Report on the Deliberation Results

April 18, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Nuvaxovid Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	December 16, 2021

Results of Deliberation

In its meeting held on April 18, 2022, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. Both the vaccine product and the active substance are classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only limited information is available on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed 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. Results of the ongoing clinical studies to confirm the immunogenicity and safety of the booster dose of the product, should be submitted promptly to PMDA. Also, the applicant is required to take actions necessary to ensure that the updated efficacy and safety information on the product is easily accessible to healthcare professionals.
4. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

Review Report

April 11, 2022
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Nuvaxovid Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	December 16, 2021
Dosage Form/Strength	Injection: Each vial contains 50 μg of SARS-CoV-2 rS
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

Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 3 weeks apart.
Booster dose: A single dose of 0.5 mL is injected intramuscularly.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only limited information is available on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed 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. Results of the ongoing clinical studies to confirm the immunogenicity and safety of the booster dose of the product should be submitted promptly to PMDA. Also, the applicant is required to take actions necessary to ensure that the updated efficacy and safety information on the product is easily accessible to healthcare professionals.
4. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

Attachment

Review Report (1)

March 8, 2022

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

Product Submitted for Approval

Brand Name	Nuvaxovid Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	December 16, 2021
Dosage Form/Strength	Injection: Each vial contains 50 μg of SARS-CoV-2 rS
Proposed Indication	Prevention of disease caused by SARS-CoV-2 infection (COVID-19)
Proposed Dosage and Administration	Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 3 to 4 weeks apart. Booster dose: A single dose of 0.5 mL is injected intramuscularly usually ≥6 months after the second dose of the primary series.

Table of Contents

List of Abbreviations

See Appendix.

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

World Health Organization (WHO) declared COVID-19 as a global pandemic in March 2020 (https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-mediabriefing-on-covid-19---11-march-2020 [last accessed on March 8, 2022]). Since then, multiple SARS-CoV-2 vaccines have been approved in the world from the second half of 2020 through the first half of 2021. Although more than 10 billion vaccine doses have been administered as of February 28, 2022 (https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---1-march-2022), there still is a high need for effective prevention by vaccines because of emerging variants and other factors. The total number of patients infected with SARS-CoV-2 is 434,154,739 globally including 5,944,342 fatal cases as of February 28, 2022 (https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---1-march-2022). In Japan, as of March 8, 2022, the total number of patients infected with SARS-CoV-2 is 5,434,108, including 25,049 fatal cases. (https://www.mhlw.go.jp/stf/newpage_24347.html)

In Japan, as of March 8, 2022, the following vaccines have been approved for the prevention of disease caused by SARS-CoV-2 infection (COVID-19): Comirnaty Intramuscular Injection and Comirnaty Intramuscular Injection for 5 to 11 years old (Pfizer Japan Inc.), Vaxzevria Intramuscular Injection (AstraZeneca K.K.), and Spikevax Intramuscular Injection (previously COVID-19 Vaccine Moderna Intramuscular Injection, Takeda Pharmaceutical Company Limited). More than 79% of Japanese people have completed the primary series of a SARS-CoV-2 vaccine (https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html). Also, multiple drugs have been approved in Japan for the treatment of COVID-19. However, the pandemic is still ongoing and there are still unmet medical needs. A vaccine supply strategy based on multiple vaccine platforms is required because of (a) the public health emergency due to SARS-CoV-2 and its novel variants, (b) the effect of the global pandemic on medical care and its social and economic impacts, and (c) vaccine supply problems associated with worldwide vaccination.

Nuvaxovid is a recombinant SARS-CoV-2 spike protein nanoparticle vaccine (SARS-CoV-2 rS) manufactured using a cell line derived from the ovary of *Spodoptera frugiperda* (Sf9 cells). Nuvaxovid thus uses a platform different from that of SARS-CoV-2 vaccines approved in Japan (messenger ribonucleic acid [mRNA] vaccine and adenovirus vector vaccine). Nuvaxovid contains an adjuvant (Matrix-M) that contains saponin as the main component. SARS-CoV-2 rS is constructed from the full-length, wild-type SARSCoV-2 spike protein. The purified trimer of SARS-CoV-2 rS can bind to human angiotensin-converting enzyme 2 (hACE2) receptor, through which SARS-CoV-2 enters human cells.

Novavax, Inc. in the United States began to develop Nuvaxovid for the prevention of COVID-19 in May 2020 and initiated Studies 2019nCoV-301 and 2019nCoV-302 (foreign phase III studies) in December and September 2020, respectively. In Japan, Takeda Pharmaceutical Company Limited initiated a Japanese clinical study (Study TAK-019-1501) in February 2021. In EU, Nuvaxovid (2 doses) was granted conditional approval for the prevention of COVID-19 on December 20, 2021. As

of March 4, 2022, Nuvaxovid has been granted conditional approval or approval for emergency supply in at least 30 countries and regions and by WHO.

Takeda Pharmaceutical Company Limited filed an application for the marketing approval of Nuvaxovid in Japan on December 16, 2021, based on the following grounds: (a) the efficacy and safety of Nuvaxovid were demonstrated by the ongoing foreign clinical studies, (b) the immunogenicity and safety after Nuvaxovid vaccination were demonstrated in Japanese people as well, and (c) the vaccine supply in Japan has been ensured.

2. Quality and Outline of the Review Conducted by PMDA

Nuvaxovid is recombinant SARS-CoV-2 S subunit vaccine constructed from the full-length spike protein (S-protein) of SARS-CoV-2 and produced in the established Sf9 insect cell expression system. Nuvaxovid is a Matrix-M-adjuvanted vaccine consisting of SARS-CoV-2 rS, the recombinant SARS-CoV-2 S protein manufactured and purified from Sf9-baculovirus cell expression system. Matrix-M consists of Matrix-A and Matrix-C.

2.1 Active substance

2.1.1 Generation and control of cell substrate

The master cell bank (MCB) and the working cell bank (WCB) were generated based on Sf9 cell strain acclimatized to a serum-free medium.

MCB, WCB, and the end-of-production cell bank (EOPCB) were subjected to a purity test and characterization according to the Guidelines "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329 dated February 22, 2000) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Q5A Guideline), "Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products" (PMSB/ELD Notification No. 3 dated January 6, 1998), and "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873 dated July 14, 2000). Results confirmed cell proliferation characteristics and baculovirus proliferation up to the [redacted] generation. The gene sequence encoding Sf rhabdovirus (Sf-RV) was detected by characterization (RT- PCR and adventitious agent screening analysis [NGS]) conducted on WCB [see Section 2.1.4]. No other viral or nonviral adventitious agents were detected by the tests conducted.

MCB and WCB are stored in the vapor phase of liquid nitrogen. A new MCB will not be generated, but a new WCB will be generated from MCB as necessary.

2.1.2 Generation and control of virus seed

The virus seed used for the manufacture of Nuvaxovid was generated by transfecting the gene encoding SARS-CoV-2 rS protein into baculovirus. Using this virus seed as the origin, Sf9 cells cultivated from WCB were infected with the virus, and the first-generation virus, pre-master virus, master virus seed (MVS), and the working virus bank (WVB) were generated sequentially.

MVS and WVB are stored in the vapor phase of liquid nitrogen. A new MVS will not be generated, but a new WVB will be generated from MVS as necessary.

MVS and WVB were subjected to characterization and a purity test. Results confirmed viral titer and viral gene sequence. Neither viral nor nonviral adventitious agents were detected by the tests conducted [see Section 2.1.4].

2.1.3 Manufacturing process

The manufacturing process of the active substance consists of cultivation in flasks, maintenance culture, seed virus culture, expanded culture, [redacted], production culture (virus inoculation), harvest, treatment with surfactant and pH adjustment, clarification, anion exchange chromatography, nanofiltration, affinity chromatography, ultrafiltration/concentration and dialysis, filtration of stock solution, and storage.

Critical steps include seed virus culture, [redacted], production culture (virus inoculation), treatment with surfactant and pH adjustment, clarification, anion exchange chromatography, nanofiltration, affinity chromatography, ultrafiltration/concentration and dialysis, and filtration of stock solution.

The active substance manufacturing process has been validated on a commercial scale.

2.1.4 Safety evaluation of adventitious agents

Except Sf9 cells used for the manufacture of the active substance, no material of biological origin is used in the manufacturing process of the active substance.

MCB, WCB, EOPCB, MVS and WVB were subjected to tests for adventitious agents listed in Table 1 and to characterization. No adventitious viruses or nonviral adventitious agents were detected in the tests for adventitious agents. The gene sequence encoding Sf-RV was detected by characterization (reverse transcription PCR [RT-PCR] and NGS) conducted on WCB. The risk of Sf-RV contamination is discussed in Section 2.R.1.

Table 1. Adventitious agent tests and characterization conducted on MCB, WCB, EOPCB, MVS, and WVB

Test item	MCB	WCB	EOPCB	MVS	WVB
Tests for adventitious agents					
Sterility test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mycoplasma test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mycobacterium test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spiroplasma test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In vitro adventitious virus test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In vivo adventitious virus test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adventitious virus test (NGS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retrovirus test (reverse transcriptase activity test [redacted] and coculture)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contaminant virus [redacted] test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Characterization					
Sf-RV gene detection (RT-PCR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adventitious agent screening analysis (NGS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The production culture fluid before harvesting is subjected to in-process control tests consisting of a mycoplasma test, a Spiroplasma test, and an adventitious virus test.

A viral clearance test was performed for the purification processes using model viruses. The results showed that the purification processes had a certain level of viral clearance capacity (Table 2).

Table 2. Results of viral clearance studies

Manufacturing process [redacted]	Viral reduction factor (log_{10})					
	Baculovirus	Vesicular stomatitis virus	Bovine viral diarrhea virus	Xenotropic murine leukemia virus	Porcine parvovirus	Reovirus type 3
Surfactant/pH treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anion-exchange chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nanofiltration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Affinity chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total viral reduction factor	**>16.21**	**≥14.70**	**≥13.53**	**≥15.67**	**7.26**	**≥11.18**

[redacted]

2.1.5 Manufacturing process development

Table 3 shows the main changes made in the manufacturing process during the development of the active substance. The active substance used in nonclinical studies and early clinical studies were manufactured by Process a, b, or c. The active substance used in the phase III clinical studies was manufactured by Process d. The active substance in the to-be-marketed formulation in Japan is manufactured by Process e. With each change of the manufacturing process, the quality attributes of pre-change and post-change active substances were assessed and shown to be comparable.

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

Process	Changes
Process a to b	[redacted]
Process b to c	[redacted]
Process c to d	[redacted]
Process d to e	[redacted]

[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. Characterization items

Primary/higher order structure	Amino acid sequence ([redacted]), N- and C-terminal amino acid sequences, disulfide bonds ([redacted]), secondary structure ([redacted]), tertiary structure ([redacted]), higher-order structure ([redacted])
Physicochemical properties	Size variants ([redacted]), charge variants ([redacted]), particle size ([redacted]), thermal stability ([redacted])
Structure of carbohydrate	N-linked carbohydrate chain profile ([redacted]), glycosylation site ([redacted])
Biological properties	[redacted]

[redacted]

2.1.6.2 Product-related substances/product-related impurities

Degradation fragments of recombinant S protein, post-translational oxidation products, deamidated products, and succinimide form were identified as product-related impurities. As for the degradation fragments [redacted] adequately controlled by the specifications for the active substance. [redacted].

2.1.6.3 Process-related impurities

The following were identified as process-related impurities: residual host cell protein, baculovirus protein, host DNA, baculovirus DNA, infectious baculovirus, Sf-RV RNA, reverse transcriptase, Impurity A, Impurity B, Impurity C, and Impurity D. All process-related impurities were shown to be adequately removed by the manufacturing process.

Residual host cell protein, baculovirus protein, host DNA, baculovirus DNA, and infectious baculovirus are controlled by the specifications for the active substance. Sf-RV is controlled within the manufacturing process by quantitative polymerase chain reaction (qPCR) and by the infection test [see Section 2.R.1].

2.1.7 Control of active substance

The proposed specifications for the active substance are as follows: appearance; identification (Western blotting); pH; purity test (1) (purity and impurities [polyacrylamide gel electrophoresis]); purity test (2) (residual DNA [[redacted]]); purity test (3) (residual baculovirus [[redacted]]); endotoxin; microbial limits; relative potency (enzyme-linked immunosorbent assay [ELISA]); protein content (spectrophotometry); and [redacted] ([redacted]).

2.1.8 Stability of active substance

Table 5 shows a summary of the main stability studies for the active substance.

Table 5. Summary of the main stability studies for the active substance

	Manufacturing process of active substance	Number of batches	Storage conditions	Test period	Storage form
Long-term	Process d	2	−70 ± 10°C	9 months*	[redacted]
	Process e	3	≤−60°C	1 month*	

*: The stability studies are ongoing up to 36 months.

The long-term test of the active substance manufactured by Process d and Process e showed no clear tendency of changes over time in test parameters throughout the test period, demonstrating conformity to the specifications. Results of the ongoing long-term test of the active substance manufactured by Process e are described in the Review Report (2).

2.2 Vaccine product

2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is available in a vial. Each vial contains 50 µg of SARS-CoV-2 rS, the active ingredient, for 10 doses. The labeled volume is 5 mL, but each vial is overfilled to [redacted] mL to ensure withdrawal of 10 doses. The vaccine product contains excipients: Matrix-A, Matrix-C, disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, polysorbate 80, sodium hydroxide, hydrochloric acid, and water for injection. The primary container is a glass vial (volume 16.5 mL) with [redacted] rubber cap, and the secondary packaging is a paper box.

2.2.2 Manufacturing process

The manufacturing process of the vaccine product consists of thawing of the active substance, preparation of buffer, weighing and storage of the active substance, preparation of Matrix-M, preparation of vaccine product solution, sterile filtration, sterile filling, inspection/test, and packaging/labeling/storage.

Critical steps include preparation of buffer, preparation of vaccine product solution, sterile filtration, and sterile filling.

The manufacturing process of the vaccine product has been validated on a commercial scale.

2.2.3 Manufacturing process development

Table 6 shows the main changes made in the manufacturing process during the development of the vaccine product. In clinical studies, the vaccine product manufactured by Process A, B, or C was used, and the active substance manufactured by Process a, b, c, or d was used. The to-be-marketed formulation in foreign countries is manufactured by Process D developed by Novavax using the active substance manufactured by Process d. The to-be-marketed formulation in Japan is manufactured by Process E developed by the applicant using the active substance manufactured by Process e. With each change of the manufacturing process, the quality attributes of pre-change and post-change vaccine products were assessed and shown to be comparable by batch analysis and characterization.

Table 6. Main changes in the manufacturing process of the vaccine product

Manufacturing process	Changes
Process A to B	[redacted]
Process B to C	
Process C to D	
Process C to E	

2.2.4 Control of vaccine product

The proposed specifications for the vaccine product include appearance, identification (Western blotting), pH, osmolality, endotoxin, extractable volume, insoluble foreign matters, insoluble particulate matters, sterility, relative potency (ELISA), protein content ([redacted]), [redacted] ([redacted]), Matrix-A content ([redacted]), and Matrix-C content ([redacted]).

2.2.5 Stability of vaccine product

Table 7 shows a summary of the main stability studies for the vaccine product.

Table 7. Summary of the main stability studies for the vaccine product

	Manufacturing process of active substance	Manufacturing process of vaccine product	Number of batches	Storage conditions	Test period	Storage form
Long-term	Process d	Process C	2	2°C to 8°C (upright and inverted)	9 months*	Glass vial with [redacted] rubber stopper
	Process e	Process E	3		<1 month*	

*: The stability studies are ongoing up to 24 months.

Long-term tests were conducted on 2 batches manufactured by Process C (one batch was for the foreign global phase III study [Study 2019nCoV-301 (Study 301)] and the Japanese phase I/II study [Study TAK-019-1501 (Study 1501)] and the other batch was for Study 301). Both batches conformed to the specification up to 9 months. Results of the ongoing long-term test on Process-E batches are described in the Review Report (2).

2.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following reviews, PMDA concluded that there was no serious quality problem affecting the evaluation of nonclinical and clinical studies of Nuvaxovid. PMDA has instructed the applicant to promptly submit the results of batch analysis of the vaccine product and of the long-term tests of the active substance and the vaccine product. Results of the review are described in the Review Report (2).

2.R.1 Risk and control of Sf-RV contamination in vaccine product

A literature published in 2014 reported that RT-PCR and NGS analyses of Sf9 cells suggested contamination of a novel virus Sf-RV (*J Virol.* 2014;88:6576-85). During the process of the development of Nuvaxovid, a gene sequence identical to that of the above-reported Sf-RV was detected by the characterization analysis (RT-PCR and NGS) of WCB used for the manufacture of the active substance [see Section 2.1.4].

PMDA asked the applicant to explain the characteristics of Sf-RV and its infectivity and pathogenicity in humans.

The applicant's explanation:
Sf-RV is an enveloped RNA virus of rhabdovirus family. It is homologous to known rhabdoviruses only in L (large polymerase) gene (*J Virol*. 2014;88:6576-85). The amino acid sequence of L protein in Sf-RV is highly homologous to that of L protein of rhabdoviruses derived from insects and other invertebrates, suggesting that Sf-RV is a rhabdovirus that proliferates only in insect cells (*J Virol*. 2019;93:1-14).

As for the replication capacity of Sf-RV, coculture of Sf-RV with mammal-derived cells or insect-derived cells showed that Sf-RV was replicated in insect-derived cells but not in mammal-derived cells including human-derived cells (*J Virol*. 2014;88:6576-85, *Protein Expr Purif.* 2018;144:25-32). In a similar manner, the applicant investigated the replication capacity by coculture [redacted]

[redacted] confirmed that Sf-RV was not replicated in human-derived cells.

The applicant conducted a joint study with University of Kentucky. In the study, Sf-RV gene was detected in all of adult specimens of *Spodoptera frugiperda*, which inhabits in the eastern part of United States and in all of the specimens derived from *S. frugiperda* colonies bred in the laboratory (*J Virol.* 2019;93:02028-18). The applicant therefore considered that *S. frugiperda* was infected with Sf-RV persistently and endogenously. *S. frugiperda* is known to be an euryphagous insect pest distributed worldwide including Japan and causes damage to agricultural crops such as sugar cane, rice, and greenstuff[1)] (https://www.cabi.org/isc/datasheet/29810 [last accessed on March 8, 2022]). These facts suggest that Sf-RV endogenous to *S. frugiperda* is distributed worldwide and that humans are exposed to Sf-RV indirectly through familiar plants such as vegetables. In fact, in an experiment conducted by the applicant, Sf-RV RNA was detected frequently in vegetables touched by the larvae of *S. frugiperda* (in 37 out of 42 vegetable samples) by qPCR (in-house material). In addition, some tribes in North and South America historically eat *S. frugiperda* (*J Ethnobiology Ethnomedicine.* 2011. https://doi.org/10.1186/1746-4269-7-2) but, up to now adverse events or infection due to Sf-RV have not been observed in these regions. Furthermore, the joint study by the applicant and University of Kentucky has confirmed that Sf-RV was not replicated in plants.

