conducted a for-cause inspection of Study U0232 in accordance with the provisions of Article 80-2, Paragraph 7 and Article 80-5, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960) to check data integrity and evaluate results from Study U0232.

1. For-cause Inspection of Study U0232

1.1 GCP compliance status and data integrity at study site

[redacted] in [redacted], Vietnam, had the largest numbers of subjects enrolled and those with a disease caused by novel coronavirus (SARS-CoV-2) infection (COVID-19). This site was selected as the site subject to the for-cause inspection and inspected for the GCP compliance status and data integrity. The GCP compliance status was found to have no particular problems. Some discrepancies were identified between case report forms provided by Shionogi & Co., Ltd. (applicant) in advance and source documents retained at the inspected site, but none of them were considered to affect the efficacy evaluation. However, the following were identified as events potentially affecting the efficacy evaluation.

(a) Many of the subjects with COVID-19 were handled as dropouts from the study, because they were quarantined according to local regulations, precluding the study site from performing examinations for definitive diagnosis and collecting specimens as specified in the study protocol.

(b) Specimen collection kits for SARS-CoV-2 strain identification were not sufficiently provided by the sponsor and were run out early. The causative strain could not be identified in most of the subjects with COVID-19.

(c) Many subjects were found to have had subclinical infection (who did not report information on COVID-19-like symptoms but tested positive for anti-SARS-CoV-2 N-protein antibody at a follow-up visit ≥4 weeks after the second dose of the study vaccine).

(d) Some of the subjects who tested positive by PCR were not assessed for onset of COVID-19.

1.2 GCP compliance status and data integrity of the applicant

The GCP compliance status of the applicant was found to have no particular problems. For the above (a) to (d), the following were confirmed.

(a)

On-site inspection revealed that 11 subjects in the Covgoze group and 4 subjects in the placebo group at [redacted] (Site 1010, which underwent the for-cause inspection) and 1 subject in the placebo group at [redacted] (Site 1005), were handled as dropouts from the study, because they were quarantined owing to onset of COVID-19 according to local regulations, precluding the study sites from performing examinations for definitive diagnosis and collecting specimens as specified in the study protocol.

(b)

Of 441 subjects who developed COVID-19 by the first data cutoff (included in the primary analysis), 74 subjects had their specimens collected for SARS-CoV-2 strain identification, and many of them were infected by the Omicron variant (66 subjects: 34 in the Covgoze group, 32 in the placebo group). Most of the subjects who developed COVID-19 with unidentified strain were also likely to have been infected by the Omicron variant. The number of subjects with the strain identified differed from study site to study site. At Sites 1005, 1006, and 1010, many subjects had COVID-19 but most of them did not have their strain identified. When this study was initiated in Vietnam, the official vaccination program had already progressed in the urban area. The study was therefore conducted mainly at medical institutions located in rural regions in Vietnam where official vaccination had not progressed. This means that there are limitations, to some extent, of assuming that most of the subjects with COVID-19 at the above sites were infected by the Omicron variant as those at sites in the other regions.

Site No.: Study site	Vaccine	No. of subjects mITT	No. of subjects with COVID-19	No. of subjects with the strain identified	Delta	Omicron	Unknown
1001: [redacted]	Covgoze	153	4	4		3	1
	Placebo	53	7	7	1	6	
1002: [redacted]	Covgoze	13	2	2		2	
	Placebo	7	1	1		1	
1003: [redacted]	Covgoze	218	6	3		3	
	Placebo	121	11	6		6	
1004: [redacted]	Covgoze	150	5	3		3	
	Placebo	66	1				
1005: [redacted]	Covgoze	359	24				
	Placebo	194	20				
1006: [redacted]	Covgoze	780	60	3		3	
	Placebo	405	39	3		3	
1007: [redacted]	Covgoze	54					
	Placebo	27	1	1	1		
1008: [redacted]	Covgoze	27	1	1		1	
	Placebo	15	1	1	1		
1009: [redacted]	Covgoze	264	20	4		4	
	Placebo	131	16	3		3	
1010: [redacted]	Covgoze	974	96	1			1
	Placebo	485	79	3	1	1	1
1012: [redacted]	Covgoze	805	6	4		3	1
	Placebo	384	3	3		3	
1013: [redacted]	Covgoze	210	3	3		3	
	Placebo	115	3	3		3	
1014: [redacted]	Covgoze	633	6	3		3	
	Placebo	327	3	1		1	
1015: [redacted]	Covgoze	178	11	6		6	
	Placebo	92	12	5		5	
1016: [redacted]	Covgoze	313					
	Placebo	158					
1017: [redacted]	Covgoze	101					
	Placebo	47					
1019: [redacted]	Covgoze	24					
	Placebo	6					
Total	Covgoze	5,256	244	37		34	3
	Placebo	2,633	197	37	4	32	1
	Overall	7,889	441	74	4	66	4

(c) and (d)

Up to the first data cutoff, 388 subjects in the Covgoze group and 254 subjects in the placebo group were found to have had subclinical infection. The incidence of subclinical infection did not show any certain trend.

Of subjects who tested positive by PCR, 9 in the Covgoze group and 7 in the placebo group were not assessed as having with COVID-19. These subjects were suspected of having COVID-19 and underwent a PCR test but did not visit the site for follow-up. Therefore whether they met the definition of COVID-19 was not judged. They discontinued the study with unknown status of COVID-19.

Site No.: Study site	Vaccine	No. of subjects mITT	No. of subjects with COVID-19	Subjects with subclinical infection	PCR-positive subjects without COVID-19 assessment
1001: [redacted]	Covgoze	153	4	2	1
	Placebo	53	7		1
1002: [redacted]	Covgoze	13	2		
	Placebo	7	1		
1003: [redacted]	Covgoze	218	6	14	
	Placebo	121	11	15	
1004: [redacted]	Covgoze	150	5	31	
	Placebo	66	1	17	
1005: [redacted]	Covgoze	359	24	17	4
	Placebo	194	20	9	3
1006: [redacted]	Covgoze	780	60	77	
	Placebo	405	39	58	
1007: [redacted]	Covgoze	54		1	
	Placebo	27	1	2	
1008: [redacted]	Covgoze	27	1		
	Placebo	15	1		
1009: [redacted]	Covgoze	264	20	2	1
	Placebo	131	16	2	
1010: [redacted]	Covgoze	974	96	96	3
	Placebo	485	79	51	3
1012: [redacted]	Covgoze	805	6	35	
	Placebo	384	3	17	
1013: [redacted]	Covgoze	210	3	41	
	Placebo	115	3	31	
1014: [redacted]	Covgoze	633	6	58	
	Placebo	327	3	45	
1015: [redacted]	Covgoze	178	11	14	
	Placebo	92	12	7	
1016: [redacted]	Covgoze	313			
	Placebo	158			
1017: [redacted]	Covgoze	101			
	Placebo	47			
1019: [redacted]	Covgoze	24			
	Placebo	6			
Total	Covgoze	5,256	244	388	9
	Placebo	2,633	197	254	7
	Overall	7,889	441	642	16

1.3 Result of for-cause inspection

The for-cause inspection of Study U0232 revealed no critical problems that would affect the efficacy or safety evaluation of Covgoze. The efficacy evaluation of Covgoze based on results from Study U0232 was considered acceptable.

2. Summary of Large-scale Disease-preventive Study in Vietnam (Study U0232)

Study period: December 25, 2021 to July 19, 2023

Data cutoff or DBL date

First data cutoff (primary analysis with unblinding): March 31, 2022

Second data cutoff (second interim analysis): September 30, 2022

Final DBL (final analysis): September 28, 2023

A randomized, observer-blind, placebo-controlled, parallel-group study was conducted to investigate the COVID-19-preventive effect of 2 doses of Covgoze in healthy adults aged ≥18 years (target sample size, 54,915 subjects [36,610 in the Covgoze group, 18,305 in the placebo group]) at 24 study sites in Vietnam (17 study sites enrolled subjects by the time of primary analysis and 21 study sites by the time of final analysis). In this study, 2 doses of Covgoze (10 μg of the antigen) or placebo were intramuscularly injected 28 days apart. The protocol at the start of the study specified that the primary analysis with unblinding should be performed when 66 subjects are confirmed to have COVID-19. In late February 2022, COVID-19 started to outbreak in Vietnam, allowing rapid accrual of subjects with COVID-19 earlier than predicted. The data were cut off on March 31, 2022 for the first data-base lock (DBL) and subjected to the primary analysis.

The median follow-up period for the primary endpoint at the time of the primary analysis was as short as 35.0 days in the Covgoze group and 27.0 days in the placebo group, the analysis plan was revised (statistical analysis plan version 3 dated December 13, 2022), and accordingly the second interim analysis was performed with the data cutoff on September 30, 2022, 6 months after the first data cutoff. The final analysis including ≥6-month follow-up data in all the participants was performed with the DBL on September 28, 2023.

In the primary analysis after the first data cutoff, of 8,594 randomized subjects (5,727 in the Covgoze group, 2,867 in the placebo group), 7,889 subjects (5,256 in the Covgoze group, 2,633 in the placebo group) were included in the modified intent-to-treat (mITT) population, which also served as the primary efficacy analysis population. The remining 705 subjects (471 in the Covgoze group, 234 in the placebo group) were excluded because they did not receive the study vaccine, had SARS-CoV-2 infection before the first dose of the study vaccine or had a history of SARS-CoV-2 infection, or had other reasons. The primary endpoint was the vaccine efficacy (VE) based on the number of subjects who had COVID-19 ≥14 days after the second dose of the study vaccine. The VE of Covgoze to placebo [two-sided 95% confidence interval (CI)] was 39.1% [26.6%, 49.5%], which did not achieve the prespecified criterion (lower limit of two-sided 95% CI >30%).

Number of subjects who had COVID-19 ≥14 days after the second dose of the study vaccine (primary analysis, mITT population)

	Covgoze	Placebo
Number of subjects analyzed	5,256	2,633
Number of subjects with COVID-19	244	197
Total follow-up period (person-years)	314.27	154.77
Incidence rate per 1,000 person-years [two-sided 95% CI][a)]	776.41 [682.04, 880.19]	1272.87 [1101.32, 1463.57]
VE [two-sided 95% CI][b)]	39.1 [26.6, 49.5]	

a) The two-sided 95% CI was estimated by the exact method based on a Poisson distribution.
b) Estimated by a Poisson regression model with a robust error variance, using the age (continuous variable) at baseline (before the first dose) as a covariate. The logarithmically transformed follow-up period was used as an offset.

A total of 8,562 randomized subjects (5,710 in the Covgoze group, 2,852 in the placebo group) who received at least 1 dose of the study vaccine were included in the full analysis set (FAS) population, which also served as the safety analysis population in the primary analysis. The incidence of solicited local adverse events was 34.6% (1,977 of 5,710 subjects, 3,243 events) in the Covgoze group and

12.2% (347 of 2,852 subjects, 406 events) in the placebo group. The incidence of solicited systemic adverse events was 29.8% (1,704 of 5,710 subjects, 4353 events) in the Covgoze group and 20.5% (584 of 2,852 subjects, 1,368 events) in the placebo group. The incidences of solicited adverse events by event term and number of doses are as follows.

Incidences of solicited adverse events occurring within 7 days after each dose of the study vaccine by event term and number of doses (primary analysis, FAS)

Event		No. of doses	Covgoze			Placebo		
			No. of subjects evaluated N	All events n (%)	Grade ≥3 n (%)	No. of subjects evaluated N	All events n (%)	Grade ≥3 n (%)
Local	Overall	1	5710	1523 (26.7)	1 (0.0)	2852	225 (7.9)	0
		2	4539	1070 (23.6)	2 (0.0)	2274	159 (7.0)	0
	Pain	1	5710	1485 (26.0)	1 (0.0)	2852	219 (7.7)	0
		2	4539	1043 (23.0)	1 (0.0)	2274	156 (6.9)	0
	Erythema/redness	1	5710	72 (1.3)	0	2852	7 (0.2)	0
		2	4539	64 (1.4)	0	2274	6 (0.3)	0
	Induration	1	5710	124 (2.2)	0	2852	2 (0.1)	0
		2	4539	87 (1.9)	1 (0.0)	2274	0	0
	Swelling	1	5710	169 (3.0)	0	2852	4 (0.1)	0
		2	4539	159 (3.5)	1 (0.0)	2274	5 (0.2)	0
Systemic	Overall	1	5710	1208 (21.2)	11 (0.2)	2852	439 (15.4)	1 (0.0)
		2	4539	914 (20.1)	17 (0.4)	2274	257 (11.3)	4 (0.2)
	Pyrexia	1	5710	161 (2.8)	7 (0.1)	2852	55 (1.9)	1 (0.0)
		2	4539	241 (5.3)	13 (0.3)	2274	44 (1.9)	4 (0.2)
	Nausea/vomiting	1	5710	195 (3.4)	0	2852	95 (3.3)	0
		2	4539	107 (2.4)	0	2274	43 (1.9)	0
	Diarrhoea	1	5710	110 (1.9)	0	2852	45 (1.6)	0
		2	4539	37 (0.8)	1 (0.0)	2274	27 (1.2)	0
	Headache	1	5710	574 (10.1)	1 (0.0)	2852	235 (8.2)	0
		2	4539	494 (10.9)	0	2274	124 (5.5)	0
	Malaise	1	5710	710 (12.4)	4 (0.1)	2852	242 (8.5)	0
		2	4539	597 (13.2)	3 (0.1)	2274	157 (6.9)	0
	Myalgia	1	5710	605 (10.6)	0	2852	142 (5.0)	0
		2	4539	336 (7.4)	0	2274	66 (2.9)	0

The incidence of unsolicited adverse events was 9.9% (566 of 5,710 subjects, 867 events) in the Covgoze group and 11.0% (315 of 2,852 subjects, 514 events) in the placebo group. Blood pressure increased (3.0% [169 subjects] in the Covgoze group, 2.9% [83 subjects] in the placebo group) was the only unsolicited adverse event with an incidence of ≥2% in either group. Of the events of blood pressure increased, those in 0.4% (21 subjects) in the Covgoze group and 0.5% (15 subjects) in the placebo group were considered related to the study vaccine.

Deaths occurred in 4 subjects (0.1%) in the Covgoze group (completed suicide, meningioma, craniocerebral injury, unknown cause) and 3 subjects (0.1%) in the placebo group (cachexia, hepatic encephalopathy, pneumonia), but all of them were considered unrelated to the study vaccine.

Other serious adverse events occurred in 13 subjects (0.2%) with 13 events in the Covgoze group and 21 subjects (0.7%) with 25 events in the placebo group, and all of them were considered unrelated to the study vaccine. The other serious adverse events in the Covgoze group were wound and COVID-19 in 2 subjects each, and angina pectoris, epilepsy, hepatic enzyme increased, vertigo, pneumonia,

synovial cyst, alcoholic psychosis, ureterolithiasis, and tonsillitis in 1 subject each. Except hepatic enzyme increased that did not resolve at the time of data cutoff, all the events resolved or were resolving.

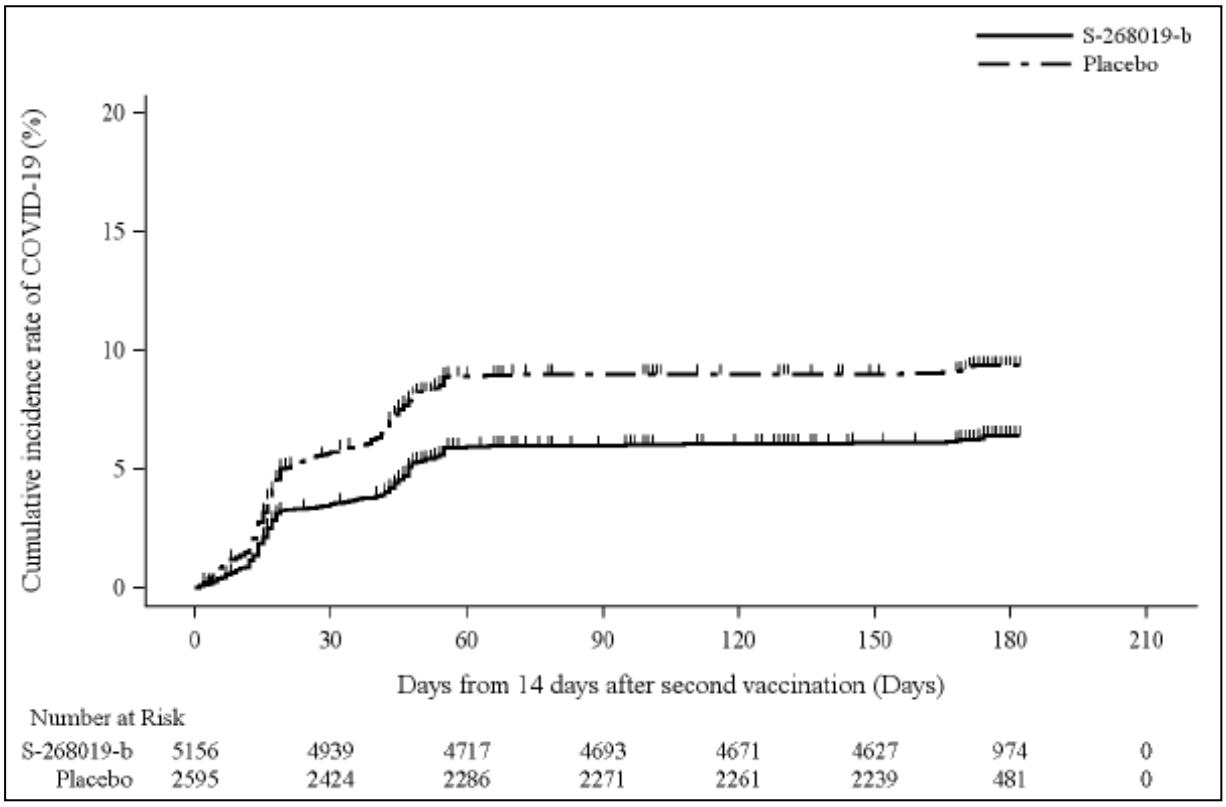
In the final analysis, of 9,902 randomized subjects (6,600 in the Covgoze group, 3,302 in the placebo group), 8,401 subjects (5,596 in the Covgoze group, 2,805 in the placebo group) were included in the mITT population, which also served as the efficacy analysis population. The remaining 1,501 subjects (1,004 in the Covgoze group, 497 in the placebo group) were excluded because they did not receive the study vaccine, had SARS-CoV-2 infection before the first dose of the study vaccine or had a history of SARS-CoV-2 infection, or had other reasons.

In the final analysis, the VE [two-sided 95% CI] based on the number of subjects who developed COVID-19 ≥14 days after the second dose of the study vaccine was 34.2% [21.9%, 44.6%], which did not achieve the prespecified criterion (lower limit of two-sided 95% CI >30%).

Number of subjects who had COVID-19 ≥14 days after the second dose of the study vaccine (final analysis, mITT population)

	Covgoze	Placebo
Number of subjects analyzed	5,596	2,805
Number of subjects with COVID-19	323	239
Total follow-up period (person-years)	2272.76	1107.40
Incidence rate per 1,000 person-years [two-sided 95% CI][a)]	142.12 [127.04, 158.49]	215.82 [189.32, 244.99]
VE [two-sided 95% CI][b)]	34.2 [21.9, 44.6]	

a) The two-sided 95% CI was estimated by the exact method based on a Poisson distribution.
b) Estimated by a Poisson regression model with a robust error variance, using the age (continuous variable) at baseline (before the first dose) as a covariate. The logarithmically transformed follow-up period was used as an offset.



Cumulative incidence of COVID-19 occurring ≥14 days after the second dose of the study vaccine (final analysis, mITT population)

Results of Study U0232

As described above, the VE [two-sided 95% CI] of Covgoze to placebo was 39.1% [26.6%, 49.5%] in the primary analysis (interim analysis) and 34.2% [21.9%, 44.6%] in the final analysis, both of which did not achieve the prespecified criterion (lower limit of two-sided 95% CI >30%). As presented in Section "1. For-cause Inspection of Study U0232," Study U0232 is deemed to have conducted in the prevalence of the Omicron variant in which the VE of Covgoze, a vaccine against the original strain, is supposed to be low. Two doses of Covgoze 4 weeks apart were deemed to have demonstrated the preventive effect against COVID-19 to a certain extent in subjects who had not previously received SARS-CoV-2 vaccines with no history of SARS-CoV-2 infection.

3. Summary of Clinical Study of Covgoze (Omicron variant XBB.1.5, Development No. S-268023)

The applicant presented the summary of the clinical study of Covgoze vaccine adapted for Omicron variant XBB.1.5.

Population	Adults aged ≥20 years who had received at least 2 doses of approved SARS-CoV-2 vaccines
Target sample size	Covgoze (Omicron variant XBB.1.5) group: 300 subjects Comirnaty RTU (Omicron variant XBB.1.5) group: 300 subjects
Study design	Randomized, observer-blind, active-controlled study
Dosage regimen	Covgoze: A dose of 0.5 mL (10 μg of the antigen) is intramuscularly injected Comirnaty RTU: A dose of 0.3 mL is intramuscularly injected
Primary endpoints	GMT of neutralizing antibody against variant XBB.1.5, antibody response rate 28 days after vaccination (Day 29) Criteria for non-inferiority ➢ With the non-inferiority margin of 0.67, the lower limit of two-sided 95% CI of the GMT ratio exceeds 0.67. ➢ With the non-inferiority margin of −10%, the lower limit of two-sided 95% CI of the difference in antibody response rate exceeds −10%.
Studied period	From November 2023

Results of the primary endpoints

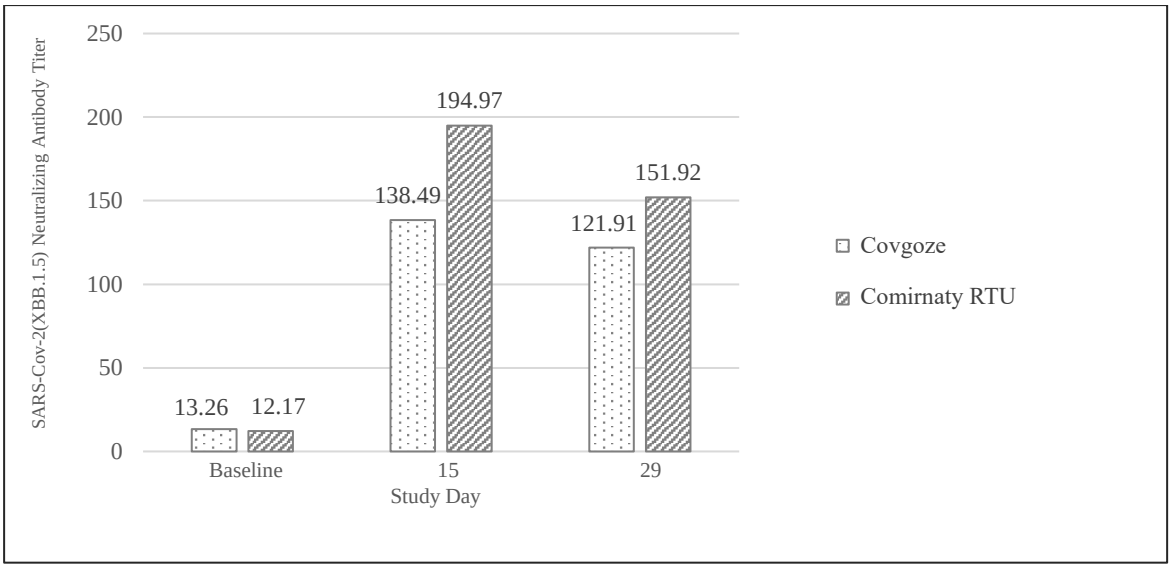
- Geometric mean titer ratio (GMTR) of neutralizing antibody (testing facility, Testing Facility C)
  The lower limit of 95% CI of the GMTR was below 0.67, resulting in a failure to demonstrate the non-inferiority.

Time point	Statistic	S-268023 N = 303	Comirnaty N = 297
Day 29	n	283	281
	GMT [95% CI]	1494.85 [1306.44, 1710.42]	2161.94 [1889.64, 2473.48]
	GMTR [95% CI]	0.69 [0.58, 0.83]	

- Antibody response rate of neutralizing antibody (testing facility, Testing Facility C)
  The lower limit of 95% CI of the difference in antibody response rate was below −10%, resulting in a failure to demonstrate the non-inferiority.

Time point	Statistic	S-268023 N = 303	Comirnaty N = 297
Day 29	n	283	281
	Antibody response rate [95% CI]	78.1 [72.9, 82.5]	85.8 [81.2, 89.4]
	Difference in antibody response rate [95% CI]	−7.7 [−14.0, −1.3]	

Reference: Results of neutralizing antibody titer assay at Testing Facility A



4. Results of Additional Investigation

As described above, 2 doses of Covgoze were shown to have the preventive effect against COVID-19 to a certain extent in subjects who had not previously received SARS-CoV-2 vaccines with no history of SARS-CoV-2 infection. The Committee has concluded that Covgoze may be approved after modifying the proposed dosage and administration as shown below.

In November 2023, a clinical study of the Covgoze booster dose was initiated in adults aged ≥20 years who had previously received 2 doses of SARS-CoV-2 vaccines to test non-inferiority of Covgoze (against the Omicron variant XBB.1.5) to Comirnaty RTU (against the Omicron variant XBB.1.5) in terms of the increase in neutralizing antibody titer after vaccination. As described in Section "3. Summary of Clinical Study of Covgoze (Omicron variant XBB.1.5, Development No. S-268023)," Covgoze was not shown to be non-inferior to Comirnaty RTU in either of the following primary endpoints: GMT ratio of neutralizing antibody and antibody response rate. Use of Covgoze for booster doses is considered to warrant further clinical study evaluation.

Indication

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

Dosage and Administration

The antigen preparation and the proprietary solution 0.75 mL are added and mixed.
For the primary series, 2 doses of 0.5 mL each are intramuscularly injected usually 4 weeks apart.

Review Report

May 17, 2023
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Covgoze Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Shionogi & Co., Ltd.
Date of Application	November 24, 2022
Dosage Form/Strength	An emulsion for injection prepared in 2 separate vials: A vial of the antigen preparation and a vial of the proprietary solution (0.75 mL) to be mixed prior to administration. After mixing, each vaccine dose (0.5 mL) contains 10 μg of the recombinant SARS-CoV-2 spike protein as the 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 the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare). A prior assessment consultation was conducted on the product.
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

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

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

Indication

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

Dosage and Administration

The proprietary solution 0.75 mL is added to the antigen preparation and then mixed.
For the primary series, 2 doses of 0.5 mL each are intramuscularly injected usually 4 weeks apart.
For a booster dose, a dose of 0.5 mL is intramuscularly injected.

Approval Conditions

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

Attachment

Review Report (1)

April 7, 2023

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

Product Submitted for Approval

Brand Name	Covgoze Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Shionogi & Co., Ltd.
Date of Application	November 24, 2022
Dosage Form/Strength	An emulsion for injection prepared in 2 separate vials: A vial of the antigen preparation and a vial of the proprietary solution (0.75 mL) to be mixed prior to administration. After mixing, each vaccine dose (0.5 mL) contains 10 μg of the recombinant SARS-CoV-2 spike protein as the active ingredient.

Proposed Indication

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

Proposed Dosage and Administration

The antigen preparation and the proprietary solution are mixed.
For the primary series, 2 doses of 0.5 mL each are intramuscularly injected usually 4 weeks apart.
For a booster dose, a dose of 0.5 mL is intramuscularly injected.

Table of Contents

List of Abbreviations

See Appendix.

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

Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) is a single-strand positive-chain ribonucleic acid (RNA) virus belonging to the family *Coronaviridae* in the order *Nidovirales* and was identified as a novel coronavirus infectious and pathogenic in humans in 2019 (*Lancet.* 2020;395:565-74, *Nat Microbiol.* 2020;5:536-44, etc.)

The disease caused by SARS-CoV-2 infection (COVID-19) was designated as a Public Health Emergency of International Concern[1)] by the World Health Organization (WHO) in January 2020 and remains to be resolved as of March 2023. In response to the global COVID-19 pandemic, multiple therapeutic drugs and preventive vaccines have been developed, and various measures against the infection have been taken, but SARS-CoV-2 variants with varied infectivity and transmissibility have been emerging one after another, resulting in multiple waves of COVID-19. Omicron variant emerged at the end of 2021 and brought the world into a pandemic in 2022. It differs from the original strain in antigenicity and thus can evade the immunity induced by the vaccines administered in the vaccination program starting in 2021, resulting in reduced efficacy of the vaccines. To address the repeated waves of COVID-19 and the reduced efficacy of vaccines, several booster vaccination programs have been implemented to reactivate the immune response. Furthermore, bivalent vaccines with the increased immunogenicity against Omicron variant have been used for booster vaccination.

Vaccines approved for prevention of COVID-19 in Japan as of March 31, 2023 are Comirnaty Intramuscular Injection and other 3 products (Pfizer Japan Inc.), Vaxzevria Intramuscular Injection (AstraZeneca K.K.), Spikevax Intramuscular Injection (Moderna Japan Co., Ltd.), Nuvaxovid Intramuscular Injection (Takeda Pharmaceutical Company Limited), and Jcovden Intramuscular Injection (Janssen Pharmaceutical K.K.). In September 2022, a booster vaccination program using Omicron-adapted bivalent vaccines was initiated. Under the official vaccination programs with these vaccine products (except Jcovden Intramuscular Injection), approximately 80% of the Japanese population have completed the primary series of a vaccine against SARS-CoV-2 and approximately 70% have completed the first booster dose.[2)] All of the Omicron-adapted vaccines available for distribution in Japan are messenger RNA (mRNA) vaccines that are intended only for booster doses. Therefore only vaccines using the original strain protein as the target antigen are used for the primary series and booster doses in people ineligible for mRNA vaccines (HSB Notification No. 0308-15 "Partial revision of 'Vaccination against COVID-19 [instruction] [in Japanese]'" Ministry of Health, Labour and Welfare [MHLW] dated March 8, 2023; and Interim Guidelines for Vaccination against COVID-19 [in Japanese] [updated on March 8, 2023]). Importance should be attached to being able to supply multiple vaccines of various origins developed in and outside Japan from a viewpoint of public health, because (1) options of vaccines available for the primary series and ones for people ineligible for mRNA vaccines are limited; (2) supply of vaccines in Japan relies on imports even at present when 2 years have passed since the first marketing approval of a vaccine against SARS-CoV-2, and (3) vaccination against SARS-CoV-2 is supposed to be continuously encouraged in the future. The government's "Strategy for Strengthening the Vaccine Development and Production System" (adapted

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 public health risk to other States through the international spread of disease; and
(b) An extraordinary event which is determined to potentially requires a coordinated international response.

2) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html (released on March 30, 2023) (last accessed on March 31, 2023)

Cabinet on June 1, 2021) also underlines the importance of vaccine development and production in Japan.

Covgoze is a recombinant protein vaccine containing the active substance of a spike protein (stabilized mutated protein) of SARS-CoV-2 (original strain) manufactured using *Trichoplusia ni*-derived cells and a baculovirus expression system. Covgoze can be used after mixing the antigen preparation with a proprietary solution containing the adjuvant mainly comprised of squalene, tocopherol, and polysorbate 80. Covgoze is adopted as a "Vaccine development against novel coronavirus infection (COVID-19) (n Japanese)" (open recruitment) under the Project Promoting Support for Drug Discovery by the Japan Agency for Medical Research and Development and an "Urgent improvement project for vaccine manufacturing systems" (open recruitment) by MHLW, and being developed as a vaccine that is based on a platform different from that of mRNA vaccines mainly used in Japan to date and manufactured within the country. The applicant has submitted the application for marketing approval because the phase III studies in Japanese adults and other studies demonstrated the efficacy and safety of Covgoze and studies for manufacture gained certain knowledge and technologies. As of March 2023, Covgoze is not approved outside Japan.

2. Quality and Outline of the Review Conducted by PMDA

Covgoze is a vaccine containing the active substance of the recombinant coronavirus (SARS-CoV-2) spike protein antigen produced in *Trichoplusia ni*-derived [redacted] cells with the baculovirus expression system and purified from this culture. An oil-in-water emulsion adjuvant mainly containing squalene, tocopherol, and polysorbate 80 is used.

2.1 Active substance

2.1.1 Generation and control of cell substrate

[redacted] cells were adapted to suspension culture in a serum-free medium. The master cell bank (MCB) and working cell bank (WCB) were prepared from the adapted cells.

The MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) were subjected to purity test and characterization according to the International council for harmonisation of technical requirements for pharmaceuticals for human use (ICH) Q5A, ICH Q5B, and ICH Q5D guidelines. The genetic stability, cell growth property, virus replication, and expression of the target protein in the cells up to [redacted] passages were confirmed. Within the scope of items tested, neither adventitious viruses nor nonviral adventitious agents were detected [see Section 2.1.4].

The MCB and WCB are stored in the vapor phase of liquid nitrogen. No regeneration of the MCB is scheduled, and a new WCB will be prepared from the MCB and generated where necessary.

2.1.2 Preparation and control of virus seed

The virus seed used in manufacture of Covgoze was prepared by introducing the SARS-CoV-2 (Wuhan-Hu-1 strain) spike protein[3)] gene into baculovirus. From this virus seed, the master virus bank (MVB) was prepared through [redacted] passages of the WCB harboring this recombinant virus, and the working virus bank (WVB) was then prepared through additional [redacted] passages.

The MVB and WVB were subjected to characterization and purity tests. The gene sequence, protein expression, and virus titer were confirmed. Within the scope of items tested, neither adventitious viruses nor nonviral adventitious agents were detected [see Section 2.1.4].

The MVB and WVB are stored in the vapor phase of liquid nitrogen. No regeneration of the MVB is scheduled, and a new WVB will be prepared from the MVB and generated where necessary.

2.1.3 Manufacturing process

The manufacturing process for the active substance consists of expansion culture, virus pre-culture, virus culture, expression culture, cell harvesting/extraction/crude filtration, affinity chromatography, hydrophobic chromatography, anion-exchange chromatography, ultrafiltration/diafiltration (UF/DF), active substance preparation, and testing/storage.

Expression culture, cell harvesting/extraction/crude filtration, affinity chromatography, hydrophobic chromatography, anion-exchange chromatography, and UF/DF were defined as critical steps.

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

2.1.4 Safety evaluation of adventitious agents

In the manufacturing process of the active substance, no raw materials of biological origin are used except [redacted] cells, which are used for manufacture.

The MCB, WCB, and CAL as well as MVB and WVB were subjected to the tests for adventitious agents as shown in Table 1. Within the scope tested, no contamination with adventitious viruses or nonviral adventitious agents was detected.

3) To stabilize the structure, amino acid substitutions were made in the amino-terminal region of the spike protein containing the RBD (S1)/carboxyl-terminal region of the spike protein containing the membrane spanning domain (S2) cleavage site and central helix domain (CH domain).

Table 1. Tests for adventitious agents performed with the MCB, WCB, CAL, MVB, and WVB

Test items	MCB	WCB	CAL	MVB	WVB
Adventitious agent testing					
Sterility					
Mycoplasma					
Mycobacteria					
Spiroplasma					
In vitro adventitious virus					
In vivo adventitious virus					
Retrovirus (electron microscopy, reverse transcriptase activity test)					
Characterization					
Whole-genome sequencing					

The expression culture medium (unpurified bulk) in the expression culture process is subjected to tests for mycoplasma, *Spiroplasma*, and *in vitro* adventitious virus as in-process control tests.

The purification process was subjected to viral clearance studies that used related viruses and model viruses, and was demonstrated to have certain robustness (Table 2).

Table 2. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	BCV	BVDV	EMCV	PPV
Extraction				
Affinity chromatography				
Hydrophobic chromatography				
Anion-exchange chromatography				
Overall reduction factor	≥ 11.31	≥ 9.31	7.35	6.23

2.1.5 Manufacturing process development

Table 3 shows major changes made to the manufacturing process of the active substance during development. The active substance used in non-clinical studies were manufactured by Process a or b, the active substance used in clinical studies were manufactured by Process a or c, and the active substance used in the intended commercial product is manufactured by Process c. In response to each change of the manufacturing process, the quality attributes of the pre-change and post-change active substances were assessed and demonstrated to be comparable.

Table 3. Major changes in the manufacturing process of the active substance

Manufacturing process	Changes
From Process a to Process b	[redacted]
From Process a to Process c	[redacted]

2.1.6 Characterization of active substance

2.1.6.1 Structure, physicochemical properties, and biological properties

The active substance was subjected to characterization shown in Table 4.