The above findings show that Sf-RV does not infect, or proliferate or multiply in, human-derived cells. Humans probably have been exposed to Sf-RV via crops touched by *S. frugiperda*, but there are no data suggesting its pathogenicity in human.

PMDA asked the applicant to explain the removal of Sf-RV during the manufacturing process of Nuvaxovid and the risk of Sf-RV contamination, based on ICH Q5A Guideline.

The applicant's explanation:
Based on ICH Q5A Guideline, virus clearance capacity of the manufacturing process of the active substance was evaluated by a spike test that detects vesicular stomatitis virus, a model virus specific to Sf-RV, by qPCR. Results showed that the purification process of the active substance achieved a virus reduction factor of ≥14.66 log. The residual amount of Sf-RV in the active substance was evaluated based on the genome copy number of Sf-RV in the production culture of the vaccine product using the same manufacturing technique. The results suggest that the clearance level achieved is sufficient to inactivate/remove Sf-RV present in the culture fluid. Treatment with surfactant/low pH treatment was found to be useful as a viral inactivation step, and anion exchange chromatography, nanofiltration, and affinity chromatography were useful as removal steps. Thus, the manufacturing process contains multiple viral inactivation/removal steps required by ICH Q5A, and therefore has a high virus clearance capacity.

In fact, qPCR detected no residual Sf-RV gene in the active substance manufactured by the proposed process for marketing in Japan.

---

1) The website of Ministry of Agriculture, Forestry and Fisheries states that "Spodoptera frugiperda is harmless to humans and animals. Eating plants to which Spodoptera frugiperda is attached does not injure the health of humans." (https://www.maff.go.jp/j/syouan/syokubo/keneki/k_kokunai/tumajiro.html [last accessed on March 8, 2022]).

These results show that Sf-RV, even if present in WCB, is completely inactivated/removed during the purification process of the active substance; this suggests that the finished product is extremely unlikely to be contaminated with infectious Sf-RV.

PMDA concluded that the status of Nuvaxovid corresponds to Case C (when the cells or unprocessed bulk are known to contain a virus, other than a rodent retrovirus, for which there is no evidence of capacity for infecting humans) defined in ICH Q5A Guideline. Also, in order to investigate the necessity of using said cell substrate, PMDA asked the applicant to explain the possibility of changing the manufacturing process to use Sf-RV-uninfected cell substrate.

The applicant's explanation:
Nuvaxovid is manufactured by using the cell bank supplied by Novavax, the developer of Nuvaxovid. In order realize GMP production of Nuvaxovid using Sf-RV-uninfected cells, it is necessary to develop a GMP-compatible cell strain in house. It will take several years to establish a new cell bank and investigate an additional manufacturing process. There is also a risk that the new manufacturing process, even if established, may not achieve the quality and productivity as those established in the current vaccine product. Nuvaxovid is a conventional recombinant protein vaccine containing SARS-CoV-2 rS as the antigen manufactured using a platform different from that used in the manufacture of the approved mRNA vaccines and adenovirus vector vaccine. From the standpoint of public health, it is the maximum priority to develop Nuvaxovid as promptly as possible. The applicant therefore decided to use the manufacturing process proposed in the present application.

As explained above, Sf-RV is completely removed during the manufacturing process of Nuvaxovid, and Sf-RV has not been detected in the vaccine product so far manufactured. Furthermore, the safety of Nuvaxovid has been confirmed in clinical studies in which Nuvaxovid was vaccinated to not less than 30,000 people including Japanese people. In addition, multiple drugs manufactured using Sf9 cells have been approved in foreign countries. Among them, a vaccine against seasonal influenza approved in 2013 in the U.S. is marketed by several million doses every year, including the sales in Europe and Australia and, up until now, no safety concerns attributable to Sf-RV have been identified. These situations suggest that the safety risk is low in manufacturing Nuvaxovid using the Sf9 cell bank. Nevertheless, the necessity of changing the present cell substrate to Sf-RV-free cell substrate will be investigated continuously.

PMDA accepted the applicant's plan to continue to investigate the necessity of changing the cell substrate. At the same time, PMDA concluded that the amount of residual Sf-RV gene in the active substance and in the vaccine product should be controlled continuously. PMDA instructed the applicant to control the amount of residual Sf-RV gene in the manufacturing process of the active substance and the vaccine product, and to check the infectivity of the residual gene.

The applicant's explanation:
[redacted] Sf-RV [redacted] will be measured in all batches of the active substance manufactured in Japan according to the request of PMDA. Also, an infectivity test will be conducted

on all batches of the active substance to confirm that the residual Sf-RV gene is not derived from infectious particles. [redacted] to determine the infectivity.

PMDA's view:
For the reasons listed below, using the Sf9 cell bank is acceptable, provided that the potential risk associated with Sf-RV is adequately controlled in the manufacturing process:

(a) Although the situation of Nuvaxovid corresponds to Case C in ICH Q5A Guideline, there is only an extremely low risk of contamination of infectious Sf-RV in the finished product, as explained by the applicant.
(b) Sf-RV gene was not detected in the active substance manufactured by the applicant using the proposed commercial process for marketing in Japan.
(c) Development of SARS-CoV-2 vaccines is urgently needed.
(d) A favorable risk-benefit balance of Nuvaxovid has been demonstrated [see Section 7.R.4].

2.R.2 Novel excipients

The vaccine product contains adjuvants Matrix-M (Matrix-A and Matrix-C), which are new excipients. Both Matrix-A and Matrix-C are registered by Novavax AB and AGC Biologics A/S in MF (MF registration number [304MF20004], MF registration number [304MF20002], MF registration number [304MF20003], and MF registration number [304MF20005]).

2.R.2.1 Specifications and stability

Results of the review on the documents on MF are reported in Supplement to Review Report (2).

2.R.2.2 Safety

Based on the submitted data, PMDA concluded that the excipients are unlikely to cause safety problems at the clinical dose of Nuvaxovid. Despite this conclusion, the use of these excipients should not be handled as a precedent, because these excipients have immunostimulatory activity as adjuvants [see Section 3.1.1] and cause inflammatory changes at the site of administration (within muscles) [see Section 5.2].

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

The applicant submitted the results of primary pharmacodynamic studies on the active substance and Matrix-M contained in the vaccine product. The studies were conducted in mice, hamsters, cynomolgus monkeys, and rhesus monkeys.

3.1 Primary pharmacodynamics

Table 8 shows the outline of the studies submitted (evaluation data).

Table 8. Summary of primary pharmacodynamics studies (evaluation data)

Animal species Sex	Number of animals	Dosage regimen (intramuscular administration in all animals)	Primary endpoint	Attached document CTD
Balb/c mice Female	6 per group (3 in the placebo group)	• SARS-CoV-2 rS (10 μg) + Matrix-M (0, 5 μg), 2 doses • Placebo, 2 doses (21 days apart between 2 doses)	Immunogenicity	4.2.1.1-2
Balb/c mice Female	10 per group	• SARS-CoV-2 rS (1, 10 μg) + Matrix-M (5 μg), 2 doses • SARS-CoV-2 rS (1, 10 μg) + aluminum hydroxide (200 μg), 2 doses • SARS-CoV-2 rS (1, 10 μg), 2 doses (21 days apart between 2 doses)	Immunogenicity	4.2.1.1-3
Balb/c mice Female	8 per group (4 in the placebo group)	• SARS-CoV-2 rS (1, 10 μg) + Matrix-M (0, 5 μg), 2 doses • BV2365 (1, 10 μg) + Matrix-M (0, 5 μg), 2 doses • BV2369 (1, 10 μg) + Matrix-M (0, 5 μg), 2 doses • Placebo, 2 doses (14 days apart between 2 doses)	Immunogenicity Prevention of infection	4.2.1.1-5
Balb/c mice Female	10 per group	• SARS-CoV-2 rS (0.01, 0.1, 1, 10 μg) + Matrix-M (5 μg), 1 or 2 doses • SARS-CoV-2 rS (10 μg), 2 doses • Placebo, 2 doses (14 days apart between 2 doses)	Immunogenicity Prevention of infection	4.2.1.1-6
Syrian hamsters Male and female	8 per group	• SARS-CoV-2 rS (10 μg) + Matrix-M (15 μg), 1 dose • SARS-CoV-2 rS (1, 10 μg) + Matrix-M (15 μg), 2 doses • Placebo, 2 doses (14 days apart between 2 doses)	Immunogenicity Prevention of infection	4.2.1.1-7
Cynomolgus monkeys Male and female	4 per group	• SARS-CoV-2 rS (5 μg) + Matrix-M (25, 50 μg), 1 dose • SARS-CoV-2 rS (2.5 μg) + Matrix-M (25 μg), 2 doses • SARS-CoV-2 rS (5, 25 μg) + Matrix-M (50 μg), 2 doses • Placebo, 2 doses (21 days apart between 2 doses)	Immunogenicity Prevention of infection	4.2.1.1-8
Rhesus monkeys Male and female	5 per group (2 in the placebo group)	• SARS-CoV-2 rS (5, 25 μg) + Matrix-M (50 μg), 1 or 2 doses • Placebo, 1 or 2 doses (21 days apart between 2 doses)	Immunogenicity Prevention of infection	4.2.1.1-9

Placebo: 25 mM sodium phosphate, pH 7.2, 300 mM sodium chloride, 0.01% polysorbate 80
BV2365: A protease-resistant vaccine candidate antigen generated by mutating and modifying the putative furin cleavage site within the S1/S2 cleavage domain of the full-length S protein.
BV2369: A protease-resistant vaccine candidate antigen generated by mutating and modifying the putative furin cleavage site within the S1/S2 cleavage domain of the full-length S protein and by deleting the hydrophobic fusion peptide.

3.1.1 Immunogenicity of SARS-CoV-2 rS and Matrix-M (CTD 4.2.1.1-2, 4.2.1.1.3, 4.2.1.1.6 to 9)

The following measurements were conducted in mice, hamsters, and monkeys on 13 to 35 days after the first dose of the test substance: (a) S-protein-specific antibody by ELISA, (b) hACE2 binding inhibitory antibody by ELISA, and (c) neutralizing antibody by cytopathic effect (CPE) using severe SARS-CoV-2 or by plaque neutralization test. Also, immunoglobulin G (IgG) subclass analysis was conducted by ELISA using mouse serum. In order to evaluate antigen-specific T cell response to stimulation by SARS-CoV-2 rS or S-protein peptide pool in mice, spleen was isolated on Day 28 after the first dose of the test substance, and Th1-type cytokines (interferon-gamma [IFN-γ], tumor necrosis factor-alpha [TNF-α], and interleukin [IL]-2) and Th2-type cytokine (IL-5) were measured by enzyme-linked immune absorbent spot (ELISpot) assay and intracellular cytokine staining.

Coadministration of SARS-CoV-2 rS and Matrix-M induced antibody production and Th1-dominant T cell response, as shown below, demonstrating the immunogenicity of SARS-CoV-2 rS.

3.1.1.1 Antibody production (CTD 4.2.1.1-3, 4.2.1.1-6 to -9)

In mice, hamsters, and monkeys, co-administration of SARS-CoV-2 rS and Matrix-M induced antibody in a SARS-CoV-2 dose-dependent manner. The antibody titer was higher in animals receiving 2 doses than in those receiving 1 dose at the same dose level (CTD4.2.1.1-6 to 9).

The difference in the immunogenicity between SARS-CoV-2 rS alone and SARS-CoV-2 rS + Matrix-M was investigated in mice. S-protein specific antibody titer, hACE2 receptor binding inhibitory antibody titer, and neutralizing antibody titer were higher in the SARS-CoV-2 rS + Matrix-M group than in the SARS-CoV-2 rS alone group (CTD 4.2.1.1-6). In the SARS-CoV-2 rS alone group and the SARS-CoV-2 rS + aluminum hydroxide (adjuvant) group, IgG1 antibody was mainly induced, showing a Th2-dominant response. In the SARS-CoV-2 rS + Matrix-M group, IgG1 and IgG2a antibodies were induced, showing a well-balanced Th1/Th2 response as suggested by IgG subclass analysis (CTD 4.2.1.1-3).

3.1.1.2 T cell response (CTD 4.2.1.1-2)

In the placebo group, neither IFN-γ-producing cells nor IL-5-producing cells were observed. In the SARS-CoV-2 rS + Matrix-M group, the number of IFN-γ-producing cells (310 cells/10^6 spleen cells) was greater than the number of IL-5-producing cells (214 cells/10^6 spleen cells), showing Th1-dominant cellular immune response.

In the SARS-CoV-2 rS + Matrix-M group, the number of cytokine (IFN-γ, TNF-α, and IL-2)-producing cells was higher than in the SARS-CoV-2 rS alone group. The percentage of multi-functional CD4- and CD8-positive T cells producing multiple cytokines (IFN-γ, TNF-α, and IL-2) in the same cells, was higher in the SARS-CoV-2 rS + Matrix-M group (CD4, 2 types in 41% and 3 types in 23%; CD8, 2 types in 39% and 3 types in 28%) than in the SARS-CoV-2 rS alone group (CD4, 2 types in 35% and 3 types in 7%; CD8, 2 types in 33% and 3 types in 24%). Furthermore, the frequency of follicular helper T cells and germinal center B cells were 3.3 and 13 times higher, respectively, in the SARS-CoV-2 rS + Matrix-M group than in the SARS-CoV-2 rS alone group. These results suggested that co-administration of SARS-CoV-2 rS and Matrix-M induces (a) multifunctional effector T cells and (b) immune response favorable for continuous production of high-affinity antibodies.

3.1.2 Infection-preventing effect of SARS-CoV-2 rS and Matrix-M (CTD 4.2.1.1-6 to 9)

Mice, hamsters, cynomolgus monkeys, and rhesus monkeys were vaccinated with the first dose of each test substance, followed by intranasal administration (or nasal and intratracheal administration in monkeys) of SARS-CoV-2 strain WA1 (Wuhan strain) after 56, 35, 35, and 38 days, respectively. After the viral exposure, laboratory tests, virological tests, and histopathological tests were conducted. In the virological test, the viral load was measured by plaque assay in mice and, in other animals, by RT-PCR targeted at SARS-CoV-2 sub-genome mRNA, which suggests virus replication. In order to make mice susceptible to SARS-CoV-2 infection, they were given adenovirus vector expressing hACE2 on Day 52 after the initial vaccination.

Results showed infection-preventing effect of SARS-CoV-2 rS + Matrix-M (see Tables 9 to 11).

Table 9. Laboratory tests

Animal species	Results	Attached document CTD
Mice	The percent weight loss during 7 days after viral infection was smaller in the SARS-CoV-2 rS + Matrix-M group than in the placebo group, showing a tendency of dose-dependent suppression of weight loss in the SARS-CoV-2 rS + Matrix-M group.	4.2.1.1-6
Hamsters	The percent weight loss during 9 days after viral infection was smaller in the SARS-CoV-2 rS + Matrix-M group than in the placebo group. Motility decreased in all groups during 2 days after viral infection. In the placebo group, motility decreased for 7 days after viral infection, whereas in the SARS-CoV-2 rS + Matrix-M group, motility returned to the pre-infection level 6 to 7 days after viral infection.	4.2.1.1-7
Cynomolgus monkeys	During the 7 days after viral infection, neither the placebo group nor theSARS-CoV-2 rS + Matrix-M group showed the following findings, demonstrating no significant differences between the 2 groups: changes in clinical signs, a marked decrease in body weight, a marked increase in body temperature, adverse reactions at the vaccination site, and changes in hematological parameters (except transient changes that resolved to baseline level before the end of the study).	4.2.1.1-8
Rhesus monkeys	During 7 to 8 days after viral infection, changes in clinical symptoms, vaccination site, body weight, and hematological parameters (except transient changes in red blood cells) were mild in both the placebo and SARS-CoV-2 rS + Matrix-M groups, showing no significant differences between the two groups. Lung X-ray conducted 3 days after viral infection showed very mild to mild findings in both the SARS-CoV-2 rS + Matrix-M and placebo groups but did not detect abnormality in the lung parenchyma, showing no significant differences between the two groups.	4.2.1.1-9

Table 10. Virological tests

Animal species	Results	Attached document CTD
Mice	The viral load in the pulmonary tissue 4 days after viral infection was lower in the SARS-CoV-2 rS + Matrix-M group than in the placebo group, showing a tendency of decrease in viral load in a manner dependent on the dose and the number of vaccinations.	4.2.1.1-6
Hamsters	From 2 days up to 14 or 15 days after viral infection, the viral load in oral swab was lower in the SARS-CoV-2 rS + Matrix-M group than in the placebo group. In the placebo group, the virus in oral swab was detectable up to 14 to 15 days after viral infection, whereas in the SARS-CoV-2 rS + Matrix-M group (2 vaccinations), the viral load decreased below the detection limit before 7 days after viral infection.	4.2.1.1-7
Cynomolgus monkeys	In the placebo group, the viral load in the nasal swab from 1 to 7 days after viral infection tended to increase in 2 of 4 animals, suggesting viral proliferation in the nasal cavity, whereas in the SARS-CoV-2 rS + Matrix-M group, the viral load was below the detection limit (50 copies/mL). The viral load in the bronchoalveolar lavage fluid 2 days after viral infection was high (1,272 to 16,143 copies/mL) in the placebo group but below the detection limit in the SARS-CoV-2 rS + Matrix-M group except in 1 animal (99 copies/mL).	4.2.1.1-8
Rhesus monkeys	The viral load in the nasal washes 2 to 8 days after viral infection was high (7,060 to 881,000 copies/mL) in the placebo group. In the SARS-CoV-2 rS + Matrix-M group (2-dose vaccination), the viral load was below the detection limit (14 copies/mL) from 4 days after viral infection although the virus was detected (5,160 to 20,300 copies/mL) in some animals 2 days after viral infection. In 2 and 4 days after viral infection, the viral load in bronchoalveolar lavage fluid was high (3,640 to 174,000 copies/mL) in the placebo group, but was below the detection limit in the SARS-CoV-2 rS + Matrix-M group (2-dose vaccination).	4.2.1.1-9

Table 11. Histopathological tests

Animal species	Results	Attached document CTD
Mice	On Day 4 and 7 after viral infection, inflammation was observed throughout the entire pulmonary interstitium, in the perivascular area, and in the bronchiolar area in the placebo group. In the SARS-CoV-2 rS + Matrix-M group, inflammatory scores at each area were significantly lower than in the placebo group.	4.2.1.1-6
Hamsters	On Day 4 after viral infection, the lungs in the placebo group showed interstitial infiltration of mononuclear cells, hyperplasia of alveolar epithelium and, in rare cases, mild to moderate pathological changes accompanied by syncytial cells. In the SARS-CoV-2 rS + Matrix-M group, no marked histopathological changes were observed except very mild to mild alveolar inflammation caused by mixed cell infiltration in 1 animal. On Day 14 or 15 after viral infection, the placebo group showed mononuclear cell infiltration in the perivascular area and in the interstitium, pleural fibrilization, hyperplasia of alveolar epithelium, moderate alveolar macrophage infiltration, and syncytial cells. In contrast, the SARS-CoV-2 rS + Matrix-M group showed a mild to moderate increase in pulmonary macrophages but no other findings.	4.2.1.1-7
Cynomolgus monkeys	On Day 7 after viral infection, the placebo group showed mild to moderate mixed cell infiltration in the area surrounding the pulmonary vessels and inflammatory reactions accompanied by macrophages and neutrophils in the alveoli and the bronchial mucosa. The SARS-CoV-2 rS + Matrix-M group showed milder pathological changes than the placebo group. Nasal cavity samples collected 7 days after viral infection did not show any significant changes in either group.	4.2.1.1-8
Rhesus monkeys	On Day 7 or 8 after viral infection, both groups showed increased alveolar macrophage count, hyperplasia of type 2 alveolar epithelial cells and, in rare cases, inflammation accompanied by syncytial cells. Histopathological changes were very mild to mild and observed only in limited parts of the lung, and no clear difference was observed between the two groups.	4.2.1.1-9

3.2 Safety pharmacology

No safety pharmacology study of Nuvaxovid was conducted. Instead, the safety pharmacology of Nuvaxovid was evaluated based on clinical signs of rabbits in the repeated dose toxicity study. The applicant explained that Nuvaxovid had no effect on the physiological functions of the cardiovascular, respiratory, or central nervous systems, etc., and that the WHO Guidelines on nonclinical studies[2)] generally exempt specific safety pharmacology studies for vaccines.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of SARS-CoV-2 rS + Matrix-M

The applicant's explanation about the mechanism of action of SARS-CoV-2 rS + Matrix-M:

The immunogenicity and infection-preventive effect of SARS-CoV-2 rS + Matrix-M were evaluated by studies in mice, hamsters, and monkeys. These animal species receiving SARS-CoV-2 rS + Matrix-M showed production of (a) S-protein-specific antibody, (b) antibody that inhibits binding to hACE2 receptor, and (c) neutralizing antibody, and showed induction of T cell response accompanied by production of Th1 cytokines (IFN-γ, TNF-α, and IL-2). Also, when these animals with humoral and cellular immunity activated by SARS-CoV-2 rS + Matrix-M were exposed to SARS-CoV-2, they showed decreased virus replication in the nasal cavity, lung, etc., decreased histopathological change in the lung, suppression of body weight loss, and suppression of motility decrease. These observations suggest that SARS-CoV-2 rS + Matrix-M has immunogenicity and can prevent infection.

2) "WHO Technical Report Series No.927 Annex 1 Guidelines on nonclinical evaluation of vaccines. WHO; 2005"

The immunostimulatory effect of Matrix-M was evaluated by a study using Matrix-M-adjuvanted SARS-CoV-2 rS and other antigens. The following results show that Matrix-M exhibits immunostimulatory effects by inducing immune cell mobilization and activation at the site of administration.

- When Matrix-M and an antigen (Ebola virus protein) were administered to mice at different sites or different timings, no adjuvant effect was observed. In contrast, when Matrix-M was administered with the antigen to mice at the same site and timing, it enhanced antibody induction by targeting the same draining lymph nodes, showing a local adjuvant effect (CTD 4.2.1.1-11).
- In mice receiving Matrix-M-adjuvanted influenza virus vaccine, production of various cytokines and chemokines at the administration site increased transiently, showing mobilization and activation of various immune cells (neutrophils, monocytes, dendritic cells, CD4-positive T cells, CD8-positive T cells, B cells, NK cells, and macrophages) at the administration site and in the draining lymph nodes (CTD 4.2.1.1-12, 4.2.1.1-13).
- Mice receiving SARS-CoV-2 rS + Matrix-M showed a higher antibody response than those receiving SARS-CoV-2 rS alone or aluminum-adjuvanted SARS-CoV-2 rS. Also, the mice showed antibody response with an increase in IgG2a/IgG1 ratio, production of IFN-γ, TNF-α, and IL-2, an increase in CD4-positive T cells and CD8-positive T cells, and an increase in the percentage of multifunctional effector cells that produce 2 to 3 types of cytokines. In addition, they showed an optimal Th1-dominant immune response when infected with the virus (CTD 4.2.1.1-2, 4.2.1.1-3).

PMDA accepted the explanation of the applicant.

3.R.2 Risk of Nuvaxovid-associated enhanced disease

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

Administration of Matrix-M-adjuvanted SARS-CoV-2 rS to mice, hamsters, and monkeys induced a high neutralizing antibody titer and Th1-dominant cellular immunity. IgG2a/IgG1 ratio was higher in mice receiving SARS-CoV-2 rS + Matrix-M than in those receiving SARS-CoV-2 rS adjuvanted with aluminum hydroxide, which induces Th2-dominant immune response; this shows that SARS-CoV-2 rS + Matrix-M induces Th1-dominant immune response. The applicant concluded that Nuvaxovid does not induce antibody-dependent enhanced disease or vaccine-associated enhanced respiratory disease, for the following reasons: (a) Mice, hamsters, and monkeys exposed to SARS-CoV-2 after receiving SARS-CoV-2 rS + Matrix-M did not showed worse clinical signs than those receiving placebo; (b) enhancement of virus infection or replication in the nasal cavity, lung, etc., was not observed; and (c) histopathological evaluation of the lung showed only limited immune cell infiltration and no eosinophilic inflammatory reactions. The above results of clinical studies suggest that Nuvaxovid is unlikely to induce enhanced disease.

PMDA accepted the explanation of the applicant. Risk of enhanced disease in humans receiving Nuvaxovid is discussed also in Section 7.R.3.3.1.

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

No non-clinical pharmacokinetics study was conducted in the present application. WHO Guidelines on nonclinical studies[3)] generally exempt non-clinical pharmacokinetics studies for vaccines.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of a repeated-dose toxicity study and a reproductive and developmental toxicity study of Nuvaxovid, and a toxicity study (genotoxicity study), etc., of Matrix-M adjuvant.

5.1 Single-dose toxicity

No single dose toxicity study of Nuvaxovid was conducted. Instead, the single dose toxicity (acute toxicity) of Nuvaxovid was evaluated from the results obtained after the first dose in the repeated intramuscular dose toxicity study in rabbis (CTD 4.2.3.2-1). After a single dose of Nuvaxovid, no death occurred but body temperature increased within the normal range.

5.2 Repeated-dose toxicity

A repeated intramuscular dose toxicity study was conducted in rabbits using SARS-CoV-2 rS + Matrix-M (Table 12). The main finding was inflammatory change at the injection site.

Table 12. Repeated-dose toxicity study using Nuvaxovid

Test system	Route of administration	Administration period	Dose (μg/body)	Main findings	No observed adverse effect level (μg/body)	Attached document CTD
Male and female rabbits (NZW)	i.m.	36 days (4 times [a)]) + 21-day withdrawal periods	SARS-CoV-2 rS (50 μg),[b)] SARS-CoV-2 rS (50 μg) + Matrix-M (50 μg),[b)] or PBS	SARS-CoV-2 rS (50 μg) [c)]: Inflammation at the administration site SARS-CoV-2 rS (50 μg) + Matrix-M (50 μg) [c)]: Inflammation at the administration site, increased CRP and fibrinogen Reversibility: Yes	SARS-CoV-2 rS (50 μg) + Matrix-M (50 μg)	4.2.3.2-1

a) Administered to a single site of a hind leg at 0.5 mL on Days 1, 8, 15, and 36 of the study.
b) 25 mM sodium phosphate (pH 7.2), 300 mM sodium chloride, and 0.01% polysorbate 80
c) S-protein-specific IgG production was observed on Days 7, 14, 35, and 57 of the study.

5.3 Genotoxicity

No genotoxicity study of Nuvaxovid was conducted. The applicant concluded that Nuvaxovid has no genotoxicity, based on the results of *in vitro* genotoxicity studies of Matrix-M (Table 13).

3) "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"

Table 13. Genotoxicity studies

Test substance	Study type		Test system	S9 (treatment duration)	Dose	Results	Attached document CTD
Matrix-M	in vitro	Test for gene mutation in bacteria	Salmonella typhimurium: TA98, TA100 TA1535, TA1537 *Escherichia coli*: WP2uvrA	+ (2 to 3 days)	0[a], 100, 250, 500, 750, 1000, 2500, 3450, 4400 µg/plate	Negative	4.2.3.3.1-3
				− (2 to 3 days)			
		Micronucleus assay in mammalian cells	Chinese hamster cells (CHO)	± (4 hours)	0,[a] 0,[b] 50, 100, 220, 440 µg/mL	Negative	4.2.3.3.1-4
				− (24 hours)			

a) PBS
b) No treatment

5.4 Carcinogenicity

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

5.5 Reproductive and developmental toxicity

A reproductive and developmental toxicity study of SARS-CoV-2 rS + Matrix-M was conducted in rats (Table 14). SARS-CoV-2 rS + Matrix-M had no effect on parental animals or their offspring.

Table 14. Reproductive and developmental toxicity study

Study types	Test system	Route of admini-stration	Administration period	Dose (µg/body)	Main findings	No observed adverse effect level (µg/body)	Attached document CTD
Studies of fertility and early embryonic development to implantation, embryofetal development, and pre- and postnatal development, including maternal function	Male rats (SD)	i.m.	27 days before mating to gestation day 15 (4 doses[a])	SARS-CoV-2 rS (5 µg) + Matrix-M (10 µg),[b] Matrix-M (10 µg),[c] or PBS	SARS-CoV-2 rS (5 µg) + Matrix-M (10 µg)[d] Maternal animals: None Embryos, fetuses: None F1 offspring: None	SARS-CoV-2 rS (5 µg) + Matrix-M (10 µg)	4.2.3.5.3-1

a) One dose each of 0.1 mL/site was administered to a single site of a hind leg on Days 27 and 13 before mating and on gestation days 7 and 15.
b) 25 mM sodium phosphate (pH 7.2), 300 mM sodium chloride, and 0.01% polysorbate 80
c) PBS
d) S-protein-specific IgG production was observed in maternal animals on Day 13 before mating, on the day of mating, on post-mating day 21 (at the time of Caesarean section), and on postpartum day 21. S-protein-specific IgG was detected in fetuses on gestation day 21 (at the time of Caesarean section) and in F1 offspring on Day 21 after birth.

5.6 Local tolerance

The local tolerance of Nuvaxovid was evaluated from the results of the repeated intramuscular dose toxicity study in rabbits (CTD 4.2.3.2-1). Reversible inflammatory changes were observed at the injection site.

5.R Outline of the review conducted by PMDA

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

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

6.1 Biopharmaceutic Studies and Associated Analytical Methods

In the evaluation of baseline serum reactions in subjects, viral gene in serum was measured by RT-PCR, and anti-nucleocapsid protein (N-protein) antibody in serum by electrochemiluminescence immunoassay.

In the evaluation of humoral immunity, anti-S protein antibody in serum of subjects was measured by ELISA, and neutralizing antibody by microneutralization method using SARS-CoV-2 (original Wuhan strain [Wuhan-Hu-1]). In the evaluation of cellular immunity, mononuclear cells were isolated from peripheral blood of subjects in Part 1 and Part 2 of Study 2019nCoV-101 (Study 101), and Th1 cytokines (IFN-γ, TNF-α, and IL-2) and Th2 cytokines (IL-5 and IL-13) were measured by ELISpot and cytokine staining.

Virological confirmation of COVID-19 was done by RT-PCR.

6.2 Clinical pharmacology study

No clinical pharmacology study was conducted in the present application.

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

The applicant submitted efficacy and safety evaluation data from 4 clinical studies shown in Table 15.

Table 15. List of clinical studies on efficacy and safety (evaluation data)

Region	Study	Phase	Population	No. of subjects enrolled	Summary of dosage regimen	Main endpoints
Japan	TAK-019-1501	I/II	Healthy adults ≥20 years old	200	Intramuscular administration of Nuvaxovid or placebo, 2 doses 21 days apart	Safety, immunogenicity
Foreign countries	2019nCoV-301	III	Healthy adults ≥18 years old	29,582	Intramuscular administration of Nuvaxovid or placebo, 2 doses 21 days apart	Efficacy, safety, immunogenicity
	2019nCoV-302	III	Subjects ≥18 and ≤84 years old who are healthy or have stable chronic disease	15,139	Intramuscular administration of Nuvaxovid or placebo, 2 doses 21 days apart	Efficacy, safety, immunogenicity
	2019nCoV-101	I/II	Part 1: Healthy adults ≥18 and ≤59 years old Part 2: Healthy adults ≥18 and ≤84 years old	Part 1: 131 Part 2: 1,283	<u>Part 1:</u> (a) Intramuscular administration of Nuvaxovid, SARS-CoV-2 rS 25 µg, SARS-CoV-2 rS 25 µg + Matrix-M 50 µg, or placebo, 2 doses 21 days apart; or (b) Intramuscular administration of SARS-CoV-2 rS 25 µg +Matrix-M 50 µg and then placebo, 1 dose each 21 days apart <u>Part 2:</u> *Primary series*: (a) Intramuscular administration of Nuvaxovid, SARS-CoV-2 rS 25 µg + Matrix-M 50 µg, or placebo, 2 doses 21 days apart; or (b) Intramuscular administration of Nuvaxovid or SARS-CoV-2 rS 25 µg + Matrix-M 50 µg and then placebo, 1 dose each 21 days apart *Booster dose:* A single intramuscular dose of Nuvaxovid or placebo on Day 168 after the primary series	Safety, immunogenicity

7.1 Phase I/II studies

7.1.1 Japanese phase I/II study (CTD 5.3.5.1.1: Study TAK-019-1501, study period, ongoing since February 2021; data cutoff date, [redacted])

A randomized, observer-blinded,[4] placebo-controlled, parallel-group study is ongoing at 2 study sites in Japan to investigate the safety and immunogenicity of Nuvaxovid in healthy Japanese people ≥20 years old (target sample size, 200; 150 in the Nuvaxovid group [100 subjects <65 years old, 50 subjects ≥65 years old], 50 in the placebo group [40 subjects <65 years old, 10 subjects ≥65 years old]).

[4] The study vaccine storage managers and the persons in charge of study vaccine dispensing at the study sites and some staff members at the external contract organization, were unblinded to the study.

Two doses of Nuvaxovid (0.5 mL each) or physiological saline were administered intramuscularly 21 days apart (allowable period, + 3 days). In response to the approval of a SARS-CoV-2 vaccine in Japan in February 2021, the study protocol was amended as follows to ensure that the subjects in the placebo group do not miss the opportunity of receiving the approved SARS-CoV-2 vaccine:

> Blindness is to be lifted by providing the assignment information to subjects after the data lock for the primary analysis of safety and immunogenicity (Day 28 after the second dose) (Protocol ver. 2.0, [redacted], 20[redacted]).

Of the 326 subjects enrolled, 200 were randomized, received at least 1 dose of the study vaccine, and were included in the Full Analysis Set (FAS) and the safety analysis set. Of the 200 subjects, 199 (150 in the Nuvaxovid group, 49 in the placebo group) were included in the per-protocol set and handled as the analysis set for immunogenicity. The remaining 1 subject in the placebo group was excluded because the subject did not receive the second dose due to an adverse event (tinnitus).

After all subjects completed the visit on Day 28 after the second dose of the study vaccine, the primary safety and immunogenicity analyses were to be performed.

The primary endpoint was specific IgG antibody titer (ELISA) against SARS-CoV-2 rS protein on Day 14 after the second dose. The geometric mean titer (GMT) [2-sided 95% confidence interval (CI)] was 31,036.8 [26,837.1, 35,893.7] in the Nuvaxovid group and 132.3 [109.6, 159.5] in the placebo group; the geometric mean fold rise (GMFR) [2-sided 95% CI] was 258.8 [218.8, 306.0] in the Nuvaxovid group and 1.0 [1.0,1.1] in the placebo group. In the Nuvaxovid group, both the seroconversion rate and antibody response rate were 100% (150 of 150 subjects). In the placebo group, the seroconversion rate was 0% (0 of 49) and the antibody response rate was 8.2% (4 of 49).

Table 16 shows changes over time in the neutralizing antibody titer against SARS-CoV-2 (original Wuhan strain) on Day 21 after the first dose and on Days 14 and 28 after the second dose.

Table 16. Neutralizing antibody titer against original Wuhan strain (Study 1501: per-protocol set)

		Nuvaxovid			Placebo		
		All ages	≥20 to <65 years old	≥65 years	All ages	≥20 to <65 years old	≥65 years
Baseline	Number of subjects	150	100	50	49	39	10
	GMT [a]	**10.0**	**10.1**	**10.0**	**10.1**	**10.2**	**10.0**
	[2-sided 95%CI]	[10.0, 10.1]	[9.9, 10.2]	[10.0, 10.0]	[9.9, 10.4]	[9.8, 10.6]	[10.0, 10.0]
Day 21 after first dose	Number of subjects	150	100	50	49	39	10
	GMT	**50.2**	**68.2**	**27.1**	**10.4**	**10.5**	**10.0**
	[2-sided 95%CI]	[41.2, 61.0]	[54.0, 86.2]	[20.2, 36.5]	[9.9, 10.9]	[9.9, 11.2]	[10.0, 10.0]
	GMFR	**5.0**	**6.8**	**2.7**	**1.0**	**1.0**	**1.0**
	[2-sided 95%CI]	[4.1, 6.1]	[5.3, 8.6]	[2.0, 3.6]	[1.0, 1.1]	[1.0, 1.1]	[1.0, 1.0]
	Seroconversion rate % (n)	**67.3 (101)**	**77.0 (77)**	**48.0 (24)**	**0**	**0**	**0**
	[2-sided 95%CI] [b]	[59.2, 74.8]	[67.5, 84.8]	[33.7, 62.6]	[0.0, 7.3]	[0.0, 9.0]	[0.0, 30.8]
Day 14 after second dose	Number of subjects	150	100	50	49	39	10
	GMT	**884.4**	**1061.5**	**613.9**	**10.4**	**10.4**	**10.7**
	[2-sided 95%CI]	[749.0, 1044.4]	[899.4, 1252.8]	[427.8, 881.1]	[9.9, 10.9]	[9.9, 10.9]	[9.2, 12.5]
	GMFR	**88.0**	**105.4**	**61.4**	**1.0**	**1.0**	**1.1**
	[2-sided 95%CI]	[74.5, 104.0]	[89.2, 124.6]	[42.8, 88.1]	[1.0, 1.1]	[1.0, 1.1]	[0.9, 1.3]
	Seroconversion rate % (n)	**99.3 (149)**	**100 (100)**	**98.0 (49)**	**0**	**0**	**0**
	[2-sided 95%CI] [b]	[96.3, 100]	[96.4, 100]	[89.4, 99.9]	[0.0, 7.3]	[0.0, 9.0]	[0.0, 30.8]
Day 28 after second dose	Number of subjects	149	99	50	49	39	10
	GMT	**509.5**	**580.2**	**394.0**	**10.4**	**10.5**	**10.0**
	[2-sided 95%CI]	[422.5, 614.6]	[471.2, 714.5]	[269.9, 575.0]	[9.9, 10.9]	[9.9, 11.2]	[10.0, 10.0]
	GMFR	**50.7**	**57.6**	**39.4**	**1.0**	**1.0**	**1.0**
	[2-sided 95%CI]	[42.0, 61.2]	[46.7, 71.0]	[27.0, 57.5]	[1.0, 1.1]	[1.0, 1.1]	[1.0, 1.0]
	Seroconversion rate % (n)	**98.0 (146)**	**99.0 (98)**	**96.0 (48)**	**0**	**0**	**0**
	[2-sided 95%CI] [b]	[94.2, 99.6]	[94.5, 100]	[86.3, 99.5]	[0.0, 7.3]	[0.0, 9.0]	[0.0, 30.8]

a) The lower quantitation limit was 20. Values below the lower quantitation limit were converted to "0.5 × lower quantitation limit."
b) Clopper-Pearson method

The safety observation period was as follows:

- Solicited adverse events[5] (local [injection site pain, tenderness, erythema/redness, induration, swelling] and systemic [pyrexia, fatigue, malaise, myalgia, arthralgia, nausea/vomiting, headache]) were collected from the subject diary until Day 7 after each dose.
- All unsolicited adverse events were collected until Day 49 after the first dose (Day 21 after the first dose and Day 28 after the second dose).
- Serious adverse events, adverse events of special interest (AESIs), adverse events requiring treatment, and adverse events leading to study discontinuation were collected between the first dose and 12 months after the last dose.