Table 4. Parameters for characterization

Primary and higher order structure	Amino acid sequence, amino acid sequence including N-terminal and C-terminal post-translational modifications, disulfide bonds, secondary structure, distribution of molecular mass
Physicochemical properties	Ultraviolet absorption spectroscopy, [redacted]
Carbohydrate structure	Carbohydrate analysis, glycopeptide
Biological properties	[redacted]

2.1.6.2 Product-related substances/product-related impurities

The product-related impurity is Related Substance 1, which is appropriately controlled by the specifications for the active substance. The product-related substance is Related Substance 2, which is appropriately controlled by the specifications for the active substance.

2.1.6.3 Process-related impurities

The process-related impurities are host cell deoxyribonucleic acid (DNA), baculovirus DNA, host cell protein, sodium dihydrogen phosphate hydrate, dibasic sodium phosphate hydrate, sodium chloride, Impurity 1, Impurity 2, Impurity 3, sodium hydroxide, Impurity 4, Impurity 5, Impurity 6, Impurity 7, and Impurity 8. These impurities were demonstrated to be adequately removed by the chromatography and filtration in the manufacturing process.

The host cell DNA, baculovirus DNA, and host cell protein are controlled by the specifications for the active substance.

2.1.7 Control of active substance

The proposed specifications for the active substance include the description, identification (1) (sodium dodecyl sulfate-polyacrylamide gel electrophoresis [SDS-PAGE]), identification (2) (Western blotting), pH, purity (SDS-PAGE), residual DNA ([redacted]), host cell protein (SDS-PAGE), baculovirus ([redacted]), bacterial endotoxins, microbial limits, [redacted] ([redacted]), assay (1) protein content ([redacted]), and assay (2) titer (enzyme-linked immunosorbent assay [ELISA]).

2.1.8 Stability of active substance

Table 5 shows main stability studies of the active substance.

Table 5. Main stability studies of the active substance

	Manufacturing process of the active substance	Number of batches	Storage condition	Test period	Storage form
Long-term	Process c	3	5°C ± 3°C, protected from light	6 months[a)]	[redacted]

a) The testing is ongoing and continued for 12 months

The active substance manufactured by Process c under the long-term condition showed no definite time-dependent changes in the parameters tested throughout the period tested. Based on the above, a shelf life of 6 months has been proposed for the active substance stored in [redacted] protected from light at 2°C to 8°C.

2.2 Vaccine product

Covgoze consists of the antigen preparation containing the active substance and the proprietary solution containing the adjuvant, which are filled in separate vials. The filling volume in each vial is enough for 2 doses. Just before use, The proprietary solution 0.75 mL is transferred to the vial of the antigen preparation followed by mixing. The secondary package is a carton.

2.2.1 Antigen preparation

2.2.1.1 Description and composition of vaccine product and formulation development

The antigen preparation is an aqueous injection, and each glass vial ([redacted] mL) contains 30 μg of the recombinant coronavirus (SARS-CoV-2) spike protein antigen (the spike protein antigen) per 0.75 mL. The concerned preparation contains sodium dihydrogen phosphate hydrate, dibasic sodium phosphate hydrate, sodium chloride, polysorbate 20, and water for injection as excipients.

2.2.1.2 Manufacturing process

The manufacturing process of the antigen preparation consists of preparation of an excipient solution, preparation of the drug solution, sterile filtration/filling/crimping, inspection, testing, labeling/packaging, and testing/storage.

Preparation of the drug solution and sterile filtration/filling/crimping are defined as critical steps.

The manufacturing process was subjected to process validation at a commercial scale.

2.2.1.3 Manufacturing process development

Table 6 shows major changes made to the manufacturing process of the antigen preparation during development. The antigen preparation used in non-clinical studies was manufactured by Process A or B, and the antigen preparation used in clinical studies was manufactured by Process B or C. Process A used the active substance manufactured by Process b, Process B used the active substance manufactured by Process a, and Process C used the active substance manufactured by Process a or c. The intended commercial antigen preparation is manufactured by Process C. In response to each change of the manufacturing process, the quality attributes of the pre-change and post-change antigen preparations were assessed and demonstrated to be comparable by test results in the batch analysis.

Table 6. Major changes in the manufacturing process of the antigen preparation

Manufacturing process	Changes
From Process A to Process B	[redacted]
From Process B to Process C	[redacted]

2.2.1.4 Control of antigen preparation

The proposed specifications for the antigen preparation include the strength, description, identification (1) (SDS-PAGE), identification (2) (Western blotting), pH, purity (SDS-PAGE), bacterial endotoxins, mass variation, foreign insoluble matters, insoluble particulate matters, sterility, assay (1) protein content ([redacted]), and assay (2) titer (ELISA).

2.2.1.5 Stability of antigen preparation

Table 7 shows main stability studies of the antigen preparation.

Table 7. Main stability studies of the antigen preparation

	Manufacturing process of the active substance	Manufacturing process of the antigen preparation	Number of batches	Storage condition	Studied period	Storage package
Long-term	Process a	Process C	1	5°C ± 3°C, protected from light (upright and inverted)	12 months[a)]	Glass vial with [redacted] rubber stopper
	Process c		2		12 months[b)]	

a) The testing is ongoing and continued for 18 months
b) The testing is ongoing and continued for 36 months

Three batches of the antigen preparation manufactured by Process C using Process a- or c-derived active substance were placed on stability under long-term conditions and showed no definite time-dependent changes in the parameters tested throughout the period tested. Based on the above, a shelf life of 12 months has been proposed for the antigen preparation stored in a glass vial with [redacted] rubber stopper protected from light at 2°C to 8°C.

2.2.2 Proprietary solution

2.2.2.1 Description and composition of vaccine product and formulation development

The proprietary solution is an oil-in-water emulsion adjuvant. Each glass vial ([redacted] mL) of the proprietary solution contains 32.070 mg of squalene, 35.580 mg of tocopherol, and 14.580 mg of polysorbate 80 per 0.75 mL. The proprietary solution also contains other excipients: sodium dihydrogen phosphate hydrate, dibasic sodium phosphate hydrate, sodium chloride, and water for injection. The vials are overfilled to ensure that 0.75 mL proprietary solution is added to the antigen preparation to make 2 doses available.

2.2.2.2 Manufacturing process

The manufacturing process of the proprietary solution consists of liquid preparation, emulsification, bulk filling/bulk packaging/labeling, testing and storage of proprietary solution bulk, sterile filtration/filling/crimping, inspection, testing, labeling/packaging, and testing/storage.

Emulsification and sterile filtration/filling/crimping are defined as critical steps.

The manufacturing process was subjected to process validation at a commercial scale.

2.2.2.3 Manufacturing process development

Table 8 shows major changes made to the manufacturing process of the proprietary solution during development. The proprietary solutions used in non-clinical studies were manufactured by Process 1 or 2, and the proprietary solutions used in clinical studies were manufactured by Process 2 or 3. The intended commercial proprietary solution is manufactured by Process 3. In response to each change of the manufacturing process, the quality attributes of pre-change and post-change proprietary solutions were assessed and demonstrated to be comparable by test results in the batch analysis.

Table 8. Major changes in the manufacturing process of the proprietary solution

Manufacturing process	Changes
Process 1 → Process 2	[redacted]
Process 2 → Process 3	[redacted]

2.2.2.4 Control of proprietary solution

The proposed specifications for the proprietary solution include the description, identification (1) tocopherol and squalene (liquid chromatography), identification (2) polysorbate 80 (liquid chromatography), pH, bacterial endotoxins, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, [redacted] ([redacted]), content (1) tocopherol and squalene (liquid chromatography), content (2) polysorbate 80 (liquid chromatography).

2.2.2.5 Stability of proprietary solution

Table 9 shows main stability studies of the proprietary solution.

Table 9 Main stability studies of the proprietary solution

	Manufacturing process of the proprietary solution	Number of batches	Storage condition	Studied period	Storage package
Long-term	Process 3	3	5°C ± 3°C, protected from light (upright and inverted)	6 months[a)]	[redacted] rubber stopper, glass vial

a) The testing is ongoing and continued for 36 months

Three batches of the proprietary solution manufactured by Process 3 were placed on stability under long-term conditions and showed no definite time-dependent changes in the parameters tested throughout the period tested. Based on the above, a shelf life of 6 months has been proposed for the proprietary solution stored in a glass vial with [redacted] rubber stopper protected from light at 2°C to 8°C.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that there were no critical quality problems that may affect evaluation of non-clinical and clinical study results of Covgoze at present.

2.R.1 Structure and control method of active substance in Covgoze

[redacted] are observed in SDS-PAGE and Western blotting performed for identification. The applicant controls [redacted] as the active substance of Covgoze.

PMDA asked the applicant to explain the appropriateness of structure and control method of the antigen protein, the active substance.

The applicant's explanation:

The primary structure of the antigen protein was identified as the coronavirus (SARS-CoV-2) spike protein according to an amino acid sequence analysis using peptide mapping. In addition, an analysis of the antigen protein by [redacted] showed [redacted], suggesting presence of [redacted]. Further, investigation of [redacted] the antigen protein [redacted]. Since [redacted] detected by [redacted] considered to have antigenicity of the spike protein. During development of Covgoze, however, the applicant concluded that [redacted], and decided to proceed with the development [redacted] as the nature of the active substance.

To establish the identification and purity tests as part of the specifications of the active substance, [redacted] investigated, but [redacted] was difficult. Because of such properties of the antigen protein, the identification and purity tests employed a method detecting and assaying [redacted]. In addition to [redacted] by the identification and purity tests, [redacted] was included to control [redacted].

PMDA's view:

It is desirable to control quality of the active substance [redacted], but the property of the antigen protein [redacted], and thus Covgoze [redacted]. Concerning the concept of the active substance in Covgoze, samples for identification [redacted], and the identification test alone does not [redacted]. However, in light of [redacted]

[redacted], the applicant's explanation (i.e., [redacted] in the identification test) is acceptable. Further, since the active substance [redacted], the applicant proposed a plan to control the active substance by multiple specifications including the purity test and [redacted] ([redacted]). PMDA accepted the plan.

2.R.2 Novel excipient (squalene)

Covgoze (vaccine product) uses squalene different from that previously used in terms of the specifications, but PMDA considered it no particular problem based on the following views.

2.R.2.1 Specifications and stability

Based on the submitted data, PMDA has concluded that squalene has no particular problems in terms of the specifications and stability.

2.R.2.2 Safety

Based on the submitted data, PMDA considered that the use of Covgoze at the clinical dosage regimen was unlikely to pose problems associated with the concerned excipient. The excipient, however, has an immunostimulatory action as an adjuvant [see Section 3.1] and induces inflammatory changes in the administration site (in the muscle) [see Section 5.2]. Thus, its use as a general excipient should not serve as a precedent for other products to be developed in the future.

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

The applicant submitted results from studies in mice and monkeys, which serve as data on primary pharmacodynamic of the spike protein antigen and adjuvant A-910823 (containing squalene, tocopherol, and polysorbate 80). Table 10 shows a summary of major studies.

Table 10. Summary of primary pharmacodynamic studies

Animal species Sex	Number of animals	Dosage regimen/virus exposure method in SARS-CoV-2 infection study	Main endpoints	Attached document CTD
BALB/c mouse Female	n = 7-8/group	• Spike protein antigen (0.1, 1, or 10 μg) + A-910823[a)] • Spike protein antigen (0.1, 1, or 10 μg) • Placebo[b)] Two intramuscular doses of 50 μL each 14 days apart	Immunogenicity	4.2.1.1-01
BALB/c mouse Female	n = 3-6/group	• Spike protein antigen (0.01, 0.1, or 1 μg) + A-910823[a)] • Spike protein antigen (0.01, 0.1, or 1 μg) • Placebo[b)] Two intramuscular doses of 50 μL each 14 days apart Intranasal inoculation of mouse-adapted B.1 variant[c)] (2.3×10^4 $TCID_{50}$/30 μL) 21 days after the second dose	Immunogenicity Prevention of SARS-CoV-2 infection	4.2.1.1-02 4.2.1.1-03 4.2.1.1-04
BALB/c mouse Female	n = 5-8/group	• Spike protein antigen (0.01, 0.1, or 1 μg) + A-910823[a)] • Spike protein antigen (0.01, 0.1, or 1 μg) • Placebo[b)] Two intramuscular doses of 50 μL each 14 days apart Intranasal inoculation of Beta variant[d)] (2.3×10^4 $TCID_{50}$/50 μL[e)] or 2.3×10^5 $TCID_{50}$/50 μL[f)]) 20 days after the second dose	Prevention of SARS-CoV-2 infection	4.2.1.1-05
Cynomolgus monkey Female	n = 4/group	• Spike protein antigen (1, 2.5, 5, 10, or 25 μg) + A-910823[a)] • Spike protein antigen (10 μg)[b)] • Placebo Two intramuscular doses of 0.5 mL each 21 days apart	Immunogenicity	4.2.1.1-06 4.2.1.1-07 4.2.1.1-08
Cynomolgus monkey Female	n = 4/group	• Spike protein antigen (10 μg) + A-910823[a)] • Spike protein antigen (10 μg) • Placebo[b)] Two intramuscular doses of 0.5 mL each 21 days apart Intranasal and transtracheal inoculation of the original strain[g)] ($10^{6.5}$ $TCID_{50}$/1.8 mL) 8 or 13 weeks[h)] after the second dose	Immunogenicity Prevention of SARS-CoV-2 infection	4.2.1.1-09 4.2.1.1-10

a) 21.38 mg/mL squalene, 23.72 mg/mL tocopherol, 9.72 mg/mL polysorbate 80, 0.10 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.77 mg/mL sodium chloride (concentrations after mixing with the spike protein antigen)
b) 0.20 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.77 mg/mL sodium chloride
c) QHmusX variant that was derived from hCoV-19/Japan/QH-329-037/2020 strain, isolated from a clinical specimen in 2020, and adapted to mice to increase its infectivity in mice. BALB/c mice infected with this variant exhibited virus-induced acute respiratory diseases such as diffuse alveolar damage and pathological findings indicative of pneumonia accompanied by eosinophilic infiltration (*Sci Adv.* 2022;8:eabh3827).
d) hCoV-19/Japan/TY8-612/2021 strain, isolated from a clinical specimen in 2021. This strain has infectivity in mice, and infected BALB/c mice exhibited weight decreased.
e) Inoculation dose in a group for evaluation of inhibition against virus replication
f) Inoculation dose in a group for evaluation of survival and changes in body weight over time
g) hCoV-19/Japan/TY-WK-521/2020 strain isolated from a clinical specimen in 2020
h) Because of the limited animal-housing capacity of the testing facility, each group was divided into 2 sub-groups of 2 animals each, which were inoculated with the original strain 8 or 13 weeks after administration of the test article.

3.1 Primary pharmacodynamics

3.1.1 Immunogenicity study (CTD 4.2.1.1-01, CTD 4.2.1.1-06 to 4.2.1.1-08)

For humoral immunity evaluation, anti-SARS-CoV-2 spike protein total immunoglobulin G (IgG) antibody titer, IgG1 antibody titer, and IgG2 antibody titer (only total IgG antibody titer in monkeys) as well as anti-receptor-binding domain (RBD) IgG antibody titer (only in monkeys) were determined by ELISA, and SARS-CoV-2 neutralizing antibody titer was determined by the microtiter method using the original strain.

For cell-mediated immunity evaluation, the number of cells producing cytokines (interferon gamma [IFN-γ], interleukin [IL]-4, and IL-5) after stimulation with the antigen (mixture of peptides derived from the SARS-CoV-2 spike protein) was determined by the enzyme-linked immune absorbent spot (ELISPOT) assay, using spleen cells in mice and peripheral blood mononuclear cells isolated from blood specimens in monkeys.

As shown below, administration of the spike protein antigen mixed with A-910823 induced production of IgG antibody and neutralizing antibody as well as helper T cell (Th)1-dominant cell-mediated immunity.

3.1.1.1 Antibody production (evaluation for humoral immunity)

In mice, the anti-SARS-CoV-2 spike protein total IgG antibody titer, IgG1 antibody titer, IgG2 antibody titer, and neutralizing antibody titer were higher 14 or 15 days after the second dose than those 13 days after the first dose in all the groups. At any dose, these titers were higher in the group receiving the spike protein antigen mixed with A-910823 (hereinafter, "the spike protein antigen + A-910823 group") than in the spike protein antigen alone group. In the spike protein antigen alone group and the spike protein antigen + A-910823 group, antibody production was induced in a dose-dependent manner.

In monkeys, the anti-SARS-CoV-2 spike protein total IgG antibody titer, anti-RBD IgG antibody titer, and neutralizing antibody titer were higher 14 days after the second dose than those 20 days after the first dose in all groups. Comparison between the groups receiving the same amount of the spike protein antigen (10 μg) showed that all the antibody titers were higher in the spike protein antigen + A-910823 group than in the spike protein antigen alone group. The neutralizing antibody titer after the second dose in the spike protein antigen + A-910823 group receiving 5 to 25 μg of the spike protein antigen was similar to that of the WHO reference sample (neutralizing antibody titer, 1473 IU/mL), which was used as the positive control.

3.1.1.2 T-cell response (evaluation for cell-mediated immunity)

In mice, the number of cells producing cytokines IFN-γ, IL-4, and IL-5 was also higher in the spike protein antigen + A-910823 group than in the spike protein antigen alone group.

In monkeys, cells producing cytokines were hardly detected in the spike protein antigen alone group, but cells producing IFN-γ, IL-4, and IL-5 were detected in the spike protein antigen + A-910823 group and the number of such cells was higher 14 days after the second dose than 20 days after the first dose. In the spike protein antigen + A-910823 group, dose-dependent increases in the number of cells producing IFN-γ were observed 14 days after the second dose, and at any dose, that number was higher than the numbers of cells producing IL-4 and cells producing IL-5.

3.1.2 SARS-CoV-2 challenge study (CTD 4.2.1.1-02 to 4.2.1.1-05 and CTD 4.2.1.1-09 to 4.2.1.1-10)

Monkeys exposed to SARS-CoV-2 were evaluated for (1) clinical signs based on scores given to food consumption, water intake, and feces, (2) inhibition against virus replication based on loads of virus genome RNA and sub-genome RNA in the nasal swab and lung sample determined by quantitative reverse transcription polymerase chain reaction (RT-PCR), and (3) the lung based on the histopathological findings.

Mice exposed to SARS-CoV-2 were evaluated for (1) prevention of the severe disease based on the survival and changes in body weight over time 10 days after the virus challenge and (2) inhibition

against virus replication based on the virus load in lung homogenate after the virus challenge, determined by the 50% tissue culture infective dose ($TCID_{50}$) method.[4)] The extent of eosinophilic infiltration was evaluated by histopathological examination of lung tissue obtained 10 days after the virus challenge (only in studies challenged with the original strain).

As shown below, the administration of the spike protein antigen mixed with A-910823 prevented clinical signs and inhibited virus replication.

3.1.2.1 Clinical observation

- Evaluation in monkeys

In the evaluation using the original strain, the clinical sign score was recorded for 7 days after the virus challenge. In the placebo group, the scores at ≤2 days post-challenge was lower than the pre-challenge score, and the scores thereafter tended to improve. In the spike protein antigen + A-910823 group, however, the pre- and post-challenge scores were almost the same. After the virus challenge, all the animals in the placebo group and the spike protein antigen + A-910823 group survived.

- Evaluation in mice

In the evaluation using the mouse-adapted strain of B.1 lineage, the placebo group showed a decrease in body weight starting 2 days after the virus challenge. In the spike protein antigen + A-910823 group, however, animals in the 0.1 or 1 μg sub-group did not show any clear decrease in body weight after the virus challenge. In the placebo group, 5 of 6 animals died 6 days after the virus challenge, but all in the spike protein antigen + A-910823 group survived.

In the evaluation using the Beta variant, the placebo group and the 0.01 and 0.1 μg sub-groups in the spike protein antigen + A-910823 group showed a decrease in body weight up to 2 to 4 days after the virus challenge followed by the increase. In the 1 μg sub-group in the spike protein antigen + A-910823 group, however, a decrease in body weight was hardly observed. After the virus challenge, all the animals in the placebo group and the spike protein antigen + A-910823 group survived.

3.1.2.2 Virological examinations

- Evaluation in monkeys

In the evaluation using the original strain, loads of virus genome RNA and sub-genome RNA in the nasal swabs 1, 4, and 7 days after the virus challenge were smaller in the spike protein antigen + A-910823 group than in the placebo group. At 7 days after the virus challenge, the virus genome RNA and sub-genome RNA in the lung were detected in the placebo group, but hardly detected in the spike protein antigen + A-910823 group, demonstrating the inhibition against virus replication.

- Evaluation in mice

In the evaluation using the mouse-adapted strain of B.1 lineage, the virus loads in the lung homogenate at 6 hours, 1 and 3 days after the virus challenge were smaller in the spike protein antigen

[4)] The virus load in lung homogenate after the virus challenge was evaluated in the spike protein antigen + A-910823 group and placebo group.

+ A-910823 group than in the placebo group. The spike protein antigen + A-910823 group showed inhibition against virus replication in a manner dependent on the amount of the spike protein antigen administered.

In the evaluation using the Beta variant, the virus loads in the lung homogenate at 6 hours, 1 and 3 days after the virus challenge were smaller in the spike protein antigen + A-910823 group than in the placebo group. The spike protein antigen + A-910823 group showed inhibition against virus replication in a manner dependent on the amount of the spike protein antigen administered.

3.1.2.3 Histopathological examinations

- Evaluation in monkeys

In the evaluation using the original strain, the lung scores (i.e., scores for thrombus, lymphoid tissue lesion, acute interstitial pneumonia, and bronchitis) at 7 days after the virus challenge were lower in the spike protein antigen + A-910823 group than in the placebo group. The score for eosinophilic pneumonia in the spike protein antigen + A-910823 group was similar to that in the placebo group.

- Evaluation in mice

In the evaluation using the mouse-adapted strain of B.1 lineage, the lung at 10 days after the virus challenge in the placebo group showed an inflammatory finding, namely diffuse alveolar damage with extensive infiltration of inflammatory cells such as neutrophils, lymphocytes, and macrophages into peribronchiolar and alveolar tissues. In the spike protein antigen + A-910823 group, however, the inflammation was limited to the peribronchiolar tissue, and no findings indicative of diffuse alveolar damage were obtained. Eosinophilic infiltration in the lung was not observed in the placebo group, but observed in the spike protein antigen alone group and the spike protein antigen + A-910823 group. The eosinophil count was lower in the groups receiving 0.1 or 1 μg of the spike protein antigen than in those receiving 0.01 μg, either with or without A-910823.

3.2 Safety pharmacology

No safety pharmacology studies using Covgoze have been conducted. The applicant explained that safety pharmacology of Covgoze was evaluated through clinical observations in a repeated-dose toxicity study in rats, and that Covgoze had no effects on physiological functions in the cardiovascular, respiratory, or central nervous system.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of Covgoze

The applicant's explanation about mechanisms of actions of Covgoze and the adjuvant (A-910823) contained in Covgoze:

To examine whether an interaction between the spike protein antigen and A-910823 would affect the adjuvant activity of A-910823, immunoreactions were evaluated in mice that had received a mixture of the spike protein antigen and A-910823 and in mice that had received them separately. No differences in immunoreaction were observed between these different administration methods (CTD 4.2.1.1-11). In addition, production of cytokines and chemokines at the administration site of A-910823 in mice was investigated, and the amounts of cytokines and chemokines such as IL-6, monocyte chemotactic

protein 1 (MCP-1), and macrophage inflammatory proteins 1 α/β (MIP-1α/β) produced in the A-910823 group were greater than those in the placebo group (CTD 4.2.1.1-12). There are data suggesting that AS03, an adjuvant of a similar composition to that of A-910823, enhances immunity only at the administration site and its draining lymph nodes, not mediated by its direct binding to the antigen (Review Report on Emulsion-adjuvanted Cell-culture Derived Influenza HA Vaccine H5N1 for Intramuscular Injection "KAKETSUKEN," dated February 17, 2014). In light of the investigation results of A-910823 in mice, as with AS03, A-910823 is considered to function without forming a complex with the spike protein antigen. Specifically, A-910823 induces cytokines and chemokines into the administration site and thereby enhances migration of immune cells including monocytes and neutrophils, consequently contributing to the potentiated immunogenicity. In combination with A-910823, the spike protein antigen is considered to induce production of anti-SARS-CoV-2 spike protein IgG antibody and neutralizing antibody against SARS-CoV-2 and cell-mediated immune response, thereby contributing to prevention of COVID-19.

PMDA accepted the applicant's explanation.

3.R.2 Risk of Covgoze-induced disease aggravation

The applicant's explanation about a risk of disease aggravation owing to Covgoze administration:
Analyses of the number of cells producing cytokines using spleen cells from mice and peripheral blood mononuclear cells from monkeys did not show induction of Th2-dominant cell-mediated immunity in the spike protein antigen + A-910823 group. In SARS-CoV-2 challenge studies in mice and monkeys, animals receiving spike protein antigen + A-910823 showed inhibition of virus replication, inhibition of weight loss, and reduction in lung lesions, compared with those receiving placebo, without findings suggestive of aggravated infection or worsened symptoms. In the SARS-CoV-2 challenge study in mice, the spike protein antigen alone group and the spike protein antigen + A-910823 group had a similar level of eosinophilic infiltration in the lung, and its severity did not increase with increasing dose of the spike protein antigen in either group; this finding is, therefore, not considered to suggest an increased risk of Covgoze-induced disease aggravation. Based on the above non-clinical pharmacology study results, Covgoze is unlikely to induce enhanced disease.

PMDA's view:
The risk of Covgoze-associated enhanced disease has not been suggested by the non-clinical pharmacology study results, but it should be further discussed based on clinical study results.

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

No non-clinical pharmacokinetic studies have been conducted for the present application. The WHO's non-clinical study guidelines[5)] do not usually require conduct of non-clinical pharmacokinetic studies for vaccines

5) "WHO Technical Report Series No.927 Annex 1 Guidelines on nonclinical evaluation of vaccines. WHO; 2005" and "WHO Technical Report Series No. 987 Annex 2 Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. WHO; 2014"

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data of Covgoze in the form of results from a repeated-dose toxicity study, reproductive and developmental toxicity study, and local tolerance study of Covgoze as well as a genotoxicity study of adjuvant A-910823.

5.1 Single-dose toxicity

No single-dose toxicity studies of Covgoze have been conducted, but toxicity after a single dose of Covgoze (acute toxicity) was evaluated based on results collected after the initial dose in the repeated intramuscular dose toxicity study in rats (CTD 4.2.3.2-01) and the local tolerance study in rabbits (CTD 4.2.3.6-01). Neither deaths nor changed clinical signs were observed after the Covgoze administration.

5.2 Repeated-dose toxicity

The repeated intramuscular dose toxicity study of Covgoze was conducted in rats. The repeated-dose toxicity of Covgoze was also evaluated in an immunogenicity study in monkeys (Table 11). The major findings were inflammatory changes at the administration site.

Table 11. Repeated-dose toxicity study and immunogenicity study

Test system		Route of administration	Treatment duration	Dose (mL/body)	Main findings	NOAEL (mL/body)	Attached document CTD
Repeated-dose toxicity	Male and female rats (SD)	Intramuscular	2 weeks (2 doses[b]) + 15-day withdrawal	Covgoze (0.2[d),e]), A-910823 (0.2[e]) or negative control (0.2[f])	Covgoze[i]: Inflammation and edema at the administration site; high leukocyte, neutrophil, monocyte, and eosinophil counts; high fibrinogen value, etc. Reversible	Covgoze: 0.2	4.2.3.2-01
Immunogenicity study[a]	Female cynomolgus monkey	Intramuscular	9 weeks (4 doses[c]) + No withdrawal	Covgoze (0.5[g), h])	Covgoze[j]: Inflammation at the administration site; high eosinophil count; high C-reactive protein and fibrinogen values, etc.		4.2.3.2-02 (reference)

a) Under non-GLP-compliant conditions, clinical observation, body weight measurement, and hematology were performed in accordance with the drug toxicity study guideline (PMSB/ELD Notification No. 655 "Partial revision of the guideline for repeated-dose toxicity study [in Japanese]" dated April 5, 1999); and body temperature measurement and histopathological examination were performed in accordance with the WHO guidelines (Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. 2013).
b) 0.2 mL/site administered to the hindlimb (1 site) on Days 1 and 15
c) 0.5 mL/site administered to the hindlimb (1 site) on Days 1, 22, 43, and 61
d) Spike protein antigen 27.58 μg/body
e) 21.05 mg/mL squalene, 23.2 mg/mL tocopherol, 9.4 mg/mL polysorbate 80, 0.1 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.765 mg/mL sodium chloride
f) 0.2 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.765 mg/mL sodium chloride
g) Spike protein antigen 10 μg/body
h) 21.38 mg/mL squalene, 23.72 mg/mL tocopherol, 9.72 mg/mL polysorbate 80, 0.1 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.766 mg/mL sodium chloride
i) Production of IgG specific to the spike protein antigen was confirmed on Days 17 and 30.
j) Production of IgG specific to the SARS-CoV-2 spike protein was confirmed on Days 15 to 57.

5.3 Genotoxicity

No genotoxicity studies of Covgoze have been conducted, but Covgoze is considered negative for genotoxicity based on experience from precedent uses of squalene, tocopherol, and polysorbate 80 contained in A-910823, and results from the *in vivo* genotoxicity study of A-910823 (Table 12).

Table 12. Genotoxicity

Test article	Type of study		Test system	Dose (mL/kg)	Study result	Attached document CTD
A-910823	*In vivo*	Rodent micronucleus assay	Male rat (SD) Bone marrow	A-910823 (1.25, 2.5, or 5[a)]) Negative control (5[b)]) (intravenous, once daily for 2 days)	Negative	4.2.3.7.7-03

a) 43.9 mg/mL squalene, 45.9 mg/mL tocopherol, 18.9 mg/mL polysorbate 80, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.766 mg/mL sodium chloride
b) Physiological saline

5.4 Carcinogenicity

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

5.5 Reproductive and developmental toxicity

Reproductive and developmental toxicity studies of Covgoze were conducted in rats (Table 13). Covgoze is considered to raise no safety concerns in parent animals or offspring.

Table 13. Reproductive and developmental toxicity

Type of study	Test system	Route of administration	Treatment duration	Dose (mL/body)	Main findings	NOAEL (mL/body)	Attached document CTD
Embryo-fetal development	Female rat (SD)	Intramuscular	12 days before mating to Gestation Day 17 (4 doses[a)])	Covgoze (0.2[c), d)]), A-910823 (0.2[d)]) or negative control (0.2[e)])	Covgoze[f)] Dam: None Embryo/fetus: None	Covgoze: 0.2	4.2.3.5.2-01
Effects on pre- and postnatal development, including maternal function			12 days before mating to Postpartum Day 7 (5 doses[b)])		Covgoze[g)] Dam: None F1 offspring: None	Covgoze: 0.2	4.2.3.5.3-01

a) 0.2 mL/site administered to the hindlimb (1 site) 12 days before mating and Gestation Days 1, 7, and 17
b) 0.2 mL/site administered to the hindlimb (1 site) 12 days before mating, Gestation Days 1, 7, and 17, and Postpartum Day 7
c) Spike protein antigen: 3.9 μg/body
d) 21.05 mg/mL squalene, 23.25 mg/mL tocopherol, 9.55 mg/mL polysorbate 80, 0.1 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.765 mg/mL sodium chloride
e) 0.2 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.765 mg/mL sodium chloride
f) IgG specific to the spike protein antigen was detected in dams on Gestation Days 7 and 20 (caesarean section) and fetuses on Gestation Day 20 (caesarean section).
g) IgG specific to the spike protein antigen was detected in dams and F1 offspring on Postpartum Day 21.

5.6 Local tolerance

A local tolerance study of intramuscular administration of Covgoze was conducted in rabbits (Table 14). Covgoze was well tolerated at the administration site.

Table 14. Local tolerance

Test system	Application site	Test method	Main findings	Attached document CTD
Male rabbit (JW)	Intramuscular	Covgoze,[a), b)] A-910823,[b)] or negative control[c)] was intramuscularly administered (2 doses[d)]), and the administration site was examined histopathologically.[e)]	Covgoze: Mild edema and inflammatory cell infiltration Reversible	4.2.3.6-01

a) Spike protein antigen, 68.95 μg/site
b) 21.05 mg/mL squalene, 23.2 mg/mL tocopherol, 9.4 mg/mL polysorbate 80, 0.1 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.766 mg/mL sodium chloride
c) 0.2 mg/mL polysorbate 20, 0.24 mg/mL sodium dihydrogen phosphate hydrate, 4.84 mg/mL dibasic sodium phosphate hydrate, and 8.766 mg/mL sodium chloride
d) 0.5 mL/site administered to the hindlimb (1 site) on Days 1 and 15
e) Performed on Days 17 and 29

5.R Outline of the review conducted by PMDA

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

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

No data related to biopharmaceutic or clinical pharmacology have been submitted for the present application. Matters related to data on the assay method for immunogenicity of Covgoze in clinical studies presented in the present application are described in Section 7 where necessary.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from clinical studies shown in Table 15.

Table 15. Summary of clinical studies (evaluation data)

Region	Study ID	Phase	Population	No. of subjects enrolled	Dosage regimen	Study objective
Japan	U0221	I/II	Healthy adults aged ≥20 and ≤64 years without previous SARS-CoV-2 vaccination	60	2 intramuscular doses of Covgoze (5 or 10 μg of the antigen) or placebo 3 weeks apart	Safety Tolerability Immunogenicity
Japan	U0222	II/III	Cohort A Adults aged ≥20 years[a)b)]	3,166	Main part 2 intramuscular doses of Covgoze (10 μg of the antigen) 4 weeks apart Sub-part A single intramuscular dose of Covgoze (10 μg of the antigen) on Day 211 in some subjects in the main part who wished	Safety Immunogenicity
			Cohort B Adults aged ≥65 years without previous SARS-CoV-2 vaccination[b)]	118		
Japan	U0223	II/III	Adults[b)] aged ≥20 years who had received the primary series[c)] of Comirnaty ≥6 months before	206	A single intramuscular dose of Covgoze (10 μg of the antigen) or Comirnaty (30 μg of tozinameran)	Immunogenicity Safety
Japan	U0231	III	Adults aged ≥18 years without previous SARS-CoV-2 vaccination[b)]	1,225	2 intramuscular doses of Covgoze (10 μg of the antigen) or Vaxzevria (COVID-19 [SARS-CoV-2] vaccine [recombinant chimpanzee adenovirus vector] 5×10^{10} virus particles) 4 weeks apart	Immunogenicity Safety
Japan	U0224	III	Cohort A Adults aged ≥20 and ≤64 years who had received the primary series[d)] of Spikevax ≥6 and ≤8 months before[b)]	103	A single intramuscular dose of Covgoze (10 μg of the antigen)	Safety Immunogenicity
			Cohort B Adults aged ≥65 years who had received the primary series[c)] of Comirnaty ≥6 and ≤8 months before[b)]	29		
			Cohort C Adults aged ≥65 years who had received the primary series[d)] of Spikevax ≥6 and ≤8 months before[b)]	23		

a) In addition to adults (20-64 years) without history of SARS-CoV-2 infection and previous SARS-CoV-2 vaccination, a small number of those with previous SARS-CoV-2 vaccination irrespective of a history of SARS-CoV-2 infection and those with a history of SARS-CoV-2 infection and without previous SARS-CoV-2 vaccination were enrolled.
b) Including adults with stable underlying diseases
c) 2 doses of tozinameran 30 μg
d) 2 doses of elasomeran 100 μg

7.1 Phase I/II study

7.1.1 Japanese phase I/II study (CTD 5.3.5.1-01, Study U0221, ongoing since August 2021, data cutoff on October 7, 2021)

A randomized, observer-blind,[6)] placebo-controlled study was conducted to investigate the safety, tolerability, and immunogenicity of Covgoze in adults aged ≥20 to ≤64 years without previous SARS-CoV-2 vaccination and SARS-CoV-2 infection (target sample size,[7)] 60 subjects; 48 in the Covgoze group, 12 in the placebo group) at a single study site in Japan.

6) Sponsor, subjects, investigators, sub-investigators, and study site staff (except those who prepared the study vaccine and those who administered it) were blinded.
7) The target sample size was specified based on the precision of safety evaluation (in a safety analysis population of 24 subjects for each of the Covgoze 5 μg and 10 μg groups, at least 1 subject would experience an adverse event with the true probable incidence of 10% and 15% at the probability of 92% and 98%, respectively).

Two doses of the study vaccine (Covgoze 5 μg,[8] Covgoze 10 μg,[9] or placebo [physiological saline]) were intramuscularly administered 3 weeks apart. The subjects were randomized to the Covgoze 5 μg group, the Covgoze 10 μg group, or the placebo group in a 2:2:1 ratio.

All of randomized 60 subjects (24 in the Covgoze 5 μg group, 24 in the Covgoze 10 μg group, and 12 in the placebo group) received 2 doses of the study vaccine and were included in the full analysis set (FAS) and safety analysis population. The FAS was used as the immunogenicity analysis population.

For immunogenicity, Table 16 shows the geometric mean titer (GMT) of SARS-CoV-2 neutralizing antibody (micro-neutralization assay against the SARS-CoV-2 original strain[10]) and seroconversion rate (percentage of subjects who showed a ≥4-fold increase in antibody titer from the pre- to post-study vaccination points[11]) after each dose of the study vaccine. Table 17 shows changes in GMT of anti-spike protein IgG antibody (ELISA) over time.

Table 16. GMT of SARS-CoV-2 neutralizing antibody and seroconversion rate (Study U0221, FAS)

Neutralizing antibody titer	Covgoze 5 μg (N = 24)	Covgoze 10 μg (N = 24)	Placebo (N = 12)
	GMT [two-sided 95% CI][a)]	GMT [two-sided 95% CI][a)]	GMT [two-sided 95% CI][a)]
Baseline	2.57 [2.42, 2.73]	2.50 [-, -]	2.50 [-, -]
21 days after the first dose	2.97 [2.08, 4.25]	2.57 [2.42, 2.73]	2.50 [-, -]
14 days after the second dose	37.75 [25.94, 54.95]	46.21 [34.72, 61.51]	2.50 [-, -]
28 days after the second dose	21.81 [15.23, 31.23]	28.28 [21.53, 37.16]	2.50 [-, -]

Seroconversion rate	Covgoze 5 μg (N = 24)		Covgoze 10 μg (N = 24)		Placebo (N = 12)	
	n	Seroconversion rate[b)] [two-sided 95% CI][c)] (%)	n	Seroconversion rate[b)] [two-sided 95% CI][c)] (%)	n	Seroconversion rate[b)] [two-sided 95% CI][c)] (%)
21 days after the first dose	1	4.2 [0.1, 21.1]	0	0.0 [0.0, 14.2]	0	0.0 [0.0, 26.5]
14 days after the second dose	22	91.7 [73.0, 99.0]	24	100.0 [85.8, 100.0]	0	0.0 [0.0, 26.5]
28 days after the second dose	22	91.7 [73.0, 99.0]	24	100.0 [85.8, 100.0]	0	0.0 [0.0, 26.5]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the lower limit of quantification (LLOQ) were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects who experienced seroconversion
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% confidence interval (CI) in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.
b) The percentage of subjects who showed a ≥4-fold increase in antibody titer from the pre- to post-study vaccination points.
c) The two-sided 95% CI was estimated by the Clopper-Pearson method.

Table 17. GMT of anti-spike protein IgG antibody (Study U0221, FAS)

	Covgoze 5 μg (N = 24)	Covgoze 10 μg (N = 24)	Placebo (N = 12)
	GMT [two-sided 95% CI][a)]	GMT [two-sided 95% CI][a)]	GMT [two-sided 95% CI][a)]
Baseline	54.5 [45.6, 65.2]	50.0 [-, -]	50.0 [-, -]
21 days after the first dose	1037.5 [652.8, 1,648.8]	1131.4 [747.9, 1711.5]	50.0 [-, -]
14 days after the second dose	28735.0 [21676.5, 38092.0]	38356.7 [27797.6, 52926.6]	50.0 [-, -]
28 days after the second dose	15667.9 [11156.7, 22003.2]	23475.3 [17560.5, 31382.3]	63.0 [42.6, 93.1]

ELISA
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 100).
N, Number of subjects analyzed
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.

[8)] Containing 5 μg of S-910823 (antigen) and 0.25 mL of A-910823 (adjuvant).
[9)] Containing 10 μg of S-910823 (antigen) and 0.25 mL of A-910823 (adjuvant).
[10)] 2019-nCoV/Japan/TY/WK-521/2020 (virus strain isolated from a clinical specimen in 2020)
[11)] The antibody titer at baseline below the LLOQ was handled as the baseline value of 0.5 × LLOQ.

For safety, the observation period was specified for each of the following event categories.

- Solicited adverse events[12] (local [pain, erythema and redness, induration, and swelling] and systemic [pyrexia, nausea and vomiting, diarrhoea, headache, malaise, and myalgia]) were collected for 7 days after each study vaccination
- Unsolicited adverse events[13] (other than the solicited adverse events) were collected between the first dose of the study vaccine and 12 months after the second dose

Table 18 shows solicited adverse events reported within 7 days after each study vaccination.

Table 18. Solicited adverse events occurring within 7 days after each study vaccination (Study U0221, safety analysis population)

		First dose			Second dose		
		Covgoze 5 µg (N = 24)	Covgoze 10 µg (N = 24)	Placebo (N = 12)	Covgoze 5 µg (N = 24)	Covgoze 10 µg (N = 24)	Placebo (N = 12)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local	Overall	22 (91.7)	21 (87.5)	3 (25.0)	23 (95.8)	22 (91.7)	3 (25.0)
	Pain	21 (87.5)	21 (87.5)	3 (25.0)	23 (95.8)	22 (91.7)	3 (25.0)
	Erythema/redness	2 (8.3)	0	0	6 (25.0)	6 (25.0)	0
	Induration	3 (12.5)	1 (4.2)	0	9 (37.5)	8 (33.3)	0
	Swelling	2 (8.3)	0	0	9 (37.5)	5 (20.8)	0
Systemic	Overall	10 (41.7)	13 (54.2)	2 (16.7)	21 (87.5)	19 (79.2)	2 (16.7)
	Pyrexia[a)]	0	0	0	5 (20.8)	12 (50.0)	0
	Nausea/vomiting	0	4 (16.7)	0	8 (33.3)	11 (45.8)	0
	Diarrhoea	1 (4.2)	0	0	1 (4.2)	0	0
	Headache	6 (25.0)	7 (29.2)	0	13 (54.2)	15 (62.5)	1 (8.3)
	Malaise	7 (29.2)	7 (29.2)	2 (16.7)	21 (87.5)	18 (75.0)	1 (8.3)
	Myalgia	1 (4.2)	7 (29.2)	0	7 (29.2)	11 (45.8)	1 (8.3)

N, Number of subjects analyzed; n, Number of subjects with events
a) Based on axillary temperature

Incidences of the unsolicited adverse events and adverse reactions reported between the first dose of the study vaccine and the data-cutoff date (median observation period: 48.0 days in the Covgoze 5 µg group, 47.0 days in the Covgoze 10 µg group, 48.0 days in the placebo group) were 16.7% (4 of 24 subjects) and 4.2% (1 of 24 subjects) in the Covgoze 5 µg group, 20.8% (5 of 24 subjects) and 12.5% (3 of 24 subjects) in the Covgoze 10 µg group, and 8.3% (1 of 12 subjects) and 0% in the placebo group. The unsolicited adverse events reported by ≥2 subjects in any group were nasopharyngitis (2 subjects [8.3%] in the Covgoze 5 µg group, 1 subject [4.2%] in the Covgoze 10 µg group, 0 subjects in the placebo group) and vaccination site pain (0 subjects in the Covgoze 5 µg group, 2 subjects [8.3%] in the Covgoze 10 µg group, 0 subjects in the placebo group). Of these events, vaccination site pain (2 subjects [8.3%] in the Covgoze 10 µg group) was assessed as adverse reactions.

No serious adverse events, adverse events leading to study discontinuation, or deaths occurred up to the data-cutoff date.

12) Severity of solicited adverse events were classified based on the Food and Drug Administration (FDA) guidance (Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007).
13) Severity of unsolicited adverse events were classified based on the Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0, Nov 27, 2017) defined by the National Cancer Institute (NCI).

7.2 Phase II/III studies

7.2.1 Japanese phase II/III study (CTD 5.3.5.2-01, Study U0222; main part ongoing since October 2021, the first and second data cutoff on January 24, 2022 and August 31, 2022, respectively; sub-part ongoing since April 2022, data cutoff on August 31, 2022)

7.2.1.1 Main part

An uncontrolled study was conducted to investigate the safety and immunogenicity of Covgoze in adults aged ≥20 years (Cohort A) and adults aged ≥65 years without previous SARS-CoV-2 vaccination and SARS-CoV-2 infection (Cohort B) (target sample size,[14] 3,100 subjects [3,000 in Cohort A, 100 in Cohort B[15]]) at 23 study sites in Japan.

Two doses of Covgoze (10 μg of the antigen) were intramuscularly administered 4 weeks apart.

This study consists of 2 cohorts, Cohort A and Cohort B. Of 3,284 subjects enrolled, 3,279 (3,161 in Cohort A [2,952 in the naïve adult group,[16] 76 in the previously-vaccinated adult group,[17] 68 in the previously-infected adult group,[18] 60 in the other adult group,[19] and 5 in the other elderly group[20]] and 118 in Cohort B [115 in the naïve elderly group[21] and 3 in the non-naïve elderly group[22]]) received at least 1 dose of Covgoze and were included in the safety analysis population. The immunogenicity analysis population included subjects who received at least 1 dose of Covgoze with available immunogenicity assay data (a secondary endpoint) obtained at ≥1 sampling point after the vaccination.

For safety, the observation period was specified for each of the following event categories.

- Solicited adverse events[12] (local [pain, erythema and redness, induration, and swelling] and systemic [pyrexia, nausea and vomiting, diarrhoea, headache, malaise, and myalgia]) were collected for 7 days after each Covgoze vaccination
- Unsolicited adverse events[13] (other than the solicited adverse events) were collected between the first dose of Covgoze and 12 months after the second dose (until 28 days after the second dose for events other than serious adverse events, adverse events of special interest, and adverse events leading to medical care)

Table 19 shows solicited adverse events reported within 7 days after each Covgoze vaccination.

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14) The target sample size in Cohort A was specified based on the precision of safety evaluation (in a safety analysis population of 3,000 subjects, at least 1 subject would experience an adverse event with the probable incidence of 0.10% at the probability of 95%), and that in Cohort B was specified in light of the feasibility. In a safety analysis population of 100 subjects, at least 1 subject would experience an adverse event with the probable incidence of 3% at the probability of 95%.

15) In Cohort A, at least 2,000 adults aged ≥20 years without any history of SARS-CoV-2 infection and previous SARS-CoV-2 vaccination, at least 30 adults with previous SARS-CoV-2 vaccination irrespective of a history of SARS-CoV-2 infection, and at least 30 adults with a history of SARS-CoV-2 infection and without previous SARS-CoV-2 vaccination were enrolled. Elderly aged ≥65 years ineligible for Cohort B were enrolled in Cohort A.

16) Adults aged ≥20 and ≤64 years without history of SARS-CoV-2 infection and previous SARS-CoV-2 vaccination who have tested negative for anti-SARS-CoV-2 N-protein antibody at screening

17) Adults aged ≥20 and ≤64 years who had previously received SARS-CoV-2 vaccines irrespective of a history of SARS-CoV-2 infection

18) Adults aged ≥20 and ≤64 years who had a history of SARS-CoV-2 infection but had not received SARS-CoV-2 vaccines

19) Adults aged ≥20 and ≤64 years without history of SARS-CoV-2 infection and previous SARS-CoV-2 vaccination who have tested positive for anti-SARS-CoV-2 N-protein antibody at screening

20) Individuals aged ≥65 years who were not included in Cohort B

21) Individuals aged ≥65 years without history of SARS-CoV-2 infection and previous SARS-CoV-2 vaccination who have tested negative for anti-SARS-CoV-2 N-protein antibody at screening

22) Individuals aged ≥65 years without history of SARS-CoV-2 infection and previous SARS-CoV-2 vaccination who did not have tested positive for anti-SARS-CoV-2 N-protein antibody at screening

Table 19. Solicited adverse events occurring within 7 days after each Covgoze vaccination (Study U0222, safety analysis population)

		First dose		Second dose	
		Cohort A (N = 3,161)	Cohort B (N = 118)	Cohort A (N = 3,114)	Cohort B (N = 115)
		n (%)	n (%)	n (%)	n (%)
Local	Overall	2,781 (88.0)	81 (68.6)	2,787 (89.5)	85 (73.9)
	Pain	2,744 (86.8)	77 (65.3)	2,728 (87.6)	77 (67.0)
	Erythema/redness	443 (14.0)	21 (17.8)	945 (30.3)	45 (39.1)
	Induration	553 (17.5)	20 (16.9)	1,033 (33.2)	42 (36.5)
	Swelling	470 (14.9)	20 (16.9)	991 (31.8)	43 (37.4)
Systemic	Overall	1,819 (57.5)	41 (34.7)	2,241 (72.0)	47 (40.9)
	Pyrexia[a)]	103 (3.3)	0	671 (21.5)	9 (7.8)
	Nausea/vomiting	337 (10.7)	5 (4.2)	772 (24.8)	9 (7.8)
	Diarrhoea	161 (5.1)	6 (5.1)	181 (5.8)	4 (3.5)
	Headache	816 (25.8)	17 (14.4)	1,381 (44.3)	26 (22.6)
	Malaise	1,055 (33.4)	22 (18.6)	1,825 (58.6)	34 (29.6)
	Myalgia	1,023 (32.4)	17 (14.4)	1,085 (34.8)	15 (13.0)

N, Number of subjects analyzed; n, Number of subjects with events
a) Based on axillary temperature

Incidences of unsolicited adverse events and unsolicited adverse reactions reported between the first dose of Covgoze and the first data-cutoff date[23)] (median observation period [range]; 57.0 [4-90] days in Cohort A, 57.0 [8-63] days in Cohort B) were 19.8% (625 of 3,161 subjects) and 7.9% (249 of 3,161 subjects), respectively, in Cohort A; and 35.6% (42 of 118 subjects) and 14.4% (17 of 118 subjects), respectively, in Cohort B. Table 20 shows unsolicited adverse events and unsolicited adverse reactions with an incidence of ≥1% in either cohort.

Table 20. Unsolicited adverse events and unsolicited adverse reactions reported during the observation period (Study U0222, safety analysis population)

	Cohort A (N = 3,161)		Cohort B (N = 118)	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions
	n (%)	n (%)	n (%)	n (%)
Nasopharyngitis	83 (2.6)	2 (0.1)	6 (5.1)	0
Pruritus	52 (1.6)	47 (1.5)	7 (5.9)	7 (5.9)
Vaccination site pruritus	41 (1.3)	41 (1.3)	4 (3.4)	4 (3.4)
Headache	29 (0.9)	4 (0.1)	2 (1.7)	0
Chills	18 (0.6)	17 (0.5)	2 (1.7)	1 (0.8)
Back pain	17 (0.5)	2 (0.1)	2 (1.7)	0
Rhinorrhoea	9 (0.3)	1 (0.0)	2 (1.7)	1 (0.8)
Eczema	7 (0.2)	3 (0.1)	2 (1.7)	0
Pyrexia	4 (0.1)	0	2 (1.7)	0

N, Number of subjects analyzed; n, Number of subjects with events; Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) Version 24.0

Up to the first data cutoff, serious adverse events occurred in 12 subjects (0.4%) in Cohort A (angina pectoris, cerebral haemorrhage, testis cancer, osteoarthritis, traumatic fracture, rectal cancer, clavicle fracture, peritonsillar abscess, thyroid neoplasm, appendicitis, colitis ischaemic, and inguinal hernia in 1 subject each) and in 1 subject (0.8%) in Cohort B (prostate cancer). A causal relationship to Covgoze was ruled out for all the events. The outcome of these events was “resolved” or “resolving.”

Adverse events leading to study discontinuation occurred in 13 subjects (0.4%) in Cohort A (12 in the naïve adult group [erythema, nausea, bronchitis, cerebral haemorrhage, neuropathy peripheral,

23) After completion of the evaluation of data up to 28 days after the second dose in all the subjects

dyspnoea, urticaria, sudden hearing loss, traumatic fracture, back pain, abdominal discomfort, and dermatitis allergic in 1 subject each], 1 in the previously-infected adult group [pyrexia]) and in 1 subject (0.8%) in Cohort B (fatigue). All the events were non-serious except cerebral haemorrhage and traumatic fracture. Of the adverse events leading to study discontinuation, a causal relationship to Covgoze could not be ruled out for all the events except bronchitis, cerebral haemorrhage, dyspnoea, sudden hearing loss, traumatic fracture, back pain, and abdominal discomfort in Cohort A. The outcome of the adverse events for which a causal relationship to Covgoze could not be ruled out, was "resolving" or "resolved" except neuropathy peripheral. No deaths occurred.

Between the first and second data-cutoff dates, serious adverse events occurred in 18 subjects in Cohort A (pyrexia in 2 subjects, COVID-19, diabetic gangrene, abortion spontaneous, abortion missed, cardiac failure, eosinophilic pneumonia chronic, cervix carcinoma stage 0, enterocolitis, breast cancer recurrent, gingivitis, back pain, type 2 diabetes mellitus, cholelithiasis, postoperative wound infection, foot fracture, atrial fibrillation, and tendon rupture in 1 subject each [1 subject had more than 1 event]) and in 2 subjects in Cohort B (endometrial cancer and cardiac failure acute in 1 subject each). A causal relationship to Covgoze was ruled out for all the events. For outcome, cardiac failure acute resulted in death; diabetic gangrene, breast cancer recurrent, and endometrial cancer were under treatment and thus did not resolve; and all the remaining events resolved or were resolving.

7.2.1.2 Sub-part

While the main part in this study was ongoing, a sub-part was introduced to investigate the immunogenicity and safety of a Covgoze booster dose in subjects who had received 2 doses of Covgoze in the main part and wished for the third dose (Protocol ver. 3, April 22, 2022).

A booster dose (i.e., the third dose) of Covgoze (10 μg of the antigen) was intramuscularly administered 210 days after the first dose in the main part (Day 211).

A total of 2,379 subjects who received the third dose of Covgoze (2,291 in Cohort A [2,137 in the naïve adult group, 55 in the previously-vaccinated adult group, 51 in the previously-infected adult group, 48 in the other adult group and other elderly group], 88 in Cohort B) were included in the safety analysis population. A total of 389 subjects who received the third dose of Covgoze with available immunogenicity endpoint results obtained at ≥1 sampling point after the third dose (311 in Cohort A [207 in the naïve adult group, 54 in the previously-vaccinated adult group, 50 in the previously-infected adult group], 78 in Cohort B) were included in the booster-dose immunogenicity analysis population.

The protocol included a plan to test the non-inferiority of the third Covgoze dose to the second Covgoze dose in terms of immunogenicity.[24)] As the primary endpoint, SARS-CoV-2 neutralizing antibody titers in the naïve adult group in Cohort A and naïve elderly group in Cohort B were determined. The third dose was considered non-inferior to the second dose if the above titers met both the following non-inferiority criteria (a) and (b):

[24)] The sample size required for non-inferiority test for the immunogenicity was 70 each in Cohort A and Cohort B based on the following considerations:

(a) The lower limit of the two-sided 95% confidence interval (CI) of the ratio of GMT of neutralizing antibodies 28 days after the third dose of Covgoze to that 28 days after the second dose exceeds 0.67, the non-inferiority margin.

(b) The lower limit of the two-sided 95% CI of the difference between the seroconversion rate based on the neutralizing antibody titer 28 days after the second dose of Covgoze (percentage of subjects who showed a ≥4-fold increase in SARS-CoV-2 neutralizing antibody titer from baseline) and the antibody response rate based on the neutralizing antibody titer 28 days after the third dose (percentage of subjects who showed a ≥4-fold increase in SARS-CoV-2 neutralizing antibody titer from the pre-third dose point) exceeds the non-inferiority margin of −10%.

Table 21 shows SARS-CoV-2 neutralizing antibody titers 28 days after the second and third doses of Covgoze. In both naïve adult group and naïve elderly group, the lower limit of two-sided 95% CI of the GMT ratio exceeded the non-inferiority margin of 0.67, meeting the prespecified criterion for non-inferiority.

Table 21. SARS-CoV-2 neutralizing antibody titer after Covgoze vaccination (Study U0222, booster-dose immunogenicity analysis population)

	Naïve adult group in Cohort A (N = 207)		Naïve elderly group in Cohort B (N = 78)	
Sampling point	n	GMT [two-sided 95% CI][a)]	n	GMT [two-sided 95% CI][a)]
28 days after the second dose	206	28.67 [25.59, 32.11]	78	19.13 [15.33, 23.87]
Pre-third dose	201	4.97 [4.45, 5.54]	77	3.55 [3.06, 4.13]
28 days after the third dose	205	154.16 [138.40, 171.71]	78	113.14 [95.24, 134.40]
GMT ratio	n	GMT ratio [two-sided 95% CI][b)]	n	GMT ratio [two-sided 95% CI][b)]
28 days after the third dose /28 days after the second dose	205	5.37 [4.74, 6.08]	78	5.91 [4.82, 7.25]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects who had no missing data up to the time of evaluation
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.
b) The GMT ratio and its two-sided 95% CI were estimated by anti-logarithmically transforming the difference between sampling points determined by paired t-test on logarithmically transformed antibody titers and its two-sided 95% CI

Table 22 shows results of the seroconversion rate based on neutralizing antibody titers 28 days after the second dose of Covgoze and the antibody response rate based on those 28 days after the third dose. The lower limit of two-sided 95% CI of the difference between the antibody response rate after the third dose and the seroconversion rate after the second dose in both naïve adult group and naïve elderly group exceeded the non-inferiority margin of −10%, meeting the prespecified criterion for non-inferiority.

(a) Non-inferiority test using GMTs of neutralizing antibody is planned as comparison of neutralizing antibody titers between different sampling points by paired t-test with the non-inferiority margin of 0.67. For the test to provide 90% statistical power at a one-sided significance level of 0.025, the sample size required is determined to be 68 on the assumption that the standard deviation (SD) of differences in natural logarithmically transformed neutralizing antibody titer between sampling points is 1.0; and the GMTs of neutralizing antibody at 2 sampling points agree.

(b) Non-inferiority test using the antibody response rate based on neutralizing antibody titers is planned as comparison of the antibody response rates at different sampling points by paired-ratio comparison test with the non-inferiority margin of −10%. For the test to provide 90% statistical power at a one-sided significance level of 0.025, the sample size required is 63 on the assumption that the antibody response rate 28 days after the third dose is 99%, and the seroconversion rate 28 days after the second dose is 95%.

Table 22. Seroconversion rate or antibody response rate based on SARS-CoV-2 neutralizing antibody titer after Covgoze vaccination (Study U0222, booster-dose immunogenicity analysis population)

	Naïve adult group in Cohort A (N = 207)		Naïve elderly group in Cohort B (N = 78)	
	n/N_1	Seroconversion rate[a] or antibody response rate[b] [two-sided 95% CI][c] (%)	n/N_1	Seroconversion rate[a] or antibody response rate[b] [two-sided 95% CI][c] (%)
28 days after the second dose (seroconversion rate[a])	195/206	94.7 [90.6, 97.3]	66/78	84.6 [74.7, 91.8]
28 days after the third dose (antibody response rate[b])	194/201	96.5 [93.0, 98.6]	75/77	97.4 [90.9, 99.7]
Difference between the third dose and the second dose	N_1	Difference (third dose − second dose) [two-sided 95% CI][d] (%)	N_1	Difference (third dose − second dose) [two-sided 95% CI][d] (%)
	201	2.0 [-2.1, 6.4]	77	11.7 [2.9, 21.7]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; N_1, Number of subjects who had no missing data up to the time of evaluation; n, Number of subjects who showed seroconversion or antibody response
a) Percentage of subjects who showed a ≥4-fold increase in SARS-CoV-2 neutralizing antibody titer from baseline to 28 days after the second dose of Covgoze
b) Percentage of subjects who showed a ≥4-fold increase in SARS-CoV-2 neutralizing antibody titer from the pre-third dose point to 28 days after the third dose of Covgoze
c) The two-sided 95% CI was estimated by the Clopper-Pearson method.
d) Differences between the antibody response rate and the seroconversion rate based on the neutralizing antibody titer and its two-sided 95% CI were estimated according to the paired-ratio comparison test.

For safety, the observation period was specified for each of the following event categories.

- Solicited adverse events[12] (local [pain, erythema and redness, induration, and swelling] and systemic [pyrexia, nausea and vomiting, diarrhoea, headache, malaise, and myalgia]) were collected for 7 days after the third dose of Covgoze
- Unsolicited adverse events[13] (other than the solicited adverse events) were collected for 6 months after the third dose of Covgoze (Day 211) (until 28 days after the third dose for events other than serious adverse events, adverse events of special interest, and adverse events leading to medical care)

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

Table 23. Solicited adverse events reported within 7 days after Covgoze vaccination (Study U0222, safety analysis population)

		Cohort A overall (N = 2,291)	Cohort B (N = 88)
		n (%)	n (%)
Local	Overall	2,080 (90.8)	73 (83.0)
	Pain	2,038 (89.0)	65 (73.9)
	Erythema/redness	796 (34.7)	41 (46.6)
	Induration	869 (37.9)	41 (46.6)
	Swelling	887 (38.7)	37 (42.0)
Systemic	Overall	1,916 (83.6)	49 (55.7)
	Pyrexia[a]	748 (32.6)	11 (12.5)
	Nausea/vomiting	881 (38.5)	18 (20.5)
	Diarrhoea	164 (7.2),	2 (2.3)
	Headache	1,264 (55.2)	21 (23.9)
	Malaise	1,659 (72.4)	40 (45.5)
	Myalgia	1,169 (51.0)	24 (27.3)

N, Number of subjects analyzed; n, Number of subjects with events
a) Based on axillary temperature

Incidences of unsolicited adverse events and unsolicited adverse reactions reported up to the data-cutoff date in the sub-part (median observation period [range]; 29.0 [1-80] days in Cohort A, 29.0

[1-38] days in Cohort B) were 7.9% (180 of 2,291 subjects) and 4.0% (91 of 2,291 subjects) in Cohort A and 9.1% (8 of 88 subjects) and 5.7% (5 of 88 subjects) in Cohort B. The unsolicited adverse events with an incidence of ≥1% in either cohort were vaccination site pruritus (1.7% in Cohort A, 3.4% in Cohort B), pruritus (0.9%, 2.3%), urticaria (0.1%, 2.3%), and brain neoplasm (0%, 1.1%). The unsolicited adverse reactions with an incidence of ≥1% in either cohort were vaccination site pruritus (1.7%, 3.4%) and pruritus (0.9%, 2.3%).

Up to the data-cutoff date (median observation period [range]; 29.0 [1-80] days in Cohort A, 29.0 [1-38] days in Cohort B), serious adverse events occurred in 7 subjects (0.3%) in Cohort A (urticaria, tuberculosis, cholecystitis, upper limb fracture, radial head dislocation, varicocele, and vertigo in 1 subject each) and 1 subject (1.1%) in Cohort B (brain neoplasm). A causal relationship to Covgoze was ruled out for all the events. The outcome of all of them was "resolved" or "resolving," except cholecystitis and brain neoplasm that did not resolve.[25)] Neither deaths nor adverse events leading to study discontinuation occurred.

7.2.2 Japanese phase II/III study (CTD 5.3.5.1-03, Study U0223, ongoing since December 2021, the first and second data cutoff on February 4, 2022 and August 31, 2022, respectively)

A randomized, observer-blind,[26)] active-controlled study was conducted to investigate the immunogenicity and safety of a Covgoze booster dose in adults aged ≥20 years who had completed the primary series (2 doses) of Comirnaty ≥6 months before (target sample size,[27)] 204 subjects; 102 per group) at a single study site in Japan.

A dose of the study vaccine (Covgoze [10 μg of the antigen] or Comirnaty [30 μg of tozinameran]) was intramuscularly administered.

All of the randomized[28)] 206 subjects (102 in the Covgoze group, 104 in the Comirnaty group) received the study vaccine, and 204 subjects (101 in the Covgoze group, 103 in the Comirnaty group) were included in the safety analysis population; the remaining 2 subjects were excluded because which study vaccine they received was unknown. From the above population, 203 subjects (101 in the Covgoze group, 102 in the Comirnaty group) were included in the modified intent-to-treat (mITT) population; the remaining 1 subject was excluded because the subject tested positive for anti-SARS-CoV-2 N-protein antibody at screening. All of them had immunogenicity endpoint results obtained at ≥1 sampling point after the study vaccination and were thus included in the immunogenicity analysis population.

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25) Outcomes of tuberculosis, cholecystitis, and radial head dislocation were not reported at the time of data cutoff, but recovery from tuberculosis and radial head dislocation was confirmed.

26) Sponsor, subjects, investigators, sub-investigators, and study site staff (except those who prepared the study vaccine and those who administered it) were blinded.

27) To test non-inferiority of Covgoze to Comirnaty using GMT of SARS-CoV-2 neutralizing antibody 28 days after the study vaccination (Day 29) and the antibody response rate with 80% statistical power at a one-sided significance level of 0.025, the sample size required is 100 subjects per group or 200 subjects in total. The following assumption was applied: The GMT ratio of the Covgoze group to the Comirnaty group is 1.0; the SD of logarithmically transformed (base 10) SARS-CoV-2 neutralizing antibody titers is 0.4; and the antibody response rate is 95% in both Covgoze group and Comirnaty group. In view of the multi-dose vial of Comirnaty, each providing 6 doses, the target sample size of 204 was determined.

28) Subjects were stratified by age (<40 years, ≥40 years) and sex at randomization.

The primary endpoint for immunogenicity was a GMT ratio based on SARS-CoV-2 neutralizing antibody 28 days after the study vaccination (Day 29) and a difference in antibody response rate. Covgoze was considered non-inferior to Comirnaty if the above titers met both the following non-inferiority criteria (a) and (b):

(a) The lower limit of the two-sided 95% CI of the ratio of GMT of neutralizing antibodies 28 days after the study vaccination in the Covgoze group to that in the Comirnaty group exceeds 0.67, the non-inferiority margin.

(b) The lower limit of the two-sided 95% CI of a difference in neutralizing antibody response rate 28 days after the study vaccination between the Covgoze group and the Comirnaty group exceeds −10%, the non-inferiority margin.

Table 24 and Table 25 show results of GMT of neutralizing antibodies 28 days after the study vaccination and antibody response rate. The lower limit of the two-sided 95% CI of the GMT ratio exceeded 0.67, and the lower limit of the two-sided 95% CI of the difference in antibody response rate exceeded −10%, demonstrating non-inferiority of Covgoze to Comirnaty.

Table 24. SARS-CoV-2 neutralizing antibody titers (Study U0223, immunogenicity analysis population)

Day of sampling	Covgoze (N = 101)		Comirnaty (N = 102)		GMT ratio (Covgoze/Comirnaty) [two-sided 95% CI]
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	
Before study vaccination	101	5.47 [4.81, 6.21][a)]	102	6.65 [5.73, 7.72][a)]	-
28 days after study vaccination	101	124.98 [107.98, 144.66][b)]	101[c)]	109.71 [94.79, 126.99][b)]	1.14 [0.94, 1.39][b)]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects who had no missing data up to the time of evaluation
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group were calculated and then anti-logarithmically transformed for estimation.
b) To logarithmically transformed neutralizing antibody titers, the analysis of the covariance (ANCOVA) model using the study vaccine group as a fixed effect and age (continuous variable) and sex as covariates was applied to obtain estimates, which were then anti-logarithmically transformed to determine the value.
c) The test excluded 1 subject who became positive for anti-SARS-CoV-2 N protein antibody on Day 17.

Table 25. Antibody response rate based on SARS-CoV-2 neutralizing antibody titers 28 days after the study vaccination (Study U0223, immunogenicity analysis population)

Covgoze (N = 101)		Comirnaty (N = 102)		Difference in antibody response rate (Covgoze − Comirnaty) [two-sided 95% CI][a)]
n/N	Antibody response rate [two-sided 95% CI][b)]	n/N	Antibody response rate [two-sided 95% CI][b)]	
101/101	100.0 [96.4, 100.0]	101/101[c)]	100.0 [96.4, 100.0]	0.0 [-5.9, 5.9]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed, n: Number of subjects meeting the criterion for an antibody responder (≥4-fold increase in antibody titer from the pre- to post-vaccination points)
a) The two-sided 95% CI was estimated by the Farrington-Manning method.
b) The two-sided 95% CI was estimated by the Clopper-Pearson method.
c) The test excluded 1 subject who became positive for anti-SARS-CoV-2 N protein antibody on Day 17.

For safety, the observation period was specified for each of the following event categories.

- Solicited adverse events[12)] (local [pain, erythema and redness, induration, and swelling] and systemic [pyrexia, nausea and vomiting, diarrhoea, headache, malaise, myalgia, arthralgia, and chills]) were collected for 7 days after the study vaccination
- Unsolicited adverse events[13)] (other than the solicited adverse events) were collected until 12 months after the study vaccination

Table 26 shows solicited adverse events reported within 7 days after the study vaccination.

Table 26. Solicited adverse events reported within 7 days after the study vaccination (Study U0223, safety analysis population)

		Covgoze (N = 101)	Comirnaty (N = 103)
		n (%)	n (%)
Local	Overall	68 (67.3)	75 (72.8)
	Pain	66 (65.3)	75 (72.8)
	Erythema/redness	6 (5.9)	10 (9.7)
	Induration	0	0
	Swelling	1 (1.0)	1 (1.0)
Systemic	Overall	70 (69.3)	82 (79.6)
	Pyrexia[a)]	39 (38.6)	61 (59.2)
	Nausea/vomiting	5 (5.0)	5 (4.9)
	Diarrhoea	4 (4.0)	6 (5.8)
	Headache	25 (24.8)	43 (41.7)
	Malaise	43 (42.6)	56 (54.4)
	Myalgia	40 (39.6)	50 (48.5)
	Arthralgia	8 (7.9)	12 (11.7)
	Chills	4 (4.0)	7 (6.8)

N, Number of subjects analyzed; n, Number of subjects with events
a) Based on axillary temperature

Incidences of unsolicited adverse events and unsolicited adverse reactions reported up to the first data-cutoff date (median observation period [range]; 30.0 [26-42] days in the Covgoze group, 29.0 [26-39] days in the Comirnaty group) were 84.2% (85 of 101 subjects) and 82.2% (83 of 101 subjects) in the Covgoze group and 84.5% (87 of 103 subjects) and 82.5% (85 of 103 subjects) in the Comirnaty group. Table 27 shows unsolicited adverse events and unsolicited adverse reactions reported by ≥2 subjects in either group. There were no deaths, serious adverse events, or adverse events leading to study discontinuation.

Table 27. Unsolicited adverse events and unsolicited adverse reactions reported by ≥2 subjects after the study vaccination (Study U0223, safety analysis population)

	Covgoze (N = 101)		Comirnaty (N = 103)	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions
	n (%)	n (%)	n (%)	n (%)
Neutrophil percentage increased	77 (76.2)	77 (76.2)	80 (77.7)	80 (77.7)
C-reactive protein increased	33 (32.7)	33 (32.7)	46 (44.7)	46 (44.7)
White blood cell count increased	9 (8.9)	9 (8.9)	11 (10.7)	11 (10.7)
Dysmenorrhoea	2 (2.0)	0	2 (1.9)	0
Coronavirus infection	1 (1.0)	0	2 (1.9)	0

N, Number of subjects analyzed; n, Number of subjects with events; MedDRA/J Version 24.1

7.3 Phase III studies

7.3.1 Japanese phase III study (CTD 5.3.5.1-02, Study U0231, ongoing since January 2022, data cutoff on April 20, 2022)

A randomized, observer-blind,[29)] active-controlled study was conducted to investigate the immunogenicity and safety of Covgoze in adults aged ≥18 years without previous SARS-CoV-2

[29)] Sponsor, subjects, investigators, sub-investigators, and study site staff (except those who prepared the study vaccine and those who administered it) were blinded.

vaccination and SARS-CoV-2 infection (target sample size, approximately 1,000 subjects[30]; approximately 500 in each group) at 20 study sites in Japan.

Two doses of the study vaccine (Covgoze [10 μg of the antigen] or Vaxzevria [COVID-19 (SARS-CoV-2) vaccine containing 5×10^{10} virus particles of recombinant chimpanzee adenovirus vector]) were intramuscularly administered 4 weeks apart.

Of the randomized[31] 1,225 subjects (613 in the Covgoze group, 612 in the Vaxzevria group), 1,221 (611 in the Covgoze group, 610 in the Vaxzevria group) were included in the safety analysis population; the remaining 4 subjects were excluded (2 in the Covgoze group who were left unvaccinated [including 1 subject who was double-allocated and left unvaccinated], 2 in the Vaxzevria group [One was left unvaccinated. The other was allocated to the Covgoze group and received Covgoze, but then was double-allocated to the Vaxzevria group at another site and received Vaxzevria]). Of the randomized 1,225 subjects, 1,220 were included in the FAS; the remaining 5 subjects were excluded (3 in the Covgoze group [2 who were left unvaccinated (including 1 left unvaccinated because of the later found double-allocation) and 1 who received the first dose in the Covgoze group, but then was double-allocated to the Vaxzevria group at another site and received Vaxzevria]; 2 in the Vaxzevria group [1 subject who were left unvaccinated and 1 subject who was allocated to the Covgoze group for the first dose, but then was double-allocated to the Vaxzevria group for the second dose and received Vaxzevria]). Of the FAS, 1,161 subjects (573 in the Covgoze group, 588 in the Vaxzevria group) were included in the mITT population; the remaining 59 subjects (37 in the Covgoze group, 22 in the Vaxzevria group) were excluded because they tested positive for RT-PCR or for anti-SARS-CoV-2 N-protein antibody at screening. Of the mITT population, 1,141 subjects (562 in the Covgoze group, 579 in the Vaxzevria group) were included in the immunogenicity analysis population or the primary analysis of immunogenicity; the remaining 20 subjects (11 in the Covgoze group, 9 in the Vaxzevria group) were excluded because they never underwent blood sampling for the immunogenicity analysis after the first dose of the study vaccine.