Table 17 shows solicited adverse events occurring by Day 7 after each dose of the study vaccine in the safety analysis set.

5) The severity of solicited adverse events was evaluated based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

Table 17. Solicited adverse events occurring by Day 7 after the first and second doses (Study 1501: Safety analysis set)

	All ages		≥20 to <65 years old		≥65 years old	
	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)
Local (after first dose)						
	(N = 150)	(N = 50)	(N = 100)	(N = 40)	(N = 50)	(N = 10)
Injection site pain	44 (29.3)	2 (4.0)	36 (36.0)	1 (2.5)	8 (16.0)	1 (10.0)
Tenderness	65 (43.3)	2 (4.0)	52 (52.0)	1 (2.5)	13 (26.0)	1 (10.0)
Erythema/redness	4 (2.7)	0	4 (4.0)	0	0	0
Induration	5 (3.3)	0	3 (3.0)	0	2 (4.0)	0
Swelling	4 (2.7)	0	4 (4.0)	0	0	0
Local (after second dose)						
	(N = 150)	(N = 49)	(N = 100)	(N = 39)	(N = 50)	(N = 10)
Injection site pain	75 (50.0)	1 (2.0)	53 (53.0)	1 (2.6)	22 (44.0)	0
Tenderness	94 (62.7)	2 (4.1)	68 (68.0)	2 (5.1)	26 (52.0)	0
Erythema/redness	23 (15.3)	0	16 (16.0)	0	7 (14.0)	0
Induration	17 (11.3)	0	9 (9.0)	0	8 (16.0)	0
Swelling	26 (17.3)	0	20 (20.0)	0	6 (12.0)	0
Systemic (after first dose)						
	(N = 150)	(N = 50)	(N = 100)	(N = 40)	(N = 50)	(N = 10)
Pyrexia	0	0	0	0	0	0
Fatigue	13 (8.7)	3 (6.0)	11 (11.0)	2 (5.0)	2 (4.0)	1 (10.0)
Malaise	15 (10.0)	2 (4.0)	11 (11.0)	2 (5.0)	4 (8.0)	0
Myalgia	26 (17.3)	2 (4.0)	21 (21.0)	1 (2.5)	5 (10.0)	1 (10.0)
Arthralgia	7 (4.7)	0	5 (5.0)	0	2 (4.0)	0
Nausea/vomiting	1 (0.7)	0	0	0	1 (2.0)	0
Headache	16 (10.7)	1 (2.0)	10 (10.0)	1 (2.5)	6 (12.0)	0
Systemic (after second dose)						
	(N = 150)	(N = 49)	(N = 100)	(N = 39)	(N = 50)	(N = 10)
Pyrexia	9 (6.0)	0	7 (7.0)	0	2 (4.0)	0
Fatigue	31 (20.7)	4 (8.2)	29 (29.0)	4 (10.3)	2 (4.0)	0
Malaise	44 (29.3)	3 (6.1)	37 (37.0)	3 (7.7)	7 (14.0)	0
Myalgia	49 (32.7)	2 (4.1)	35 (35.0)	2 (5.1)	14 (28.0)	0
Arthralgia	20 (13.3)	0	17 (17.0)	0	3 (6.0)	0
Nausea/vomiting	8 (5.3)	0	7 (7.0)	0	1 (2.0)	0
Headache	32 (21.3)	1 (2.0)	29 (29.0)	1 (2.6)	3 (6.0)	0

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

Up to Day 49 after the first dose of the study vaccine, unsolicited adverse events were observed in 54 of 150 subjects (36.0%) in the Nuvaxovid group and in 9 of 50 subjects (18.0%) in the placebo group. Among these events, those occurring in 39 subjects (26.0%) in the Nuvaxovid group and in 3 subjects (6.0%) in the placebo group were considered related to the study vaccine. Table 18 shows unsolicited adverse events occurring in ≥2 subjects in either group and those for which causal relationship to the study vaccine could not be ruled out.

There were no serious adverse events, adverse events leading to discontinuation of study, or death up to Day 28 after the second dose.

Table 18. Unsolicited adverse events occurring in ≥2 subjects in either group occurring by Day 49 after the first dose and unsolicited adverse events for which causal relationship to the study vaccination could not be ruled out (Study 1501: Safety analysis set)

Event name in PT (MedDRA/J Ver.24.0)	Unsolicited adverse events		Unsolicited adverse events for which causal relationship to the study vaccine could not be ruled out	
	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)
	(N = 150)	(N = 50)	(N = 150)	(N = 50)
Diarrhoea	5 (3.3)	0	2 (1.3)	0
Dental caries	2 (1.3)	0	0	0
Injection site pruritus	26 (17.3)	0	26 (17.3)	0
Chills	5 (3.3)	0	5 (3.3)	0
Injection site warmth	4 (2.7)	0	4 (2.7)	0
Injection site swelling	2 (1.3)	0	2 (1.3)	0
Nasopharyngitis	4 (2.7)	0	0	0
Headache	2 (1.3)	0	0	0
Urticaria	2 (1.3)	0	1 (0.7)	0

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

7.1.2 Foreign phase I/II study (CTD 5.3.5.1.4: Study 2019nCoV-101: study period: Part 1, ongoing since May 2020 [data cut-off on [redacted], 20[redacted]]; Part 2, ongoing since [redacted], 20[redacted] [data cut-off on [redacted], 20[redacted]])

(a) Part 1

A randomized, observer-blinded,[6] placebo-controlled, parallel-group study is ongoing at 2 study sites in Australia to investigate the safety and immunogenicity of Nuvaxovid in healthy subjects ≥18 to ≤59 years old (maximum target sample size, 131 [100 in the Nuvaxovid group, 25 in the placebo group, 6 open-label sentinel subjects in the Nuvaxovid group]).

The study vaccine was administered intramuscularly at the dosage regimen shown in Table 19.

Table 19. Study vaccine, dose interval, and target number of subjects in Part 1 of Study 101

Group	Study vaccine, number of doses	Dose interval (acceptable range)	Target sample size
A	Placebo, 2 doses	21 days (+ 5 days)	25 randomized subjects
B	SARS-CoV-2 rS 25 μg, 2 doses		25 randomized subjects
C [a)]	Nuvaxovid, 2 doses		25 randomized subjects and 3 sentinel subjects [b)]
D	SARS-CoV-2 rS 25 μg + Matrix-M 50 μg, 2 doses		25 randomized subjects and 3 sentinel subjects [b)]
E	SARS-CoV-2 rS 25 μg + Matrix-M 50 μg and then placebo, 1 dose each		25 randomized subjects

a) Proposed dosage of Nuvaxovid
b) Six sentinel subjects were randomly assigned to Group C and Group D at a 1 : 1 ratio under unblinded conditions.

A total of 265 subjects were enrolled in the study. Among them, 114 failed the screening test and 17 withdrew informed consent. The remaining 134 subjects were randomized, and 131 of them who received at least 1 dose of the study vaccine were included in the safety analysis set.

6) The study vaccine storage managers and the persons in charge of study vaccine dispensing at the study sites and some staff members at the external contract organization, were unblinded to the study.

Safety observation period was as follows:

- Solicited adverse events[7] (local [pain, tenderness, erythema, and swelling/induration] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after each dose.[8]
- All unsolicited adverse events were collected until Day 49 after the first dose.
- Adverse events requiring treatment were collected until Day 105 after the first dose.
- Adverse events requiring treatment for which a causal relationship to the study vaccine could not be ruled out, serious adverse events, and adverse events of special interest (AESIs), were collected until Day 265 after the second dose.

Table 20 shows solicited adverse events occurring by Day 7 after each dose of study vaccination.

Table 20. Solicited adverse events occurring by Day 7 after each dose of study vaccination (Part 1 of Study 101: Safety analysis set)

	Event name	Dose No.	Group A (N1 = 23, N2 = 21)	Group B (N1 = 25, N2 = 25)	Group C (N1 = 26, N2 = 26)	Group D (N1 = 25, N2 = 24)	Group E (N1 = 26, N2 = 26)
			n (%)	n (%)	n (%)	n (%)	n (%)
Local reactions	Pain	1	3 (13.0)	6 (24.0)	10 (38.5)	11 (44.0)	14 (53.8)
		2	2 (9.5)	2 (8.0)	15 (57.7)	15 (62.5)	3 (11.5)
	Tenderness	1	7 (30.4)	5 (20.0)	17 (65.4)	13 (52.0)	16 (61.5)
		2	2 (9.5)	3 (12.0)	21 (80.8)	19 (79.2)	2 (7.7)
	Erythema	1	0	0	0	0	1 (3.8)
		2	1 (4.8)	1 (4.0)	2 (7.7)	0	1 (3.8)
	Swelling/induration	1	0	0	0	0	0
		2	0	1 (4.0)	1 (3.8)	2 (8.3)	0
Systemic reactions	Nausea/Vomiting	1	1 (4.3)	4 (16.0)	1 (3.8)	1 (4.0)	4 (15.4)
		2	0	2 (8.0)	2 (7.7)	3 (12.5)	0
	Headache	1	7 (30.4)	10 (40.0)	6 (23.1)	8 (32.0)	6 (23.1)
		2	6 (28.6)	7 (28.0)	12 (46.2)	14 (58.3)	5 (19.2)
	Fatigue	1	4 (17.4)	4 (16.0)	8 (30.8)	10 (40.0)	7 (26.9)
		2	3 (14.3)	3 (12.0)	12 (46.2)	12 (50.0)	4 (15.4)
	Malaise	1	2 (8.7)	1 (4.0)	3 (11.5)	7 (28.0)	4 (15.4)
		2	3 (14.3)	2 (8.0)	9 (34.6)	9 (37.5)	1 (3.8)
	Myalgia	1	2 (8.7)	3 (12.0)	6 (23.1)	8 (32.0)	8 (30.8)
		2	3 (14.3)	2 (8.0)	12 (46.2)	13 (54.2)	1 (3.8)
	Arthralgia	1	1 (4.3)	1 (4.0)	1 (3.8)	2 (8.0)	4 (15.4)
		2	2 (9.5)	1 (4.0)	7 (26.9)	3 (12.5)	1 (3.8)
	Pyrexia	1	0	0	0	0	0
		2	0	0	0	1 (4.2)	0

N 1 = Number of subjects analyzed after the first dose, N 2 = Number of subjects analyzed after the second dose,
n = number of subjects with events

Table 21 shows the incidences of adverse events and adverse reactions. Unsolicited adverse events observed in ≥5 subjects (including events observed up to Day 168 after the second dose) were upper respiratory tract infection (1 in Group A, 0 in Group B, 4 in Group C, 1 in Group D, 2 in Group E; the same order applies hereinafter) and headache (1, 1, 2, 1, 0).

7) The severity of solicited adverse events was evaluated based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

8) Grade ≥1 events persisting until Day ≥7 after the vaccination were collected again from Day 7 until they resolved. From Day 7 onward, they were classified as unsolicited adverse events.

Table 21. Unsolicited adverse events and adverse reactions observed by Day 28 after the second dose (Part 1 of Study 101: Safety analysis set)

	Group A (placebo) (N = 23)	Group B (N = 25)	Group C (N = 26)	Group D (N = 25)	Group E (N = 26)
	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	9 (39.1)	11 (44.0)	14 (53.8)	12 (48.0)	11 (42.3)
Adverse reactions	1 (4.3)	4 (16.0)	7 (26.9)	4 (16.0)	8 (30.8)

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

There were no deaths, serious adverse events, or adverse events leading to study discontinuation up to Day 168 after the second dose. An adverse event led to the discontinuation of the study vaccination in 1 subject of Group D (cellulitis), but it was considered unrelated to the study vaccination.

(b) Part 2

A randomized, observer-blinded,[9)] placebo-control, parallel-group study is ongoing at 17 study sites in the United States and Australia to investigate the safety and immunogenicity of Nuvaxovid in healthy subjects ≥18 to ≤84 years old (target sample size 1,500 at the maximum).

The study vaccine was administered intramuscularly at the dosage regimen shown in Table 22.

Table 22. Study vaccine, dose interval, and target number of subjects in Part 2 of Study 101

Group	Study vaccine, number of doses	Dose interval (acceptable range)	Target sample size
A	Placebo, 2 doses	21 days (−1 to +3 days)	150 to 300 per group
B [a)]	Nuvaxovid, 2 doses		
C	Nuvaxovid and then placebo, 1 dose each		
D	SARS-CoV-2 rS 25 μg + Matrix-M 50 μg, 2 doses		
E	SARS-CoV-2 rS 25 μg + Matrix-M 50 μg and then placebo, 1 dose each		

a) Proposed dosage of Nuvaxovid

Subjects were stratified by study site and age (<60 years, ≥60 years). The percentage of subjects seropositive for SARS-CoV-2 at baseline was not to exceed 15%. A total of 1,288 randomized subjects (257 in Group A, 258 in Group B, 257 in Group C, 258 in Group D, 258 in Group E) were included in the intent-to-treat (ITT) analysis set, and 1,283 (255, 257, 257, 258, 256) of them who received at least 1 dose of the study vaccine was included in FAS and in the safety analysis set. Among them, 1,198 (238, 240, 241, 236, 243) who met the criteria (e.g., having received 2 doses with available data on specific IgG antibody titer in serum at least at baseline and on Day 14 after the second dose) were included in the per protocol (PP) immunogenicity analysis set, and subjected to the primary immunogenicity analysis. Also, in the evaluation of other immunogenicity, subject who met the following criteria were included in the PP analysis set.[10)]

- Analysis up to Day 21 after the first dose: Subjects who received the first dose with available serum samples at baseline and at ≥1 time point after vaccination.
- Analysis after Day 7 after the second dose: Subjects who received 2 doses with available serum samples at baseline and at ≥1 time point after vaccination.

9) The study vaccine storage managers and the persons in charge of study vaccine dispensing at the study sites and some staff members at the external contract organization, were unblinded to the study.

10) Subjects who tested positive for SARS-CoV-2 by PCR during the period from screening up to an evaluation time point, were excluded from the PP analysis set of that time point.

A total of 1,256 subjects (250, 254, 255, 251, 246) received 2 doses of the study vaccine.

At the data cut-off point, 1,252 subjects were participating in the study. Main reasons for study discontinuation in 31 subjects (5, 8, 3, 9, 6) were lost to follow-up (12), withdrawal of consent (11) and adverse events (7).

The primary endpoint was the specific IgG antibody response (GMT, GMFR, and seroconversion rate) against SARS-CoV-2 rS protein on Day 14 after the second dose. Table 23 shows the results of the primary endpoint in the PP immunogenicity analysis set.

Table 23. IgG antibody reaction specific to SARS-CoV-2 rS protein
(Study 101, Part 2: PP immunogenicity analysis set)

		Group A	Group B	Group C	Group D	Group E
Baseline	No. of subjects	238	240	241	236	243
	GMT [a]	120.5	115.2	120.9	120.7	126.5
	[2-sided 95% CI]	[110.6, 131.4]	[106.9, 124.1]	[111.2, 131.5]	[111.2, 131.0]	[115.8, 138.2]
Day 14 after second dose	No. of subjects	238	240	241	236	243
	GMT	**126.1**	**44420.9**	**894.0**	**46459.3**	**1951.3**
	[2-sided 95% CI]	[114.0, 139.4]	[37929.1, 52023.8]	[744.1, 1074.0]	[40839.4, 52852.5]	[1658.3, 2296.1]
	GMFR	**1.0**	**385.6**	**7.4**	**384.9**	**15.4**
	[2-sided 95% CI]	[1.0, 1.1]	[325.5, 456.8]	[6.3, 8.7]	[334.7, 442.7]	[13.3, 17.9]
	Seroconversion rate % (n)	**1.3 (3)**	**98.3 (236)**	**67.6 (163)**	**99.6 (235)**	**86.8 (211)**
	[2-sided 95% CI] [b]	[0.3, 3.6]	[95.8, 99.5]	[61.3, 73.5]	[97.7, 100]	[81.9, 90.8]

a) The lower quantitation limit was 200 EU/mL. Values below the lower quantitation limit were converted to "0.5 × lower quantitation limit."
b) Clopper-Pearson method

Table 24 shows the neutralizing antibody titer against the original Wuhan strain on Day 21 after the first dose and on Day 14 after the second dose in the PP analysis set.

Table 24. Neutralizing antibody titer against original Wuhan strain
(Study 101, Part 2: PP analysis set)

		Group A	Group B	Group C	Group D	Group E
Baseline	Number of subjects	51	51	57	49	48
	GMT [a]	**10.0**	**10.6**	**10.0**	**10.0**	**10.0**
	[2-sided 95% CI]	[10.0, 10.0]	[9.5, 11.8]	[10.0, 10.0]	[10.0, 10.0]	[10.0, 10.0]
Day 21 after first dose	Number of subjects	21	21	22	21	20
	GMT	**10.0**	**40.0**	**30.1**	**67.8**	**44.4**
	[2-sided 95% CI]	[10.0, 10.0]	[20.3, 78.7]	[20.2, 44.9]	[37.3, 123.3]	[22.9, 85.8]
	GMFR	**1.0**	**3.5**	**3.0**	**6.8**	**4.4**
	[2-sided 95% CI]	[1.0, 1.0]	[2.0, 6.0]	[2.0, 4.5]	[3.7, 12.3]	[2.3, 8.6]
	Seroconversion rate % (n)	**0**	**42.9 (9)**	**50.0 (11)**	**71.4 (15)**	**60.0 (12)**
	[2-sided 95% CI] [b]	[0.0, 16.1]	[21.8, 66.0]	[28.2, 71.8]	[47.8, 88.7]	[36.1, 80.9]
Day 14 after second dose	Number of subjects	51	49	55	49	47
	GMT	**10.7**	**1433.0**	**20.8**	**1335.5**	**37.7**
	[2-sided 95% CI]	[9.3, 12.3]	[978.2, 2099.4]	[16.3, 26.5]	[973.8, 1831.6]	[26.9, 52.8]
	GMFR	**1.1**	**143.3**	**2.1**	**133.5**	**3.8**
	[2-sided 95% CI]	[0.9, 1.2]	[97.8, 209.9]	[1.6, 2.6]	[97.4, 183.2]	[2.7, 5.3]
	Seroconversion rate % (n)	**2.0 (1)**	**100 (49)**	**34.5 (19)**	**98.0 (48)**	**55.3 (26)**
	[2-sided 95% CI] [b]	[0.0, 10.4]	[92.7, 100]	[22.2, 48.6]	[89.1, 99.9]	[40.1, 69.8]

a) The lower quantitation limit was 20. Values below the lower quantitation limit were converted to "0.5 × lower quantitation limit."
b) Clopper-Pearson method

Safety observation period was as follows:

- Solicited adverse events[11)] (local [pain, tenderness, erythema, and swelling/induration] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after each dose.[12)]
- All unsolicited adverse events were collected between the first dose and the second dose, until Day 14 after the second dose, and until Day 28 after the booster dose (which was administered on Day 168 after the second dose).
- Adverse events requiring treatment were collected until Day 217 after the first dose (Day 357 after the first dose for events related to the study vaccine).
- Serious adverse events and AESIs were collected until Day 357 after the first dose.