The primary endpoint for immunogenicity was the GMT of neutralizing antibodies based on the SARS-CoV-2 neutralizing antibody titer 28 days after the second dose of the study vaccine (Day 57). The protocol included a plan to test the superiority of Covgoze to Vaxzevria in terms of the GMT. Table 28 shows results of the GMT based on the SARS-CoV-2 neutralizing antibody 28 days after the second dose of the study vaccine. The lower limit of 95% CI of the GMT ratio of Covgoze to Vaxzevria exceeded 1.0, achieving the prespecified criterion for superiority.

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30) On the assumption that the SD of natural logarithmically transformed SARS-CoV-2 neutralizing antibody titers is 1.2, and the true GMT ratio of Covgoze to Vaxzevria is 1.3, to test superiority of Covgoze to Vaxzevria with ≥90% statistical power at a two-sided significance level of 0.05 in the primary analysis of immunogenicity, 882 subjects who are included in the immunogenicity analysis population and would provide the neutralizing antibody titer 28 days after the second dose are required. In light of potential early discontinuations, the target sample size was determined to be 1,000 subjects who would be included in the immunogenicity analysis and did not serologically test positive for SARS-CoV-2 at baseline (before the first dose of the study vaccine).

31) Subjects were stratified by age (18-39 years, 40-64 years, ≥65 years) at randomization.

Table 28. SARS-CoV-2 neutralizing antibody titers 28 days after the second dose (Study U0231, immunogenicity analysis population)

	Covgoze (N = 562)		Vaxzevria (N = 579)		GMT ratio (Covgoze/Vaxzevria) [two-sided 95% CI]
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	
Baseline	562	2.61 [2.54, 2.68][a)]	579	2.59 [2.53, 2.66][a)]	-
28 days after the second dose	497	19.92 [18.68, 21.23][b)]	514	3.63 [3.41, 3.87][b)]	5.48 [5.01, 6.00][b)]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects who had no missing data at any sampling point
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group were calculated and then anti-logarithmically transformed for estimation.
b) To logarithmically transformed neutralizing antibody titers, an ANCOVA model using the study vaccine group as a fixed effect and age (continuous variable) as a covariate was applied to obtain estimates, which were then anti-logarithmically transformed to determine the value.

For safety, the observation period was specified for each of the following event categories.

- Solicited adverse events[12)] (local [pain, erythema and redness, induration, and swelling] and systemic [pyrexia, nausea and vomiting, diarrhoea, headache, malaise, and myalgia]) were collected for 7 days after each study vaccination
- Unsolicited adverse events[13)] (other than the solicited adverse events) were collected between the first dose of the study vaccine and 12 months after the second dose (until 28 days after the second dose for events other than serious adverse events, adverse events of special interest, and adverse events leading to medical care)

Table 29 shows solicited adverse events reported within 7 days after each study vaccination.

Table 29. Solicited adverse events reported within 7 days after study vaccination (Study U0231, safety analysis population)

		First dose		Second dose	
		Covgoze (N = 611)	Vaxzevria (N = 610)	Covgoze (N = 571)	Vaxzevria (N = 574)
		n (%)	n (%)	n (%)	n (%)
Local	Overall	485 (79.4)	487 (79.8)	469 (82.1)	322 (56.1)
	Pain	477 (78.1)	480 (78.7)	457 (80.0)	312 (54.4)
	Erythema/redness	34 (5.6)	60 (9.8)	79 (13.8)	31 (5.4)
	Induration	43 (7.0)	39 (6.4)	72 (12.6)	12 (2.1)
	Swelling	50 (8.2)	44 (7.2)	104 (18.2)	27 (4.7)
Systemic	Overall	304 (49.8)	470 (77.0)	373 (65.3)	240 (41.8)
	Pyrexia[a)]	38 (6.2)	178 (29.2)	113 (19.8)	15 (2.6)
	Nausea/vomiting	50 (8.2)	111 (18.2)	85 (14.9)	29 (5.1)
	Diarrhoea	37 (6.1)	82 (13.4)	32 (5.6)	36 (6.3)
	Headache	142 (23.2)	288 (47.2)	223 (39.1)	112 (19.5)
	Malaise	172 (28.2)	349 (57.2)	280 (49.0)	146 (25.4)
	Myalgia	153 (25.0)	236 (38.7)	183 (32.0)	99 (17.2)

N, Number of subjects analyzed; n, Number of subjects with events
a) Based on oral or axillary temperature

Incidences of unsolicited adverse events and unsolicited adverse reactions reported up to the data-cutoff date (median observation period [range]; 57.0 [1-75] days in the Covgoze group, 57.0 [1-72] days in the Vaxzevria group) were 19.0% (116 of 611 subjects) and 5.4% (33 of 611 subjects) in the Covgoze group and 14.9% (91 of 610 subjects) and 4.3% (26 of 610 subjects) in the Vaxzevria group. Table 30 shows unsolicited adverse events and unsolicited adverse reactions with an incidence of ≥1% in either group.

Table 30. Unsolicited adverse events and unsolicited adverse reactions reported by ≥1% of the subjects after the study vaccination (Study U0231, safety analysis population)

	Covgoze (N = 611)		Vaxzevria (N = 610)	
	Adverse events	Adverse reactions	Adverse events	Adverse reactions
	n (%)	n (%)	n (%)	n (%)
Pyrexia	12 (2.0)	7 (1.1)	8 (1.3)	3 (0.5)
Headache	10 (1.6)	0	8 (1.3)	0
Diarrhoea	8 (1.3)	0	5 (0.8)	0
Nasopharyngitis	7 (1.1)	0	5 (0.8)	0
Pruritus	7 (1.1)	7 (1.1)	1 (0.2)	1 (0.2)
Rhinorrhoea	6 (1.0)	2 (0.3)	6 (1.0)	1 (0.2)

N, Number of subjects analyzed; n, Number of subjects with events; MedDRA/J Version 24.1

Adverse events leading to study discontinuation occurred in 1 subject (0.2%) in the Covgoze group (cerebral haemorrhage) and 1 subject (0.2%) in the Vaxzevria group (cough and non-cardiac chest pain in 1 subject), and a causal relationship to the study vaccine was ruled out for all of them. For outcome, the events in 1 subject in the Vaxzevria group did not resolve, but both of them were non-serious. Serious adverse events occurred in 6 subjects (1.0%) in the Covgoze group (COVID-19 in 4 subjects, and duodenal ulcer and cerebral haemorrhage in 1 subject each) and in 1 subject (0.2%) in the Vaxzevria group (COVID-19); a causal relationship to the study vaccine was ruled out for all of them. For outcome, the events resolved or were resolving. No deaths occurred until the data-cutoff date.

7.3.2 Japanese phase III study (CTD 5.3.5.2-02, Study U0224, ongoing since February 2022, data cutoff on April 27, 2022)

An uncontrolled study was conducted to investigate the safety and immunogenicity of a Covgoze booster dose in adults aged ≥20 and ≤64 years who had no history of SARS-CoV-2 infection and had completed the primary series (2 doses) of Spikevax ≥6 and ≤8 months before (target sample size in Cohort A,[32)] 100 subjects) and in elderly subjects aged ≥65 years who had no history of SARS-CoV-2 infection and had completed the primary series (2 doses) of Comirnaty or Spikevax ≥6 and ≤8 months before (target sample size in Cohort B or Cohort C, 25 subjects[32)] in each cohort) at a single study site in Japan.

Covgoze (10 μg of the antigen) was intramuscularly administered once.

All of the enrolled 155 subjects (103 in Cohort A, 29 in Cohort B, 23 in Cohort C) received Covgoze and were included in the safety analysis population. Of the safety analysis population, 150 subjects (100 in Cohort A, 29 in Cohort B, 21 in Cohort C) were included in the mITT population; the remaining 5 subjects (3 in Cohort A, 2 in Cohort C) were excluded because they tested positive for anti-SARS-CoV-2 N-protein antibody at screening. Of the mITT population, all subjects had immunogenicity endpoint results obtained at ≥1 sampling point after Covgoze vaccination and were thus included in the immunogenicity analysis population.

32) The target sample size of 100 for adults in Cohort A (20-64 years) was specified to perform the evaluation at precision similar to that in Study U0223. The sample size of 25 each for elderly in Cohort B and Cohort C was specified in light of the feasibility. In a safety analysis population of 150 subjects, at least 1 subject would experience an adverse event with the probable incidence of 2% at the probability of 95%.

For immunogenicity, Table 31 shows the GMT of SARS-CoV-2 neutralizing antibody after Covgoze vaccination and the antibody response rate (percentage of subjects who showed a ≥4-fold increase in antibody titer from baseline [0.5 × LLOQ was used if the baseline titer was below LLOQ] to post-vaccination points).

Table 31. GMT of SARS-CoV-2 neutralizing antibody after Covgoze vaccination and antibody response rate (Study U0224, immunogenicity analysis population)

Neutralizing antibody titer	Cohort A (N = 100)			Cohort B (N = 29)			Cohort C (N = 21)		
	GMT [two-sided 95% CI][a)]			GMT [two-sided 95% CI][a)]			GMT [two-sided 95% CI][a)]		
Pre-vaccination	12.14 [10.53, 14.00]			3.41 [2.93, 3.97]			10.34 [6.13, 17.44]		
14 days post-vaccination	92.16 [79.70, 106.56]			52.52 [38.39, 71.84]			115.22 [86.99, 152.61]		
28 days post-vaccination	99.35 [83.44, 118.29]			76.14 [55.38, 104.67]			129.96 [88.79, 190.22]		
Antibody response rate	Cohort A (N = 100)			Cohort B (N = 29)			Cohort C (N = 21)		
	n1	n2	Antibody response rate [two-sided 95% CI][b)] (%)	n1	n2	Antibody response rate [two-sided 95% CI][b)] (%)	n1	n2	Antibody response rate [two-sided 95% CI][b)] (%)
14 days post-vaccination	98	83	84.7 [76.0, 91.2]	28	28	100.0 [87.7, 100.0]	19	17	89.5 [66.9, 98.7]
28 days post-vaccination	96	83	86.5 [78.0, 92.6]	28	28	100.0 [87.7, 100.0]	20	19	95.0 [75.1, 99.9]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed, n1: Number of subjects who had no missing data at any sampling point; n2, Number of subjects meeting the criterion for an antibody responder (≥4-fold increase in antibody titer from the pre- to post-vaccination points)
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.
b) The two-sided 95% CI was estimated by the Clopper-Pearson method.

For safety, the observation period was specified for each of the following event categories.

- Solicited adverse events[12)] (local [pain, erythema and redness, induration, and swelling] and systemic [pyrexia, nausea and vomiting, diarrhoea, headache, malaise, myalgia, arthralgia, and chills]) were collected for 7 days after Covgoze vaccination.
- Unsolicited adverse events[13)] (other than the solicited adverse events) were collected up to 12 months after Covgoze vaccination.

Table 32 shows solicited adverse events reported within 7 days after each Covgoze vaccination.

Table 32. Solicited adverse events reported within 7 days after Covgoze vaccination (Study U0224, safety analysis population)

		Cohort A (N = 103)	Cohort B (N = 29)	Cohort C (N = 23)
		n (%)	n (%)	n (%)
Local	Overall	97 (94.2)	23 (79.3)	20 (87.0)
	Pain	95 (92.2)	22 (75.9)	18 (78.3)
	Erythema/redness	46 (44.7)	11 (37.9)	10 (43.5)
	Induration	31 (30.1)	10 (34.5)	8 (34.8)
	Swelling	32 (31.1)	8 (27.6)	4 (17.4)
Systemic	Overall	70 (68.0)	10 (34.5)	13 (56.5)
	Pyrexia[a)]	21 (20.4)	0[b)]	1 (4.3)
	Nausea/vomiting	21 (20.4)	2 (6.9)	4 (17.4)
	Diarrhoea	10 (9.7)	1 (3.4)[b)]	2 (8.7)
	Headache	34 (33.0)	7 (24.1)	4 (17.4)
	Malaise	51 (49.5)	5 (17.2)	8 (34.8)
	Myalgia	9 (8.7)	1 (3.4)	2 (8.7)
	Arthralgia	19 (18.4)	1 (3.4)	2 (8.7)
	Chills	23 (22.3)	4 (13.8)	2 (8.7)

N, Number of subjects analyzed; n, Number of subjects with events
a) Based on axillary temperature
b) Instead of "pyrexia," "diarrhoea" was reported by mistake and included in the tabulation. In the final report, correction to pyrexia in 1 subject (3.4%) and diarrhoea in 0 subjects is planned.

Incidences of unsolicited adverse events and unsolicited adverse reactions reported up to the data-cutoff date (median observation period [range]; 30.0 [2-31] days in Cohort A, 29.0 [2-31] days in Cohort B, 30.0 [10-31] days in Cohort C) were 13.6% (14 of 103 subjects) and 4.9% (5 of 103 subjects) in Cohort A, 6.9% (2 of 29 subjects) and 0% in Cohort B, and 13.0% (3 of 23 subjects) and 0% in Cohort C. Unsolicited adverse events reported by ≥2 subjects in any group were headache (2 subjects in Cohort A, 0 subjects in Cohort B, 1 subject in Cohort C), oropharyngeal pain (2 subjects, 0 subjects, 0 subjects), arthralgia (2 subjects, 0 subjects, 1 subject), vaccination site pruritus (2 subjects, 0 subjects, 0 subjects), and blood pressure increased (2 subjects, 0 subjects, 0 subjects). Unsolicited adverse reactions were vaccination site pruritus in 2 subjects, oropharyngeal pain, arthralgia, and contusion in 1 subject each (all in Cohort A). A serious adverse event occurred in 1 subject in Cohort C (pancreatic carcinoma), but its causal relationship to Covgoze was ruled out. For outcome, the event did not resolve. Neither adverse events leading to study discontinuation nor deaths occurred up to the data-cutoff date.

7.R Outline of the review conducted by PMDA

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

The applicant's explanation about the clinical data package:

Since the initial phase of the SARS-CoV-2 pandemic, the International Coalition of Medicines Regulatory Authorities (ICMRA),[33)] WHO,[34)] and local regulatory authorities[35)] have published guidance for vaccine development to accelerate development of vaccines. In Japan, the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2"[36)] was published on September 2, 2020, and since then, multiple appendices have been published to reflect subsequent accumulation of scientific knowledge and changes in development environments.

33) "Global regulatory workshop on COVID-19 vaccine development" (March 18, 2020 and June 22, 2020)
34) "Target Product Profiles for COVID-19 Vaccines, WHO R&D Blueprint, 29 April 2020" and "An international randomised trial of candidate vaccines against COVID-19, WHO R&D Blueprint, 28 May 2020"
35) FDA "Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, CBER FDA, June 2020," EMA "EMA considerations on COVID-19 vaccine approval," etc.
36) https://www.pmda.go.jp/files/000236327.pdf (last accessed on March 31, 2023)

The "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 3): Evaluation of the vaccines based on Immunogenicity" (hereinafter, "Principles [Appendix 3]") published on October 22, 2021 states that in development of SARS-CoV-2 vaccines, the efficacy of a vaccine can be evaluated using an immunogenicity bridging approach, which evaluates vaccine efficacy based on immunogenicity using an approved SARS-CoV-2 vaccine with proven efficacy in preventing COVID-19 as an active comparator, because a correlation between neutralizing antibody titer after SARS-CoV-2 vaccination and COVID-19-preventive effect has become increasingly clear (*Vaccine.* 2021;39:4423-8, *Nat Med.* 2021;27:1205-11).

In accordance with this guidance, the applicant decided to plan and conduct clinical studies to investigate the immunogenicity and safety of Covgoze in Japan, and based on results from these studies, evaluate the efficacy and safety, taking into account that (1) clinical studies of Covgoze were to be conducted while an official vaccination program with approved SARS-CoV-2 vaccines was ongoing; and (2) the situation either in or outside Japan would not allow conduct of any placebo controlled study to evaluate the disease-preventive effect. In addition, the applicant examined whether a placebo-controlled study to investigate the clinical efficacy of Covgoze was feasible in countries outside Japan where the SARS-CoV-2 vaccination rate was low. In parallel to the clinical development in Japan, the applicant is currently conducting a foreign placebo-controlled phase III study for comparison of the preventive effect (Study U0232).[37)]

For the present application, the applicant prepared a clinical data package comprised of (1) the evaluation data on the Covgoze primary series from the Japanese phase I/II study (Study U0221), Japanese phase II/III study (Study U0222), and Japanese phase III study (Study U0231), which was designed to enable the immunogenicity bridging with approved SARS-CoV-2 vaccines, and (2) the evaluation data on the booster dose from the Japanese phase II/III studies (Studies U0222 and U0223) and Japanese phase III study (Study U0224). The applicant does not include data from the foreign phase III study (Study U0232) in the clinical data package for the present application, considering the sufficiency of the clinical data package and timing when results from each study would become available for submission.

PMDA's view on the data for review on Covgoze:
Since the global outbreak of COVID-19 pandemic in January 2020, multiple therapeutic drugs and vaccines have been developed. In Japan, many people have received the primary series and booster doses of SARS-CoV-2 vaccines through official vaccination programs. People who have not received SARS-CoV-2 vaccines and thus are eligible for studies for the primary series are limited; and an active-controlled study to verify the non-inferiority of a study vaccine to approved active SARS-CoV-2 vaccines in terms of the disease-preventive effect, requires 2 to 3 times more person-years follow-up than a placebo-controlled study (*Clin Trials.* 2021;18:335-42). Therefore, studies for development of a new SARS-CoV-2 vaccine have problems in terms of feasibility. In view of this situation, the applicant's evaluation approach (i.e., evaluating the efficacy of Covgoze versus approved SARS-CoV-2 vaccines that have been demonstrated to prevent COVID-19, based on the

[37)] https://clinicaltrials.gov/ct2/show/NCT05212948 (last accessed on March 31, 2023)

prespecified immunogenicity bridging success criteria) is acceptable in accordance with the "Principles (Appendix 3)."

Even if the immunogenicity bridging approach is employed, the efficacy evaluation based on immunogenicity data should be supported by incidences of clinical events wherever possible. PMDA thus decided to review not only incidences of COVID-19 in the conducted clinical studies but also results of the disease-prevention effect of Covgoze in the ongoing foreign clinical study (Study U0232) submitted during the review for the present application.

For safety, PMDA decided to review all the evaluation data submitted. However, it should be noted that the major results of the safety of Covgoze in the submitted data only cover a limited period up to the data-cutoff date in each study, and the adequate long-term safety data after Covgoze vaccination are not available at present. PMDA, therefore, reviewed the safety data of Covgoze additionally submitted during the review too.

7.R.2 Efficacy

7.R.2.1 Efficacy endpoints and criteria

The applicant's explanation about the efficacy endpoints for Covgoze and the evaluation criteria:
In principle, the efficacy of vaccines in preventing infectious diseases is evaluated based on the disease-preventive effect, which serves as the primary endpoint (PFSB/ELD Notification No. 0527-5 "Guidelines for Clinical Studies of Preventive Vaccines for Infectious Diseases" dated May 27, 2010). Around November 2021, however, when the applicant was planning a pivotal clinical study to evaluate the efficacy of the Covgoze primary series (Study U0231) and another pivotal clinical study to evaluate the efficacy of a booster dose (Study U0223), the Delta variant was predominant in Japan. Based on the prevalence of COVID-19 at that time, the applicant estimated that an enormous sample size would be required for a placebo-controlled study to evaluate the disease-preventive effect of the Covgoze primary series. In addition, official vaccination programs for the primary series and booster doses of SARS-CoV-2 vaccines were ongoing in and outside Japan, and therefore a placebo-controlled study was deemed unfeasible from ethical considerations. Furthermore, conduct of an active-controlled study to verify the disease-preventive effect of the primary series and booster dose was also deemed difficult, because it required a greater sample size than that for a placebo-controlled study. Based on the above views and the "Principles (Appendix 3)," the applicant designed Study U0231 as a study employing the immunogenicity bridging approach and thereby performed comparison of Covgoze with approved vaccines using anti-SARS-CoV-2 neutralizing antibody titer as the endpoint. The "Principles (Appendix 3)" recommends that the control vaccine should be an approved SARS-CoV-2 vaccine in the same modality. At the time of planning Studies U0231 and U0223, however, recombinant protein vaccines in the same modality as that of Covgoze were not approved in Japan, and thus there was no choice but to use SARS-CoV-2 vaccines in a different modality as the control vaccines. Because official vaccination was ongoing, availability of approved SARS-CoV-2 vaccines to be used as the control vaccine in the clinical studies was limited in terms of the type and timing. In these circumstances, Study U0231 (for the efficacy evaluation of the primary series) used Vaxzevria as the control vaccine to test the superiority of Covgoze in immunogenicity. Vaxzevria is a virus vector vaccine that has been demonstrated to have a moderate disease-preventive

effect when used for the primary series (vaccine efficacy [VE] [two-sided 95.84% CI], 70.42% [54.84%, 80.63%]) and is widely used in multiple countries and regions including Japan. In Study U0223 for the efficacy evaluation of a booster dose, Comirnaty was used as the control vaccine to test non-inferiority of Covgoze in immunogenicity. Comirnaty is a mRNA vaccine that has been demonstrated to have a high disease-preventive effect (VE [95% credible interval], 94.6% [89.9%, 97.3%]) and is also used as a booster dose.

To evaluate the efficacy of Covgoze in comparison with the control vaccines based on immunogenicity, the immunogenicity endpoints were defined based on the following recommendations in the "Principles (Appendix 3)":

- When developers of vaccine candidates decide to use indicators of immunogenicity to assess efficacy of the candidates, the primary endpoint in the confirmatory clinical trial should be the geometric mean of the neutralizing antibody titer (GMT) against the origin of each SARS-CoV-2 strain.
- If a non-inferiority study is carried out with GMT serving as a primary endpoint, non-inferiority to the active comparator needs to be verified as primary endpoint also in terms of the seroconversion rate for neutralizing antibody.

In accordance with these recommendations, Study U0231 (for the efficacy evaluation of the primary series) used (a) GMT of neutralizing antibodies against the SARS-CoV-2 original strain 28 days after the second dose as the primary and (b) the seroconversion rate as an important secondary endpoint. Study U0223 (for the efficacy evaluation of the booster dose) used the primary endpoints of (a) the GMT of neutralizing antibodies against the SARS-CoV-2 original strain 28 days after the booster dose and (b) the antibody response rate 28 days after the booster dose. Study U0222 (to evaluate the efficacy of a Covgoze booster dose in individuals who had received the Covgoze primary series) tested the non-inferiority of the immunogenicity data after the booster dose (third dose) to the corresponding data after the second dose of the primary series.

The seroconversion rate and antibody response rate were defined as "Percentage of subjects who showed a ≥4-fold increase in antibody titer from baseline (before the first dose of the study vaccine for the seroconversion rate and before the booster dose for the antibody response rate)" with reference to "Principles (Appendix 3)."

PMDA's view:

The following applicant's strategy is acceptable:

In Study U0231, a pivotal clinical study for the primary series, Vaxzevria was used as the control vaccine because no approved vaccines in the same modality were available at the time of planning, In this study, the applicant planned to explain the efficacy of the Covgoze primary series by demonstrating the superiority of Covgoze to Vaxzevria in the following primary endpoint: GMT of neutralizing antibodies against the SARS-CoV-2 original strain, which has the antigen used in both Covgoze and Vaxzevria.

For the efficacy of Covgoze, as discussed in Section 7.R.1, the applicant is also conducting a foreign clinical study to investigate the disease-preventive effect based on clinical events. PMDA further

evaluated the efficacy of Covgoze by additionally reviewing results from Study U0232 that became available during the review.

The following applicant's strategy is also acceptable:

In Study U0223, a pivotal clinical study for the booster dose, subjects who had completed the Comirnaty primary series received Covgoze or Comirnaty once as a booster dose. In the study, the applicant planned to explain the efficacy of the Covgoze booster dose by demonstrating the non-inferiority of Covgoze to Comirnaty in the following primary endpoints: the GMT of neutralizing antibodies against the SARS-CoV-2 original strain and the antibody response rate 28 after the booster dose.

An approach to evaluate the efficacy of the booster dose of a variant-adapted vaccine in comparison with the primary series of parent vaccine based on immunogenicity, is presented in the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2 (Appendix 1): Evaluation of vaccines against variants" (Office of Vaccines and Blood Products, PMDA, dated April 5, 2021). This approach is applicable for evaluating the efficacy in subjects in Study U0222 who had completed the primary series and subsequently received the same vaccine as the booster dose. This evaluation strategy is acceptable.

In addition to Comirnaty, other SARS-CoV-2 vaccines are used for the primary series in Japan. PMDA therefore decided to evaluate the efficacy of the booster dose by reviewing not only Study U0223, the pivotal study, but also the sub-part in Study U0222 and Study U0224, which evaluated the immunogenicity of the Covgoze booster dose in subjects who had completed the primary series of a SARS-CoV-2 vaccine other than Comirnaty such as Spikevax or Covgoze.

7.R.2.2 Efficacy of the primary series

The applicant's explanation about the efficacy of the Covgoze primary series:

7.R.2.2.1 Efficacy of the primary series against SARS-CoV-2 (original strain)

In all of Study U0221, the main part in Study U0222, and Study U0231, the GMT of neutralizing antibodies against SARS-CoV-2 (original strain) increased from baseline (before the first dose of the study vaccine) to 28 days after the second dose.

In Study U0231 for comparison with Vaxzevria based on immunogenicity, the GMT ratio of neutralizing antibody (Covgoze group/Vaxzevria group) met the prespecified criterion for superiority (Table 28). According to the protocol, if the superiority Covgoze to Vaxzevria in GMT was demonstrated, the applicant would perform a test for non-inferiority of Covgoze to Vaxzevria in the seroconversion rate (percentage of subjects who showed a ≥4-fold increase in SARS-CoV-2 neutralizing antibody titer from baseline to 28 days after the second dose), which is the important secondary endpoint. The test was conducted and the results are shown in Table 33. The lower limit of 95% CI of difference in the seroconversion rate between Vaxzevria and Covgoze exceeded −10%, achieving the prespecified criterion for non-inferiority.

Table 33. Seroconversion rate based on SARS-CoV-2 neutralizing antibody titer 28 days after the second dose of the study vaccine (Study U0231, immunogenicity analysis population)

	Covgoze (N = 562)			Vaxzevria (N = 579)			Difference in seroconversion rate [two-sided 95% CI][b]
	n1	n2	Seroconversion rate [two-sided 95% CI][a] (%)	n1	n2	Seroconversion rate [two-sided 95% CI][a] (%)	
28 days after the second dose	497	453	91.1 [88.3, 93.5]	514	42	8.2 [6.0, 10.9]	83.0 [76.8, 89.1]

Micro-neutralization assay against the SARS-CoV-2 original strain
N, Number of subjects analyzed; n1, Number of subjects evaluated; n2, Number of subjects meeting the criterion for seroconversion (≥4-fold increase in antibody titer from the pre- to post-vaccination points [titer below the LLOQ at the pre-vaccination point is handled as "0.5 × LLOQ"])
a) The two-sided 95% CI was estimated by the Clopper-Pearson method.
b) The two-sided 95% CI was estimated by the Farrington-Manning method.

The applicant considers that these results in Study U0231 have demonstrated the efficacy of the Covgoze primary series against SARS-CoV-2 (original strain). In many subjects in the Vaxzevria group in Study U0231, neutralizing antibody titers after the study vaccination were low and failed to meet the criterion for seroconversion; this finding is discussed in Section 7.R.2.2.2.

The immunogenicity profile obtained from the Covgoze primary series was further analyzed by sub-group (by age group and by presence/absence of a risk factor of severe COVID-19) and for sustainability of the antibody titer.

Table 34 shows GMTs and geometric mean fold rise (GMFR) of SARS-CoV-2 neutralizing antibody at sampling points and seroconversion rates up to approximately 6 months after the second dose of Covgoze by subgroup in the immunogenicity analysis population in the main part in Study U0222.

Table 34. GMT of SARS-CoV-2 neutralizing antibody and seroconversion rate after Covgoze vaccination (main part in Study U0222, immunogenicity analysis population)

Neutralizing antibody titer		Naïve adult (N = 304)		Previously-vaccinated adult (N = 76)		Previously-infected adult (N = 68)		Naïve elderly (N = 115)	
		n1	GMT [two-sided 95% CI][a)]	n1	GMT [two-sided 95% CI][a)]	n1	GMT [two-sided 95% CI][a)]	n1	GMT [two-sided 95% CI][a)]
Baseline		304	2.52 [2.50, 2.54]	76	5.33 [4.51, 6.30]	68	6.01 [4.72, 7.64]	115	2.53 [2.47, 2.59]
First dose	Day 28	303	2.72 [2.57, 2.88]	76	69.77 [60.14, 80.95]	65	90.92 [71.19, 116.11]	112	2.64 [2.49, 2.81]
Second dose	Day 14	296	46.14 [41.91, 50.80]	75	106.54 [89.70, 126.55]	66	125.67 [105.70, 149.40]	110	26.56 [21.72, 32.47]
	Day 28	294	30.72 [27.97, 33.73]	76	108.09 [92.10, 126.87]	66	117.99 [98.84, 140.86]	110	20.38 [16.89, 24.60]
	Day 68	284	13.44 [12.34, 14.63]	70	68.96 [57.73, 82.37]	64	79.14 [63.70, 98.32]	109	8.86 [7.44, 10.56]
	Day 182	246	5.13 [4.62, 5.70]	63	43.68 [36.43, 52.37]	59	51.19 [40.22, 65.17]	99	3.70 [3.21, 4.27]

GMFR		Naïve adult (N = 304)		Previously-vaccinated adult (N = 76)		Previously-infected adult (N = 68)		Naïve elderly (N = 115)	
		n1	GMFR [two-sided 95% CI][b)]	n1	GMFR [two-sided 95% CI][b)]	n1	GMFR [two-sided 95% CI][b)]	n1	GMFR [two-sided 95% CI][b)]
First dose	Day 28	303	1.08 [1.03, 1.14]	76	13.09 [10.87, 15.77]	65	14.85 [10.69, 20.63]	112	1.04 [1.00, 1.09]
Second dose	Day 14	296	18.33 [16.67, 20.15]	75	19.97 [16.30, 24.48]	66	20.37 [15.17, 27.36]	110	10.49 [8.59, 12.81]
	Day 28	294	12.20 [11.13, 13.38]	76	20.28 [16.81, 24.46]	66	19.13 [14.18, 25.80]	110	8.05 [6.67, 9.72]
	Day 68	284	5.35 [4.92, 5.82]	70	12.62 [10.32, 15.42]	64	12.61 [9.16, 17.35]	109	3.50 [2.95, 4.15]
	Day 182	246	2.05 [1.84, 2.27]	63	7.91 [6.37, 9.82]	59	8.29 [5.83, 11.79]	99	1.46 [1.28, 1.67]

Seroconversion rate		Naïve adult (N = 304)			Previously-vaccinated adult (N = 76)			Previously-infected adult (N = 68)			Naïve elderly (N = 115)		
		n1	n2	Seroconversion rate [two-sided 95% CI][c)] (%)	n1	n2	Seroconversion rate [two-sided 95% CI][c)] (%)	n1	n2	Seroconversion rate [two-sided 95% CI][c)] (%)	n1	n2	Seroconversion rate [two-sided 95% CI][c)] (%)
First dose	Day 28	303	8	2.6 [1.1, 5.1]	76	75	98.7 [92.9, 100.0]	65	60	92.3 [83.0, 97.5]	112	3	2.7 [0.6, 7.6]
Second dose	Day 14	296	286	96.6 [93.9, 98.4]	75	74	98.7 [92.8, 100.0]	66	63	95.5 [87.3, 99.1]	110	94	85.5 [77.5, 91.5]
	Day 28	294	282	95.9 [93.0, 97.9]	76	76	100.0 [95.3, 100.0]	66	64	97.0 [89.5, 99.6]	110	94	85.5 [77.5, 91.5]
	Day 68	284	236	83.1 [78.2, 87.3]	70	66	94.3 [86.0, 98.4]	64	57	89.1 [78.8, 95.5]	109	61	56.0 [46.1, 65.5]
	Day 182	246	64	26.0 [20.6, 32.0]	63	55	87.3 [76.5, 94.4]	59	50	84.7 [73.0, 92.8]	99	13	13.1 [7.2, 21.4]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n1, Number of subjects who had no missing data at the sampling point; n2, Number of subjects who showed seroconversion

a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.
b) Of changes in logarithmically transformed antibody titers from baseline (before the first dose), the mean and its two-sided 95% CI in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.
c) The two-sided 95% CI was estimated by the Clopper-Pearson method.

Results by age group in Study U0222 showed that GMT [two-sided 95% CI] of SARS-CoV-2 neutralizing antibody 28 days after the second dose of Covgoze was 30.72 [27.97, 33.73] in the group aged 20 to 64 years (naïve adult group) and 20.38 [16.89, 24.60] in the group aged ≥65 years (naïve elderly group). The GMT in the group aged ≥65 years tended to be lower than that in the group aged 20 to 64 years, but SARS-CoV-2 neutralizing antibody was induced after the second dose in either age group (Table 34). In the immunogenicity analysis population in Study U0231, GMT [two-sided 95% CI] of SARS-CoV-2 neutralizing antibody 28 days after the second dose of the study vaccine was 20.12 [18.71, 21.63] in the group aged 20 to 64 years (476 subjects) and 15.87 [11.35, 22.21] in the group aged ≥65 years (21 subjects) in the Covgoze group; and 3.65 [3.44, 3.87] in the group aged 20 to 64 years (492 subjects) and 3.22 [2.69, 3.85] in the group aged ≥65 years (22 subjects) in the Vaxzevria group. No substantial difference was observed between the age groups in either Covgoze or Vaxzevria group, although the number of subjects aged ≥65 years in the immunogenicity analysis population was limited.

Results in subjects with and without a risk factor of severe COVID-19[38] showed that, in the naïve adult group in the main part in Study U0222, GMT [two-sided 95% CI] of SARS-CoV-2 neutralizing antibody 28 days after the second dose of Covgoze was 26.22 [22.56, 30.49] in the sub-group with a risk factor of severe COVID-19 (110 subjects) and 33.76 [30.00, 38.00] in the sub-group without (184 subjects). No substantial difference was observed between the sub-groups with and without a risk factor of severe COVID-19. In Study U0231, GMT [two-sided 95% CI] of SARS-CoV-2 neutralizing antibody 28 days after the second dose of the study vaccine in the Covgoze group was 17.83 [15.86, 20.04] in subjects with a risk factor of severe COVID-19 (193 subjects) and 21.37 [19.57, 23.33] in those without (304 subjects); and that in the Vaxzevria group was 3.52 [3.26, 3.81] in subjects with a risk factor of severe COVID-19 (210 subjects) and 3.71 [3.43, 4.02] in those without (304 subjects). In either the Covgoze or Vaxzevria group, no substantial difference was observed between subjects with and without a risk factor of severe COVID-19.

Based on the above, the Covgoze primary series is expected to have efficacy even in the elderly and individuals with a risk factor of severe COVID-19.

In the naïve adult group and naïve elderly group of Study U0222 (see Table 34), GMTs of SARS-CoV-2 neutralizing antibody at sampling points after Covgoze vaccination increased from baseline (before the first dose) to 14 days after the second dose and then decreased with time. The GMT 182 days after the second dose was similar to the baseline value in both groups. The GMTs in the previously-vaccinated adult group and previously-infected adult group were higher than those in the naïve adult group at all the sampling points, followed by a slow decrease with time at ≥28 days after the second dose. In all groups, changes in the GMFR and seroconversion rate over time after Covgoze vaccination showed a similar trend to that of the GMT. Changes in GMT of anti-spike protein IgG antibody over time (see Table 35) were similar to those of the neutralizing antibody titer.

The above results of sustainability of the immunogenicity of Covgoze showed that the antibody titer increased after Covgoze vaccination and then decreased with time, as observed with approved SARS-CoV-2 vaccines.