Table 25 shows solicited adverse events occurring by Day 7 after each dose of study vaccination.

Table 25. Solicited adverse events occurring by Day 7 after each dose of study vaccination (Study 101, Part 2: Safety analysis set)

	Event name	Dose No.	Group A (N1 = 252, N2 = 242)	Group B (N1 = 253, N2 = 250)	Group C (N1 = 255, N2 = 249)	Group D (N1 = 252, N2 = 247)	Group E (N1 = 253, N2 = 236)
			n (%)	n (%)	n (%)	n (%)	n (%)
Local reactions	Pain	1	10 (4.0)	68 (26.9)	71 (27.8)	83 (32.9)	105 (41.5)
		2	9 (3.7)	114 (45.6)	16 (6.4)	135 (54.7)	12 (5.1)
	Tenderness	1	33 (13.1)	122 (48.2)	122 (47.8)	142 (56.3)	158 (62.5)
		2	18 (7.4)	163 (65.2)	22 (8.8)	188 (76.1)	17 (7.2)
	Erythema	1	0	2 (0.8)	1 (0.4)	1 (0.4)	2 (0.8)
		2	0	12 (4.8)	0	33 (13.4)	0
	Swelling/induration	1	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.4)	3 (1.2)
		2	0	14 (5.6)	0	27 (10.9)	0
Systemic reactions	Nausea/vomiting	1	9 (3.6)	15 (5.9)	10 (3.9)	11 (4.4)	16 (6.3)
		2	9 (3.7)	18 (7.2)	5 (2.0)	27 (10.9)	6 (2.6)
	Headache	1	48 (19.1)	55 (21.6)	42 (16.5)	48 (19.0)	38 (15.0)
		2	31 (12.9)	74 (29.6)	32 (12.9)	84 (34.0)	28 (11.9)
	Fatigue	1	52 (20.7)	59 (23.1)	62 (24.3)	41 (16.3)	47 (18.6)
		2	33 (13.7)	89 (35.6)	44 (17.7)	105 (42.5)	31 (13.2)
	Malaise	1	30 (12.0)	31 (12.2)	31 (12.2)	23 (9.1)	26 (10.3)
		2	19 (7.9)	66 (26.4)	19 (7.6)	74 (30.0)	11 (4.7)
	Myalgia	1	27 (10.8)	51 (20.0)	52 (20.4)	59 (23.4)	48 (19.0)
		2	16 (6.6)	77 (30.8)	18 (7.2)	101 (40.9)	5 (2.1)
	Arthralgia	1	15 (6.0)	17 (6.7)	21 (8.2)	12 (4.8)	16 (6.3)
		2	9 (3.7)	37 (14.8)	8 (3.2)	47 (19.0)	4 (1.7)
	Pyrexia	1	6 (2.4)	6 (2.4)	6 (2.4)	3 (1.2)	3 (1.2)
		2	2 (0.8)	11 (4.4)	1 (0.4)	20 (8.2)	1 (0.4)

N1 = Number of subjects analyzed after the first dose, N2 = number of subjects analyzed after the second dose, n = number of subjects with events

Table 26 shows the incidences of adverse events and adverse reactions. Unsolicited adverse events observed in ≥3 subjects in at least 1 group were urinary tract infection (2 in Group A, 2 in Group B, 1 in Group C, 2 in Group D, 3 in Group E; the same order applies hereinafter), skin laceration (1, 0, 0, 0, 3), injection site pruritus (0, 3, 0, 5, 0), arthralgia (2, 3, 0, 1, 1), headache (2, 3, 1, 2, 1), lymphadenopathy (1, 3, 1, 1, 2), and hypertension (1, 2, 0, 0, 3).

11) The severity of solicited adverse events was evaluated based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

12) Grade ≥1 events persisting until Day ≥7 after the vaccination were collected again from Day 7 until they resolved. From Day 7 onward, they were classified as unsolicited adverse events.

Table 26. Unsolicited adverse events and adverse reactions occurring by Day 35 after the first dose (Study 101, Part 2: safety analysis set)

	Group A (N = 255)	Group B (N = 258)	Group C (N = 256)	Group D (N = 256)	Group E (N = 255)
	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	42 (16.5)	51 (19.8)	35 (13.7)	52 (20.1)	43 (16.9)
Adverse reactions	6 (2.4)	5 (1.9)	2 (0.8)	15 (5.8)	3 (1.2)

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

No death occurred up to the data cut-off date. Adverse events leading to study discontinuation were observed in 7 subjects (2, 0, 1, 4, 0), and events in 1 subject in Group D (pyrexia, myalgia, and malaise) were considered related to the study vaccination. Adverse events leading to discontinuation of the study vaccination were observed in 13 subjects (4, 1, 3, 4, 1). Events in 1 subject in Group A (multiple sclerosis) and in 1 subject in Group C (colitis) were considered related to the study vaccination, as was the case in 1 subject in Group D who discontinued the study. Serious adverse events were observed in 9 subjects (2, 0, 5, 1, 1), and events in 1 subject in Group A (multiple sclerosis) and in 1 subject in Group C (colitis) were considered related to the study vaccination.

(c) Part 2 (booster dose)

As a secondary evaluation in Part 2, the immunogenicity and safety of a booster dose of Nuvaxovid administered 6 months after the primary series were investigated in some subjects from Group B (2-dose primary series of Nuvaxovid) and Group C (single-dose primary series of Nuvaxovid). On Day 168 (± 15 days) after the second dose, subjects in Group B were randomly re-assigned to Group B1 or B2 (1 : 1 ratio) and those in Group C to Group C1 or C2 (1 : 1 ratio). Subjects were to receive an intramuscular booster dose at the dosage shown in Table 27 (Protocol ver. 8.0, [redacted], 20[redacted]).

Table 27. Study vaccines and target sample size in Part 2 of Study 101 (booster dose)

Group (dosage regimen in the primary series)	Study vaccine, number of doses	Target sample size
Group A (placebo, 2 doses)	Placebo, 1 dose	150 to 300 per group
Group B1 (Nuvaxovid, 2 doses)	Placebo, 1 dose	
Group B2 (Nuvaxovid, 2 doses)	Nuvaxovid, 1 dose	
Group C1 (Nuvaxovid and then placebo, 1 dose each)	Placebo, 1 dose	
Group C2 (Nuvaxovid and then placebo, 1 dose each)	Nuvaxovid, 1 dose	
Group D (Nuvaxovid 25 µg + Matrix-M 50 µg, 2 doses)	Placebo, 1 dose	
Group E (Nuvaxovid 25 µg + Matrix-M 50 µg and then placebo, 1 dose each)	Placebo, 1 dose	

In total, 257 subjects were assigned to Group B for the primary series and received 2 doses of Nuvaxovid. Of them, 210 were randomly re-assigned to Group B1 (106 subjects) and Group B2 (104 subjects) on Day 168 after the second dose. Of them, 102 (Group B1) and 104 (Group B2) received the third dose. Among them, 2 in Group B1 received Nuvaxovid and 1 in Group B2 received placebo.

Table 28 shows changes over time in the neutralizing antibody titer against the original Wuhan strain: on the day of study vaccination, on Day 168 after the second dose (before the booster dose), and on Day 196 after the second dose (Day 28 after the booster dose).

Safety observation period was as follows:

- Solicited adverse events[13)] (local [pain, tenderness, erythema, and swelling/induration] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after the booster dose.[14)]
- Unsolicited adverse events were collected until Day 28 after the booster dose.
- Adverse events requiring treatment were collected until Day 217 after the first dose.
- Study vaccine-related adverse events requiring treatment, serious adverse events, and AESIs were collected until Day 357 after the first dose.

Table 29 shows solicited adverse events occurring by Day 7 after the study vaccination in the safety analysis set.

Table 28. Neutralizing antibody titer against original Wuhan strain
(Study 101, Part 2 [booster dose]: PP analysis set)

		Day of the first dose as baseline		Day 168 after the second dose as baseline	
		Group B1	Group B2	Group B1	Group B2
Day of first dose	Number of subjects	n1 = 22	n1 = 24	-	-
	GMT [a)]	**10.0**	**10.0**	-	-
	[2-sided 95% CI]	[10.0, 10.0]	[10.0, 10.0]	-	-
Day 168 after second dose	Number of subjects	n1 = 22	n1 = 24	n2 = 86	n2 = 84
	GMT	**80.0**	**67.3**	**74.4**	**63.0**
	[2-sided 95% CI]	[48.9, 131.0]	[44.0, 102.9]	[58.6, 94.4]	[49.1, 80.8]
	GMFR	**8.0**	**6.7**	-	-
	[2-sided 95% CI]	[4.9, 13.1]	[4.4, 10.3]	-	-
	Seroconversion rate % (n)	**86.4 (19)**	**83.3 (20)**	-	-
	[2-sided 95% CI] [b)]	[65.1, 97.1]	[62.6, 95.3]	-	-
Day 196 after second dose (Day 28 after booster dose)	Number of subjects	n1 = 17	n1 = 22	n2 = 67	n2 = 64
	GMT	**55.4**	**6185.4**	**65.0**	**6023.2**
	[2-sided 95% CI]	[34.0, 90.5]	[4640.4, 8244.8]	[49.5, 85.5]	[4541.7, 7987.8]
	GMFR	**5.5**	**618.5**	**1.0**	**86.7**
	[2-sided 95% CI]	[3.4, 9.0]	[464.0, 824.5]	[0.8, 1.3]	[59.6, 126.1]
	Seroconversion rate % (n)	**82.4 (14)**	**100 (22)**	**11.9 (8)**	**95.3 (61)**
	[2-sided 95% CI] [b)]	[56.6, 96.2]	[84.6, 100]	[5.3, 22.2]	[86.9, 99.0]

a) The lower quantitation limit was 20. Measured values below the lower quantitation limit were recorded as 10.
In the primary series of vaccination in Part 2 of Study 101, neutralizing antibody titer on the day of the first dose was measured in 256 subjects (including 51 subjects in Group B) who were extracted randomly but evenly from each group, out of 1,288 subjects in total. All subjects who had been in Group B, including those who were tested for neutralizing antibody titer on the day of the first dose (22 in Group B1, 24 in Group B2), were subjected to neutralizing antibody titer testing after the booster dose.
b) Clopper-Pearson method
n1 = the number of subjects with available data at baseline (day of the first dose) and on the visit day among the PP analysis set of each visit
n2 = the number of subjects with available data at baseline (Day 168 after the second dose) and on the visit day among the PP analysis set of each visit

13) The severity of solicited adverse events was evaluated based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).
14) Grade ≥1 events persisting until Day ≥7 after the vaccination were collected again from Day 7 until they resolved. From Day 7 onward, they were classified as unsolicited adverse events.

Table 29. Solicited adverse events occurring by Day 7 after study vaccination (Study 101, Part 2 [booster dose]: safety analysis set)

	Event name	Primary series		Booster dose	
		Group B (Nuvaxovid)		Group B1 (placebo) (N = 97)	Group B2 (Nuvaxovid) (N = 97)
		After first dose (N = 253)	After second dose (N = 250)		
		n (%)	n (%)	n (%)	n (%)
Local reactions	Pain	68 (26.9)	114 (45.6)	7 (7.2)	53 (54.6)
	Tenderness	122 (48.2)	163 (65.2)	11 (11.3)	79 (81.4)
	Erythema	2 (0.8)	12 (4.8)	1 (1.0)	10 (10.3)
	Swelling/induration	2 (0.8)	14 (5.6)	0 (0)	11 (11.3)
Systemic reactions	Nausea/vomiting	15 (5.9)	18 (7.2)	2 (2.1)	13 (13.3)
	Headache	55 (21.6)	74 (29.6)	10 (10.5)	45 (45.9)
	Fatigue	59 (23.1)	89 (35.6)	12 (12.6)	62 (63.3)
	Malaise	31 (12.2)	66 (26.4)	6 (6.3)	46 (46.9)
	Myalgia	51 (20.0)	77 (30.8)	5 (5.3)	50 (51.0)
	Arthralgia	17 (6.7)	37 (14.8)	3 (3.2)	28 (28.6)
	Pyrexia	6 (2.4)	11 (4.4)	0 (0)	17 (17.3)

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

In the safety analysis set, the incidence of unsolicited adverse events up to Day 28 after the third dose was 12.7% (13 of 102) in Group B1 and 12.4% (13 of 105) in Group B2. The incidence of unsolicited adverse events for which causal relationship to the study vaccination could not be ruled out was 1.0% of subjects in Group B1 (varicose vein) and in 3.8% of subjects in Group B2 (injection site pruritus, lymphadenitis, drug hypersensitivity, myalgia/diarrhoea/nausea/headache in 1 subject each).

There were no deaths, AESIs, or adverse events leading to study discontinuation. Serious adverse events were observed in 2 subjects in Group B1 (atrial fibrillation, lumbar spinal stenosis) and in 1 subject in Group B2 (abscess bacterial and cellulitis), all of which were considered to be unrelated to the study vaccination.

7.2 Phase II study

7.2.1 Foreign phase IIa/b study (CTD 5.3.5.1.5: Study 2019nCoV-501, ongoing since August 2020, data cut-off date, [redacted], 20[redacted] [primary analysis], [redacted], 20[redacted] [last analysis of primary endpoint] (reference data)

A randomized, observer-blinded,[15] placebo-controlled, parallel-group study is ongoing at 16 study sites in Republic of South Africa to investigate the efficacy, safety, and immunogenicity of Nuvaxovid. Subjects are human immunodeficiency virus (HIV)-negative adults ≥18 years old and HIV-positive, medically stable adults ≥18 years old (target sample size: approx. 2,960 to 4,164 HIV-negative adults, approx. 240 HIV-positive adults[16]).

Two doses of Nuvaxovid 0.5 mL or physiological saline were administered intramuscularly, 21 days apart (allowable period: + 7 days). The study consisted of the following 2 cohorts based on the presence/absence of HIV infection, and subjects in both cohorts were assigned to the Nuvaxovid group and the placebo group at a ratio of 1:1.

[15] The study vaccine storage managers and the persons in charge of study vaccine dispensing at the study sites and some staff members at the external contract organization independent from study staff, were unblinded to the study.

[16] In order to evaluate whether the primary endpoint VE exceeds 0%, the event rate in the placebo group is assumed to be 2% to 6%, VE to be 80%, the percentage of unevaluable subjects to be 10%. Under these assumptions, the power is approximately 90% at a 2-sided significance level of 5% and the event number of 23. By taking into account the possibility of VE exceeding 30%, the necessary event number was set at 23 to 50. On the basis of the above, the target sample size was determined to be approximately 3,200 to 4,404 (approximately 2,960 to 4,164 HIV-negative adults, approximately 240 HIV-positive adults).

- Cohort 1: HIV-negative subjects ≥18 to <85 years old
- Cohort 2: HIV-positive, medically stable subjects ≥18 to <65 years old

The study enrolled (a) 6,324 subjects (5,844 HIV-negative subjects, 480 HIV-positive subjects) at the data cut-off point for the primary efficacy analysis, and (b) 6,350 subjects (5,867 HIV-negative subjects, 483 HIV-positive subjects) at the data cut-off point for the final analysis of the primary endpoint (described later). Among them, (a) 4,406 subjects (4,160 HIV-negative subjects, 246 HIV-positive subjects) and (b) 4,419 subjects (4,173 HIV-negative subjects, 246 HIV-positive subjects) were included in the ITT analysis set.

Efficacy populations:
At the time of primary efficacy analysis, 2,684 subjects in the ITT analysis set (1,357 in the Nuvaxovid group, 1,327 in the placebo group; the same order applies hereinafter) were included in the per-protocol efficacy (PP-EFF) analysis set and the primary efficacy analysis set, because they (a) were seronegative to SARS-CoV-2 at baseline, (b) received 2 doses of the study vaccine, and (b) had no serious protocol deviation affecting the evaluation of the primary endpoint. The remaining 1,722 subjects (849, 873) were excluded from the PP-EFF analysis set, mainly because of a positive PCR result obtained by Day 7 after the second dose (1,455 subjects [715, 740]). After the primary analysis, the final analysis of the primary endpoint was conducted to obtain results based on more data. At the final analysis of the primary endpoint, 2,770 subjects (1,408, 1,362) were included in the PP-EFF analysis set and in the primary efficacy analysis set.

Safety populations:
Among subjects in the ITT analysis set at the final analysis of the primary endpoint, 4,408 subjects (2,209, 2,199) who received the study vaccine were included in FAS, and 4,408 (2,211, 2,197) were included in the safety analysis set based on the study vaccine actually administered.

Immunogenicity population:
A total of 4,090 subjects (2,046, 2,044) who met the following criteria were included in the PP immunogenicity analysis set.

(a) Hepatis B and C viruses negative at baseline
(b) Received 2 doses of the study vaccine
(c) Serum samples available at least at baseline and at the visit, and
(d) No serious protocol deviation affecting the immunogenicity reaction at the visit

The primary efficacy endpoint was “Occurrence of symptomatic mild, moderate, or severe COVID-19 confirmed by PCR for SARS-CoV-2 between Day 7 after the second dose and the completion of event accrual in all subjects (including medically stable HIV-positive subjects) who were seronegative to SARS-CoV-2 at baseline” (for the definition of severity, see Table 58). The primary efficacy analysis was to be conducted in the PP-EFF analysis set when 23 to 50 symptomatic COVID-19 events were observed. After discussion with the regulatory agency, the study was unblinded to perform the primary analysis, but was continued to evaluate the immunogenicity and safety, regardless of whether the primary endpoint was achieved or not.

As for efficacy, the incidence of COVID-19 events from Day 7 after the second dose in the PP-EFF analysis set, at the data cut-off point for the primary analysis, was 1.11% (15 of 1,357 subjects) in the Nuvaxovid group and 2.19% (29 of 1,327) in the placebo group, with the vaccine efficacy (VE) of Nuvaxovid [2-sided 95% CI] being 49.4% [6.1%, 72.8%]. All COVID-19 events were mild or moderate, except for 1 case of severe COVID-19 in the placebo group. At the data cut-off point for the final analysis of the primary endpoint, COVID-19 events occurred in 147 subjects (51 [3.62%] in the Nuvaxovid group, 96 [7.05%] in the placebo group), with VE [2-sided 95% CI] of Nuvaxovid being 48.6% [28.4%, 63.1%].

The safety observation period was as follows:

- Solicited adverse events[17)] (local [pain, tenderness, erythema, and swelling/induration] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after each dose.[18)]
- All unsolicited adverse events were collected between the first dose and Day 14 after the second dose.
- Adverse events requiring treatment were collected between the first dose and Day 14 after the second dose (up to 12 months after the second dose for events considered related to the study vaccine).
- Serious adverse events and AESIs were collected between the first dose and 12 months after the second dose.

Tables 30 and 31 show solicited adverse events occurring by Day 7 after each dose of study vaccination in HIV-negative and HIV-positive subjects in the safety analysis set (by baseline serostatus).

In the safety analysis set, the incidence of unsolicited adverse events up to Day 49 after the first dose was 14.9% (329 of 2,211) in the Nuvaxovid group and 14.9% (327 of 2,197) in the placebo group. Among them, the incidence of unsolicited adverse events for which causal relationship to the study vaccination could not be ruled out was 3.2% (70 subjects) in the Nuvaxovid group and 2.3% (51 subjects) in the placebo group.

Table 32 shows unsolicited adverse events with an incidence of ≥0.5% in either group in the safety analysis set. The unsolicited, study vaccination-related adverse event with an incidence of ≥0.5% in either group was headache (0.8% [17 subjects] in the Nuvaxovid group, 0.6% [14 subjects] in the placebo group).

17) The severity of solicited adverse events was evaluated based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).
18) Grade ≥1 events persisting until Day ≥7 after the vaccination were collected again from Day 7 until they resolved. From Day 7 onward, they were classified as unsolicited adverse events.

Table 30. Solicited adverse events occurring by Day 7 after each dose of study vaccination (Study 501: Safety analysis set, HIV-negative subjects, by baseline serostatus)

	Event name	Dose No.	Seronegative for SARS-CoV-2		Seropositive for SARS-CoV-2	
			Nuvaxovid (N1/N2=1,397/1,350)	Placebo (N1/N2=1,345/1,302)	Nuvaxovid (N1/N2=692/672)	Placebo (N1/N2=730/705)
			n (%)	n (%)	n (%)	n (%)
Local reactions	Pain	1	390 (27.9)	157 (11.7)	180 (26.0)	88 (12.1)
		2	361 (26.7)	107 (8.2)	178 (26.5)	66 (9.3)
	Tenderness	1	223 (16.0)	104 (7.7)	117 (16.9)	54 (7.4)
		2	246 (18.2)	74 (5.7)	107 (15.9)	51 (7.2)
	Erythema	1	7 (0.5)	3 (0.2)	7 (1.0)	1 (0.1)
		2	27 (2.0)	1 (<0.1)	5 (0.7)	2 (0.3)
	Swelling/ induration	1	8 (0.6)	5 (0.4)	8 (1.2)	0
		2	33 (2.5)	2 (0.2)	10 (1.5)	2 (0.3)
Systemic reactions	Nausea/ vomiting	1	82 (5.9)	67 (5.0)	45 (6.5)	41 (5.6)
		2	68 (5.0)	41 (3.1)	44 (6.5)	39 (5.5)
	Headache	1	246 (17.6)	224 (16.7)	121 (17.5)	119 (16.3)
		2	214 (15.8)	137 (10.5)	95 (14.1)	87 (12.3)
	Fatigue	1	165 (11.8)	123 (9.2)	80 (11.6)	66 (9.0)
		2	138 (10.2)	88 (6.8)	65 (9.7)	43 (6.1)
	Malaise	1	98 (7.0)	82 (6.1)	57 (8.2)	43 (5.9)
		2	95 (7.0)	50 (3.8)	49 (7.3)	35 (5.0)
	Myalgia	1	175 (12.5)	103 (7.7)	77 (11.1)	61 (8.4)
		2	164 (12.1)	68 (5.2)	77 (11.5)	41 (5.8)
	Arthralgia	1	122 (8.7)	92 (6.8)	60 (8.7)	58 (7.9)
		2	121 (9.0)	62 (4.8)	54 (8.0)	41 (5.8)
	Pyrexia	1	19 (1.4)	21 (1.6)	12 (1.7)	10 (1.4)
		2	23 (1.7)	16 (1.2)	19 (2.8)	10 (1.4)

N1 = number of subjects analyzed after the first dose, N2 = number of subjects analyzed after the second dose
n = number of subjects with events

Table 31. Solicited adverse events occurring by Day 7 after each dose of study vaccination (Study 501: Safety analysis set, HIV-positive subjects, by baseline serostatus)

	Event name	Dose No.	Seronegative for SARS-CoV-2		Seropositive for SARS-CoV-2	
			Nuvaxovid (N1/N2=79/78)	Placebo (N1/N2=82/75)	Nuvaxovid (N1/N2=43/40)	Placebo (N1/N2=40/38)
			n (%)	n (%)	n (%)	n (%)
Local reactions	Pain	1	17 (21.5)	10 (12.2)	8 (18.6)	6 (15.0)
		2	23 (29.5)	9 (11.8)	8 (20.0)	2 (5.3)
	Tenderness	1	12 (15.2)	6 (7.3)	8 (18.6)	2 (5.0)
		2	12 (15.4)	7 (9.2)	4 (10.0)	1 (2.6)
	Erythema	1	1 (1.3)	1 (1.2)	2 (4.7)	0
		2	2 (2.6)	0	0	0
	Swelling/induration	1	0	0	2 (4.7)	0
		2	2 (2.6)	0	0	0
Systemic reactions	Nausea/vomiting	1	6 (7.6)	1 (1.2)	5 (11.6)	0
		2	4 (5.1)	1 (1.3)	2 (5.0)	0
	Headache	1	11 (13.9)	11 (13.4)	6 (14.0)	2 (5.0)
		2	6 (7.7)	5 (6.6)	3 (7.5)	3 (7.9)
	Fatigue	1	12 (15.2)	9 (11.0)	5 (11.6)	1 (2.5)
		2	5 (6.4)	4 (5.3)	1 (2.5)	2 (5.3)
	Malaise	1	7 (8.9)	1 (1.2)	2 (4.7)	1 (2.5)
		2	3 (3.8)	2 (2.6)	1 (2.5)	1 (2.6)
	Myalgia	1	6 (7.6)	4 (4.9)	3 (7.0)	3 (7.5)
		2	6 (7.7)	0	2 (5.0)	1 (2.6)
	Arthralgia	1	8 (10.1)	4 (4.9)	6 (14.0)	4 (10.0)
		2	3 (3.8)	4 (5.3)	2 (5.0)	2 (5.3)
	Pyrexia	1	2 (2.5)	1 (1.2)	0	0
		2	3 (3.8)	0	3 (7.5)	1 (2.6)

N1 = number of subjects analyzed after the first dose, N2 = number of subjects analyzed after the second dose
n = number of subjects with events

Table 32. Unsolicited adverse events with an incidence of ≥0.5% in the Nuvaxovid or placebo group that occurred between the first dose and Day 28 after the second dose [a)]

(Study 501: Safety analysis set)

Event name PT (MedDRA/J Ver.23.0)	Nuvaxovid	Placebo
	N = 2,211	N = 2,197
	n (%)	n (%)
Headache	69 (3.1)	50 (2.3)
Anosmia	5 (0.2)	11 (0.5)
Upper respiratory tract infection	26 (1.2)	19 (0.9)
Gastroenteritis	13 (0.6)	12 (0.5)
Influenza like illness	14 (0.6)	24 (1.1)
Fatigue	12 (0.5)	15 (0.7)
Diarrhoea	20 (0.9)	20 (0.9)
Nausea	11 (0.5)	7 (0.3)
Myalgia	14 (0.6)	19 (0.9)
Arthralgia	12 (0.5)	11 (0.5)
Respiratory rate increased	15 (0.7)	20 (0.9)
Blood pressure increased	13 (0.6)	15 (0.7)
Cough	13 (0.6)	11 (0.5)
Nasal congestion	14 (0.6)	9 (0.4)
Oropharyngeal pain	11 (0.5)	7 (0.3)
Lymphadenopathy	11 (0.5)	6 (0.3)

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

a) All unsolicited adverse events were collected up to Day 14 after the second dose, and some of unsolicited adverse events (serious adverse events, vaccination-related adverse events requiring treatment, and AESIs) were collected up to Day 28 after the second dose, and were subjected to analysis.

At the data cut-off point for the final analysis of the primary endpoint, 4 subjects (2 in the Nuvaxovid group, 2 in the placebo group) had died, but the deaths were considered unrelated to the study vaccination by the investigator. An adverse event leading to discontinuation of vaccination was observed in 1 subject in the placebo group (vaccine complication). Adverse events leading to study discontinuation were observed in 4 subjects in the Nuvaxovid group (abortion spontaneous, COVID-19, death, gastroenteritis) and in 4 subjects in the placebo group (COVID-19, gastroenteritis, nasal congestion, upper respiratory tract infection). Causal relationship to Nuvaxovid was ruled out for all of the 4 subjects in the Nuvaxovid group.

Serious adverse events were observed in 11 subjects (0.5%) in the Nuvaxovid group and in 18 subjects (0.8%) in the placebo group, all of which were considered unrelated to the study vaccination by the investigator.

7.3 Phase III studies

7.3.1 Foreign global phase III study (CTD 5.3.5.1.2: Study 2019nCoV-301, ongoing since December 2020, data cut-off on [redacted], 20[redacted] [primary analysis])

A randomized, observer-blinded,[19)] placebo-controlled, parallel-group study is ongoing at 119 study sites in the United States and Mexico to investigate the efficacy, safety, and immunogenicity of Nuvaxovid. Two doses of Nuvaxovid or placebo are administered intramuscularly 21 days apart (allowable period: + 7 days) to subjects ≥18 years old (target sample size, approximately 30,000[20)]: 20,000 in the Nuvaxovid group, 10,000 in the placebo group). In response to the emergency use

19) Only the following staff were unblinded to the study: (a) the study vaccine storage managers and the persons in charge of study vaccine dispensing at the study sites; (b) some of statisticians and programmers at the external contract organization independent from study staff; (c) persons in charge of subject assignment; and (d) DSMB.

20) For evaluating whether the lower limit of 2-sided CI of VE (primary endpoint) exceeds 30% and the point estimate of VE is ≥50%, the power is ≥90% at a 2-sided significance level of 5%, assuming the total event number to be 144 and VE to be 60%. Accordingly, the target sample size was set at 30,000 (20,000 in the Nuvaxovid group, 10,000 in the placebo group).

authorization of another SARS-CoV-2 vaccine in the United States after the start of the study, a blinded crossover period was added in which placebo is administered to subjects in the Nuvaxovid group and Nuvaxovid to those in the placebo group (2 doses at a 21-day interval) (Protocol ver. 4.0, January 11, 2021). Subsequently, when 2-month (median) safety data became available and statistically significant VE was demonstrated ([redacted], 20[redacted]), the study proceeded to the blinded crossover period.

Subjects were stratified by age (<65, ≥65) to Nuvaxovid and placebo at a 2 : 1 ratio. A total of 31,588 subjects were enrolled in the study. Among them, 29,949 (19,965 in the Nuvaxovid group, 9,984 in the placebo group; the same order applies hereinafter) were randomized and included in the ITT analysis set. The remaining 1,639 subjects (1,367 who violated inclusion/exclusion criteria, 193 who withdrew informed consent) were excluded. Of the 29,949 subjects, 29,582 (19,729, 9,868) who received at least 1 dose of the study vaccine were included in the safety analysis set, and 28,256 (19,104, 9,422) of them received 2 doses of the study vaccine.

Among the subjects in the ITT analysis set, 25,452 (17,312, 8,140) were included in the PP-EFF analysis set and subjected to the primary efficacy analysis. The remaining 4,497 subjects were excluded for reasons including the following:

(a) Seropositive for SARS-CoV-2 (1,076 [5.4%], 609 [6.1%]) at baseline
(b) Withdrawal from the study before Day 7 after the second dose (unblinded, study discontinuation, death, etc.) (652 [3.3%], 701 [7.0%])
(c) Not received the second dose (705 [3.5%], 479 [4.8%])
(d) Protocol deviation (415 [2.1%], 576 [5.8%])

Immunogenicity was measured in the immunogenicity population (approximately 1,200 subjects at the maximum who were randomly extracted by a statistician of Novavax blinded to treatment group to minimize potential bias in age group and country). Among them, subjects who met the following criteria were included in the PP immunogenicity analysis set at each visit after randomization:

(a) Blood samples were available at baseline and at 1 or more time points after baseline
(b) No serious protocol deviation likely to affect immunogenicity reaction at said visit
(c) Received 2 doses of the study vaccine (only for visits Day ≥21 after the first dose)

At the data cut-off point for the primary (final) efficacy analysis, among 29,949 randomized subjects, 26,939 (18,346 [91.9%], 8,593 [86.1%]) are continuing the study. The remaining 3,010 discontinued the study, mainly because of withdrawal of consent (1,097 [5.5%], 1,103 [11.0%]) and lost to follow-up (418 [2.1%], 213 [2.1%]). A total of 5,376 subjects (3,038 [15.2%], 2,338 [23.4%]) were unblinded; the main reason was vaccination of the approved vaccine (3,021 [15.1%], 2,330 [23.3%]).

The primary efficacy endpoint was defined as “The first occurrence of PCR-confirmed symptomatic (mild, moderate, or severe) COVID-19 in adult subjects who were seronegative to SARS-CoV-2 at baseline” (for the definition of severity, see Table 58). The definition of symptoms suggestive of COVID-19 is shown in Table 59. All subjects who were confirmed to have SARS-CoV-2 infection by PCR were subjected to assessment of COVID-19 event, according to the algorithm based on

physicians' assessment including severity, symptoms reported by the subject, body temperature, and oxygen saturation.

According to the original study protocol, the final analysis was to be conducted when 144 symptomatic COVID-19 events were observed in the PP-EFF analysis set, and 2 interim analyses were to be conducted when approximately 50% and 75% of events accrued. Subsequently, the study protocol was amended to conduct only the final analysis (Protocol ver. 7.0, March 31, 2021), for the following reasons:

(a) The U.S. government instructed that the approved vaccine be available for all adults on and after May 1, 2021 under the emergency use authorization,
(b) The incidence of COVID-19 in the United States decreased, and
(c) Other studies showed the efficacy of Nuvaxovid.

The main analysis of the primary efficacy endpoint and important secondary endpoints was carried out by the statistician and the programmer who were independent from the study staff and unblinded to the study. The study site and each subject were blinded to the data of subjects.

At the time of the primary (final) analysis, the median follow-up period (from Day 7 after the second dose) in the PP-EFF analysis set was 64.0 days in the Nuvaxovid group and 58.0 days in the placebo group. As for safety in each subject, the data at the cut-off point or at the start of blinded crossover period, whichever came faster, were evaluated. In the safety analysis set, the follow-up period (mean ± standard deviation) from Day 7 after the second dose was 76.5 ± 21.3 days in the Nuvaxovid group and 76.2 ± 24.8 days in the placebo group.

As for the primary efficacy endpoint, Table 33 and Figure 1 show the occurrence of COVID-19 events and the cumulative event rate in the PP-EFF analysis set (the primary analysis set.) Results showed that the study subjects achieved the prespecified efficacy criteria "the lower limit of the 2-sided 95% CI of VE exceeds 30% and the point estimate of VE is ≥50%."[21)]

Table 33. Efficacy of vaccine against COVID-19 events from Day 7 after the second dose (Study 301: PP-EFF analysis set)

	Nuvaxovid	Placebo
Number of subjects	17,312	8,140
Number of subjects with COVID-19 events (%)	14 (0.1)	63 (0.8)
VE (%) [2-sided 95%CI][a)]	90.40 [82.88, 94.62]	

a) Poisson regression model with explanatory variables of vaccination group and age (18-64, ≥65)

[21)] The eligibility of each subject for the PP-EFF analysis set was assessed under blinded conditions. After the primary efficacy analysis, an error was found in the eligibility assessment of some subjects (for details, see Section 7.R.2.2 (a)).

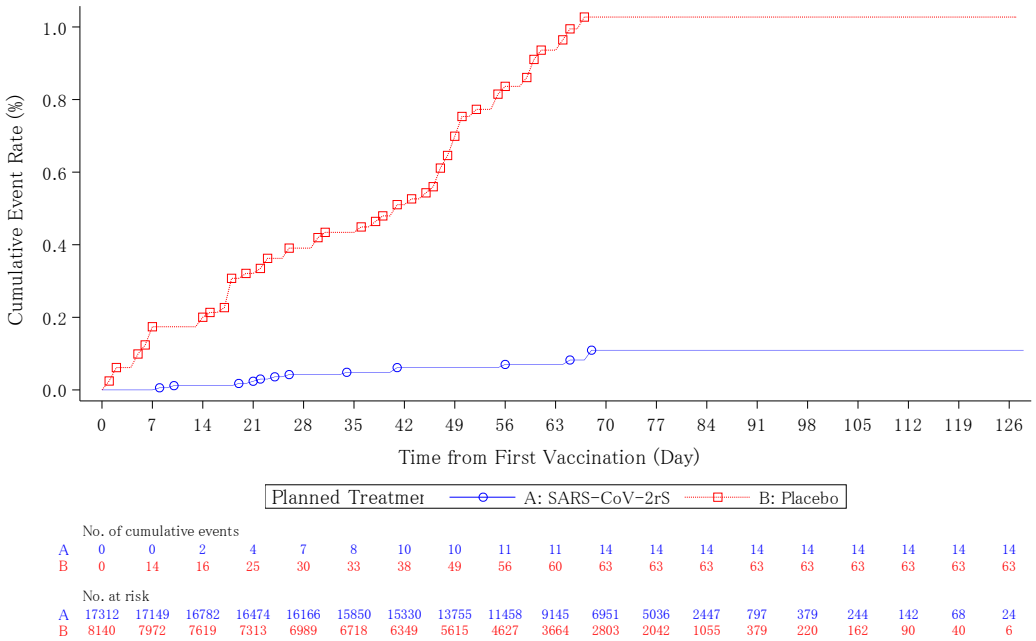

Figure 1. Cumulative COVID-19 event rate in the primary analysis (PP-EFF analysis set)

The safety observation period was as follows:

- Solicited adverse events[22)] (local [pain, tenderness, erythema, and swelling/induration] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after each dose.[23)]
- All unsolicited adverse events were collected between the first dose and Day 28 after the second dose.
- Adverse events requiring treatment were collected between the first dose and Day 28 after the second dose (up to Day 720 after the second dose for events considered related to the study vaccine).
- Serious adverse events and AESIs were collected between the informed consent and Day 720 after the second dose.

Table 34 shows solicited adverse events occurring by Day 7 after each dose of study vaccination.

22) The severity of solicited adverse events was evaluated based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

23) Grade ≥1 events persisting until Day ≥7 after the vaccination were collected again from Day 7 until they resolved. From Day 7 onward, they were classified as unsolicited adverse events.