[38] The elderly aged ≥65 years, malignancies, chronic obstructive pulmonary disease, chronic renal disease, diabetes mellitus, hypertension, dyslipidaemia, obesity with body mass index (BMI) ≥30, smoking, immunodeficiency after solid organ transplantation, late pregnancy

Table 35. GMT of anti-spike protein IgG antibody
(main part in Study U0222, immunogenicity analysis population)

		Naïve adult (N = 304)		Previously-vaccinated adult (N = 76)		Previously-infected adult (N = 68)		Naïve elderly (N = 115)	
		n	GMT [two-sided 95% CI][a)]	n	GMT [two-sided 95% CI][a)]	n	GMT [two-sided 95% CI][a)]	n	GMT [two-sided 95% CI][a)]
Baseline		304	61.7 [57.9, 65.7]	76	2028.2 [1681.4, 2446.4]	68	1616.4 [1154.9, 2262.3]	115	53.1 [48.7, 58.0]
First dose	Day 28	303	655.6 [577.1, 744.8]	76	17138.0 [14730.1, 19939.4]	65	25600.0 [19413.7, 33757.5]	112	506.1 [400.7, 639.1]
Second dose	Day 14	296	32430.7 [29448.8, 35714.5]	75	26564.1 [21649.2, 32594.8]	66	30284.3 [24834.3, 36930.2]	110	12880.9 [10083.1, 16455.1]
	Day 28	294	29213.2 [26314.9, 32430.7]	76	44653.6 [38151.3, 52264.0]	66	65877.2 [54707.7, 79327.2]	110	27093.8 [22548.2, 32555.7]
	Day 68	284	7073.6 [6431.4, 7779.9]	70	20588.8 [17136.6, 24736.4]	64	19740.3 [15888.8, 24525.4]	109	5599.9 [4627.4, 6776.9]
	Day 182	246	3111.1 [2755.1, 3513.1]	63	16852.6 [13769.1, 20626.5]	59	18423.8 [14487.1, 23430.1]	99	2030.0 [1645.4, 2504.6]

ELISA
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 100).
N, Number of subjects analyzed; n, Number of subjects who had no missing data up to the time of evaluation
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.

7.R.2.2.2 Immunogenicity evaluation in Study U0231

In Study U0231, 2 doses of Covgoze or Vaxzevria for the primary series were administered to adults and the elderly to evaluate the superiority of Covgoze to Vaxzevria in immunogenicity and the clinical efficacy of Covgoze versus Vaxzevria, as the major efficacy evaluation of the Covgoze primary series. The primary endpoint was the GMT of SARS-CoV-2 neutralizing antibody 28 days after the second dose of the study vaccine. The GMT ratio [two-sided 95% CI] of Covgoze to Vaxzevria was 5.48 [5.01, 6.00], achieving the prespecified criterion for superiority (lower limit of two-sided 95% CI of the GMT ratio of Covgoze to Vaxzevria should exceed 1.0) (Table 28). Then, an analysis of the seroconversion rate, the important secondary endpoint, was performed according to the fixed-sequence procedure; the results met the criterion for non-inferiority of Covgoze to Vaxzevria (lower limit of two-sided 95% of difference in the seroconversion rate between Vaxzevria and Covgoze should exceed −10%) (Table 33).

In Study U0231, SARS-CoV-2 neutralizing antibody titers were measured at Testing Facility A, and the GMT of SARS-CoV-2 neutralizing antibody 28 days after the second dose of the study vaccine in the Vaxzevria group, the control group, was 3.63 (Table 28) with the seroconversion rate of 8.2% (Table 33). Although strict comparison is difficult because of the assay method differing among studies, the seroconversion rate in the Vaxzevria group in Study U0231 was extremely lower than that in a Japanese phase I/II study (67.5% in the group aged 18-55 years and 57.0% in the group aged ≥56 years) published in the Japanese package insert of Vaxzevria (last accessed on March 31, 2023). In Study U0231, the percentage of subjects with the neutralizing antibody titer 28 days after the second dose of the study vaccine being below the LLOQ was 2.2% in the Covgoze group and 63.4% in the Vaxzevria group, and none of these subjects met the definition of seroconversion. The immunogenicity results in the Vaxzevria group in Study U0231 were thus different from those expected from the past clinical study results of Vaxzevria at the time of planning the study. A possible reason for the low seroconversion rate in the Vaxzevria group in Study U0231 was that the neutralizing antibody titer assay performed at Testing Facility A may have had a low sensitivity for measuring the SARS-CoV-2 neutralizing antibody titer after a dose of Vaxzevria. To examine if the analytical sensitivity in Study

U0231 was enough to support an active-controlled study design using Vaxzevria as the control vaccine, the following post hoc investigations (a) to (c) were conducted.

(a) Investigation of anti-spike protein (S1/S2) IgG antibody titer, the secondary endpoint

Table 36 and Table 37, respectively, show the GMT of anti-spike protein (S1/S2) IgG antibody (chemiluminescence immunoassay) and the seroconversion rate 28 days after the second dose of the study vaccine in Study U0231. The GMT increased 149.57-fold from baseline (before the first dose) in the Covgoze group and 29.3-fold in the Vaxzevria group.

Table 36. Anti-spike protein (S1/S2) IgG antibody titer 28 days after the second dose of the study vaccine (Study U0231, immunogenicity analysis population)

	Covgoze (N = 562)		Vaxzevria (N = 579)		GMT ratio[a] (Covgoze/Vaxzevria) [two-sided 95% CI]
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	
Baseline	561	2.56 [2.38, 2.77]	579	2.61 [2.43, 2.80]	-
28 days after the second dose	497	370.05 [346.73, 394.93]	514	77.92 [73.09, 83.08]	4.75 [4.34, 5.20]

Chemiluminescence immunoassay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 3.8 AU/mL).
N, Number of subjects analyzed; n, Number of subjects who had no missing data up to the time of evaluation
a) To logarithmically transformed anti-spike protein (S1/S2) IgG antibody titers, an ANCOVA model using the study vaccine group as a fixed effect and age (continuous variable) as a covariate was applied to obtain estimates, which were then anti-logarithmically transformed to determine the value.

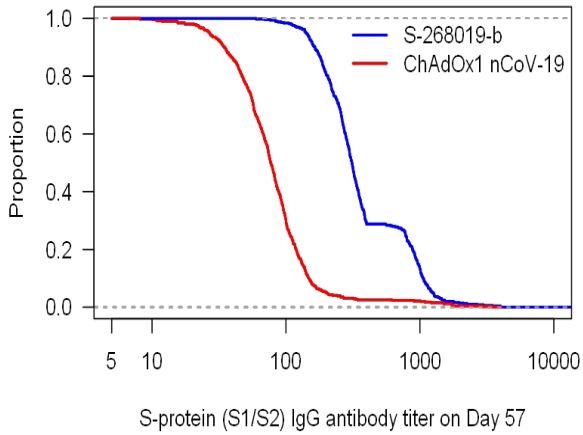
Table 37. Seroconversion rate based on anti-spike protein (S1/S2) IgG antibody titer 28 days after the second dose of the study vaccine (Study U0231, immunogenicity analysis population)

	Covgoze (N = 562)			Vaxzevria (N = 579)			Difference in seroconversion rate [two-sided 95% CI]
	n1	n2	Seroconversion rate[a] [two-sided 95% CI][b] (%)	n1	n2	Seroconversion rate[a] [two-sided 95% CI][b] (%)	
28 days after the second dose	496	495	99.8 [98.9, 100.0]	514	505	98.2 [96.7, 99.2]	1.5 [0.3, 2.7]

Chemiluminescence immunoassay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 3.8 AU/mL).
N, Number of subjects analyzed; n1, Number of subjects evaluated; n2, Number of subjects who experienced seroconversion
a) The percentage of subjects who showed a ≥4-fold increase in antibody titer from the pre- to post-study vaccination points.
b) The two-sided 95% CI was estimated by the Clopper-Pearson method.

Figure 1-(A) shows the inverse cumulative distribution curves of anti-spike protein (S1/S2) IgG antibody titers 28 days after the second dose of the study vaccine. The curve of Covgoze is generally plotted above that of Vaxzevria. Figure 1-(B) shows scatter plots of the anti-spike protein (S1/S2) IgG antibody titer against the SARS-CoV-2 neutralizing antibody titer of the same subject in each group. Titers of these 2 different antibodies were analyzed for a correlation. The Pearson correlation coefficient for the logarithmically transformed values was 0.7146 in the Covgoze group and 0.7658 in the Vaxzevria group, suggesting a correlation between the titers of the 2 different antibodies in both groups.

(A)



S-268019: Covgoze

ChAdOx1 nCoV-19: Vaxzevria

n, Number of applicable subjects

(B)

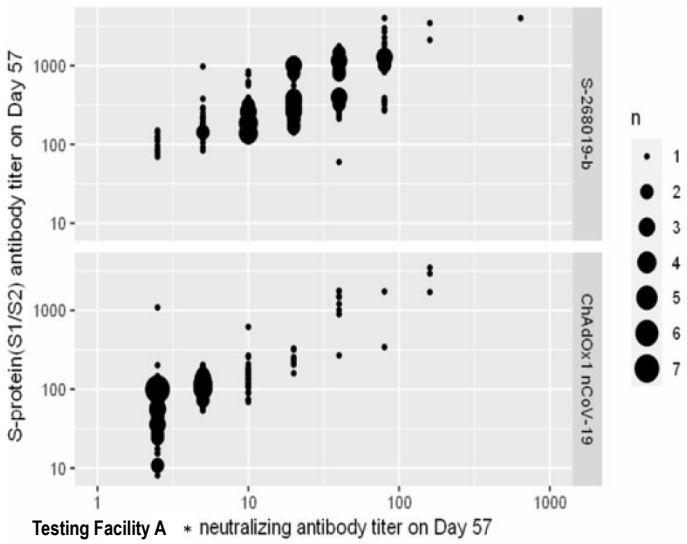


Figure 1. Investigation of anti-spike protein (S1/S2) IgG antibody titer 28 days after the second dose of the study vaccine
(Study U0231, immunogenicity analysis population)

(A) This shows inverse cumulative distribution curves of anti-spike protein (S1/S2) IgG antibody titers 28 days after the second dose of the study vaccine. Because assay systems with different quantitation ranges were used for assay of IgG antibody titer <400 and ≥400 (quantified in standard units [AU/mL]), the curves appear to lack the accumulation around the IgG antibody titer of 400. (B) This shows scatter plots of anti-spike protein (S1/S2) IgG antibody titer and SARS-CoV-2 neutralizing antibody titer in double logarithmic scale. Neutralizing antibody titers (horizontal axis) below the LLOQ that were measured at Testing Facility A were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5). Anti-spike protein (S1/S2) IgG antibody titers (vertical axis) determined to be below the LLOQ were handled as "0.5 × LLOQ" and those determined to be above the upper limit of quantification (ULOQ) were handled as the ULOQ value (LLOQ = 3.8, ULOQ = 4000).

(b) Investigation of titers in variant pseudovirus neutralization assay on a WHO international standard basis

Samples from 48 subjects (24 in each group) in the immunogenicity analysis population in Study U0231 were subjected to variant pseudovirus neutralization assay to measure neutralizing antibody titers against the D614G variant (reference variant)[39] and other variants. The results are shown in Table 38. The GMT (50% neutralization titer [NT_{50}]) of SARS-CoV-2 neutralizing antibody against the D614G variant 28 days after the second dose was 906 in the Covgoze group and 96 in the Vaxzevria group, and the values obtained by conversion into the WHO international standard units (WHO-IU values) were 381 IU/mL and 40 IU/mL, respectively. On the other hand, the GMT of SARS-CoV-2 neutralizing antibody (pseudovirus-based neutralizing antibody assay[40]) 28 days after the second dose in clinical studies conducted for development of Vaxzevria, was 103.0 in the primary analysis of the Japanese phase I/II study and 180.881 in a pooled analysis of 4 foreign studies (Report on Special Approval for Emergency of Vaxzevria Intramuscular Injection, dated May 13, 2021). The corresponding WHO-IU values (conversion factor, 0.1458 [*Nat Med.* 2021;27:2032-40]) were 15.02 IU/mL and 26.37 IU/mL, respectively, which were comparable to or lower than the value (40 IU/mL) measured by the variant pseudovirus neutralization assay in the Vaxzevria group in Study U0231.

[39] Variant pseudovirus with infectivity increased by introducing mutation (D614G) in the spike protein amino acid sequence of SARS-CoV-2 original strain

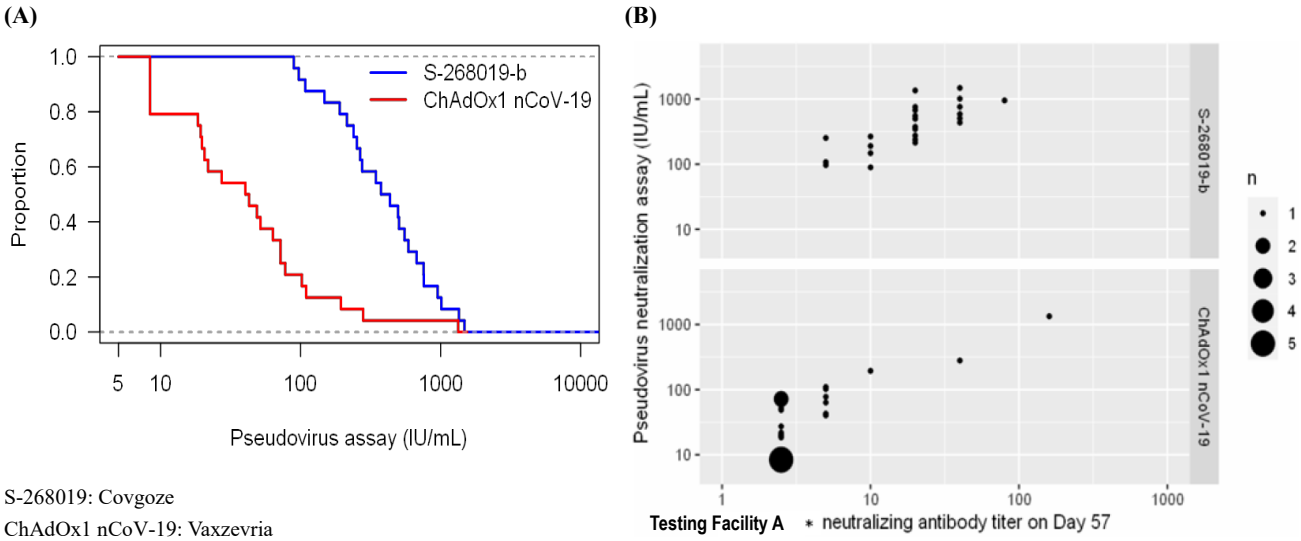
[40] Measured at Monogram Biosciences, Inc (*Lancet.* 2021;397:881-91)

Table 38. SARS-CoV-2 neutralizing antibody titer against variants 28 days after the second dose of the study vaccine
(Study U0231, a part of the immunogenicity analysis population)

	Covgoze (N = 24)		Vaxzevria (N = 24)	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
D614G variant (reference variant)	24	906 [645, 1273]	24	96 [56, 163]
Delta variant	24	825 [592, 1148]	24	43 [25, 75]
Omicron variant (BA.1)	24	59 [37, 94]	24	29 [18, 44]
Omicron variant (BA.2)	24	43 [27, 68]	24	27 [18, 40]

Variant pseudovirus neutralization assay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 40).
N, Number of subjects analyzed; n, Number of subjects evaluated

Figure 2-(A) shows the inverse cumulative distribution curves of WHO-IU values calculated from variant pseudovirus neutralization assay values 28 days after the second dose of the study vaccine in 48 subjects. The curve of Covgoze is generally plotted above that of Vaxzevria. Figure 2-(B) shows scatter plots of the WHO-IU value calculated from the variant pseudovirus neutralization assay value against the SARS-CoV-2 neutralizing antibody titer of the same subject. Values of these different assays were analyzed for a correlation. The Pearson correlation coefficient for the logarithmically transformed values was 0.7762 in the Covgoze group and 0.8304 in the Vaxzevria group, suggesting a correlation between results from the different assays in either group.



S-268019: Covgoze
ChAdOx1 nCoV-19: Vaxzevria
n, Number of applicable subjects

Figure 2. Investigation of WHO-IU values calculated from the variant pseudovirus neutralization assay values 28 days after the second dose of the study vaccine
(Study U0231, a part of the immunogenicity analysis population)

(A) This shows the inverse cumulative distribution curves of WHO-IU values calculated from the variant pseudovirus neutralization assay values 28 days after the second dose of the study vaccine (number of subjects analyzed, 24 in each group) (B) This shows scatter plots of WHO-IU value calculated from variant pseudovirus neutralization assay value and SARS-CoV-2 neutralizing antibody titer (measured at Testing Facility A) in double logarithmic scale. Neutralizing antibody titers (horizontal axis) below the LLOQ that were measured at Testing Facility A were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).

(c) Investigation of SARS-CoV-2 neutralizing antibody titers measured post hoc at another testing facility (Testing Facility B)

SARS-CoV-2 neutralizing antibody titers 28 days after the second dose of the study vaccine in Study U0231 were measured post hoc by the method (micro-neutralization assay against the SARS-CoV-2

original strain[41]) of a testing facility (Testing Facility B) other than Testing Facility A. The measured values are shown in Table 39. The lower limit of 95% CI of the GMT ratio of Covgoze to Vaxzevria was 6.55, which exceeds the prespecified criterion for superiority in the primary analysis in Study U0231. As shown in Table 40, the seroconversion rate in the Vaxzevria group was similar to the values in the Japanese phase I/II study (67.5% in the group aged 18-55 years and 57.0% in the group aged ≥56 years) disclosed in the package insert of Vaxzevria in Japan (last accessed on March 31, 2023).

Figure 3-(A) shows the inverse cumulative distribution curves of SARS-CoV-2 neutralizing antibody titers 28 days after the second dose of the study vaccine measured at Testing Facility B. The curve of Covgoze is generally plotted above that of Vaxzevria. Figure 3-(B) shows scatter plots of SARS-CoV-2 neutralizing antibody titers 28 days after the second dose of the study vaccine in the same subject, measured at Testing Facilities A and B. Values measured at these 2 different facilities were analyzed for a correlation. The Pearson correlation coefficient for the logarithmically transformed values was 0.6877 in the Covgoze group and 0.7275 in the Vaxzevria group, suggesting a correlation between results from the 2 different facilities in both groups.

Table 39. SARS-CoV-2 neutralizing antibody titer 28 days after the second dose of the study vaccine (Study U0231, immunogenicity analysis population) (values measured post hoc at Testing Facility B)

	Covgoze (N = 562)		Vaxzevria (N = 579)		GMT ratio[a)] (Covgoze/Vaxzevria) [two-sided 95% CI]
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	
Baseline	562	5.45 [5.23, 5.68]	579	5.37 [5.17, 5.58]	-
28 days after the second dose	497	183.25 [168.04, 199.84][a)]	514	24.79 [22.77, 27.00][a)]	7.39 [6.55, 8.35]

Micro-neutralization assay against the SARS-CoV-2 original strain
LLOQ = 11.22
N, Number of subjects analyzed; n, Number of subjects who had no missing data up to the time of evaluation
a) These values are anti-logarithmically transformed estimates. The estimates before logarithmical transformation were obtained by applying an ANCOVA model using the study vaccine group as a fixed effect and age (continuous variable) as a covariate, to logarithmically transformed neutralizing antibody titers.

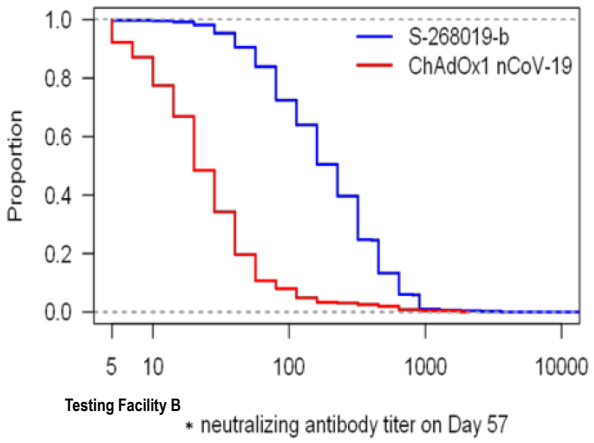
Table 40. Seroconversion rate[a)] based on SARS-CoV-2 neutralizing antibody titer 28 days after the second dose of the study vaccine (Study U0231, immunogenicity analysis population) (values measured post hoc at Testing Facility B)

	Covgoze (N = 562)			Vaxzevria (N = 579)			Difference in seroconversion rate [two-sided 95% CI][c)] (%)
	n1	n2	Seroconversion rate [two-sided 95% CI][b)] (%)	n1	n2	Seroconversion rate [two-sided 95% CI][b)] (%)	
28 days after the second dose	497	491	98.8 [97.4, 99.6]	514	339	66.0 [61.7, 70.0]	32.8 [27.8, 37.9]

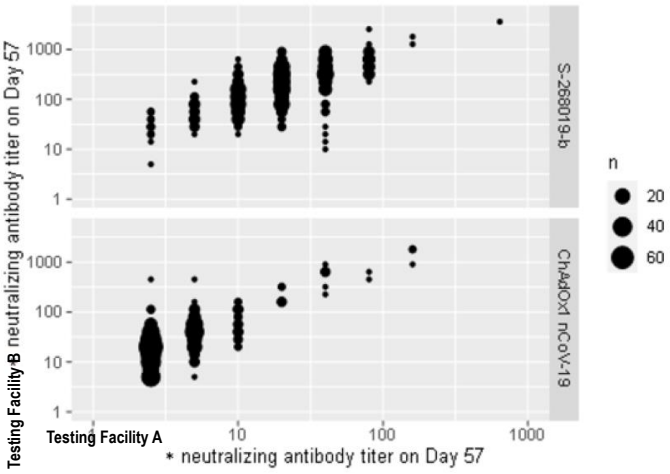
Micro-neutralization assay against the SARS-CoV-2 original strain
LLOQ = 11.22
n1, Number of subjects evaluated; n2, Number of subjects who experienced seroconversion
a) The percentage of subjects who showed a ≥4-fold increase in antibody titer from the pre- to post-study vaccination points.
b) The two-sided 95% CI was estimated by the Clopper-Pearson method.
c) The two-sided 95% CI was estimated by the Farrington-Manning method.

41) 2019-nCoV/USA-WA1/2020 (virus strain isolated from a clinical specimen in 2020)

(A)



(B)



S-268019: Covgoze

ChAdOx1 nCoV-19: Vaxzevria

n, Number of applicable subjects

Figure 3. Investigation of SARS-CoV-2 neutralizing antibody titer 28 days after the second dose of the study vaccine, measured at Testing Facility B (Study U0231, immunogenicity analysis population)

(A) This shows the inverse cumulative distribution curves of SARS-CoV-2 neutralizing antibody titers 28 days after the second dose of the study vaccine, measured at Testing Facility B. (B) This shows scatter plots of SARS-CoV-2 neutralizing antibody titer, measured at Testing Facilities A and B, in double logarithmic scale. Neutralizing antibody titers below the LLOQ measured at Testing Facility A (horizontal axis) were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5). The LLOQ of neutralizing antibody titers measured at Testing Facility B (vertical axis) was 11.22.

Based on the results of multiple endpoints and assays presented in (a) to (c), the applicant considers that Vaxzevria, the control vaccine, induced immune response appropriately in Study U0231, and the analytical sensitivity in this study was enough to support the active-controlled study design.

Appropriateness of the primary analysis in Study U0231 was further investigated as shown below.

Table 41 shows distribution of SARS-CoV-2 neutralizing antibody titers (Testing Facility A) 28 days after the second dose, the primary endpoint of Study U0231, by group. As described above, the percentage of subjects whose SARS-CoV-2 neutralizing antibody titer 28 days after the second dose was below the LLOQ, was as high as 63.4% in the Vaxzevria group in Study U0231; therefore logarithmically transformed antibody titers in the Vaxzevria group in the analysis population for comparison of the primary endpoint between the groups had a truncated distribution, which was different from a normal distribution. In the primary analysis of the primary endpoint, hypothesis testing according to the t-test procedure and calculation of the CI were performed using logarithmically transformed SARS-CoV-2 neutralizing antibody titers, and thus the data should be assumed to have the normal distribution. However, if the data have a skew distribution such as a truncated distribution, different from the normal distribution but the sample size is about 100 in each group, distribution of the mean values can be approximated to the normal distribution by central limit theorem, and the t-test can provide robust conclusion (*Contemp Clin Trials.* 2009;30:490-6, *BMC Med Res Methodol.* 2012;12:78), and thus, the primary analysis according to the t-test procedure was considered applicable.

Table 41. Distribution of SARS-CoV-2 neutralizing antibody titer (Testing Facility A) 28 days after the second dose of the study vaccine (Study U0231, immunogenicity analysis population)

Neutralizing antibody titer 28 days after the second dose (Testing Facility A)	Covgoze (N = 497)	Vaxzevria (N = 514)
	n (%)	n (%)
<5	11 (2.2)	326 (63.4)
5	32 (6.4)	140 (27.2)
10	114 (22.9)	28 (5.4)
20	181 (36.4)	7 (1.4)
40	115 (23.1)	8 (1.6)
80	41 (8.2)	2 (0.4)
160	2 (0.4)	3 (0.6)
640	1 (0.2)	0

Micro-neutralization assay against the SARS-CoV-2 original strain
LLOQ = 5
N, Number of subjects analyzed; n, Number of applicable subjects

In Study U0231, a post hoc analysis was performed by applying Wilcoxon rank-sum test procedure, a nonparametric analysis method without hypothesis of the data distribution, to SARS-CoV-2 neutralizing antibody titer (Testing Facility A) 28 days after the second dose, the primary endpoint. The distribution of GMT in the Covgoze group was plotted above that in the Vaxzevria group with a nominal significance ($P < 0.0001$, Wilcoxon rank-sum test [two-sided test]), supporting the result from the primary analysis (Table 28). Based on the above, the applicant considered that Covgoze was shown to be superior to Vaxzevria in the primary endpoint of Study U023.

7.R.2.2.3 Clinical efficacy of the primary series

The efficacy of Covgoze was evaluated based on the immunogenicity endpoints [see Sections 7.R.1 and 7.R.2.1]. In addition, the clinical studies conducted were designed to evaluate incidences of COVID-19[42)] and SARS-CoV-2 infection as secondary or exploratory endpoints.

Table 42 shows numbers of subjects who had COVID-19 and of subjects who had asymptomatic SARS-CoV-2 infection ≥14 days after the second dose of the study vaccine in the mITT populations in Studies U0231 (follow-up period [range], 13-52 days) and U0222 (follow-up period [range], 1-276 days), both of which evaluated the primary series. In Study U0231, which used an approved SARS-CoV-2 vaccine as the control vaccine, none of the subjects had COVID-19 in either group, but similar numbers of subjects had asymptomatic SARS-CoV-2 infection in the Covgoze and Vaxzevria groups.

42) COVID-19 was defined as a pathological condition meeting at least one of COVID-19 symptoms (pyrexia [axillary temperature ≥37.5°C or oral temperature ≥38.0°C], shortness of breath, and dyspnea irrespective of duration of the symptom; chills, cough, malaise, myalgia, body pain, headache, ageusia, anosmia, sore throat, nasal congestion, runny nose, nausea, vomiting, and diarrhoea with duration of ≥2 days) or definitions of severe COVID-19 in addition to the positive result in SARS-CoV-2 RT-PCR test.
Severe COVID-19 was defined as a condition meeting one of the following pathological conditions, in addition to the positive result in SARS-CoV-2 RT-PCR test:
- Clinical signs indicative of a severe systemic disease (respiratory rate ≥30/min, heart rate ≥125/min, saturation of percutaneous oxygen (SpO_2) ≤93% or partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <300 mmHg)
- Respiratory failure (defined as a condition needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- Shock sign (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Serious acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

Table 42. Subjects who had COVID-19 or asymptomatic SARS-CoV-2 infection ≥14 days after the second dose of the study vaccine (Studies U0231 and U0222, mITT population)

	Study U0231		Study U0222	
	Covgoze (N = 573)	Vaxzevria (N = 588)	Naïve adult (N = 2,951)	Naïve elderly (N = 115)
Number of subjects with COVID-19	0	0	151	3
Total follow-up period (person-years)	65.07	67.15	1,468.73	55.62
Incidence rate per 1,000 person-years [two-sided 95% CI][a)]	0.00 [0.00, 56.70]	0.00 [0.00, 54.93]	102.81 [87.07, 120.58]	53.93 [11.12, 157.61]
Number of subjects with asymptomatic infection	20	15	130	4
Total follow-up period (person-years)	63.01	65.87	1,447.63	55.41
Incidence rate per 1,000 person-years [two-sided 95% CI][a)]	317.39 [193.87, 490.18]	227.71 [127.45, 375.58]	89.80 [75.03, 106.63]	72.19 [19.67, 184.84]

N, Number of subjects analyzed
a) The two-sided 95% CI was estimated by the exact method based on a Poisson distribution.

A phase III study (Study U0232) to verify the COVID-19-preventive effect of the Covgoze primary series is ongoing at 24 study sites in Vietnam. Study U0232 is a randomized, double-blind, placebo-controlled study in healthy adults aged ≥18 years who had no history of SARS-CoV-2 infection (target sample size,[43)] 54,915 subjects; 36,610 in the Covgoze group, 18,305 in the placebo group).[44)] The study was initiated with a plan to perform the primary analysis with unblinding when 66 subjects are confirmed to have COVID-19. Based on the concerned plan, the data were cut off on March 31, 2022 for the first data-base lock (DBL). This DBL was for the primary analysis, which was performed earlier than predicted because of COVID-19 outbreak in Vietnam, and the median follow-up period from 14 days after the second dose of the study vaccine was as short as 35 days. To evaluate the efficacy with a longer follow-up period, the analysis plan was revised (statistical analysis plan version 3 dated December 13, 2022). The second DBL was made on September 30, 2022, 6 months after the first data cutoff, and the analysis is currently ongoing.

In the analysis after the first data cutoff, of 8,594 randomized subjects (5,727 in the Covgoze group, 2,867 in the placebo group), 7,889 subjects (5,256 in the Covgoze group, 2,633 in the placebo group) were included in the mITT population, and the remaining 705 subjects (471 in the Covgoze group, 234 in the placebo group) were excluded because they did not receive the study vaccine, had SARS-CoV-2 infection before the first dose of the study vaccine or had a history of SARS-CoV-2 infection, or had other reasons.

The clinical efficacy of Covgoze versus placebo was evaluated based on the number of subjects who had COVID-19 ≥14 days after the second dose in the mITT population of the first DBL. The results are shown in Table 43. The VE [two-sided 95% CI] was 39.1% [26.6%, 49.5%], which did not meet the prespecified criterion (lower limit of two-sided 95% CI >30%).

43) On the assumption that the true VE was 70% for the primary endpoint (onset of COVID-19 ≥14 days after the second dose of the study vaccine), the test was planned to examine if the lower limit of two-sided 95% CI of the VE exceeds 30%. The total number of events required for the test to provide ≥90% of statistical power at a one-sided significance level of 0.025 was estimated to be 66. On the assumption that the incidence rate was 0.5% per year in the placebo group and 10% of subjects would be excluded because of the immunogenicity positive status at baseline and drop-out, the total number of subjects required for the study with the follow-up period of 6 months was estimated to be 54,915 (36,610 in the Covgoze group, 18,305 in the placebo group).

44) Persons involved in preparation of the study vaccine (pharmacists) and vaccination were unblinded.

Table 43. Number of subjects who had COVID-19 ≥14 days after the second dose of the study vaccine (Study U0232, primary analysis, mITT population)

	Covgoze	Placebo
Number of subjects analyzed	5,256	2,633
Number of subjects with COVID-19	244	197
Total follow-up period (person-years)	314.27	154.77
Incidence rate per 1,000 person-years [two-sided 95% CI][a)]	776.41 [682.04, 880.19]	1272.87 [1101.32, 1463.57]
VE [two-sided 95% CI][b)] (%)	39.1 [26.6, 49.5]	

a) The two-sided 95% CI was estimated by the exact method based on a Poisson distribution.
b) Estimated by a Poisson regression model with a robust error variance, using the age (continuous variable) at baseline (before the first dose) as a covariate. The logarithmically transformed follow-up period was used as an offset.

The GMT of neutralizing antibodies against the SARS-CoV-2 (original strain) 28 days after the second dose of the study vaccine increased in the Covgoze group and was similar to that observed 28 days after the second dose of Covgoze in Study U0231.

The failure to demonstrate superiority of Covgoze to placebo in the disease-preventive effect in Study U0232, despite the immune response to SARS-CoV-2 observed after Covgoze vaccination, was considered attributable to prevalence of a variant in the study country. The first onset of COVID-19 ≥14 days after the second dose of the study vaccine was reported on February 10, 2022. Because the predominant variant detected in Vietnam at the middle of February 2022 or later was the Omicron variant (https://covariants.org/per-country?country=Vietnam [last accessed on January 12, 2023]), most of the subjects with COVID-19 in this study were deemed to have been infected by the Omicron variant. In a clinical study to evaluate the disease-preventive effect of Spikevax in the prevalence of the Omicron variant, the VE [two-sided 95% CI] was 36.8% [12.5%, 54.0%] (*N Engl J Med.* 2022;387:1673-87), and a cohort study using real-world data showed that the disease-preventive effect of the primary series in the prevalence of the Omicron variant was lower than that in the prevalence of the Delta variant or its preceding variants (*N Engl J Med.* 2022;387:1865-76, COVID-19 vaccine monthly surveillance reports [weeks 39 to 48, 2021 to 2022][45)]). The VE of Covgoze in Study U0232 was considered similar to the results presented in these reports.

Based on the above, the Covgoze primary series may not be expected to exert a high disease-preventive effect in the prevalence of the Omicron variant but may have a similar effect to that of monovalent SARS-CoV-2 vaccines against the original strain available for the primary series in Japan.

7.R.2.2.4 Efficacy of the Covgoze primary series against variants

The immunogenicity of the Covgoze primary series against variants was evaluated using serum specimens from 24 subjects in the Covgoze 10 μg group in Study U0221, 24 subjects extracted from the naïve adult group in Study U0222,[46)] and 24 subjects each extracted from the Covgoze and Vaxzevria groups in Study U0231 by the same procedure as that in Study U0222. Table 44 and Table 45 show SARS-CoV-2 neutralizing antibody titers (NT_{50}) against each of the variants measured by the variant pseudovirus neutralization assay. Neutralizing antibody titers against the D614G (reference),

45) https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports (last accessed on March 31, 2023)
46) To extract a population representative of the original population in terms of SARS-CoV-2 neutralizing antibody titer and age distributions, the criterion of $P \geq 0.8$ was specified for comparison between the original and the extracted populations by Wilcoxon rank-sum test, which performs a comparison of distribution between 2 groups. A total of 24 subjects were extracted as a sample size that provided $P \geq 0.8$ to the comparisons with the original population in terms of both SARS-CoV-2 neutralizing antibody titer and age.

Alfa, Beta, Gamma, and Delta variants increased after vaccination with Covgoze, while that against the Omicron variant remained below the LLOQ in many specimens in any group.

Table 44. Neutralizing antibody titers against variants after Covgoze vaccination (Study U0221, immunogenicity analysis population)

	Covgoze 10 μg (N = 24)					
	Baseline		14 days after the second dose		28 days after the second dose	
Assay target	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
D614G variant (reference variant)[a)]	24	20 [20, 20]	24	1469 [1120, 1926]	24	895 [674, 1190]
Alfa variant	24	20 [20, 20]	24	874 [650, 1174]	-	-
Beta variant	24	20 [20, 20]	24	248 [177, 349]	24	166 [106, 260]
Gamma variant	24	20 [20, 20]	24	291 [209, 405]	-	-
Delta variant	24	20 [20, 20]	24	1023 [729, 1436]	24	1499 [994, 2260]
Omicron variant BA.1	24	20 [20, 20]	-	-	23	35 [27, 45]
Omicron variant BA.2	24	20 [20, 20]	-	-	24	30 [23, 38]
Omicron variant BA.4-5	24	20 [20, 20]	-	-	24	24 [20, 29]

Variant pseudovirus neutralization assay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 40).
N, Number of subjects analyzed; n, Number of subjects who had assay values; -, No assay performed
a) Because pseudovirus with envelope using the spike protein of the original strain does not have enough infectivity for assay, more infectious pseudovirus using the D614G-mutant spike protein with 1 amino acid substitution in the original strain sequence to increase the infectivity was used as the reference.

Table 45. Neutralizing antibody titers against variants 28 days after the second dose of the study vaccine (Studies U0222 and U0231, a part of the immunogenicity analysis population)

Assay target	Study U0222		Study U0231			
	Naïve adult (N = 24)		Covgoze (N = 24)		Vaxzevria (N = 24)	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
D614G variant (reference variant)[a)]	24	880 [612, 1266]	24	906 [645, 1273]	24	96 [56, 163]
Alfa variant	24	672 [478, 945]	-	-	-	-
Beta variant	24	181 [118, 279]	-	-	-	-
Gamma variant	24	240 [149, 386]	-	-	-	-
Delta variant	24	522 [327, 833]	24	825 [592, 1148]	24	43 [25, 75]
Omicron variant BA.1	24	38 [27, 54]	24	59 [37, 94]	24	29 [18, 44]
Omicron variant BA.2	-	-	24	43 [27, 68]	24	27 [18, 40]

Variant pseudovirus neutralization assay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 40).
N, Number of subjects analyzed; n, Number of subjects who had assay values; -, No assay performed
a) Because pseudovirus with envelope using the spike protein of the original strain does not have enough infectivity for assay, more infectious pseudovirus using the D614G-mutant spike protein with 1 amino acid substitution in the original strain sequence to increase the infectivity was used as the reference.

Furthermore, specimens from 24 subjects in the Covgoze group of Study U0231 (28 days after the second dose of the study vaccine) were also subjected to assay with variant pseudoviruses including Omicron XBB.1 lineage and BQ.1 lineage. The GMT [two-sided 95% CI] of SARS-CoV-2 neutralizing antibody (NT_{50}) was 808 [577, 1,132] for the D614G variant, 30 [20, 44] for the Omicron BA.4-5 lineage, 22 [18, 29] for the XBB.1 lineage, and 22 [18, 29] for the BQ.1.1 lineage. The GMTs of neutralizing antibody against all the Omicron BA.4-5, XBB.1, and BQ.1.1 lineages were lower than that against the D614G variant, and measured values in many specimens were below the LLOQ.

PMDA's view on the efficacy of the primary series:
In Study U0231, which evaluated the immunogenicity (efficacy) of the Covgoze primary series versus Vaxzevria (an approved vaccine used as the control), the GMT of SARS-CoV-2 neutralizing antibody, the primary endpoint, achieved the prespecified criterion for superiority. In Study U0231, however, neutralizing antibody titers of many specimens in the Vaxzevria group were below the LLOQ. The neutralizing antibody titer in the Vaxzevria group predicted at the time of planning Study U0231 was

based on the past clinical study results because no results from exploratory comparison with Covgoze were available. The predicted titer might be justified to some extent, but the result of immunogenicity after Vaxzevria vaccination in Study U0231 was not reproduction of the past results; therefore the results of comparison of Vaxzevria with Covgoze in the study should be interpreted with care. In view of the applicant's investigation of analytical sensitivity in Study U0231 [see Section 7.R.2.2.2], which showed results of multiple immunogenicity endpoints and correlation between assay results within the same subject, the applicant's discussion that differences in assay method might have affected the GMT of neutralizing antibodies in the Vaxzevria group is somewhat reasonable, and the Vaxzevria group in Study U0231 can be deemed to have immunologically responded to a certain extent. In addition to the above, the results of SARS-CoV-2 neutralizing antibody, the primary endpoint, and the other immunogenicity endpoints (Tables 36-38, Table 45) in Study U0231 can lead to an insight that immunogenicity of Covgoze tended to be higher than that of Vaxzevria. An analytical procedure that assumed that the GMT in each group have the normal distribution, was applied to the primary analysis of the primary endpoint in Study U0231, but it was inappropriate because actual data in the Vaxzevria group had an extremely truncated distribution. However, the post hoc nonparametric analysis (Wilcoxon rank-sum test) also showed that the GMT in the Covgoze group tended to be higher than that in the Vaxzevria group, supporting the primary analysis result. Based on the above findings, the immunogenicity of Covgoze can be considered higher than that of Vaxzevria.

For the clinical efficacy, the Covgoze primary series was not shown to have disease-preventive effects in Study U0232, which is ongoing to investigate prevention of disease onset. This may be due to prevalence of the SARS-CoV-2 Omicron variant, which has the antigenicity different from the original strain, in the study country when the study was conducted. In the prevalence of the Omicron variant, the primary series alone of the existing SARS-CoV-2 vaccines with proven high efficacy against the original strain, had the effectiveness of 35.9% to 71.0% against the Omicron BA.1 or BA.2 lineage (*Nat Med.* 2022;28:1063-71, *Nat Commun.* 2022;13:3082, *Morbidity and Mortality Weekly Report.* 2022;71:931-9), and their effectiveness decrease with time. Also in the investigations of neutralizing activities against various variants, the activities against the Omicron variant were lower than those against the original strain (*Nature.* 2022;603:493-6, *N Engl J Med.* 2022;386:698-700, etc.). The investigation of neutralizing activities against variant pseudoviruses demonstrated that the immunogenicity of Covgoze against the Omicron variant was greatly lower than that against the other variants close to the original strain (Tables 44 and 45). In view of the target antigen of Covgoze, which is the protein of the SARS-CoV-2 original strain, the results of the disease-preventive effect demonstrated in Study U0232 is not inconsistent with the reports on the existing SARS-CoV-2 vaccines. The efficacy of approved SARS-CoV-2 vaccines against the Omicron variant was low only with the primary series and decreased with time but the booster dose restored it (*Nat Med.* 2022;28:1063-71, *Nat Commun.* 2022;13:3082, etc.). Covgoze is also considered to have inadequate efficacy against the Omicron variant only with the primary series, requiring the booster dose. Study U0232 is not included in the clinical data package for the present application, and only a part of results of the analysis performed are available at present. The study results should be reviewed when they are compiled, and should be appropriately communicated to healthcare professionals.

In Study U0222, the SARS-CoV-2 neutralizing antibody titer 28 days after the second dose of Covgoze tended to be lower in the elderly than in the non-elderly [see Section 7.R.2.2.1]. In Study U0231, a similar trend was observed too. In both age groups, the SARS-CoV-2 neutralizing antibody titer in the Covgoze group was higher than that in the Vaxzevria group. The immunogenicity of approved COVID-19 vaccines also tended to be lower in the elderly than in the non-elderly, but their COVID-19-preventive effect has been demonstrated in the elderly as well (Review Report on Comirnaty Intramuscular Injection dated February 8, 2021, Review Report on Nuvaxovid Intramuscular Injection dated April 11, 2022, etc.). At present, PMDA therefore considers it difficult to conclude that the difference in SARS-CoV-2 neutralizing antibody titer between the age groups observed in Study U0222 is large enough to have an impact on the clinical efficacy.

In view of the above review, PMDA concluded that 2 doses of Covgoze adequately increased the neutralizing antibody titer against the original strain, and thus the primary series can be expected to have the efficacy against the original strain. As described above, Covgoze hardly induced production of neutralizing activities against the Omicron variant only with the primary series, as reported on the primary series of other SARS-CoV-2 vaccines, and therefore cannot be expected to have high efficacy for COVID-19 caused by the persistently prevalent Omicron variant. The booster dose is therefore needed. The efficacy of the Covgoze booster dose is discussed in Section 7.R.2.3.

PMDA will draw the final conclusion on the above review, taking account of comments from the Expert Discussion.

7.R.2.3 Efficacy of the Covgoze booster dose

The applicant provided the following explanation about the efficacy of the Covgoze booster dose.

7.R.2.3.1 Immunogenicity of the booster dose and its sustainability in the population who had received the primary series of mRNA vaccines

In Study U0223, the pivotal clinical study to evaluate the efficacy of the booster dose, subjects who had completed the Comirnaty primary series received a dose of Covgoze or Comirnaty. The study demonstrated the non-inferiority of Covgoze to Comirnaty in immunogenicity [see Section 7.2.2]. In Study U0223, the inclusion criterion for the age was “adults aged ≥20 years,” but adults aged ≥65 years were not enrolled, and therefore data only in adults aged 20 to 64 years are available. To investigate the safety and immunogenicity of the Covgoze booster dose in the population including adults aged ≥65 years (they were not included in Study U0223), Study U0224 was designed to enroll adults aged 20 to 64 years who had received the primary series of Spikevax and the elderly aged ≥65 years who had received the primary series of Comirnaty or Spikevax. Table 46 shows the GMTs of SARS-CoV-2 neutralizing antibody in Studies U0223 and U0224. One additional Covgoze booster dose increased the SARS-CoV-2 neutralizing antibody titer from baseline (before the booster dose). In the elderly who had completed the Comirnaty primary series, the GMT of SARS-CoV-2 neutralizing antibody tended to be lower than that in the non-elderly who had completed the same primary series, both before and after the booster dose.

Table 46. GMT of SARS-CoV-2 neutralizing antibody after the study vaccination (Studies U0223 and U0224, immunogenicity analysis population)

	Study U0223				Study U0224					
	Covgoze (N = 101)		Comirnaty (N = 102)		Cohort A (N = 100)		Cohort B (N = 29)		Cohort C (N = 21)	
Age	20-64 years		20-64 years		20-64 years		≥65 years		≥65 years	
Vaccine for primary series	Comirnaty		Comirnaty		Spikevax		Comirnaty		Spikevax	
Vaccine for booster dose (study vaccine)	Covgoze		Comirnaty		Covgoze		Covgoze		Covgoze	
Measurement timepoint	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
Before booster dose	101	5.47 [4.81, 6.21]	102	6.65 [5.73, 7.72]	100	12.14 [10.53, 14.00]	29	3.41 [2.93, 3.97]	21	10.34 [6.13, 17.44]
14 days after booster dose	101	127.57 [112.03, 145.28]	101	139.48 [122.50, 158.82]	98	92.16 [79.70, 106.56]	28	52.52 [38.39, 71.84]	19	115.22 [86.99, 152.61]
28 days after booster dose	101	124.97 [108.33, 144.18]	101	109.70 [95.73,125.70]	96	99.35 [83.44, 118.29]	28	76.14 [55.38, 104.67]	20	129.96 [88.79, 190.22]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects evaluated

For sustainability of the immunogenicity, Table 47 shows the GMTs of SARS-CoV-2 neutralizing antibody over time starting 14 days after the study vaccination in Study U0223. The GMT [two-sided 95% CI] peaked 14 days after the study vaccination in both the Covgoze and Comirnaty groups and then decreased to 49.60 [41.01, 59.99] (Covgoze) and 32.85 [27.42, 39.36] (Comirnaty) 182 days after the study vaccination; these values were still higher than those before the booster dose when ≥6 had passed since the primary series.

Table 47. GMT of SARS-CoV-2 neutralizing antibody after study vaccination (Study U0223, immunogenicity analysis population)

	Covgoze (N = 101)		Comirnaty (N = 102)	
Age	20-64 years		20-64 years	
Vaccine for primary series	Comirnaty		Comirnaty	
Booster dose (study vaccine)	Covgoze		Comirnaty	
Measurement timepoint	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
Before booster dose	101	5.47 [4.81, 6.21]	102	6.65 [5.73, 7.72]
14 days after booster dose	101	127.57 [112.03, 145.28]	101	139.48 [122.50, 158.82]
28 days after booster dose	101	124.97 [108.33, 144.18]	101	109.70 [95.73,125.70]
68 days after booster dose	97	76.10 [65.51, 88.40]	97	68.85 [60.30, 78.61]
182 days after booster dose	87	49.60 [41.01, 59.99]	88	32.85 [27.42, 39.36]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects evaluated

7.R.2.3.2 Immunogenicity of the booster dose in subjects who had received the Covgoze primary series

In the sub-part in Study U0222, Covgoze was administered as a booster dose to some subjects in the main part who wished, and the SARS-CoV-2 neutralizing antibody titer after the booster dose was compared with that after the primary dose. In both the naïve adult group and naïve elderly group, the prespecified criterion for non-inferiority was met (Tables 21 and 22). Table 48 shows the GMTs of SARS-CoV-2 neutralizing antibody in major subject groups with different characteristics enrolled in Study U0222. In all groups, the Covgoze booster dose increased the SARS-CoV-2 neutralizing antibody titer. The SARS-CoV-2 neutralizing antibody titer after the booster dose was lower in the naïve elderly group than in the naïve adult group.

Table 48. GMT of SARS-CoV-2 neutralizing antibody after Covgoze vaccination (sub-part in Study U0222, booster-dose immunogenicity analysis population)

	Naïve adult (N = 207)		Naïve elderly (N = 78)		Previously-infected adult (N = 50)		Previously-vaccinated adult (N = 54)	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
Before booster dose	201	4.97 [4.45, 5.54]	77	3.55 [3.06, 4.13]	50	50.63 [38.70, 66.24]	48	43.62 [34.67, 54.89]
28 days after booster dose	205	154.16 [138.40, 171.71]	78	113.14 [95.24,134.40]	50	173.88 [138.04, 219.02]	49	107.67 [85.25, 135.99]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects evaluated

7.R.2.3.3 Efficacy of the booster dose against variants

The immunogenicity of the Covgoze booster dose against variants was evaluated using serum specimens from 24 subjects each extracted[47] from (a) the naïve adult group in the sub-part in Study U0222, (b) the Covgoze and Comirnaty groups in Study U0223, and (c) the adult Spikevax group in Study U0224. Table 49 and Table 50 show SARS-CoV-2 neutralizing antibody titers against each of the variants measured by the variant pseudovirus neutralization assay. The Covgoze booster dose induced production of neutralizing antibodies against the Delta variant and Omicron BA.1, BA.2, BA.2.12.1, BA.4.6, and BA.4-5 lineages. Antibody titers against the Omicron BA.1, BA.2, BA.4.6, and BA.4-5 lineages were comparable to or higher than that against the D614G variant (reference variant) after the primary series. The antibody titers against the Omicron BA.2.12.1, BA.4.6, and BA.4-5 lineages after the booster dose were lower than that against the D614G variant, but those against the Omicron BA.1 and BA.2 lineages were similar (Table 49). In Study U0223, specimens 28 and 68 days after the booster dose were measured for SARS-CoV-2 neutralizing antibody titer (variant pseudovirus neutralization assay). The antibody titers 28 days after the Covgoze booster dose against D614G variant (reference variant), Delta variant, and Omicron variant (BA.1) were similar. However, the antibody titer 68 days after the booster dose was lower against the Delta variant than against the D614G variant (original strain), and those against the Omicron variant (BA.1) and the D614G variant (original strain) were similar. Antibody titers against these variants in the Covgoze group and the Comirnaty group were similar at any sampling point (Table 50).

[47] To extract a population representative of the original population, the criterion of $P \geq 0.7$ (Study U0222) or ≥ 0.8 (Studies U0223 and U0224) was specified for comparison between the original and the extracted populations by Wilcoxon rank-sum test, which performs a comparison of distribution between 2 groups. A total of 24 subjects were extracted as a sample size that provided $P \geq 0.7$ (Study U0222) or ≥ 0.8 (Studies U0223 and U0224) to the comparisons with the original population in terms of both SARS-CoV-2 neutralizing antibody titer and age.

Table 49. GMT of SARS-CoV-2 neutralizing antibody against variants (sub-part in Study U0222 and Study U0224, a part of the immunogenicity analysis population)

	Study U0222/Covgoze naïve (N = 24)				Study U0224/Cohort A (N = 24)			
Vaccine for primary series (2 doses)	Covgoze				Spikevax			
Vaccine for booster dose (third dose)	Covgoze				Covgoze			
Assay target	28 days after second dose		28 days after third dose		Before booster dose		28 days after booster dose	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
D614G (reference variant)[a)]	24	807 [610, 1068]	24	1749 [1316, 2323]	24	119 [93, 153]	24	1043 [718, 1513]
Omicron BA.1	24	41 [29, 57]	24	1113 [807, 1537]	24	24 [18, 32]	24	426 [252, 721]
Omicron BA.2	24	58 [38, 90]	24	1513 [1088, 2105]	-	-	-	-
Omicron BA.2.12.1	-	-	-	-	24	22 [18, 26]	24	169 [107, 267]
Omicron BA.4.6	24	29 [21, 40]	24	465 [331, 655]	-	-	-	-
Omicron BA.4-5	24	29 [22, 40]	24	465 [331, 652]	24	22 [18, 26]	24	149 [99, 225]

Variant pseudovirus neutralization assay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 40).
N, Number of subjects analyzed; n, Number of subjects evaluated; -, No assay performed
a) Because pseudovirus with envelope using the spike protein of the original strain does not have enough infectivity for assay, more infectious pseudovirus using the D614G-mutant spike protein with 1 amino acid substitution in the original strain sequence to increase the infectivity was used as the reference.

Table 50. GMT of SARS-CoV-2 neutralizing antibody against variants (Study U0223, a part of the immunogenicity analysis population)

	Covgoze (N = 24)				Comirnaty (N = 24)			
Vaccine for primary series	Comirnaty							
Vaccine for booster dose	Covgoze				Comirnaty			
Assay target	28 days after booster dose		68 days after booster dose		28 days after booster dose		68 days after booster dose	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
D614G (reference variant)[a)]	24	618 [428, 892]	23	737 [431, 1258]	24	659 [538, 806]	24	698 [500, 974]
Delta	24	455 [306, 678]	23	181 [108, 303]	24	387 [306, 488]	24	120 [90, 160]
Omicron BA.1	24	593 [381, 925]	23	266 [139, 509]	24	522 [373, 729]	24	289 [167, 499]

Variant pseudovirus neutralization assay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 40).
N, Number of subjects analyzed; n, Number of subjects evaluated
a) Because pseudovirus with envelope using the spike protein of the original strain does not have enough infectivity for assay, more infectious pseudovirus using the D614G-mutant spike protein with 1 amino acid substitution in the original strain sequence to increase the infectivity was used as the reference.

In ongoing Study U0224, the second Covgoze booster dose was administered to some subjects in Cohort A (adults who received 2 doses of Spikevax for the primary series) who wished, and serum specimens obtained after the vaccination were measured for SARS-CoV-2 neutralizing antibody titer using variant pseudoviruses including the Omicron XBB.1 and BQ.1 lineages. The results are shown in Table 51. The GMTs of neutralizing antibodies against the Omicron BA.4/BA.5, XBB.1, and BQ.1.1 lineages 28 days after both first and second doses were lower than those against the D614G variant (reference variant), but the antibody titer 28 days after the second booster dose (fourth dose) tended to be higher than that after the first booster dose (third dose).

Table 51. GMT of SARS-CoV-2 neutralizing antibody against variants (Cohort A in Study U0224, immunogenicity analysis population)

Assay target	Primary series (2 doses) of Spikevax and booster doses (third and fourth doses) of Covgoze (N = 24)			
	28 days after the third dose[a)]		28 days after the fourth dose[b)]	
	n	GMT [two-sided 95% CI]	n	GMT [two-sided 95% CI]
D614G variant (reference variant)[c)]	23	1087 [823, 1436]	24	1213 [884, 1664]
Omicron BA.4-5 lineage	24	129 [93, 180]	24	203 [129, 319]
Omicron XBB.1 lineage	24	43 [30, 62]	24	73 [45, 118]
Omicron BQ.1.1 lineage	24	62 [45, 88]	24	114 [69, 187]

Variant pseudovirus neutralization assay
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 40).
N, Number of subjects analyzed; n, Number of subjects evaluated
a) Third dose of SARS-CoV-2 vaccine (first dose of Covgoze [study vaccine])
b) Fourth dose of SARS-CoV-2 vaccine (second dose of Covgoze [study vaccine])
c) Because pseudovirus with envelope using the spike protein of the original strain does not have enough infectivity for assay, more infectious pseudovirus using the D614G-mutant spike protein with 1 amino acid substitution in the original strain sequence to increase the infectivity was used as the reference.

Based on the above, immunization achieved by Covgoze primary series alone cannot be expected to highly prevent the disease caused by the SARS-CoV-2 Omicron variant, which is currently predominant in Japan. However, in the population who completed the primary series, a booster dose of Covgoze can be expected to induce production of neutralizing antibodies against representative variants including the Omicron variant and thus have a certain level of efficacy as with the approved SARS-CoV-2 vaccines.

PMDA's view:
As for the efficacy of a Covgoze booster dose, Study U0223 showed that the Covgoze booster dose increased the neutralizing antibody titer against the SARS-CoV-2 original strain to a similar extent as the Comirnaty booster dose in the population who had completed the Comirnaty primary series (Tables 24 and 25). Results from Studies U0222 and U0224 showed that a Covgoze booster dose increased the neutralizing antibody titer against the SARS-CoV-2 original strain irrespective of the vaccine product used for the primary series.

For the immunogenicity against variants, the Covgoze primary series did not increase the neutralizing antibody titer against the Omicron variant, but the Covgoze booster dose induced production of neutralizing antibody against the Omicron variant to a certain extent. The primary series of approved monovalent SARS-CoV-2 vaccines tended to have lower efficacy against the Omicron variant than against the original strain, and the efficacy against the Omicron decreased with time [see Section 7.R.2.2]. On the other hand, the effectiveness of a booster dose against the Omicron variant was 56% to 84% (*Morbidity and Mortality Weekly Report.* 2022;71:931-9). Further, at 2 to 4 weeks after a booster dose, the effectiveness against the Delta and Omicron variants was 94.7% to 96.6% and 64.9% to 73.9%, respectively (*N Engl J Med.* 2022;386:1532-46). These data show that a booster dose tended to have higher effectiveness than the primary series alone even against the Omicron variant. As with approved SARS-CoV-2 vaccines, Covgoze, when used as the booster dose, was shown to restore the neutralizing antibody titer that has decreased with time after the primary series and induce production of neutralizing activities against various variants to a certain extent. PMDA considered that a Covgoze booster dose can be expected to have a certain level of efficacy against not only the original strain but also variants including the Omicron variant.

However, data on the long-term efficacy of the booster dose including the clinical efficacy are not available. When new information becomes available from the post-marketing investigations or ongoing clinical studies, it should be promptly provided to healthcare professionals.

7.R.3 Safety

The applicant explained the safety of Covgoze based on clinical study results shown in Sections 7.R.3.1 to 7.R.3.6:

The following is PMDA's view on the safety of Covgoze, based on the submitted data and the applicant's explanation covering the additional information presented during the review:

According to the clinical study results submitted, the solicited adverse events reported after Covgoze vaccination for both primary series and booster dose were mostly Grade 1 or 2 and reversible. In clinical studies, the incidence of serious adverse events including death was low for both primary series and booster dose. At present, the following data have not raised any critical safety concerns that may affect the decision of approval or non-approval of Covgoze: (a) the incidence of unsolicited adverse events [see Sections 7.1 to 7.3 and 7.R.3.1], (b) the safety data in special populations including the elderly [see Sections 7.R.3.2 and 7.R.3.5], and (c) comparison of Covgoze with approved SARS-CoV-2 vaccines used as controls [see Sections 7.2.2 and 7.3.1]. The safety of Covgoze is therefore considered tolerable. In Japan, vaccination against SARS-CoV-2 has been preferentially provided to the elderly and the population with underlying diseases, and thus only limited data are available regarding Covgoze vaccination in special populations including the elderly in Japanese clinical studies. In addition, the information about the safety in individuals excluded from the clinical studies such as pregnant women is lacking. Therefore post-marketing pharmacovigilance is required in a clinical setting, and risk-benefit evaluation covering the risk of vaccine-associated enhanced diseases (VAEDs) should be conducted continuously. Provision of additional precautions and information should be considered in response to the information about Covgoze collected in post-marketing settings and findings from the ongoing clinical studies, and other appropriate measures should be taken.

Data are available on the first booster dose of Covgoze in subjects who had completed the primary series, but investigation results of the subsequent booster doses are limited. The incidence of some adverse events (e.g., pyrexia and malaise) tended to increase with the increasing number of doses including 2 doses for the primary series. The safety profile associated with the increased number of booster doses should be appropriately evaluated based on the information obtained from ongoing clinical studies.

At present, no critical adverse reactions such as shock and anaphylaxis for which a causal relationship cannot be ruled out have been observed in individuals vaccinated with Covgoze, but the incidence of adverse events is considered unlikely to be greatly different from that with approved SARS-CoV-2 vaccines. Taking into account that the target antigen is similar to that of approved SARS-CoV-2 vaccines and Covgoze is a vaccine containing a potently immunostimulating adjuvant, myocarditis and pericarditis investigated in addition to adverse events of special interest should be carefully monitored as important potential risks of Covgoze with the focus on their incidence in post-marketing settings, and the necessity of safety measures should be considered.

PMDA will draw the final conclusion on the above review, taking account of comments from the Expert Discussion.

7.R.3.1 Safety profile

7.R.3.1.1 Adverse events with the primary series

(a) Main part in Study U0222

Table 52 shows incidences of solicited local adverse events and solicited systemic adverse events after each study vaccination in the naïve adult group, previously-vaccinated adult group, and previously-infected adult group in Cohort A as well as Cohort B in the main part (primary series) in Study U0222. The incidences of solicited local adverse events excluding pain and solicited systemic adverse events excluding diarrhoea and myalgia were higher after the second dose than after the first dose in the naïve adult group and Cohort B, but the incidences in the previously-vaccinated adult group and previously-infected adult group tended to be different from those in the naive group. The incidences in the naïve adult group tended to be higher than those in Cohort B. Table 53 shows incidences of solicited local adverse events and solicited systemic adverse events of Grade ≥3 in severity, and all the Grade ≥3 solicited adverse events were classified as adverse reactions. A Grade ≥4 solicited adverse event (Grade 4 pyrexia) occurred in 1 subject in the naïve adult group after the second dose.

Table 52. Solicited adverse events within 7 days after each study vaccination (main part in Study U0222, safety analysis population)

			Cohort A						Cohort B	
			Naïve adult		Previously-vaccinated adult		Previously-infected adult			
Event		No. of doses	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Local	Overall	1	2,952	2,580 (87.4)	76	74 (97.4)	68	65 (95.6)	118	81 (68.6)
		2	2,910	2,607 (89.6)	76	64 (84.2)	66	60 (90.9)	115	85 (73.9)
	Pain	1	2,952	2,544 (86.2)	76	74 (97.4)	68	65 (95.6)	118	77 (65.3)
		2	2,910	2,552 (87.7)	76	64 (84.2)	66	59 (89.4)	115	77 (67.0)
	Erythema /redness	1	2,952	392 (13.3)	76	23 (30.3)	68	13 (19.1)	118	21 (17.8)
		2	2,910	909 (31.2)	76	7 (9.2)	66	12 (18.2)	115	45 (39.1)
	Induration	1	2,952	494 (16.7)	76	23 (30.3)	68	16 (23.5)	118	20 (16.9)
		2	2,910	983 (33.8)	76	10 (13.2)	66	16 (24.2)	115	42 (36.5)
	Swelling	1	2,952	419 (14.2)	76	21 (27.6)	68	16 (23.5)	118	20 (16.9)
		2	2,910	948 (32.6)	76	11 (14.5)	66	11 (16.7)	115	43 (37.4)
Systemic	Overall	1	2,952	1,667 (56.5)	76	50 (65.8)	68	56 (82.4)	118	41 (34.7)
		2	2,910	2,100 (72.2)	76	50 (65.8)	66	47 (71.2)	115	47 (40.9)
	Pyrexia[a)]	1	2,952	75 (2.5)	76	8 (10.5)	68	14 (20.6)	118	0
		2	2,910	644 (22.1)	76	7 (9.2)	66	11 (16.7)	115	9 (7.8)
	Nausea /vomiting	1	2,952	291 (9.9)	76	14 (18.4)	68	16 (23.5)	118	5 (4.2)
		2	2,910	730 (25.1)	76	15 (19.7)	66	14 (21.2)	115	9 (7.8)
	Diarrhoea	1	2,952	144 (4.9)	76	5 (6.6)	68	7 (10.3)	118	6 (5.1)
		2	2,910	167 (5.7)	76	4 (5.3)	66	4 (6.1)	115	4 (3.5)
	Headache	1	2,952	742 (25.1)	76	27 (35.5)	68	30 (44.1)	118	17 (14.4)
		2	2,910	1,304 (44.8)	76	28 (36.8)	66	24 (36.4)	115	26 (22.6)
	Malaise	1	2,952	947 (32.1)	76	37 (48.7)	68	42 (61.8)	118	22 (18.6)
		2	2,910	1,711 (58.8)	76	36 (47.4)	66	40 (60.6)	115	34 (29.6)
	Myalgia	1	2,952	941 (31.9)	76	30 (39.5)	68	26 (38.2)	118	17 (14.4)
		2	2,910	1,027 (35.3)	76	20 (26.3)	66	20 (30.3)	115	15 (13.0)

N, Number of subjects evaluated; n, Number of subjects with events

a) Based on axillary temperature

Table 53. Grade ≥3 solicited adverse events within 7 days after each study vaccination (main part in Study U0222, safety analysis population)

			Cohort A						Cohort B	
			Naïve adult		Previously-vaccinated adult		Previously-infected adult			
Event		No. of doses	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Local	Overall	1	2,952	21 (0.7)	76	3 (3.9)	68	1 (1.5)	118	3 (2.5)
		2	2,910	161 (5.5)	76	1 (1.3)	66	2 (3.0)	115	10 (8.7)
	Pain	1	2,952	1 (0.0)	76	0	68	0	118	0
		2	2,910	6 (0.2)	76	0	66	0	115	0
	Erythema /redness	1	2,952	8 (0.3)	76	1 (1.3)	68	0	118	2 (1.7)
		2	2,910	107 (3.7)	76	1 (1.3)	66	0	115	8 (7.0)
	Induration	1	2,952	8 (0.3)	76	1 (1.3)	68	0	118	0
		2	2,910	49 (1.7)	76	0	66	1 (1.5)	115	5 (4.3)
	Swelling	1	2,952	6 (0.2)	76	3 (3.9)	68	1 (1.5)	118	2 (1.7)
		2	2,910	90 (3.1)	76	0	66	1 (1.5)	115	4 (3.5)
Systemic	Overall	1	2,952	4 (0.1)	76	0	68	0	118	0
		2	2,910	54 (1.9)	76	0	66	0	115	0
	Pyrexia[a)]	1	2,952	0	76	0	68	0	118	0
		2	2,910	35 (1.2)	76	0	66	0	115	0
	Nausea /vomiting	1	2,952	0	76	0	68	0	118	0
		2	2,910	0	76	0	66	0	115	0
	Diarrhoea	1	2,952	0	76	0	68	0	118	0
		2	2,910	2 (0.1)	76	0	66	0	115	0
	Headache	1	2,952	2 (0.1)	76	0	68	0	118	0
		2	2,910	4 (0.1)	76	0	66	0	115	0
	Malaise	1	2,952	0	76	0	68	0	118	0
		2	2,910	16 (0.5)	76	0	66	0	115	0
	Myalgia	1	2,952	2 (0.1)	76	0	68	0	118	0
		2	2,910	7 (0.2)	76	0	66	0	115	0

N, Number of subjects evaluated; n, Number of subjects with events
a) Based on axillary temperature

The time to onset and duration of solicited adverse events are as follows: For any event in any group, the median time to onset and duration, respectively, of solicited local adverse events were 1.0 to 2.0 days and 2.0 to 4.0 days after the vaccination, and the median time to onset and duration, respectively, of solicited systemic adverse events were 2.0 to 3.0 days and 1.0 to 3.0 days after the vaccination. For both solicited local adverse events and solicited systemic adverse events, values after the first and second doses were similar.

Table 54 shows incidences of unsolicited adverse events and unsolicited adverse reactions reported up to the data-cutoff date (median observation period [range]; 57.0 days [4-90 days] in the naïve adult group, 57.0 days [54-59 days] in the previously-vaccinated adult group, 57.0 days [12-63 days] in the previously-infected adult group, 57.0 days [28-62 days] in the other adult group, 55.0 days [53-57 days] in the other elderly group, 57.0 days [8-63 days] in Cohort B). Grade ≥3 unsolicited adverse events occurred in 13 subjects in the naïve adult group (appendicitis, peritonsillar abscess, colon cancer, testis cancer, anaemia, cerebral haemorrhage, tachycardia, angina pectoris, colitis ischaemic, osteoarthritis, vaccination site swelling, traumatic fracture, and clavicle fracture) and 1 subject in Cohort B (prostate cancer). Among these events, those occurring in 3 subjects in the naïve adult group (anaemia, tachycardia, and vaccination site swelling) were Grade ≥3 unsolicited adverse reactions for which a causal relationship to the study vaccine could not be ruled out.

Table 54. Incidences of unsolicited adverse events and unsolicited adverse reactions (main part in Study U0222, safety analysis population)

		N	Unsolicited adverse events		Unsolicited adverse reactions	
			All events, n (%)	Grade ≥3, n (%)	All events, n (%)	Grade ≥3, n (%)
Cohort A	Overall	3,161	625 (19.8)	13 (0.4)	249 (7.9)	3 (0.1)
	Naïve adult	2,952	582 (19.7)	13 (0.4)	232 (7.9)	3 (0.1)
	Previously-vaccinated adult	76	16 (21.1)	0	3 (3.9)	0
	Previously-infected adult	68	18 (26.5)	0	10 (14.7)	0
	Other adult	60	6 (10.0)	0	3 (5.0)	0
	Other elderly	5	3 (60.0)	0	1 (20.0)	0
Cohort B		118	42 (35.6)	1 (0.8)	17 (14.4)	0

N, Number of subjects evaluated; n, Number of subjects with events

(b) Study U0231

Table 55 shows incidences of solicited local adverse events, solicited systemic adverse events, and Grade ≥3 adverse events in Study U0231. In the Covgoze group and Vaxzevria group, neither Grade 4 or 5 solicited local adverse events nor Grade 5 solicited systemic adverse events occurred. Grade ≥4 pyrexia occurred in 1 subject each in both groups after the first dose of the study vaccine. In the Vaxzevria group, the incidence of solicited adverse events was higher after the first dose, while in the Covgoze group, the incidence was higher after the second dose. The time to onset and duration of solicited adverse events are as follows: For any event in any group, the median time to onset and duration, respectively, of solicited local adverse events were 1.0 to 2.0 days and 2.0 to 4.0 days after the vaccination, and the median time to onset and duration, respectively, of solicited systemic adverse events were 2.0 to 3.0 days and 2.0 to 3.0 days after the vaccination. For both solicited local adverse events and solicited systemic adverse events, values after the first and second doses were similar.

Table 55. Grade ≥3 solicited adverse events within 7 days after each study vaccination (Study U0231, safety analysis population)

Event		First dose				Second dose			
		Covgoze (N = 611)		Vaxzevria (N = 610)		Covgoze (N = 571)		Vaxzevria (N = 574)	
		All events n (%)	Grade ≥3 n (%)	All events n (%)	Grade ≥3 n (%)	All events n (%)	Grade ≥3 n (%)	All events n (%)	Grade ≥3 n (%)
Local	Overall	485 (79.4)	2 (0.3)	487 (79.8)	2 (0.3)	469 (82.1)	25 (4.4)	322 (56.1)	0
	Pain	477 (78.1)	0	480 (78.7)	1 (0.2)	457 (80.0)	3 (0.5)	312 (54.4)	0
	Erythema/redness	34 (5.6)	0	60 (9.8)	1 (0.2)	79 (13.8)	18 (3.2)	31 (5.4)	0
	Induration	43 (7.0)	1 (0.2)	39 (6.4)	1 (0.2)	72 (12.6)	6 (1.1)	12 (2.1)	0
	Swelling	50 (8.2)	2 (0.3)	44 (7.2)	0	104 (18.2)	14 (2.5)	27 (4.7)	0
Systemic	Overall	304 (49.8)	9 (1.5)	470 (77.0)	49 (8.0)	373 (65.3)	24 (4.2)	240 (41.8)	3 (0.5)
	Pyrexia[a)]	38 (6.2)	5 (0.8)	178 (29.2)	26 (4.3)	113 (19.8)	15 (2.6)	15 (2.6)	1 (0.2)
	Nausea/vomiting	50 (8.2)	1 (0.2)	111 (18.2)	1 (0.2)	85 (14.9)	1 (0.2)	29 (5.1)	0
	Diarrhoea	37 (6.1)	0	82 (13.4)	2 (0.3)	32 (5.6)	0	36 (6.3)	0
	Headache	142 (23.2)	1 (0.2)	288 (47.2)	7 (1.1)	223 (39.1)	2 (0.4)	112 (19.5)	0
	Malaise	172 (28.2)	3 (0.5)	349 (57.2)	21 (3.4)	280 (49.0)	13 (2.3)	146 (25.4)	1 (0.2)
	Myalgia	153 (25.0)	2 (0.3)	236 (38.7)	11 (1.8)	183 (32.0)	6 (1.1)	99 (17.2)	1 (0.2)

N, Number of subjects evaluated; n, Number of subjects with events
a) Based on oral or axillary temperature

During the observation period, Grade ≥3 unsolicited adverse events occurred in 2 subjects in the Covgoze group (COVID-19 and cerebral haemorrhage in 1 subject each) and 1 subject in the Vaxzevria group (hyperlipidaemia), and a causal relationship to the study vaccine was ruled out for all of them. The events in 2 subjects in the Covgoze group were both classified as serious adverse events and their outcome was “resolved” or “resolving.” The event in 1 subject in the Vaxzevria group was non-serious and its outcome was “not resolving” at the time of the data cutoff.