Table 34. Solicited adverse events occurring by Day 7 after each dose of study vaccination (Study 301: safety analysis set)

	Event name	First dose		Second dose	
		Nuvaxovid (N = 19,729)	Placebo (N = 9,853)	Nuvaxovid (N = 19,104)	Placebo (N = 9,422)
		n (%)	n (%)	n (%)	n (%)
Local reactions	Pain	6211 (34.4)	986 (11.1)	10227 (59.7)	1141 (13.8)
	Tenderness	9450 (52.3)	1494 (16.8)	12584 (73.4)	1312 (15.9)
	Erythema	164 (0.9)	27 (0.3)	1138 (6.6)	29 (0.4)
	Swelling/induration	154 (0.9)	24 (0.3)	1056 (6.2)	25 (0.3)
Systemic reactions	Nausea/vomiting	1152 (6.4)	488 (5.5)	1929 (11.3)	450 (5.4)
	Headache	4505 (24.9)	2028 (22.8)	7618 (44.5)	1625 (19.6)
	Fatigue	4632 (25.6)	1993 (22.4)	8486 (49.5)	1811 (21.9)
	Malaise	2660 (14.7)	1037 (11.7)	6674 (38.9)	1018 (12.3)
	Myalgia	4102 (22.7)	1188 (13.3)	8240 (48.1)	1001 (12.1)
	Arthralgia	1388 (7.7)	590 (6.6)	3809 (22.2)	567 (6.9)
	Pyrexia	66 (0.4)	33 (0.4)	973 (5.7)	23 (0.3)

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

In the safety analysis set, the incidence of unsolicited adverse events up to Day 49 after the first dose was 12.74% (2,514 of 19,729 subjects) in the Nuvaxovid group and 11.54% (1,137 of 9,853 subjects) in the placebo group. The incidence of unsolicited adverse events for which causal relationship to the study vaccination could not be ruled out was 3.96% (782 of 19,729) in the Nuvaxovid group and 2.36% (233 of 9,853) in the placebo group.

Tables 35 shows unsolicited adverse events with an incidence of ≥0.5% in either group and Table 36 shows unsolicited adverse events related to the study vaccination in the safety analysis set.

Table 35. Unsolicited adverse events with an incidence of ≥0.5% in either Nuvaxovid or placebo group that occurred between the first dose and Day 28 after the second dose (Study 301: safety analysis set)

Event name PT (MedDRA/J Ver.23.1)	Nuvaxovid	Placebo
	N = 19,729	N = 9,853
	n (%)	n (%)
Diarrhoea	83 (0.4)	57 (0.6)
Fatigue	185 (0.9)	65 (0.7)
Injection site pain	136 (0.7)	36 (0.4)
Pyrexia	112 (0.6)	23 (0.2)
Myalgia	105 (0.5)	28 (0.3)
Headache	265 (1.3)	120 (1.2)
Nasal congestion	100 (0.5)	63 (0.6)

Table 36. Unsolicited adverse events related to the study vaccine with an incidence of ≥0.5% in either Nuvaxovid or placebo group that occurred between the first dose and Day 28 after the second dose (Study 301: safety analysis set)

Event name PT (MedDRA/J Ver.23.1)	Nuvaxovid	Placebo
	N = 19,729	N = 9,853
	n (%)	n (%)
Fatigue	127 (0.6)	34 (0.4)
Injection site pain	132 (0.7)	30 (0.3)
Headache	122 (0.6)	42 (0.4)

Before the data cut-off point, death occurred in 9 subjects (0.05%) in the Nuvaxovid group (cardiac arrest in 3, myocardial infarction, septic shock, sudden death, gunshot wound, cerebrovascular accident, and circulatory collapse in 1 each) and in 5 subjects in the placebo group (0.05%) (cardiac

arrest in 3, myocardial infarction and COVID-19 in 1 each). Causal relationship to the study vaccine was ruled out for all of the events except in 1 subject in the placebo group (myocardial infarction). Adverse events leading to discontinuation of study vaccination were observed in 57 subjects (0.3%) in the Nuvaxovid group and in 16 subjects (0.2%) in the placebo group. Adverse events leading to study discontinuation were observed in 60 subjects (0.3%) in the Nuvaxovid group and in 13 subjects (0.1%) in the placebo group.

Serious adverse events were observed in 169 subjects (0.86%) in the Nuvaxovid group and in 94 subjects (0.95%) in the placebo group. Events with an incidence of ≥0.03% in either group were atrial fibrillation (7 subjects [0.04%] in the Nuvaxovid group, 2 subjects (0.02%) in the placebo group; the same order applies hereinafter), cardiac arrest (3 [0.02%], 3 [0.03%], chest pain [1 [0.01%], 3 [0.03%]), cholecystitis acute (5 [0.03%], 0), appendicitis (5 [0.03%], 4 [0.04%]), COVID-19 (5 [0.03%], 9 [0.09%]), COVID-19 pneumonia (0, 6 [0.06%]), prostate cancer (5 [0.03%], 0), cerebrovascular accident (7 [0.04%], 1 [0.01%]), and suicidal ideation (3 [0.02%], 3 [0.03%]). Serious adverse events for which causal relationship to the study vaccination could not be ruled out were observed in 5 subjects (0.02%) in the Nuvaxovid group and in 5 subjects (0.05%) in the placebo group. In the Nuvaxovid group, these events were angioedema, Basedow's disease/hyperthyroidism, thrombocytopenia, peroneal nerve palsy/central nervous system inflammation/neuropathy peripheral, and respiratory failure[24] in 1 subject each.

7.3.2 U.K. phase III study (CTD 5.3.5.1.3: Study 2019nCoV-302, ongoing since September 2020, data cut-off date, [redacted], 20[redacted] [interim analysis], [redacted], 20[redacted] [final analysis], [redacted], 20[redacted] [analysis of other endpoints, at the time of preparing interim analysis report])

A randomized, observer-blinded,[25] placebo-controlled, parallel-group study is ongoing at 33 study sites in the U.K. to investigate the efficacy, safety, and immunogenicity of Nuvaxovid in healthy subjects and subjects with stable chronic disease who are ≥18 to ≤84 years old (target sample size 15,000[26]: 7,500 in the Nuvaxovid group, 7,500 in the placebo group). Subjects receive 2 doses of intramuscular Nuvaxovid or placebo 21 days apart (allowable period: + 7 days). After the start of study, another SARS-CoV-2 vaccine was approved in December 2020 in the U.K. Therefore, the study protocol was amended to allow unblinding of subjects who wished to receive the newly approved vaccine (Protocol ver. 3, December 23, 2020). Also, in case when the study achieved the primary endpoint with acceptable safety profile, the study was to add a blinded crossover period in which placebo (2 doses, 21 days apart) is administered to subjects in the Nuvaxovid group, and Nuvaxovid (2 doses, 21 days apart) to subjects in the placebo group (Protocol ver. 4, February 25, 2021). The interim report contained the data obtained at 3 data cut-off dates.

---

[24] For this event, the causality assessment by the investigator was changed to "Unrelated to the study vaccination" after the data cut-off.

[25] The study vaccine storage managers and the persons in charge of study vaccine dispensing at the study sites and statisticians and some staff members at the independent external contract organization, were unblinded to the study. During the study, administration of the study vaccine by unblinded persons was permitted because of the lack of staff at many study sites, but the evaluators (investigators) remained blinded.

[26] For evaluating whether the primary endpoint VE exceeds 30%, the power is 95% at a 2-sided significance level of 5%, assuming the total event number to be 100 and VE to be ≥70%. By assuming the percentage of unevaluable cases to be 10%, the target sample size was calculated to be 15,000 in total (7,500 in each group). When the event number in the interim analysis is 50, the power of the entire study is 96%.

Subjects were stratified by study site and age (<65, ≥65). A total of 16,641 subjects were enrolled in the study, and 15,187 (7,593 in the Nuvaxovid group, 7,594 in the placebo group) were randomized. The remaining subjects were not randomized because they violated the inclusion/exclusion criteria (1,425) or withdrew consent (29). Among the randomized subjects, 15,139 (7,569, 7,570) who received the study vaccine were included in the ITT analysis set and safety analysis set, and 14,930 (7,467, 7,463) of them received the second dose.

For the interim analysis, 14,049 subjects (7,016, 7,033) in the ITT analysis set were included in the PP-EFF analysis set and in the primary efficacy analysis set. The remaining 1,086 subjects were excluded because they became seropositive before Day 7 after the second dose (621) or received only 1 dose (227). For the final analysis (described later), 14,039 subjects (7,020, 7,019) were included in the PP-EFF analysis set.[27)]

Solicited adverse events were collected from approximately 2,000 subjects who were randomized and received the study vaccine during the early stage of the study and from approximately 400 subjects of the substudy who received the study vaccine in combination with a seasonal influenza vaccine. In total, 2,714 subjects (1,364, 1,350), including 404 in the substudy, were included in the solicited adverse event analysis set.

As for immunogenicity, subjects who met the following criteria were included in the PP immunogenicity analysis set at each visit after randomization:

(a) Received 2 doses of the study vaccine at an interval of ≤45 days,
(b) Serum samples available at least at baseline and at the visit, and
(c) No serious protocol deviation clinically affecting the immunogenicity reaction at the visit.

At the data cut-off point for the interim report preparation, 14,809 (7,418, 7,391) of 15,187 subjects who had been randomized at the time of the final analysis are continuing the clinical study; the remaining 378 discontinued the study. Main reasons for the study discontinuation were withdrawal of consent (70, 107) and lost-to-follow up (19, 19). A total of 5,293 subjects (2,589, 2,704) were unblinded, and 5,197 (2,555, 2,642) of them are being followed up for safety data. The main reason for unblinding was administration of the approved vaccine (2,555, 2,680).

The primary efficacy endpoint was “The first occurrence of PCR-confirmed symptomatic (mild, moderate, or severe) COVID-19 from Day 7 after the second dose in adults who were seronegative to SARS-CoV-2 at baseline” (for the definition of severity, see Table 58). The definition of symptoms suggesting COVID-19 is described in Table 59. Identification of COVID-19 events and assessment of severity were performed under blinded conditions using the pre-defined algorithm based on (a) PCR results, (b) symptoms in the electronic diary inputted by the subject, (c) symptoms reported from the subject to the investigator, (d) the record at hospitalization, and (e) vital signs and physical findings at the visit for COVID-19 test or at hospitalization.

---

27) The following subjects were excluded: (a) subjects who tested positive for SARS-CoV-2 by IgG antibody test (against N-protein) or by PCR on Day ≤6 after the second dose and (b) subjects with a censoring event (unblinding, study discontinuation, death, etc.) on Day ≤7 after the second dose.

The protocol of this study stipulated that the final analysis of efficacy be conducted when approximately 100 cases (subjects) of symptomatic COVID-19 events, the primary efficacy endpoint, have been accrued. Also, in order to confirm efficacy early, an interim analysis was to be conducted by independent statisticians and a programming team when approximately 50 symptomatic COVID-19 events (approximately 50% of the target event number) were observed. In order to control the type 1 error associated with the interim analysis, Pocock type α-spending function according to Lan-DeMets method was used, with a 2-sided significance level of 0.031 in the interim analysis. If the pre-defined success criteria were achieved by the interim analysis, the sponsor was allowed to continue the study for the pre-scheduled period to obtain more robust safety and efficacy data, by maintaining the blindness of data at the subject level.

At the time of the interim analysis, the median follow-up period (follow-up period from Day 7 after the second dose) in the PP-EFF analysis set was 39 days in the Nuvaxovid group and 39 days in the placebo group. At the time of the final analysis, the median follow-up period in the PP-EFF analysis set was 56 days in the Nuvaxovid group and 54 days in the placebo group. At the time of the interim analysis report preparation, the follow-up period (mean ± SD) from Day 7 after the second dose in subjects who completed the second dose among subjects in the safety analysis set, was 89.9 ± 15.69 days in the Nuvaxovid group and 89.6 ± 16.47 days in the placebo group.

Results of the primary efficacy endpoint:
Table 37 shows the occurrence of COVID-19 events and Figure 2 shows the cumulative event rate in the PP-EFF analysis set (the primary analysis set) in the interim analysis. The lower limit of the 2-sided 96.9% CI of VE exceeded 30%, the predefined efficacy criterion.

Table 37. Efficacy of vaccine against COVID-19 events from Day 7 after the second dose (Study 302: Interim analysis, PP-EFF analysis set)

	Nuvaxovid	Placebo
Number of subjects	7,016	7,033
Number of subjects with COVID-19 (%)	6 (<0.1)	56 (0.8)
VE (%) [2-sided 96.9%CI][a)]	89.3 [73.0, 95.8]	

a) Poisson regression model with explanatory variables of vaccination group, region, and age (18-64, ≥65)

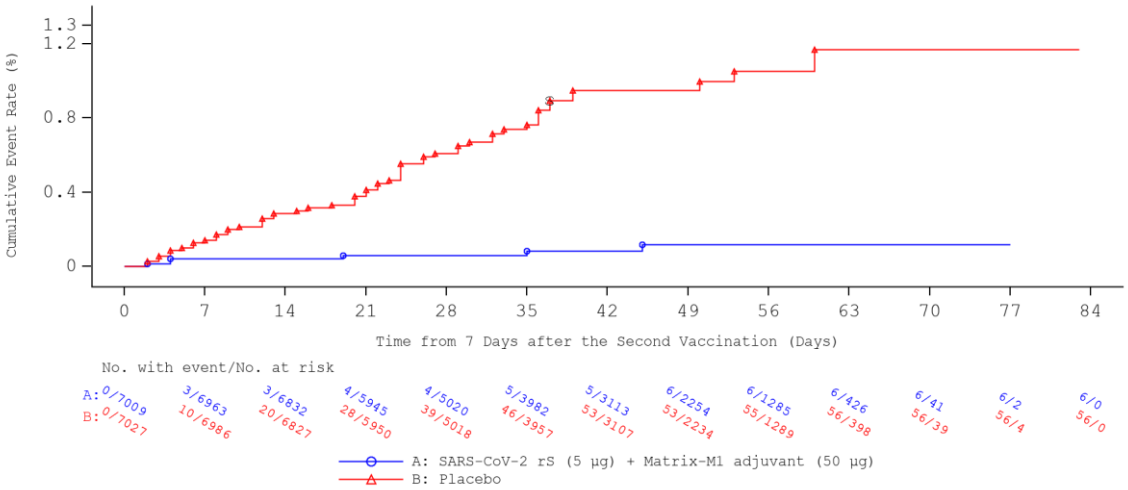

Figure 2. Cumulative rate of COVID-19 events (Study 302: Interim analysis, PP-EFF analysis set)

Table 38 shows the occurrence of COVID-19 events and Figure 3 shows the cumulative event rate in the PP-EFF analysis set (the primary analysis set) in the final analysis.

Table 38. Efficacy of vaccine against COVID-19 events from Day 7 after the second dose (Study 302: Final analysis, PP-EFF analysis set)

	Nuvaxovid	Placebo
Number of subjects	7,020	7,019
Number of subjects with COVID-19 (%)	10 (0.1)	96 (1.4)
VE (%) [2-sided 96.9%CI][a)]	89.7 [80.2, 94.6]	

a) Poisson regression model with explanatory variables of vaccination group, region, and age (18-64, ≥65)

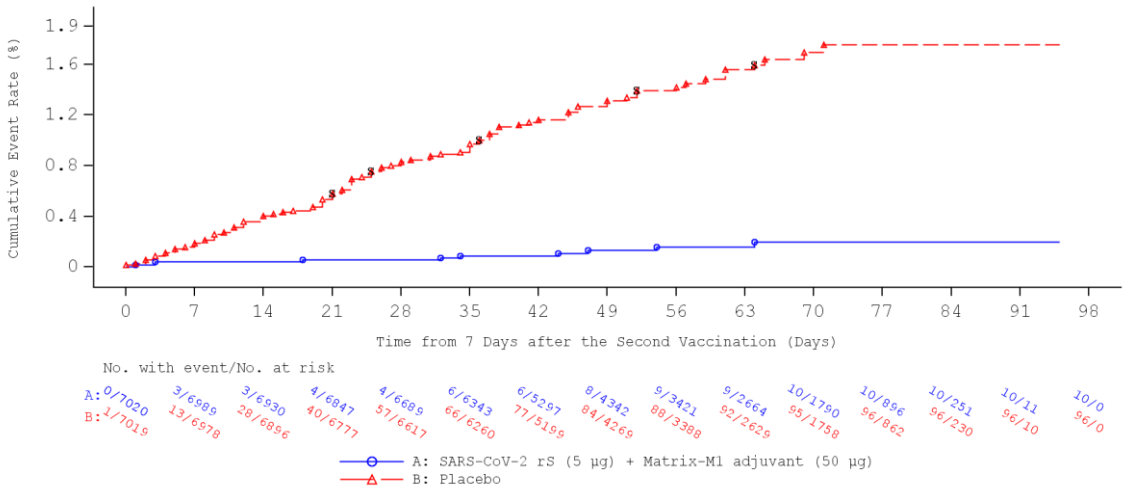

Figure 3. Cumulative rate of COVID-19 events (Study 302: Final analysis, PP-EFF analysis set)

The safety observation period was as follows:

- Solicited adverse events[28)] (local [pain, tenderness, erythema, and swelling/induration] and systemic [nausea/vomiting, headache, fatigue, malaise, myalgia, arthralgia, and pyrexia]) were collected from the subject diary until Day 7 after each dose.[29)]

28) The severity of solicited adverse events was evaluated based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

- All unsolicited adverse events were collected between the first dose and Day 28 after the second dose.
- Adverse events requiring treatment were collected between the first dose and Day 14 after the second dose (up to 12 months after the second dose for events considered related to the study vaccine).
- Serious adverse events and AESIs were collected between the informed consent and 12 months after the second dose.

Table 39 shows solicited adverse events occurring by Day 7 after each dose of study vaccination in the solicited adverse event analysis set

Table 39. Solicited adverse events occurring by Day 7 after each dose of study vaccination (Study 302: solicited adverse event analysis set)

	Event name	First dose		Second dose	
		Nuvaxovid (N = 1,364)	Placebo (N = 1,350)	Nuvaxovid (N = 1,348)	Placebo (N = 1,335)
		n (%)	n (%)	n (%)	n (%)
Local reactions	Pain	394 (30.7)	130 (10.2)	624 (51.9)	107 (9.1)
	Tenderness	705 (54.9)	223 (17.5)	922 (76.6)	164 (14.0)
	Erythema	25 (1.9)	5 (0.4)	100 (8.3)	2 (0.2)
	Swelling/induration	12 (0.9)	6 (0.5)	89 (7.4)	4 (0.3)
Systemic reactions	Nausea/vomiting	67 (5.2)	69 (5.4)	128 (10.7)	44 (3.8)
	Headache	314 (24.5)	274 (21.5)	487 (40.7)	208 (17.9)
	Fatigue	263 (20.5)	244 (19.2)	491 (41.0)	194 (16.7)
	Malaise	149 (11.6)	122 (9.6)	377 (31.5)	107 (9.2)
	Myalgia	286 (22.3)	181 (14.2)	492 (41.1)	113 (9.7)
	Arthralgia	84 (6.6)	63 (4.9)	205 (17.1)	59 (5.1)
	Pyrexia	28 (2.3)	19 (1.5)	59 (5.1)	9 (0.8)

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

In the safety analysis set, the incidence of unsolicited adverse events (events after unblinding, events after administration of another SARS-CoV-2 vaccine, and events corresponding to solicited adverse events [except preferred terms corresponding to immunogenicity occurring by Day 7 after each dose][30]) was 23.8% (1,802 of 7,569 subjects) in the Nuvaxovid group and 18.7% (1,414 of 7,570 subjects) in the placebo group. Among them, the incidence of unsolicited adverse events for which causal relationship to the study vaccination could not be ruled out was 10.8% (819 subjects) in the Nuvaxovid group and 4.5% (341 subjects) in the placebo group.