7.R.3.1.2 Adverse events with the booster dose

(a) Sub-part in Study U0222

Table 56 shows incidences of solicited local adverse events and solicited systemic adverse events in the naïve adult group, previously-vaccinated adult group, and previously-infected adult group in Cohort A as well as Cohort B in the sub-part in Study U0222. In the naïve adult group and Cohort B, incidences of erythema/redness, induration, and swelling (solicited local adverse events) and pyrexia, nausea/vomiting, headache, malaise, and myalgia (solicited systemic adverse events) tended to increase with the increasing number of doses (Tables 52 and 56). Table 57 shows incidences of solicited local adverse events and solicited systemic adverse events of Grade ≥3 in severity. The incidences of Grade 3 solicited adverse events were similar to or tended to be higher than those with the primary series (Tables 53 and 57). No Grade 4 or 5 solicited local adverse events occurred. Grade 4 solicited systemic adverse events (Grade 4 pyrexia) occurred in 3 subjects in the naïve adult group. The time to onset and duration of solicited adverse events are as follows: For any event in any group, the median time to onset and duration, respectively, of solicited local adverse events were 1.0 to 2.0 days and 2.5 to 4.0 days after the vaccination, and the median time to onset and duration, respectively, of solicited systemic adverse events were 1.0 to 3.0 days and 1.0 to 3.0 days after the vaccination.

Table 56. Incidences of solicited adverse events within 7 days after Covgoze vaccination (sub-part in Study U0222, safety analysis population)

Event		Cohort A						Cohort B	
		Naïve adult		Previously-vaccinated adult		Previously-infected adult			
		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Local	Overall	2,137	1,938 (90.7)	55	50 (90.9)	51	48 (94.1)	88	73 (83.0)
	Pain	2,137	1,899 (88.9)	55	50 (90.9)	51	46 (90.2)	88	65 (73.9)
	Erythema/redness	2,137	761 (35.6)	55	4 (7.3)	51	18 (35.3)	88	41 (46.6)
	Induration	2,137	830 (38.8)	55	9 (16.4)	51	16 (31.4)	88	41 (46.6)
	Swelling	2,137	851 (39.8)	55	6 (10.9)	51	16 (31.4)	88	37 (42.0)
Systemic	Overall	2,137	1,803 (84.4)	55	39 (70.9)	51	40 (78.4)	88	49 (55.7)
	Pyrexia[a)]	2,137	722 (33.8)	55	4 (7.3)	51	13 (25.5)	88	11 (12.5)
	Nausea/vomiting	2,137	841 (39.4)	55	11 (20.0)	51	17 (33.3)	88	18 (20.5)
	Diarrhoea	2,137	156 (7.3)	55	3 (5.5)	51	3 (5.9)	88	2 (2.3)
	Headache	2,137	1,191 (55.7)	55	22 (40.0)	51	29 (56.9)	88	21 (23.9)
	Malaise	2,137	1,564 (73.2)	55	32 (58.2)	51	35 (68.6)	88	40 (45.5)
	Myalgia	2,137	1,100 (51.5)	55	17 (30.9)	51	29 (56.9)	88	24 (27.3)

N, Number of subjects evaluated; n, Number of subjects with events

a) Axillary temperature

Table 57. Incidences of Grade ≥3 solicited adverse events within 7 days after Covgoze vaccination (sub-part in Study U0222, safety analysis population)

Event		Cohort A						Cohort B	
		Naïve adult		Previously-vaccinated adult		Previously-infected adult			
		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Local	Overall	2,137	188 (8.8)	55	1 (1.8)	51	2 (3.9)	88	7 (8.0)
	Pain	2,137	13 (0.6)	55	0	51	0	88	0
	Erythema/redness	2,137	123 (5.8)	55	0	51	1 (2.0)	88	6 (6.8)
	Induration	2,137	54 (2.5)	55	0	51	0	88	2 (2.3)
	Swelling	2,137	98 (4.6)	55	1 (1.8)	51	1 (2.0)	88	2 (2.3)
Systemic	Overall	2,137	114 (5.3)	55	1 (1.8)	51	3 (5.9)	88	1 (1.1)
	Pyrexia[a)]	2,137	64 (3.0)	55	1 (1.8)	51	1 (2.0)	88	1 (1.1)
	Nausea/vomiting	2,137	0	55	0	51	0	88	0
	Diarrhoea	2,137	0	55	0	51	0	88	0
	Headache	2,137	19 (0.9)	55	0	51	1 (2.0)	88	0
	Malaise	2,137	41 (1.9)	55	0	51	1 (2.0)	88	0
	Myalgia	2,137	15 (0.7)	55	0	51	0	88	0

N, Number of subjects evaluated; n, Number of subjects with events
a) Axillary temperature

Table 58 shows incidences of unsolicited adverse events and unsolicited adverse reactions in the sub-part in Study U0222 reported by the second data-cutoff date (median observation period [range]; 29.0 days [1-80 days] in the naïve adult group, 29.0 days [26-49 days] in the previously-vaccinated adult group, 29.0 days [15-64 days] in the previously-infected adult group, 29.0 days [1-78 days] in the other adult group, 29.0 days [27-31 days] in the other elderly group, 29.0 days [1-38 days] in Cohort B). Grade ≥3 unsolicited adverse events occurred in 7 subjects in the naïve adult group (tuberculosis, diarrhoea, cholecystitis, hepatic function abnormal, urticaria, vaccination site swelling, upper limb fracture, and radial head dislocation in 1 subject each [1 subject had mora than 1 event]), 1 subject in the other elderly group (vertigo), and 1 subject in Cohort B (brain neoplasm). Grade ≥3 unsolicited adverse reactions for which a causal relationship to the study vaccine could not be ruled out occurred in 1 subject in the naïve adult group (vaccination site swelling).

Table 58. Incidences of unsolicited adverse events and unsolicited adverse reactions after Covgoze vaccination (sub-part in Study U0222, safety analysis population)

		N	Unsolicited adverse events		Unsolicited adverse reactions	
			All events, n (%)	Grade ≥3, n (%)	All events, n (%)	Grade ≥3, n (%)
Cohort A	Overall	2,291	180 (7.9)	8 (0.3)	91 (4.0)	1 (0.0)
	Naïve adult	2,137	170 (8.0)	7 (0.3)	88 (4.1)	1 (0.0)
	Previously-vaccinated adult	55	4 (7.3)	0	1 (1.8)	0
	Previously-infected adult	51	5 (9.8)	0	2 (3.9)	0
	Other adult	44	0	0	0	0
	Other elderly	4	1 (25.0)	1 (25.0)	0	0
Cohort B		88	8 (9.1)	1 (1.1)	5 (5.7)	0

N, Number of subjects evaluated; n, Number of subjects with events

(b) Study U0224

Table 32 shows incidences of solicited local adverse events and solicited systemic adverse events in Study U0224. Grade ≥3 solicited local adverse events occurred in 3 subjects (2.9%) in Cohort A (swelling in 2 subjects, pain and erythema/redness in 1 subject each) and 1 subject (4.3%) in Cohort C (erythema/redness), and all of them were assessed as adverse reactions. In Cohort B, no Grade ≥3 solicited adverse events occurred. Neither Grade ≥4 solicited local adverse events nor Grade ≥3 solicited systemic adverse events occurred in any cohort. The time to onset and duration of solicited adverse events are as follows: For any event in any cohort, the median time to onset and duration, respectively, of solicited local adverse events were 1.0 to 2.0 days and 3.0 to 5.0 days after the

vaccination, and the median time to onset and duration, respectively, of solicited systemic adverse events were 1.0 to 3.0 days and 2.0 to 4.0 days after the vaccination.

During the observation period, unsolicited adverse events occurred in 13.6% (14 of 103 subjects) in Cohort A, 6.9% (2 of 29 subjects) in Cohort B, and 13.0% (3 of 23 subjects) in Cohort C, and unsolicited adverse reactions occurred in 5 subjects (4.9%) in Cohort A. Unsolicited adverse events of Grade ≥3 in severity were pancreatic carcinoma and pancreatitis in 1 subject (4.3%) in Cohort C, and pancreatitis resolved but pancreatic carcinoma did not. A causal relationship to Covgoze was ruled out for all of these events.

(c) Incidences of unsolicited adverse events in Study U0223

Incidences of unsolicited adverse events in Study U0223 (84.2% in the Covgoze group, 84.5% in the Comirnaty group) were greatly different from those in the sub-part in Study U0222 (7.9% in Cohort A, 9.1% in Cohort B) and Study U0224 (13.6% in Cohort A, 6.9% in Cohort B, 13.0% in Cohort C), which were conducted for evaluation of the Covgoze booster dose. Most of the unsolicited adverse events observed in Study U0223 were related to laboratory tests (neutrophil percentage increased, C-reactive protein increased, and white blood cell count increased) (Table 27), and none of them were Grade ≥3. The laboratory values became higher on the day after the study vaccination (Day 2) than those before that (baseline) but returned to the baseline values 14 days after the vaccination (Day 15). Study U0224 also showed a similar trend of changes in these laboratory values over time. Such different incidences of unsolicited adverse events among the studies were considered attributable to the design of Study U0223, which was conducted at a single study site. Identification of reportable adverse events performed by the investigators at this site was considered to have a potential impact. For the adverse events with the incidence higher than that in the other studies, the incidences in Study U0223 were similar in the Covgoze group and Comirnaty group; no Grade ≥3 events occurred; and the recovery was confirmed. Even with the incidences of unsolicited adverse events in Study U0223 taken into account, based on the above findings, the Covgoze booster dose is considered to raise no substantial safety concern.

7.R.3.2 Adverse events by age group

The safety profile of Covgoze by age group (elderly aged ≥65 years/adults aged <65 years) is as follows.

Table 59 shows a summary of adverse events by age group at the time of the primary series, and Table 60 shows incidences of solicited adverse events and Grade ≥3 solicited adverse events after each dose, in Study U0231. In the Covgoze group in Study U0231, the incidences of solicited adverse events, unsolicited adverse events, and Grade ≥3 solicited adverse events tended to be lower in the elderly aged ≥65 years than in the adults aged 20 to 64 years.

Table 59. Summary of adverse events by age group (Study U0231, safety analysis population)

	20-64 years		≥65 years	
	Covgoze (N = 585)	Vaxzevria (N = 584)	Covgoze (N = 26)	Vaxzevria (N = 26)
Solicited local adverse events	534 (91.3)	501 (85.8)	20 (76.9)	18 (69.2)
Solicited local adverse reactions	534 (91.3)	501 (85.8)	20 (76.9)	18 (69.2)
Solicited systemic adverse events	435 (74.4)	475 (81.3)	12 (46.2)	14 (53.8)
Solicited systemic adverse reactions	435 (74.4)	475 (81.3)	12 (46.2)	14 (53.8)
Unsolicited adverse events	114 (19.5)	86 (14.7)	2 (7.7)	5 (19.2)
Unsolicited adverse reactions	31 (5.3)	23 (3.9)	2 (7.7)	3 (11.5)

Number of subjects with events (%); N, Number of subjects analyzed

Table 60. Incidences of solicited adverse events after each study vaccination by age group (Study U0231, safety analysis population)

		20-64 years				≥65 years			
		Overall		Grade ≥3		Overall		Grade ≥3	
		Covgoze	Vaxzevria	Covgoze	Vaxzevria	Covgoze	Vaxzevria	Covgoze	Vaxzevria
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local	**First dose**	N = 585	N = 584	N = 585	N = 584	N = 26	N = 26	N = 26	N = 26
	Overall	469 (80.2)	470 (80.5)	2 (0.3)	2 (0.3)	16 (61.5)	17 (65.4)	0	0
	Pain	461 (78.8)	464 (79.5)	0	1 (0.2)	16 (61.5)	16 (61.5)	0	0
	Erythema/redness	34 (5.8)	56 (9.6)	0	1 (0.2)	0	4 (15.4)	0	0
	Induration	40 (6.8)	38 (6.5)	1 (0.2)	1 (0.2)	3 (11.5)	1 (3.8)	0	0
	Swelling	48 (8.2)	43 (7.4)	2 (0.3)	0	2 (7.7)	1 (3.8)	0	0
	Second dose	N = 547	N = 550	N = 547	N = 550	N = 24	N = 24	N = 24	N = 24
	Overall	452 (82.6)	309 (56.2)	24 (4.4)	0	17 (70.8)	13 (54.2)	1 (4.2)	0
	Pain	440 (80.4)	300 (54.5)	3 (0.5)	0	17 (70.8)	12 (50.0)	0	0
	Erythema/redness	76 (13.9)	29 (5.3)	17 (3.1)	0	3 (12.5)	2 (8.3)	1 (4.2)	0
	Induration	69 (12.6)	12 (2.2)	6 (1.1)	0	3 (12.5)	0	0	0
	Swelling	99 (18.1)	25 (4.5)	14 (2.6)	0	5 (20.8)	2 (8.3)	0	0
Systemic	**First dose**	N = 585	N = 584	N = 585	N = 584	N = 26	N = 26	N = 26	N = 26
	Overall	297 (50.8)	457 (78.3)	9 (1.5)	47 (8.0)	7 (26.9)	13 (50.0)	0	2 (7.7)
	Pyrexia[a)]	38 (6.5)	175 (30.0)	5 (0.9)	25 (4.3)	0	3 (11.5)	0	1 (3.8)
	Nausea/vomiting	50 (8.5)	109 (18.7)	1 (0.2)	1 (0.2)	0	2 (7.7)	0	0
	Diarrhoea	36 (6.2)	79 (13.5)	0	2 (0.3)	1 (3.8)	3 (11.5)	0	0
	Headache	140 (23.9)	281 (48.1)	1 (0.2)	7 (1.2)	2 (7.7)	7 (26.9)	0	0
	Malaise	170 (29.1)	344 (58.9)	3 (0.5)	20 (3.4)	2 (7.7)	5 (19.2)	0	1 (3.8)
	Myalgia	149 (25.5)	230 (39.4)	2 (0.3)	10 (1.7)	4 (15.4)	6 (23.1)	0	1 (3.8)
	Second dose	N = 547	N = 550	N = 547	N = 550	N = 24	N = 24	N = 24	N = 24
	Overall	362 (66.2)	231 (42.0)	24 (4.4)	3 (0.5)	11 (45.8)	9 (37.5)	0	0
	Pyrexia[a)]	112 (20.5)	14 (2.5)	15 (2.7)	1 (0.2)	1 (4.2)	1 (4.2)	0	0
	Nausea/vomiting	85 (15.5)	27 (4.9)	1 (0.2)	0	0	2 (8.3)	0	0
	Diarrhoea	32 (5.9)	34 (6.2)	0	0	0	2 (8.3)	0	0
	Headache	219 (40.0)	107 (19.5)	2 (0.4)	0	4 (16.7)	5 (20.8)	0	0
	Malaise	273 (49.9)	141 (25.6)	13 (2.4)	1 (0.2)	7 (29.2)	5 (20.8)	0	0
	Myalgia	177 (32.4)	93 (16.9)	6 (1.1)	1 (0.2)	6 (25.0)	6 (25.0)	0	0

N, Number of subjects analyzed; n, Number of subjects with events
a) Based on oral or axillary temperature

Table 61 shows a summary of adverse events by age group at the time of the primary series in the main part in Study U0222. Table 52 and Table 53 show incidences of solicited adverse events after each dose. The incidences in the elderly aged ≥65 years (Cohort B) tended to be lower than those in the non-elderly aged 20 to 64 years. The incidences of unsolicited adverse events were higher in the elderly than in the other groups, but unsolicited adverse events mainly observed in the elderly were pruritus and vaccination site pruritus (Table 20), and the profile of adverse events did not tend to differ from that in the population aged 20 to 64 years.

Table 61. Summary of adverse events by age group (main part in Study U0222, safety analysis population)

	20-64 years			≥65 years
	Naïve adult (N = 2,952)	Previously-vaccinated adult (N = 76)	Previously-infected adult (N = 68)	Cohort B (N = 118)
Solicited local adverse events	2,818 (95.5)	75 (98.7)	66 (97.1)	97 (82.2)
Solicited local adverse reactions	2,817 (95.4)	75 (98.7)	66 (97.1)	97 (82.2)
Solicited systemic adverse events	2,387 (80.9)	61 (80.3)	61 (89.7)	63 (53.4)
Solicited systemic adverse reactions	2,386 (80.8)	61 (80.3)	60 (88.2)	63 (53.4)
Unsolicited adverse events	,582 (19.7)	16 (21.1)	18 (26.5)	42 (35.6)
Unsolicited adverse reactions	,232 (7.9)	3 (3.9)	10 (14.7)	17 (14.4)

Number of subjects with events (%); N, Number of subjects analyzed

Table 62 shows a summary of adverse events by age group at the time of the booster dose in the sub-part in Study U0222. Incidences of solicited adverse events tended to be lower in the elderly than in the non-elderly.

Table 62. Summary of adverse events by age group (sub-part in Study U0222, safety analysis population)

	20-64 years			≥65 years
	Naïve adult (N = 2,137)	Previously-vaccinated adult (N = 55)	Previously-infected adult (N = 51)	Cohort B (N = 88)
Solicited local adverse events/ adverse reactions	1,938 (90.7)	50 (90.9)	48 (94.1)	73 (83.0)
Grade ≥3	188 (8.8)	1 (1.8)	2 (3.9)	7 (8.0)
Solicited systemic adverse events/ adverse reactions	1,803 (84.4)	39 (70.9)	40 (78.4)	49 (55.7)
Grade ≥3	114 (5.3)	1 (1.8)	3 (5.9)	1 (1.1)
Unsolicited adverse events	170 (8.0)	4 (7.3)	5 (9.8)	8 (9.1)
Grade ≥3	7 (0.3)	0	0	1 (1.1)
Unsolicited adverse reactions	88 (4.1)	1 (1.8)	2 (3.9)	5 (5.7)
Grade ≥3	1 (0.0)	0	0	0

Number of subjects with events (%); N, Number of subjects analyzed

Table 63 shows a summary of adverse events after the booster dose in Study U0224. Incidences of solicited adverse events tended to be lower in the elderly than in the non-elderly.

Table 63. Summary of adverse events by age group (Study U0224, safety analysis population)

	20-64 years	≥65 years	
	Cohort A (N = 103)	Cohort B (N = 29)	Cohort C (N = 23)
Solicited local adverse events	97 (94.2)	23 (79.3)	20 (87.0)
Grade ≥3	3 (2.9)	0	1 (4.3)
Solicited local adverse reactions	97 (94.2)	23 (79.3)	19 (82.6)
Grade ≥3	3 (2.9)	0	1 (4.3)
Solicited systemic adverse events/adverse reactions	70 (68.0)	10 (34.5)	13 (56.5)
Grade ≥3	0	0	0
Unsolicited adverse events	14 (13.6)	2 (6.9)	3 (13.0)
Grade ≥3	0	0	1 (4.3)
Unsolicited adverse reactions	5 (4.9)	0	0
Grade ≥3	0	0	0

Number of subjects with events (%); N, Number of subjects analyzed

The review on the above incidences of adverse events by age group indicated that the safety in the elderly aged ≥65 years after the primary series and booster doses was not greatly different from that in the adults aged <65 years, raising no critical concerns.

7.R.3.3 Serious adverse events

The following is the data (as of March 16, 2023) regarding (a) serious adverse events occurring after the data cutoff of the clinical studies included in the submitted evaluation data and (b) serious adverse events reported in Study U0232 ongoing outside Japan.

Up to the data cutoff in Study U0231, 6 serious adverse events occurred in 6 subjects in the Covgoze group (COVID-19 in 4 subjects, duodenal ulcer and cerebral haemorrhage in 1 subject each), but a causal relationship to the study vaccine was ruled out for all of them. For outcome, the events resolved or were resolving. After the data cutoff, 16 serious adverse events[48)] in 16 subjects were reported after Covgoze vaccination (lumbar spinal stenosis, tonsillar hypertrophy, cerebral infarction, abortion spontaneous, epilepsy, subarachnoid haemorrhage, gastric cancer, chronic tonsillitis, organ failure, vertigo, campylobacter gastroenteritis, osteoarthritis, hand fracture, pancreatitis necrotising, depression, and lymphoma in 1 subject each), and a causal relationship to Covgoze was ruled out for all of them. For outcome, the events in 2 subjects (lumbar spinal stenosis and lymphoma in 1 subject each) did not resolve and event in 1 subject (cerebral infarction) resolved with sequelae, but all of the rest resolved or were resolving.

Up to the second data cutoff in the main part in Study U0222, cardiac failure acute occurred and lead to death in 1 subject in Cohort B, but the causal relationship to the study vaccine was ruled out. A total of 33 serious adverse events occurred in 32 subjects (27 subjects in the naïve adult group [pyrexia in 2 subjects, COVID-19, angina pectoris, cerebral haemorrhage, diabetic gangrene, testis cancer, abortion spontaneous, osteoarthritis, abortion missed, traumatic fracture, cardiac failure, rectal cancer, clavicle fracture, eosinophilic pneumonia chronic, cervix carcinoma stage 0, peritonsillar abscess, enterocolitis, thyroid neoplasm, breast cancer recurrent, gingivitis, appendicitis, colitis ischaemic, back pain, type 2 diabetes mellitus, foot fracture, cholelithiasis, and postoperative wound infection in 1 subject each (1 subject had more than 1 event)], 2 subjects in the previously-infected adult group [atrial fibrillation and tendon rupture in 1 subject each], 1 subject in the other elderly group [inguinal hernia], 2 subjects in Cohort B [prostate cancer and endometrial cancer in 1 subject each]). A causal relationship to the study vaccine was ruled out for all of the adverse events. For outcome, all of them resolved or were resolving, except diabetic gangrene, breast cancer recurrent, and endometrial cancer. After the second data cutoff, 8 serious adverse events in 7 subjects were reported after Covgoze vaccination (tonsillitis, osteoarthritis, thoracic outlet syndrome, hypopharyngeal cancer, inguinal hernia, uterine leiomyoma, and spinal compression fracture in 1 subject each). For outcome, inguinal hernia and spinal compression fracture did not resolve, but all of the rest resolved or were resolving.

Up to the data cutoff in the sub-part in Study U0222, 8 serious adverse events occurred in 8 subjects (6 subjects in the naïve adult group [urticaria, tuberculosis, cholecystitis, upper limb fracture, radial head dislocation, and varicocele in 1 subject each], 1 subject in the other elderly group [vertigo], 1 subject in Cohort B [brain neoplasm]). A causal relationship to the study vaccine was ruled out for all of the adverse events. For outcome, all of them resolved or were resolving, except cholecystitis and brain

[48)] According to the revised protocol, a booster-dose part was planned to investigate the safety and immunogenicity of Covgoze administered as the third dose on Day 211 in the subjects in Study U0231 who wished the Covgoze booster dose (Protocol ver. 5, dated June 15, 2022). Including serious adverse events in the subjects who were initially allocated to the Vaxzevria group in this study and received Covgoze on Day 211.

neoplasm (including the information on the outcome confirmed after the data cutoff). After the data cutoff in the sub-part in this study, 9 serious adverse events occurred in 8 subjects (mechanical ileus, colon cancer, lower limb fracture, appendicitis perforated, ovarian neoplasm, invasive ductal breast carcinoma, COVID-19, and uterine cancer in 1 subject each). For outcome, all of them resolved or were resolving, except colon cancer and invasive ductal breast carcinoma.

Up to the data cutoff in Study U0223, no serious adverse events were reported. After the data cutoff in Study U0223, 2 serious adverse events occurred in 2 subjects after Covgoze vaccination (tonsillitis bacterial and atrial fibrillation in 1 subject each). For outcome, atrial fibrillation in 1 subject did not resolve, and tonsillitis bacterial in 1 subject resolved. Up to the data cutoff in Study U0224, 1 serious adverse event occurred in 1 subject (pancreatic carcinoma), but the causal relationship to Covgoze was ruled out. After the data cutoff, 2 serious adverse events occurred in 2 subjects (brain stem infarction and loose body in joint in 1 subject each); both resolved, but brain stem infarction resolved with sequelae. After the data cutoff in Study U0221, no serious adverse events occurred.

In the subjects who had received Covgoze as the most recent dose (including subjects who had been initially allocated to the placebo group and received Covgoze on Day 225 in a crossover manner) in Study U0232, 178 serious adverse events were reported in 147 subjects. Events reported by ≥2 subjects were death in 10 subjects, COVID-19 in 7 subjects, pneumonia in 6 subjects, bronchitis in 5 subjects, appendicitis, gastritis and headache in 4 subjects each, vestibular disorder, anaemia, rickettsiosis, angina pectoris, pancreatitis acute, and hypertension in 3 subjects each, and craniocerebral injury, hepatic cirrhosis, cerebrovascular accident, road traffic accident, multiple injuries, soft tissue injury, arthritis, respiratory failure, epilepsy, wound, abscess limb, chest injury, gastrooesophageal reflux disease, tuberculosis, completed suicide, back pain, cardiac failure, psychotic disorder, sciatica, and asthma in 2 subjects each. In the subjects who had been initially allocated to the Covgoze group and received the placebo on Day 225 in a crossover manner, 45 serious adverse events were reported in 42 subjects. Events reported by ≥2 subjects were pneumonia in 4 subjects, vestibular disorder in 3 subjects, and limb injury, hepatic cirrhosis, craniocerebral injury, bronchitis, and death in 2 subjects each. In Study U0232, 1 subject experienced a serious adverse event (headache). Its causal relationship to Covgoze could not be ruled out, but its outcome was “resolved.”

7.R.3.4 Adverse events of special interest

The risks identified for the other SARS-CoV-2 vaccines, including adverse events of special interest evaluated in the clinical studies, were investigated and the results are described below:

(a) Adverse events of special interest

In the clinical studies of Covgoze, which was a vaccine containing adjuvant, potential immune-mediated diseases were collected as adverse events of special interest. The potential immune-mediated diseases were defined in the protocol based on the definitions in clinical studies of the other vaccines (*Lancet Infect Dis.* 2021;21:1257-70, *Vaccine.* 2013;31:1870-6).

Adverse events of special interest were collected up to the data cutoff in each of the clinical studies. In Study U0222, such events occurred in 5 subjects who had received Covgoze for the primary series

(gout in 4 subjects in the naïve adult group, alopecia areata in 1 subject in Cohort B). A causal relationship to the study vaccine was ruled out for all the events of gout. A causal relationship to the study vaccine could not be ruled out for alopecia areata, and its outcome was "not resolved." These events were all non-serious and Grade 1 or 2 for severity. In the sub-part in Study U0222 and Studies U0223 and U0224, which were conducted for evaluation of the booster dose, no adverse events of special interest occurred.

(b) Shock and anaphylaxis

The risk of shock and anaphylaxis after Covgoze administration was evaluated, because package inserts of the existing vaccines have raised caution about this risk. Up to the data cutoff in each of the clinical studies, no adverse events corresponding to shock or anaphylaxis were reported. Furthermore, the events meeting the definitions of MedDRA SMQ "Anaphylactic reaction" (broad), which include event terms related to shock and anaphylaxis, were observed as adverse reactions in the clinical studies. The observed adverse reactions were pruritus in 58 subjects (1.6%), urticaria in 9 subjects (0.2%), and rash in 6 subjects (0.2%) in Studies U0222 and U0231 for evaluation of the primary series (3,681 subjects in total); and pruritus in 23 subjects (0.9%) and rash in 2 subjects (0.1%) in Studies U0222, U0223, and U0224 for evaluation of the booster dose (2,551 subjects in total). Although Covgoze uses a protein antigen as the active substance, it may have a risk of shock and anaphylaxis as with the other vaccines. The applicant will include a cautionary statement about the risk in the package insert and conduct post-marketing pharmacovigilance activities.

(c) Myocarditis and pericarditis

The risk management plans (RMPs) of the existing SARS-CoV-2 vaccines (mRNA vaccines [Comirnaty and Spikevax] or a recombinant protein vaccine [Nuvaxovid]) include myocarditis and pericarditis in the safety specification to raise cautions, and their incidences have been continuously evaluated. Events reported as MedDRA preferred terms of autoimmune myocarditis, eosinophilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, myocarditis, autoimmune pericarditis, pericarditis, pericarditis adhesive, pericarditis constrictive, and pleuropericarditis were defined as myocarditis and pericarditis, and their incidences in the clinical studies of Covgoze were checked. Up to the data cutoff in each of the clinical studies (up to the second data cutoff in Study U0222), no adverse events corresponding to myocarditis or pericarditis were reported.

In Japan, the RMP of the recombinant protein vaccine, which has the same modality as that of Covgoze, does not include myocarditis or pericarditis as the identified risk, and the RMP of the approved SARS-CoV-2 vaccine using virus vector does not include myocarditis or pericarditis in the safety specification. Accordingly, myocarditis and pericarditis are not considered as a common risk of SARS-CoV-2 vaccines irrespective of the modality. The applicant thus will not include myocarditis or pericarditis in the safety specification in the RMP of Covgoze, but instead will check the updated safety information of the other existing SARS-CoV-2 vaccines or incidences of myocarditis or pericarditis in the ongoing clinical studies of Covgoze, and raise caution where necessary.

7.R.3.5 Safety in special populations

The safety profiles of Covgoze in individuals with a risk factor of severe COVID-19 and pregnant or lactating women are described below.

(a) Individuals with a risk factor of severe COVID-19

The safety in individuals with a risk factor of severe COVID-19 was investigated using the results from Studies U0222 and U0231, which included individuals with a risk factor of severe COVID-19 such as those with underlying diseases in the study population.

For safety of the primary series, Table 64 and Table 65 show incidences of adverse events and adverse reactions in the main part in Study U0222 (naïve adult group, previously-infected adult group, Cohort B) and Study U0231 (Covgoze group and Vaxzevria group) in subjects with and without a risk factor of severe COVID-19 (defined as ≥65 years of age, malignancies, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, hypertension, dyslipidaemia, obesity with body mass index (BMI) ≥30, smoking, immunodeficiency after solid organ transplantation, and late pregnancy). The incidences of adverse events did not greatly differ between individuals with and without a risk factor of the severe disease. The subjects in Cohort B in Study U0222 were all aged ≥65 years and were thus collectively handled as those with a risk factor of the severe disease.

Table 64. Adverse events and adverse reactions after the primary series in subjects with and without a risk factor of severe COVID-19[a)] (main part in Study U0222, safety analysis population)

	Naïve adult		Previously-infected adult		Cohort B
	With a risk factor (N = 1,129)	Without a risk factor (N = 1,823)	With a risk factor (N = 28)	Without a risk factor (N = 40)	With a risk factor (elderly) (N = 118)
Solicited local adverse events	1,066 (94.4)	1,752 (96.1)	26 (92.9)	40 (100.0)	97 (82.2)
Solicited local adverse reactions	1,066 (94.4)	1,751 (96.1)	26 (92.9)	40 (100.0)	97 (82.2)
Solicited systemic adverse events	877 (77.7)	1,510 (82.8)	26 (92.9)	35 (87.5)	63 (53.4)
Solicited systemic adverse reactions	876 (77.6)	1,510 (82.8)	25 (89.3)	35 (87.5)	63 (53.4)
Unsolicited adverse events	222 (19.7)	360 (19.7)	6 (21.4)	12 (30.0)	42 (35.6)
Unsolicited adverse reactions	87 (7.7)	145 (8.0)	4 (14.3)	6 (15.0)	17 (14.4)

Number of subjects with events (%); N, Number of subjects analyzed

a) Elderly aged ≥65 years, malignancies, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, hypertension, dyslipidaemia, obesity with BMI ≥30, smoking, immunodeficiency after solid organ transplantation, and late pregnancy

Table 65. Adverse events and adverse reactions after the primary series in subjects with and without a risk factor of severe COVID-19[a)] (Study U0231, safety analysis population)

	With a risk factor		Without a risk factor	
	Covgoze (N = 241)	Vaxzevria (N = 256)	Covgoze (N = 370)	Vaxzevria (N = 354)
Solicited local adverse events	215 (89.2)	211 (82.4)	339 (91.6)	308 (87.0)
Solicited local adverse reactions	215 (89.2)	211 (82.4)	339 (91.6)	308 (87.0)
Solicited systemic adverse events	170 (70.5)	197 (77.0)	277 (74.9)	292 (82.5)
Solicited systemic adverse reactions	170 (70.5)	197 (77.0)	277 (74.9)	292 (82.5)
Unsolicited adverse events	42 (17.4)	44 (17.2)	74 (20.0)	47 (13.3)
Unsolicited adverse reactions	13 (5.4)	15 (5.9)	20 (5.4)	11 (3.1)

N, Number of subjects analyzed; Number of subjects with events (%)

a) Elderly aged ≥65 years, malignancies, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, hypertension, dyslipidaemia, obesity with BMI ≥30, smoking, immunodeficiency after solid organ transplantation, and late pregnancy

The safety profile of the booster dose in subjects with and without a risk factor of severe COVID-19 was analyzed in the following A to E populations, which were formed based on the study vaccine used

for the primary series and booster dose. The results are shown in Table 66. The incidences of adverse events did not greatly differ between individuals with and without a risk factor of severe COVID-19.

A) Analysis in the subjects who received 2 doses of the Comirnaty primary series and then a single Covgoze booster dose, using results in the previously-vaccinated adult group in the main part in Study U0222, the Covgoze group in Study U0223, and Cohort B in Study U0224
B) Analysis in the subjects who received 2 doses of the Spikevax primary series and then a single Covgoze booster dose, using results in Cohort A and Cohort C in Study U0224
C) Analysis in the subjects who received 2 doses of the Covgoze the primary series in the main part in Study U0222 and then a single Covgoze booster dose, using results in the naïve adult group and Cohort B in Study U0222
D) Analysis using results in the previously-infected adult group, which received 2 doses of the Covgoze primary series in the main part in Study U0222 and then a single Covgoze booster dose
E) Analysis in the subjects who received 2 doses of the Comirnaty primary series and then a single booster dose of Comirnaty, using results in the Comirnaty group in Study U0223

Table 66. Adverse events and adverse reactions with the booster dose in subjects with and without a risk factor of severe COVID-19[a)] (safety analysis population)

	A	B	C	D	E
Studies analyzed	Pool of Studies U0222, U0224, and U0223	Study U0224	Study U0222 (naïve adult + Cohort B)	Study U0222 (previously-infected)	Study U0223
Vaccine for primary series	Comirnaty	Spikevax	Covgoze	Covgoze	Comirnaty
Vaccine for booster dose	Covgoze	Covgoze	Covgoze	Covgoze	Comirnaty
With a risk factor					
	N = 95	N = 71	N = 938	N = 21	N = 46
Solicited local adverse events	78 (82.1)	65 (91.5)	821 (87.5)	20 (95.2)	34 (73.9)
Solicited local adverse reactions	78 (82.1)	64 (90.1)	821 (87.5)	20 (95.2)	34 (73.9)
Solicited systemic adverse events	55 (57.9)	46 (64.8)	741 (79.0)	16 (76.2)	35 (76.1)
Solicited systemic adverse reactions	55 (57.9)	46 (64.8)	741 (79.0)	16 (76.2)	35 (76.1)
Unsolicited adverse events	39 (41.1)	8 (11.3)	77 (8.2)	3 (14.3)	38 (82.6)
Unsolicited adverse reactions	33 (34.7)	3 (4.2)	38 (4.1)	1 (4.8)	37 (80.4)
Without a risk factor					
	N = 105	N = 55	N = 1,287	N = 30	N = 57
Solicited local adverse events	83 (79.0)	52 (94.5)	1,190 (92.5)	28 (93.3)	41 (71.9)
Solicited local adverse reactions	83 (79.0)	52 (94.5)	1,190 (92.5)	28 (93.3)	41 (71.9)
Solicited systemic adverse events	73 (69.5)	37 (67.3)	1,111 (86.3)	24 (80.0)	47 (82.5)
Solicited systemic adverse reactions	73 (69.5)	37 (67.3)	1,111 (86.3)	24 (80.0)	47 (82.5)
Unsolicited adverse events	58 (55.2)	9 (16.4)	101 (7.8)	2 (6.7)	49 (86.0)
Unsolicited adverse reactions	52 (49.5)	2 (3.6)	55 (4.3)	1 (3.3)	48 (84.2)

Number of subjects with events (%); N, Number of subjects analyzed

a) Elderly aged ≥65 years, malignancies, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, hypertension, dyslipidaemia, obesity with BMI ≥30, smoking, immunodeficiency after solid organ transplantation, and late pregnancy

(b) Pregnant women and lactating women

The clinical studies of Covgoze excluded pregnant or potentially pregnant women and lactating women. According to the information about use of Covgoze in pregnant women up to February 8, 2023, among subjects who received Covgoze in Japanese Studies U0222 and U0231, 7 subjects (6 in Study U0222 and 1 in Study U0231) were found pregnant, and abortion spontaneous in 2 subjects and abortion missed in 1 subject were reported as serious adverse events. A causal relationship to the study vaccine was ruled out for all of them. Other than these serious adverse events, adverse events occurring in the pregnant subjects were all solicited adverse events of Grade ≤2 for severity, and the outcome of all of them was “resolved.”

In Study U0232 ongoing outside Japan (because of its crossover design, the number of subjects was summed according to the most recent study vaccine administered before the pregnancy was found), up to February 8, 2023, pregnancy was found in 33 subjects who received Covgoze and 25 subjects who received placebo, as the most recent dose. Serious adverse events reported were abortion spontaneous in 2 subjects (1 subject each last vaccinated with Covgoze and placebo), mother's death and foetal death in 1 subject last vaccinated with placebo, and talipes in 1 subject last vaccinated with placebo. A causal relationship to the study vaccine was ruled out for all of them. Other than the serious adverse events, adverse events were mostly solicited adverse events, and all were at Grade ≤2 for severity except for Grade 3 pyrexia in 1 subject. An unsolicited adverse event of Grade 3 tachycardia occurred in 1 subject, but its causal relationship to the study vaccine was ruled out.

Adverse events related to pregnancy reported after Covgoze vaccination were all temporally unassociated with the study vaccination or suspected of involvement of the other factors; therefore their causal relationship with Covgoze is unclear. At present, 6 subjects reported to have had delivery (3 subjects each in Studies U0222 and U0232); none of them or their children have experienced adverse events.

As described above, the information obtained in the clinical studies and evaluation in non-clinical studies have not identified a risk of Covgoze in pregnant women, but the safety information of Covgoze in pregnant or potentially pregnant women is lacking at present. The applicant will conduct post-marketing pharmacovigilance activities, collect the information, and where necessary take appropriate safety measures. Because no information of Covgoze in lactating women is available, collection of the information and safety evaluation are considered necessary as done for vaccination in pregnant women.

7.R.3.6 Vaccine associated enhanced diseases (VAEDs)

In the clinical studies of Covgoze, (a) subjects who experienced VAED or vaccine-associated enhanced respiratory disease (VAERD) and (b) subjects who had severe COVID-19 after Covgoze vaccination were deemed as subjects with potential VAED or VAERD and analyzed, based on the Brighton Collaboration's guidelines for VAED evaluation (*Vaccine*. 2021;39:3053-66).

Neither VAED nor VAERD was reported up to the data cutoff after the Covgoze primary series in each of the clinical studies (up to the second data cutoff in Study U0222). Severe COVID-19 after the Covgoze primary series developed in 2 subjects each in Studies U0222 and U0231. The 2 subjects in Study U0222 were (a) a 5[redacted]-year old woman with comorbidities of type 2 diabetes mellitus and dyslipidaemia who developed severe COVID-19 on Day 116 of the second dose and (b) a 5[redacted]-year old man without comorbidities who developed severe COVID-19 on Day 109 of the second dose. The 2 subjects in Study U0231 were (a) a 2[redacted]-year old woman without comorbidities who developed severe COVID-19 on Day 2 of the first dose and (b) a 5[redacted]-year old woman without comorbidities who developed severe COVID-19 on Day 11 of the first dose. These cases of severe COVID-19 occurred in a subject with comorbidities or before the acquisition of immunity, except 1 case. No cases suggestive of definite VAED or VAERD have been observed. Up to the data cutoff in each of the clinical studies

for evaluation of the Covgoze booster dose, none of VAED, VAERD, and severe COVID-19 were reported.

Theoretically, the possibility of VAED occurring after Covgoze vaccination cannot be ruled out. VAED may aggravate respiratory diseases, and might lead to a critical outcome. The applicant will classify VAED and VAERD as important potential risks in the RMP and continuously monitor incidences of VAED and VAERD in post-marketing settings as well.

7.R.4 Clinical positioning and indication

The intended indication is "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)."
The applicant provided the following explanation about the clinical positioning of Covgoze:
As of March 2023, the Omicron variant of SARS-CoV-2 is predominant in Japan, and vaccines mainly used for official vaccination are bivalent, containing the active substances representative of the original strain and Omicron variant. These bivalent vaccines are used only for booster doses. For the primary series, monovalent vaccines only containing the active substance representative of the original strain are used.

Serum specimens collected from subjects in Study U0221, the main part in Study U0222, and Study U0231 for evaluation of the Covgoze primary series were measured for neutralizing antibody titers against major SARS-CoV-2 variants including previous variants of concern (VOC). Neutralizing activities against the D614G, Alfa, Beta, Gamma, and Delta variants were detected, but the neutralizing titer against the Omicron variant was below the LLOQ in many specimens [see Section 7.R.2.2.4]. Study U0232 conducted to evaluate the COVID-19-preventive effect of the Covgoze primary series revealed that the Covgoze primary series could not be expected to have a high disease-preventive effect in the prevalent of the Omicron variant but could be expected to have a similar effect to that of the primary series of approved SARS-CoV-2 vaccines [see Section 7.R.2.2.3].

Serum specimens collected from subjects who received the Covgoze booster dose in the sub-part in Study U0222 and Studies U0223 and U0224, were measured for neutralizing antibody titers against SARS-CoV-2 variants. Neutralizing activities against Omicron BA.1, BA.2, BA.2.12.1, BA.4.2, and BA.4-5 lineages were higher than those after the primary series, and similar neutralizing antibody titers were detected in the Comirnaty and Covgoze groups [see Section 7.R.2.3.3]. Based on the above results, the Covgoze booster dose can be expected to have efficacy against variants including the Omicron variant to a certain extent.

As of the end of March 2023, approximately 12 and 25 million people, respectively, in Japan are estimated to have not received the primary series (aged ≥20 years) and booster dose (aged ≥20 years, third dose).[49)] In the current SARS-CoV-2 vaccination program in Japan, Comirnaty (monovalent, original strain) and Nuvaxovid are used for the primary series (first and second doses) and Omicron-adapted bivalent vaccines (mRNA vaccines only) for booster doses (HSB Notification No. 0308-15 "Partial revision of 'Vaccination against COVID-19 [instruction] [in Japanese]'" MHLW

[49)] Calculated from "Results by age group (in Japanese)" published on March 27, 2023 (https://www.kantei.go.jp/jp/headline/kansensho/vaccine. html, last accessed on March 30, 2023)

dated March 8, 2023; and Interim Guidelines for Vaccination against COVID-19 [in Japanese] [updated on March 8, 2023]). For booster doses, Omicron-adapted bivalent vaccines are recommended, but Nuvaxovid containing the original strain-based antigen is also used as an option in individuals ineligible for mRNA vaccines owing to a medical history of allergy, etc., because a clinical study of a Nuvaxovid booster dose (third or fourth dose) showed that the booster dose (a) restored the neutralizing antibody titer that had decreased with time and (b) increased neutralizing activities against variants. Accordingly, Covgoze can be used as another option for the primary series and booster doses as with Nuvaxovid.

Although the intended target population in the present application is adults, a clinical study in individuals aged ≤19 years including children aged ≥5 years is ongoing to expand the eligible age range so that Covgoze will be offered as a new option in adolescents and children.

COVID-19 can be prevalent with repeated waves accompanying emergence of new variants and rapid spreading of the infection, and the necessity of vaccines adapted to variants currently prevalent or predicted to be prevalent is being discussed. The applicant is planning to develop a derived vaccine adapted to a new variant using Covgoze as the parent vaccine.

PMDA's view:
As of March 31, 2023, multiple drugs for treatment of SARS-CoV-2 infection and vaccines for prevention of COVID-19 are approved in Japan.

For the efficacy of the Covgoze primary series, its superiority to the control vaccine in GMT of neutralizing antibodies and its non-inferiority to the control vaccine in antibody response rate were investigated in Study U0231, a pivotal study for the efficacy evaluation [see Sections 7.3.1 and 7.R.2.2.3]. For the efficacy of the Covgoze booster dose, its non-inferiority to the control vaccine in GMT of neutralizing antibodies and antibody response rate was demonstrated in subjects who had completed the Comirnaty primary series in Study U0223, and the Covgoze booster dose was shown to restore the neutralizing antibody titer that once had decreased with time after the primary series irrespective of the vaccine modality used for the primary series [see Section 7.R.2.3]. Covgoze is considered tolerable because the safety profile presented in the clinical studies of Covgoze does not show any substantially different trend from those of approved SARS-CoV-2 vaccines.

In Japan, 80.2% of people have completed the primary series of approved SARS-CoV-2 vaccines, and 68.6% have received the first booster dose.[2)] Most of them received mRNA vaccines. On the other hand, there are some people who hesitate to receive mRNA vaccines or even vaccination itself because of concerns about adverse reactions of the mRNA vaccines and other various reasons. PMDA therefore considers it meaningful to approve Covgoze as a vaccine in a different modality from that of the mRNA vaccines and thereby add a new vaccine option for prevention of COVID-19. Under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Law), the category of COVID-19 is scheduled to be reclassified from the current Class 2 to Class 5, but the currently ongoing official vaccination is being planned to continue mainly in the elderly with a high risk of severe COVID-19 for the time being ("Action policy in

response to classification change of novel coronavirus infection under the Infectious Diseases Control Law [in Japanese]"[50] dated January 27, 2023, decided by the Novel Coronavirus Response Headquarters, the 45th Subcommittee meeting on Immunization and Vaccines of the Health Sciences Council held on March 7, 2023[51]). In view of such circumstances, introduction of Covgoze is expected to contribute to future stable supply of SARS-CoV-2 vaccines.

The efficacy of Covgoze has been evaluated mainly based on results of immunogenicity, and according to the information obtained from Study U0232, the Covgoze primary series alone cannot be expected to have high efficacy against the currently prevalent Omicron variant. However, a Covgoze booster dose in addition to the primary series of not only Covgoze but also the other SARS-CoV-2 vaccines, can induce immunization against and reactivate the immune response to SARS-CoV-2 and thus can be expected to have a certain level of efficacy. Based on the above, PMDA has concluded that, as with approved SARS-CoV-2 vaccines, the following indication of Covgoze is acceptable: "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)."

7.R.5 Dosage and administration

The proposed dosage and administration of Covgoze was "The antigen preparation and the proprietary solution are mixed. For the primary series, 2 doses of 0.5 mL (10 μg of the antigen) each are intramuscularly injected usually 4 weeks apart. For a booster dose, a dose of 0.5 mL is intramuscularly injected."

The applicant's explanation about the dose selection and the age range eligible for the vaccination:
The dose for the primary series was examined based on results of the safety and immunogenicity in Study U0221 in which healthy adults aged ≥20 years received 2 doses of Covgoze at 5 or 10 μg of the antigen 21 days apart. The evaluation of immunogenicity showed that the SARS-CoV-2 neutralizing antibody titer 28 days after the second dose of the study vaccine was higher in the Covgoze 10 μg group than in the 5 μg group (Table 16). The number of cells producing IFN-γ specific to the spike antigen, which indicates cell-mediated immunity, increased in both the Covgoze 5 μg group and 10 μg group. The evaluation of safety showed that some adverse events occurred more frequently in the Covgoze 10 μg group than in the 5 μg group (Table 18), but most of the adverse events at either dose were at Grade ≤2 for severity. All the adverse events resolved by the data cutoff date. Covgoze at either dose was well tolerated. Based on these results, the amount of the antigen per dose was specified as 10 μg in the subsequent clinical studies, because this amount raised no safety problems and provided higher neutralizing antibody titers.

The first dose and the second dose for the primary series were separated by 4 weeks in the clinical studies including pivotal Study U0231 for the efficacy evaluation of the Covgoze primary series, except Study U0221. Comparison with Vaxzevria based on immunogenicity in Study U0231 indicates that Covgoze can be expected to have a certain level of efficacy against the SARS-CoV-2 original strain [see Section 7.R.2.2]. The safety and tolerability of the Covgoze primary series were considered acceptable based on data from the clinical studies including Study U0222 [see Section 7.R.3].

[50] https://www.kantei.go.jp/jp/singi/novel_coronavirus/th_siryou/kihon_r2_050127.pdf (last accessed on March 31, 2023)
[51] Material 1-1: https://www.mhlw.go.jp/stf/newpage_31559.html (last accessed on March 31, 2023)

Therefore the following dosage and administration for the Covgoze primary series was specified: A total of 2 doses of 0.5 mL each containing 10 μg of the antigen are intramuscularly injected 4 weeks apart.

In clinical studies to evaluate the booster dose, the amount of the antigen per dose of Covgoze was 10 μg, which was the same as that for the primary series. In Study U0223, subjects who had completed the Comirnaty primary series received Covgoze as a booster dose, and the immunogenicity and safety were evaluated. Non-inferiority of Covgoze to Comirnaty was demonstrated in immunogenicity [see Section 7.R.2.3]. In addition, results from the sub-part in Study U0222 and Study U0224 also showed that the neutralizing antibody titer 28 days after the Covgoze booster dose was higher than that at baseline (before the booster dose) as observed in Study U0223 [see Sections 7.2.1.2 and 7.3.2]. The safety of the booster dose was similar to that of the primary series, with no substantial concerns. The above dosage and administration was therefore specified.

The statement in the proposed dosage and administration "The antigen preparation and the proprietary solution are mixed." was changed to "The proprietary solution 0.75 mL is added to the antigen preparation and then mixed." because the applicant considered that the procedure of adding an appropriate volume of the proprietary solution (0.75 mL) to the antigen preparation followed by mixing should be clarified in the statements of dosage and administration. The population eligible for Covgoze was specified as shown below. With reference to the package inserts of approved SARS-CoV-2 vaccines, information and precautionary statements will be included in the "Precautions Concerning Dosage and Administration" section in the package insert.

The population eligible for the primary series and Covgoze booster dose is adults aged ≥20 years, corresponding to the study population evaluated in the clinical studies for the present application. A clinical study in individuals aged ≤19 years including children aged ≥5 years is ongoing, and whether the eligible age limit for Covgoze can be lowered is to be examined.

In the clinical studies for the Covgoze booster dose included in the evaluation data in the present application, subjects who had completed the primary series received the third dose of Covgoze (the first booster dose) for evaluation [see Sections 7.2.1.2, 7.2.2, and 7.3.2]. However, the official vaccination against SARS-CoV-2 in Japan allows adults to receive the second and subsequent booster doses (fourth and subsequent doses), and a large proportion of people have received 3 doses. Based on such circumstances, the second and subsequent booster doses are being evaluated in Studies U0223 and U0224. Table 51 shows results of the second booster dose on immunogenicity against variants in Study U0224. The second booster dose induced the immune response comparable to or higher than that by the first booster dose. Furthermore, in an ongoing clinical study (Study U0226),[52)] adults aged ≥60 years who had completed the first booster dose of an approved vaccine received a single dose of Covgoze or Comirnaty to investigate its safety and immunogenicity. After the second booster dose, neutralizing antibody titer increased from baseline (before the second booster dose) (Table 67).

[52)] https://jrct.niph.go.jp/latest-detail/jRCT2031220224 (last accessed on March 31, 2023)

Table 67. GMT of SARS-CoV-2 neutralizing antibody after the second booster dose (Study U0226, immunogenicity analysis population)

	Covgoze (N = 96)		Comirnaty (N = 94)	
	n	GMT [two-sided 95% CI][a)]	n	GMT [two-sided 95% CI][a)]
Pre-vaccination	96	24.66 [20.05, 30.33]	94	24.41 [19.97, 29.82]
14 days post-vaccination	94	72.15 [59.42, 87.61]	90	133.00 [113.54, 155.78]
28 days post-vaccination	93	58.94 [48.51, 71.59]	90	91.90 [78.53, 107.54]

Micro-neutralization assay against the SARS-CoV-2 original strain
Antibody titers below the LLOQ were handled as "0.5 × LLOQ" in the analysis (LLOQ = 5).
N, Number of subjects analyzed; n, Number of subjects evaluated
a) Of logarithmically transformed antibody titers, the mean and its two-sided 95% CI in each group and at each sampling point were calculated and then anti-logarithmically transformed for estimation.

For safety of the second Covgoze booster dose in Study U0226, Table 68 shows incidences of solicited adverse events[53)] collected within 7 days after the study vaccination. The results showed no trend substantially different from the safety profile of the first Covgoze booster dose available to date. No serious adverse events occurred.

Table 68. Solicited adverse events reported within 7 days after the study vaccination (Study U0226, safety analysis population)

		Covgoze (N = 99)		Comirnaty (N = 99)	
		Overall	Grade ≥3	Overall	Grade ≥3
		n (%)	n (%)	n (%)	n (%)
Local	Overall	76 (76.8)	0	82 (82.8)	2 (2.0)
	Pain	76 (76.8)	0	80 (80.8)	0
	Erythema/redness	13 (13.1)	0	12 (12.1)	2 (2.0)
	Induration	15 (15.2)	0	14 (14.1)	0
	Swelling	13 (13.1)		11 (11.1)	0
Systemic	Overall	50 (50.5)	2 (2.0)	58 (58.6)	1 (1.0)
	Pyrexia	2 (2.0)	1 (1.0)	2 (2.0)	0
	Nausea/vomiting	8 (8.1)	0	11 (11.1)	0
	Diarrhoea	0	0	6 (6.1)	0
	Headache	18 (18.2)	0	25 (25.3)	0
	Malaise	25 (25.3)	1 (1.0)	33 (33.3)	1 (1.0)
	Myalgia	39 (39.4)	0	40 (40.4)	1 (1.0)
	Arthralgia	9 (9.1)	0	14 (14.1)	0
	Chills	4 (4.0)	0	5 (5.1)	0

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

Based on results of immunogenicity and safety available to date, Covgoze can be used for the second and subsequent booster doses as with approved SARS-CoV-2 vaccines and can be expected to have a certain level of efficacy by reactivating the immune response that once had attenuated. Study U0226 is ongoing to evaluate the fifth dose. The applicant will appropriately provide information to healthcare professionals when new data on the Covgoze booster dose become available in currently ongoing studies such as Study U0223.

PMDA's view:
In view of the applicant's explanation and review in Sections 7.R.2 and 7.R.3, the eligible population should be aged ≥20 years; and the proposed dosage and administration of Covgoze (i.e., the dosage and number of doses for the primary series and booster doses and the interval between doses for the primary series) is acceptable. Also, regarding the statement for before-use preparation, the change proposed by the applicant is acceptable to ensure proper use.

53) Solicited local adverse events (pain, erythema and redness, induration, swelling) and solicited systemic adverse events (pyrexia, nausea and vomiting, diarrhoea, headache, fatigue, myalgia, arthralgia, and chills)

The results of safety and immunogenicity after the first Covgoze booster dose in subjects who had completed the primary series are available from all of the clinical studies for the Covgoze booster dose included in the evaluation data for the present application [see Sections 7.2.1.2, 7.2.2, and 7.3.2]. The additionally submitted results from Studies U0224 and U0226 (Tables 51 and 67) showed that the second Covgoze booster dose in adults aged ≥60 years who had completed the first booster dose of an approved SARS-CoV-2 vaccine induced the immune response to a certain extent and was deemed to raise no particular safety problems. For approved SARS-CoV-2 vaccines, no acceptable number of booster doses is specified. In the current circumstances around vaccination against SARS-CoV-2 in Japan, the number of previous doses and the vaccine type used differ depending on the age and profession. In view of these matters, PMDA considers it meaningful to a certain extent to make a Covgoze booster dose available for the people who have completed the primary series of a SARS-CoV-2 vaccine, irrespective of the number of subsequent doses and the vaccine type previously used. For the timing of the Covgoze booster dose, the statement that "at least 6 months after the most recent vaccination against SARS-CoV-2" should be included in the "Precautions Concerning Dosage and Administration" to ensure that healthcare professionals can easily understand the timing and therefore do not become confused, in consideration of the following:

(1) A confirmatory study for the Covgoze booster dose was conducted in subjects who had completed the primary series at least 6 months before.
(2) A booster dose of Nuvaxovid, a recombinant coronavirus (SARS-CoV-2) vaccine approved in Japan, should be administered at least 6 months after the most recent vaccination against SARS-CoV-2.

7.R.6 Post-marketing investigations

7.R.6.1 Post-marketing surveillance etc.

The applicant's explanation about post-marketing surveillance of Covgoze:

The safety specification includes shock, anaphylaxis, VAED, and VAERD as important potential risks of Covgoze, and the safety in pregnant or lactating women as important missing information. With the safety specification, a use-results survey (target sample size, 1,000 individuals) is planned to evaluate the safety of Covgoze in clinical use. Since the currently ongoing SARS-CoV-2 vaccination program provides mainly booster doses of Omicron-adapted bivalent vaccines, the use of Covgoze, a monovalent vaccine, for booster doses is deemed to be limited. At present, it is difficult to estimate to what extent Covgoze will be used for the primary series and booster dose. Accordingly, the survey sample size for the primary series and that for booster dose have not been determined at present.

In the ongoing Study U0232, VAED and VAERD will be evaluated continuously as pharmacovigilance activities. The applicant will evaluate the safety and clinical efficacy of Covgoze when final results become available.

PMDA's view:

As discussed in Section 7.R.3, only limited data are currently available regarding the safety and efficacy in special populations (e.g., the elderly and pregnant women) and the population ineligible for the clinical studies of Covgoze. The applicant's plan to conduct a post-marketing survey as

pharmacovigilance activities in clinical use, is acceptable. Vaccination against SARS-CoV-2 will continue to be recommended for elderly people. The data from elderly people available to date has not raised any particular safety concerns, but the clinical studies could not evaluate Covgoze in an adequate number of elderly people because the vaccination against SARS-CoV-2 has been preferentially implemented in the elderly. Therefore, information regarding elderly people, in particular, should be appropriately collected in the survey to assess whether a new precautionary statement is necessary in view of data on their characteristics such as underlying disease. The applicant explained that what extent Covgoze will be used for the primary series and booster dose cannot be estimated at present. PMDA understands that to a certain extent, but since only a limited number of subjects were included in the clinical studies of the Covgoze booster dose, the safety information associated with the increasing number of booster doses should be collected in the future. The post-marketing surveillance should be planned to ensure investigation of booster doses in a certain sample size.

As discussed in Section 7.R.3, the safety specification of Covgoze should also include myocarditis and pericarditis as important potential risks. The safety specification should be evaluated based on results from additional pharmacovigilance activities such as the post-marketing surveillance and ongoing clinical studies. Only interim reports were submitted for the present application, and the safety and efficacy of Covgoze should be further evaluated based on information to be obtained from the clinical studies of Covgoze including ongoing Study U0232 as a part of the post-marketing investigations. The evaluation results should be appropriately provided to healthcare professionals.

PMDA will draw the final conclusion on the post-marketing investigations and post-marketing surveillance, taking account of comments from the Expert Discussion.

7.R.6.2 Prevention of vaccination error

Covgoze, a vaccine requiring before-use preparation, is comprised of the antigen preparation and proprietary solution. Both components are liquid filled in separate vials. As the applicant explains in Section 7.R.5, an appropriate volume of the proprietary solution must be added to the antigen preparation; this procedure must be complied with. The following potential vaccination errors can occur: (1) The antigen preparation is added to the proprietary solution; (2) the antigen preparation is mixed with a solution other than the proprietary solution; and (3) either the proprietary solution or antigen preparation alone is administered without mixing of both components.

The applicant’s explanation about preventive measures against the potential vaccination errors:

- To enhance the discrimination, vials of different components have a cap of a different color and a label of a different color that matches the cap’s color.
- Each vial is given a code, and the label includes the procedure for mixing.
- The carton packaging both vials displays the statement that the vaccine is comprised of 2 vials and liquids in both vials should be mixed before use.
- The applicant will provide information about proper use using multiple approaches such as disseminating information materials and videos that explain how to prepare Covgoze before use.

PMDA's view:
Each unit of Covgoze contains 2 doses, and the proprietary solution is provided with the antigen preparation in the same package. In these 2 points, Covgoze is different from currently available approved SARS-CoV-2 vaccines. The dosage regimen of Covgoze is thus unlikely to be confused with those of the other vaccines. Covgoze is therefore expected to be appropriately prepared and administered according to the dosage regimen presented in its package insert, etc. Still, as described above, concerns about vaccination errors remain. For introduction of Covgoze, information about how to use Covgoze and the precautions should be appropriately provided to ensure healthcare professionals' understanding. The applicant should take the above preventive measures against the potential vaccination errors as planned and, if a risk of jeopardizing proper use of Covgoze is identified, should assess the risk and take further safety measures where necessary.

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

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

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

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

The new drug application data (CTD 5.3.5.1-02, CTD 5.3.5.1-03) 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.

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

On the basis of the data submitted, PMDA considers that Covgoze has efficacy in the prevention of COVID-19 and acceptable safety in view of its benefits. PMDA considers it clinically meaningful to make Covgoze available for clinical use as an option for the primary series in people who have not received SARS-CoV-2 vaccines and thus are ineligible for approved bivalent vaccines and for use in people who cannot tolerate mRNA vaccines.

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

Review Report (2)

May 16, 2023

Product Submitted for Approval

Brand Name	Covgoze Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Shionogi & Co., Ltd.
Date of Application	November 24, 2022

List of Abbreviations
See Appendix.

1. Content of the Review

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

At the Expert Discussion, the expert advisors supported PMDA's conclusion in Section "7.R.5 Dosage and administration" in the Review Report (1).

1.1 Efficacy

At the Expert Discussion, the expert advisors made the following comments on the PMDA's conclusions in Sections "7.R.1 Clinical data package and data for review" and "7.R.2 Efficacy" in the Review Report (1).

- For the efficacy evaluation of Covgoze, there might have been no other options than using immunogenicity as an indicator. This is understandable, but results of the COVID-19-preventive effect investigated in the ongoing foreign phase III study (Study U0232) should be evaluated together. In addition, results of not only the disease-preventive effect for symptomatic COVID-19 but also a suppressive effect for severe COVID-19 should be evaluated.
- The Covgoze primary series alone cannot be expected to have high efficacy against the Omicron variant; this information should be disseminated.
- The efficacy of the Covgoze booster dose against variants has been evaluated only in a limited way. When new information (e.g., investigation results of immunogenicity and clinical efficacy from the ongoing clinical studies) is obtained, the applicant should disseminate the information appropriately.

The applicant submitted the following 2 investigation results (up to the first data-base lock) of the efficacy of Covgoze other than the primary endpoint in the foreign phase III study (Study U0232). For both results, only a limited number of subjects developed COVID-19, and therefore the results should be interpreted with care.

- At ≥14 days after the second dose of the study vaccine, severe COVID-19[54)] occurred in 0 subjects in the Covgoze group (incidence rate per 1,000 person-years [two-sided 95% CI], 0.00 [0.00, 11.31]) and 1 subject in the placebo group (incidence rate per 1,000 person-years [two-sided 95% CI], 6.06 [0.15, 33.75]) in the mITT population (5,256 subjects in the Covgoze group, 2,633 subjects in the placebo group). VE was 100.0%.
- A post hoc analysis in the mITT population revealed that the following number of subjects developed COVID-19 at ≥14 days after the second dose of the study vaccine: 1 subject in the Covgoze group (incidence rate per 1,000 person-years [two-sided 95% CI], 3.07 [0.08, 17.09]) and 3 subjects in the placebo group (incidence rate per 1,000 person-years [two-sided 95% CI], 18.18 [3.75, 53.14]). VE [two-sided 95% CI] was 83.2% [−61.5%, 98.2%].

During the development of Covgoze, the clinical efficacy of its booster doses was not investigated, but the applicant plans to survey the incidence of COVID-19 in the post-marketing surveillance and to evaluate the booster doses in the ongoing clinical studies.

In view of the above investigation results and plan for the investigations, the expert advisors supported PMDA's conclusion on the efficacy of Covgoze presented in Section "7.R.2 Efficacy."

PMDA requested that the applicant disseminate the following information appropriately:

(a) The finding that Covgoze primary series alone cannot be expected to have high efficacy against the Omicron variant
(b) Investigation results of the booster doses to be obtained

The applicant replied that they would take actions appropriately.

1.2 Safety

At the Expert Discussion, the expert advisors made the following comments and supported PMDA's conclusion presented in Section "7.R.3 Safety" of the Review Report (1):

- People who choose Covgoze for vaccination may include those who have experienced severe adverse reactions to an approved SARS-CoV-2 vaccine containing mRNA as the active substance. The safety information of Covgoze in such individuals can be useful if it can be collected.
- Covgoze may be administered to populations in whom the safety of Covgoze has not been evaluated adequately or at all (e.g., elderly people and pregnant women). As with approved SARS-CoV-2 vaccines, Covgoze should be carefully used with attention paid to serious adverse events.

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54) Severe COVID-19 was defined as a condition meeting one of the following pathological conditions:
- Clinical signs indicative of a severe systemic disease (respiratory rate ≥30/min, heart rate ≥125/min, SpO_2 ≤93% or PaO_2/FiO_2 <300 mmHg)
- Respiratory failure (defined as a condition needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)
- Shock sign (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Severe acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

Since the populations about whom only limited or no information was obtained during development may receive Covgoze, PMDA asked the applicant to (a) appropriately provide information about Covgoze to healthcare professionals and vaccine recipients, (b) collect information from the post-marketing surveillance and adverse reaction reports, (c) and evaluate the information obtained in post-marketing settings and appropriately communicate the information to healthcare professionals. The applicant replied that they would take actions appropriately.

1.3 Clinical positioning of Covgoze

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

- Making Covgoze available is meaningful because it offers another option for people who could not receive the next vaccination due to intense adverse reactions to an approved SARS-CoV-2 vaccine containing mRNA as the active substance and those who have refrained from receiving vaccination because of concerns about adverse reactions.
- Covgoze is not considered to have high efficacy against the SARS-CoV-2 Omicron variant, but it can be used for immunization against the original strain and reactivation of the immune response with a booster dose. Since the next prevalent strain is unknown, making Covgoze available for use as an option of SARS-CoV-2 vaccine is meaningful.

On May 5, 2023, WHO declared an end to COVID-19 as a public health emergency of concern, but they clearly stated that COVID-19 is an established and ongoing health issue that requires efforts to increase COVID-19 vaccination coverage, implement epidemiological monitoring, and develop new vaccines and therapeutic drugs.
(https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic, last accessed on May 9, 2023) Introduction of Covgoze, manufactured in Japan, is considered meaningful in terms of vaccine supply in Japan.

1.4 Risk management plan (draft)

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

- After the launch, the applicant is expected to collect information wherever possible, covering not only the safety of Covgoze but also evaluation of immunogenicity and efficacy of the booster dose, and clinical efficacy of Covgoze, and evaluate the collected information.
- The safety information in post-marketing settings should be collected and carefully evaluated.
- Offering another vaccine option is beneficial but may increase the risk of vaccination errors. Concerning the risk, the applicant should provide the relevant information to healthcare professionals in a simple and easy-to-understand manner.

After its launch, evaluation of the clinical efficacy of Covgoze remains important as well, and careful safety evaluation is required. PMDA instructed the applicant to collect safety and efficacy data of

Covgoze wherever possible and evaluate the risks and benefits of Covgoze continuously. The applicant replied that they would take actions appropriately.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for Covgoze should include the safety and efficacy specifications presented in Table 69, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 70 and Table 71.

Table 69. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• Shock and anaphylaxis • Myocarditis and pericarditis • Vaccine associated enhanced diseases (VAEDs) including vaccine associated enhanced respiratory diseases (VAERDs)	• Safety in pregnant or lactating women
Efficacy specification		
None		

Table 70. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General drug-use survey • Foreign clinical study (foreign phase III study [Study U0232]) • Post-marketing clinical study (Japanese phase III study [Study U0226]) • Post-marketing clinical study (Japanese phase II/III study [Study U0223])	• 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 (brochure for individuals who are going to receive Covgoze Intramuscular Injection) • Periodical publication of the occurrence of adverse reactions

Table 71. Outline of general use-results survey (draft)

Objective	To survey the safety of Covgoze used for the primary series or as a booster dose in clinical settings To survey the incidence of COVID-19 in individuals who have received Covgoze
Survey method	Central registry system
Population	Individuals who have received Covgoze for the primary series or as a booster dose
Observation period	Primary series: from the first dose of Covgoze to 24 weeks after the second dose Booster dose: from the day of the vaccination to 24 weeks after that
Planned sample size	1,000
Main survey items	Characteristics of vaccine recipients, use status of Covgoze, concomitant medication, adverse events and detailed information, onset of COVID-19, local adverse events (vaccination site pain, induration, swelling, erythema/redness) and systemic adverse events (pyrexia, nausea, vomiting, diarrhoea, headache, malaise, myalgia, arthralgia, chills) within 7 days after Covgoze vaccination, collected through a health observation diary

1.5 Quality

1.5.1 Shelf lives of active substance and proprietary solution

In the Review Report (1), the shelf life of 6 months was proposed for both active substance and proprietary solution of Covgoze stored in the respective storage container protected from light at 2°C to 8°C, based on long-term stability results presented in Tables 5 and 9 [see Sections 2.1.8 and 2.2.2.5].

The applicant additionally submitted stability data at 9 months under long-term conditions from the ongoing stability study. The data showed no changing trend in quality of the active substance or proprietary solution throughout the studied period. The applicant explained that both shelf-lives can be changed to 9 months.

In view of the submitted long-term stability data and the applicant's explanation, PMDA has concluded that the following shelf-lives for the active substance and proprietary solution are acceptable:

- Active substance: 9 months when stored in [redacted] protected from light at 2°C to 8°C
- Proprietary solution: 9 months when stored in a glass vial with [redacted] rubber stopper protected from light at 2°C to 8°C

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and the dosage and administration proposed 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

The proprietary solution 0.75 mL is added to the antigen preparation and then mixed.
For the primary series, 2 doses of 0.5 mL each are intramuscularly injected usually 4 weeks apart.
For a booster dose, a dose of 0.5 mL is intramuscularly injected.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information on the product at present, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed plan, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product.
3. The applicant is required to submit results of the ongoing Japanese and foreign clinical studies of the product to PMDA as soon as they become available and take necessary actions to ensure that the latest efficacy and safety data of the product are easily accessible to healthcare professionals and vaccine recipients.
4. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the latest efficacy and safety data of the product in

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

Appendix

List of Abbreviations

A-910823	Adjuvant containing squalene, tocopherol, and polysorbate 80
AU	arbitrary units
[redacted]	[redacted]
BCV	Baculovirus
[redacted] cells	[redacted] cell line
BMI	body mass index
[redacted]	[redacted]
BVDV	Bovine viral diarrhea virus
CAL	cells at the limit of *in vitro* cell age
CH domain	central helix domain
[redacted]	[redacted]
CI	confidence interval
Covgoze	Covgoze Intramuscular Injection
COVID-19	Coronavirus disease (COVID-19)
CTD	Common Technical Document
DNA	deoxyribonucleic acid
[redacted]	[redacted]
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immune absorbent spot
EMCV	Encephalomyocarditis Virus
FAS	full analysis set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
[redacted]	[redacted]
GMFR	geometric mean fold rise
GMT	geometric mean titer
[redacted]	[redacted]
[redacted]	[redacted]
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICMRA	International Coalition of Medicines Regulatory Authorities
IFN-γ	interferon-gamma
IgG	immunoglobulin G
IL	interleukin
IU	international units
LLOQ	lower limit of quantification
MCB	master cell bank
MCP-1	monocyte chemotactic protein 1
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MIP-1α/β	macrophage inflammatory proteins 1 α/β
mITT	modified intent-to-treat
[redacted]	[redacted]
[redacted] cells	[redacted] cell line
mRNA	messenger RNA
MVB	master virus bank
N-protein	nucleocapsid protein
NT_{50}	50% neutralization titer
PaO_2	partial pressure of oxygen
PBS	phosphate buffered saline
PCR	polymerase chain reaction
[redacted]	[redacted]

PMDA	Pharmaceuticals and Medical Devices Agency
PPV	Porcine Parvovirus
RBD	receptor binding domain
RMP	risk management plan
RNA	ribonucleic acid
RT-PCR	reverse transcription PCR
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
SDS-PAGE	sodium dodecyl sulfate -polyacrylamide gel electrophoresis
[redacted] cells	[redacted] cell line
SpO_2	saturation of percutaneous Oxygen
[redacted]	[redacted]
[redacted]	[redacted]
Spike protein antigen	Recombinant coronavirus (SARS-CoV-2) spike protein antigen
S1	Amino-terminal region of the spike protein containing the RBD
S2	Carboxyl-terminal region of the spike protein containing the membrane spanning domain
$TCID_{50}$	50% tissue culture infective dose
Th	helper T cell
UF/DF	ultrafiltration/diafiltration
ULOQ	upper limit of quantification
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VE	vaccine efficacy
[redacted] cells	[redacted] cell line
VOC	variants of concern
WCB	working cell bank
WHO	World Health Organization
WVB	working virus bank