Tables 40 shows unsolicited adverse events with an incidence of ≥0.5% in either group. Table 41 shows unsolicited adverse events related to the study vaccination.

[29] Grade ≥1 events persisting until Day ≥7 after the vaccination were collected again from Day 7 until they resolved. From Day 7 onward, they were classified as unsolicited adverse events.

[30] The following events were excluded from the collection of "all unsolicited adverse events" in order to make the safety profile of Nuvaxovid clearer: Events after unblinding, events after administration of another SARS-CoV-2 vaccine, and events corresponding to solicited adverse events (preferred terms corresponding to immunogenicity events occurring by Day 7 after each dose). On the other hand, these events were not excluded from the collection of "adverse events resulting in death," "other serious adverse events," "adverse events leading to study discontinuation," "adverse events requiring treatment," or "AESIs."

Table 40. Unsolicited adverse events with an incidence of ≥0.5% in either Nuvaxovid or placebo group between the first dose and Day 28 after the second dose
(Study 302: Safety analysis set)

Event name PT (MedDRA/J Ver.23.1)	Nuvaxovid	Placebo
	N = 7,569	N = 7,570
	n (%)	n (%)
Injection site pain	93 (1.2)	25 (0.3)
Fatigue	51 (0.7)	58 (0.8)
Influenza like illness	60 (0.8)	12 (0.2)
Injection site pruritus	50 (0.7)	4 (<0.1)
Headache	92 (1.2)	108 (1.4)
Lethargy	77 (1.0)	29 (0.4)
Dizziness	45 (0.6)	33 (0.4)
Oropharyngeal pain	103 (1.4)	106 (1.4)
Rhinorrhoea	60 (0.8)	86 (1.1)
Cough	49 (0.6)	66 (0.9)
Nasal congestion	28 (0.4)	35 (0.5)
Urinary tract infection	29 (0.4)	40 (0.5)
Diarrhoea	75 (1.0)	63 (0.8)
Back pain	41 (0.5)	42 (0.6)
Hypertension	66 (0.9)	42 (0.6)
Lymphadenopathy	60 (0.8)	41 (0.5)

Table 41. Study vaccination-related, unsolicited adverse events observed in ≥0.5% of subjects in either Nuvaxovid or placebo group between the first dose and Day 28 after the second dose
(Study 302: safety analysis set)

Event name PT (MedDRA/J Ver.23.1)	Nuvaxovid	Placebo
	N = 7,569	N = 7,570
	n (%)	n (%)
Pain	81 (1.1)	18 (0.2)
Influenza like illness	57 (0.8)	7 (<0.1)
Injection site pruritus	45 (0.6)	3 (<0.1)
Lethargy	69 (0.9)	22 (0.3)
Diarrhoea	36 (0.5)	19 (0.3)
Lymphadenopathy	45 (0.6)	29 (0.4)

In the safety analysis set, death occurred in 2 subjects in the Nuvaxovid group (COVID-19 pneumonia and morphine/fentanyl intoxication in 1 each) and 1 subject in the placebo group (COVID-19-related sepsis). The causal relationship to the study vaccine was ruled out for all of them. Adverse events leading to discontinuation of vaccination were observed in 30 subjects (0.4%) in the Nuvaxovid group and in 23 subjects in the placebo group (0.3%). Adverse events leading to study discontinuation were observed in 27 subjects (0.4%) in the Nuvaxovid group and in 17 subjects (0.2%) in the placebo group. Among them, those (mild or moderate events) observed in 14 subjects (Nuvaxovid) and 3 subjects (placebo) were considered related to the study vaccination.

Serious adverse events were observed in 44 of 7,569 subjects (0.6%) in the Nuvaxovid group and in 44 of 7,570 subjects (0.6%) in the placebo group. Serious events observed in ≥2 subjects in either group were COVID-19 pneumonia (1 in the Nuvaxovid group, 3 in the placebo group; the same order applies hereinafter), appendicitis (1, 2), COVID-19 (2, 0), pneumonia (0, 2), ankle fracture (3, 0), femoral neck fracture (0, 3), breast cancer (2, 0), migraine (3, 0), and pulmonary embolism (1, 2). A serious adverse event for which causal relationship to the study vaccination could not be ruled out was observed in 1 subject in the Nuvaxovid group (myocarditis).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical Data Package and Review Policy

Rapid development of vaccines against SARS-CoV-2 is needed amid the COVID-19 pandemic. The International Coalition of Medicines Regulatory Authorities (ICMRA),[31] WHO,[32] and the regulatory authorities in various countries[33] have published guidance, etc., to accelerate vaccine development. In Japan, PMDA published, on September 2, 2020, the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2"[34], which explains the following principles for clinical studies.

- As a rule, clinical trials to assess the preventive effect against COVID-19 must be conducted to evaluate the efficacy of SARS-CoV-2 vaccine candidates [see Section 3.1.3].
- There is a high need for evaluating the efficacy and safety of a vaccine candidate in Japanese subjects by conducting a clinical trial(s) in Japan, even if a large-scale confirmatory trial is conducted overseas to evaluate the disease-preventive effect [see Section 3].
- When a large-scale confirmatory clinical trial of a vaccine candidate is conducted overseas using the disease-preventive effect as the primary endpoint, it may be sufficient to conduct a Japanese clinical trial to confirm the immunogenicity and safety in Japanese subjects without conducting a confirmatory clinical trial in Japan to evaluate the disease-preventive effect in Japanese subjects [see Section 3.2.3].

The applicant planned and conducted a Japanese clinical study to evaluate the immunogenicity and safety of Nuvaxovid according to the above guidelines, and constructed a clinical data package for the present application with evaluation data from the following studies: 2 phase III studies evaluating the disease-preventive effect (Studies 301 and 302), a foreign phase I/II study (Study 101) and the Japanese phase I/II study (Study 1501) evaluating the safety and immunogenicity.

PMDA's view:

Taking account of the description in "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2," it is acceptable to evaluate the efficacy and safety of Nuvaxovid based on the clinical data package constructed by the applicant. The efficacy and safety of Nuvaxovid in Japanese people are assessed based on the following evaluations:

(a) The efficacy and safety of Nuvaxovid are evaluated using data from 2 foreign confirmatory studies (Studies 301 and 302) that evaluated disease preventive effect, as the pivotal study data.

(b) The immunogenicity and safety in Japanese people are evaluated based on data from the Japanese clinical study (Study 1501).

The safety of Nuvaxovid is evaluated based on submitted data from these studies and other clinical studies and based on as post-marketing data from foreign countries.

The applicant proposed the dosage and administration of a booster dose in the present application, based on the results of the booster dose of Nuvaxovid in Study 501 (reference data) and Study 101.

---

31) "Global regulatory workshop on COVID-19 vaccine development" (March 18, 2020 and June 22, 2022)

32) "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"

33) FDA "Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, CBER FDA, June 2020."
EMA "EMA considerations on COIVD-19 vaccine approval," etc.

34) https://www.pmda.go.jp/files/000236327.pdf (last accessed on March 8, 2022)

Appropriateness of the clinical data package on the booster dose is discussed in Sections 7.R.2.3 and 7.R.5.2, including the necessity of a booster dose and appropriateness of the dosage.

7.R.2 Efficacy

7.R.2.1 Primary endpoint

In the pivotal clinical studies (Studies 301 and 302) for evaluating the efficacy of Nuvaxovid, the primary efficacy endpoint was "The first occurrence of PCR-confirmed symptomatic COVID-19 (mild, moderate, or severe) from Day 7 after the second dose in subjects who were seronegative to SARS-CoV-2 at baseline."

The applicant's rationale for the primary endpoint:
The definition of COVID-19 cases is "cases of SARS-CoV-2 infection confirmed by PCR," which was established after discussion with U.S. Food and Drug Administration (FDA) and U.K. Medicines and Healthcare products Regulatory Agency (MHRA). The same definition was used in Study 301 and Study 302. Severity was classified into 3 grades of mild, moderate, and severe, based mainly on the definition of COVID-19 cases recommended by U.S. FDA (U.S. Department of Health and Human Services. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020). In addition, the definition of mild and moderate COVID-19 was established as an objective and practical measure under the pandemic, based on the experiences in the clinical development by Novavax.

COVID-19 cases in the primary endpoint include "mild, moderate, and severe" diseases to widely cover the clinical picture of symptomatic SARS-CoV-2 infection. Preventive effect against "moderate or severe" COVID-19 (i.e., events with greater severity) was evaluated as the secondary endpoint. The long-term efficacy of the already-approved vaccines against mainly mild events was shown to decrease, whereas the efficacy of the vaccines against severer events (e.g., death and hospitalization) was maintained. (*MMWR Morb Mortal Wkly Rep.* 2021;70:1337-43, *MMWR Morb Mortal Wkly Rep.* 2021;70:1156-62).

These results suggest that the above-described evaluation policy is appropriate for clarifying the efficacy profile of Nuvaxovid against events of each severity.

In Study 301, cases of PCR-confirmed COVID-19 were assessed by the algorithm based on the physician's assessment (including assessment of severity). Cases classified as severe COVID-19 by the algorithm were subjected to a more rigorous assessment of severity by blinded medical review conducted by the independent medical review committee (IMRC) consisting of specialists in infectious diseases. In Study 302, identification of COVID-19 cases (the primary endpoint) and severity assessment were conducted under blinded conditions using a prespecified algorithm. During the process of designing the algorithm, clinical reviews were conducted to confirm that the results of algorithm-based assessment were not different from the physician's assessment. After the beginning of study, however, no such clinical reviews were conducted on the final results of algorithm-based assessment in each subject. Thus, clinical reviews were conducted in both Studies 301 and 302, although the timing of the physician's intervention differed between the studies; this means that

COVID-19 cases, the primary endpoint, were assessed appropriately in both studies. The fact that both studies showed similar VE also supports that similar assessment was conducted in the studies.

Study 301 and Study 302 used different PCR test kits and assay methods, but both test kits were granted emergency use authorization in the United States, and validated assay methods were used in all testing laboratories.

The timing of starting assessment was defined as "from Day 7 after the second dose" based on the following finding: In the phase I part of Study 101 involving adults 18 to 59 years old, subjects receiving 2 doses of the proposed dose (SARS-CoV-2 rS 5 μg + Matrix-M 50 μg) (Group C) showed extremely high titers of the specific IgG antibody against SARS-CoV-2 rS protein on Day 7 after the second dose (Day 28 after the first dose) (Table 42). In addition, starting assessment at an early timing (i.e., from Day 7 after the second dose) was deemed desirable for prompt collection of COVID-19 cases and early assessment of efficacy. Thus, it is considered appropriate to have started the assessment of the primary endpoint from Day 7 after the second dose.

Table 42. Specific IgG antibody titer against SARS-CoV-2rS protein
(Study 101, Part 1: PP analysis set, Group C)

	No. of subjects	GMT [a)]	[2-sided 95%CI]
Baseline	29	113.6	[97.8, 132.0]
Day 7 after first dose	29	131.8	[107.6, 161.4]
Day 21 after first dose	29	1984.2	[1405.8, 2800.7]
Day 28 after first dose	29	15318.8	[9486.8, 24736.0]
Day 35 after first dose	29	63160.4	[47117.3, 84666.0]
Day 49 after first dose	29	41783.4	[30466.4, 57304.1]
Day 105 after first dose	28	14777.3	[11222.5, 19458.1]
Day 189 after first dose	27	5434.1	[4161.2, 7096.3]

PP analysis set: Subjects who received at least 1 dose of the study vaccine, provided serum samples at baseline and at least once after vaccination, and had no serious protocol violation affecting the immunogenicity assessment at visits.
a) The lower quantitation limit was 200 EU/m. Values below the lower quantitation limit were converted to "0.5 × lower quantitation limit."

PMDA's view:
Although the method for detecting and assessing COVID-19 cases, the primary endpoint, differed between Study 301 and Study 302, this is unlikely to pose any significant problem in the clinical assessment. The primary endpoint was defined based on the appropriate plan in both studies. It is thus acceptable to evaluate the COVID-19-preventive effect of Nuvaxovid based on these primary endpoints.

7.R.2.2 Efficacy results

The applicant's explanation about the efficacy results:

(a) Disease-preventive effect

Results of the primary endpoint in Study 301 and in Study 302 were as follows:

Study 301:

The results of VE of Nuvaxovid (see Table 33) demonstrate the COVID-19-preventive effect of Nuvaxovid. As a supplementary analysis of the primary endpoint, the efficacy was evaluated in the population including subjects seropositive to SARS-CoV-2 at baseline. Results showed that the

number of confirmed COVID-19 cases occurring on Day ≥7 after the second dose was 15 of 18,438 in the Nuvaxovid group and 64 of 8,740 in the placebo group, with VE [2-sided 95%CI] of 89.7% [82.0%, 94.15%]; these results were similar to those of the primary analysis.

The following is a summary of the error found in the eligibility assessment of some subjects for the PP-EFF analysis set in Study 301 [see footnote in Section 7.3.1]:

Whether to exclude subjects from the PP-EFF analysis set was decided under blinded conditions based on the deviation report, but the details of deviations were not confirmed before the assessment. The inspection after data extraction and unblinding revealed the following error:

Of the subjects excluded from the PP-EFF analysis set, 397 (51 in the Nuvaxovid group, 346 in the placebo group) should not have been excluded. Of the subjects included in the PP-EFF analysis set, 14 (12 in the Nuvaxovid group, 2 in the placebo group) should have been excluded because of "protocol-non-compliant vaccination."

Most of the wrong exclusions allegedly due to "deviation in study vaccination" were caused by errors in the flagging for deviation in temperature control of the study vaccine. The number of wrongly excluded subjects was greater in the placebo group, for the following reason: The physiological saline used as the placebo was allowed by the manufacturer to be stored at a low temperature, whereas the label required storage at 20ºC to 25°C, resulting in a non-uniform temperature control. Further, the wrongly included 14 subjects who should have been excluded had the deviation of protocol-non-compliant vaccination (e.g., failure to record the time of taking out of the study vaccine, the time of drawing drug solution into the syringe, the time of vaccination)

When the exclusion criteria were applied correctly, the PP-EFF analysis set consisted of 25,776 subjects (17,351 in the Nuvaxovid group, 8,425 in the placebo group). In the correct PP-EFF analysis set, the number of subjects with primary endpoint events was 14 (0.08%), which is the same as in the original assessment and 68 (0.81%) in the placebo group, with the resulting VE being 90.71% [2-sided 95% CI: 83.48%, 94.77%]. The handling of the deviation cases and exclusion assessment did not affect blinding and did not negatively affect the results of the primary endpoint. Accordingly, the description of Study 301 in this report is based on the results obtained in the original PP-EFF analysis set.

Study 302:

Table 37 shows VE of Nuvaxovid at the data cut-off point for the interim analysis ([redacted], 20[redacted]), demonstrating COVID-19-preventive effect of Nuvaxovid. VE at the final analysis ([redacted], 20[redacted]) (see Table 38) was similar to that at the interim analysis.

(b) Results of subpopulation analysis

Table 43 shows the efficacy in subpopulations of Study 301. No meaningful analysis could be performed due to insufficient number of events collected for the following subpopulations: Subjects ≥65 years old, American Indian or Alaska Native, Native Hawaiians and other Pacific Islander, multiple or unknown race, and subjects in Mexico. VE in Hispanic/Latino subjects, a subgroup of ethnicity, was lower than that in the non-Hispanic/Latino subpopulation or in the entire population. In the immunogenicity assessment, however, GMT [2-sided 95% CI] of neutralizing antibody titer on

Day 14 after the second dose was 1,124.4 [880.7, 1,435.4] in Hispanic/Latino subjects and 1,070.7 [949.2, 1,207.8] in non-Hispanic/Latino subjects, showing similar results in both groups.

Table 43. Occurrence of COVID-19 from Day 7 after the second dose by subpopulation (Study 301, PPE population)

		Nuvaxovid n/N (%)	Placebo n/N (%)	VE (%) [2-sided 95%CI][b)]
Entire population		14/17312 (0.1)	63/8140 (0.8)	90.4 [82.9, 94.6]
Age	18 to 64	12/15264 (0.1)	61/7194 (0.8)	91.5 [84.1, 95.4]
	≥65	2/2048 (0.1)	2/946 (0.2)	57.5 [−486.9, 96.9]
Sex	Male	5/9050 (0.1)	23/4131 (0.6)	90.9 [76.0, 96.5]
	Female	9/8262 (0.1)	40/4009 (1.0)	90.0 [79.4, 95.1]
Race	White	12/13140 (0.1)	48/6184 (0.8)	89.4 [80.0, 94.4]
	Black or African American	0/1893 (0)	7/905 (0.8)	100 [67.9, 100]
	American Indian or Alaska Native	0/1074 (0)	2/498 (0.4)	100 [−143.6, 100]
	Asian	0/761 (0)	5/366 (1.4)	100 [52.8, 100]
	Native Hawaiian and other Pacific Islander	0/47 (0)	0/10 (0)	NE
	Multiple	2/293	0/132	NE
	Unknown	0/104 (0)	1/45 (2.2)	100 [−1549.6, 100]
Ethnicity	Hispanic/Latino	8/3733 (0.2)	11/1751 (0.6)	67.3 [18.7, 86.8]
	Not Hispanic/Latino	6/13538 (<0.1)	52/6379 (0.8)	95.1 [88.5, 97.9]
Country	United States	14/16294 (0.1)	62/7638 (0.8)	90.4 [82.8, 94.6]
	Mexico	0/1018 (0)	1/502 (0.2)	100 [−1791.9, 100]
Comorbidity [a)]	Yes	7/8109 (0.1)	34/3910 (0.9)	90.8 [79.2, 95.9]
	No	7/9203 (0.1)	29/4230 (0.7)	89.9 [77.1, 95.6]

n = number of subjects with COVID-19, N = number of subjects analyzed
a) Obesity (BMI≥30 kg/m^2). chronic kidney disease, chronic lung disease, cardiovascular disease, type 2 diabetes mellitus
b) Poisson regression model with explanatory variables of vaccination group, age (18-64, ≥65), and region

Table 44 shows efficacy by subgroup in Study 302. The efficacy of Nuvaxovid was consistent regardless of age, sex, race, or comorbidities.

Table 44. Occurrence of COVID-19 from Day 7 after the second dose by subgroup (Study 302, PPE population, final analysis)

		Nuvaxovid n/N (%)	Placebo n/N (%)	VE (%) [2-sided 95%CI] [c)]
Entire population		10/7020 (0.1)	96/7019 (1.4)	89.7 [80.2, 94.6]
Age	18 to 64	9/5067 (0.2)	87/5062 (1.7)	89.8 [79.7, 94.9]
	≥65	1/1953 (0.1)	9/1957 (0.5)	88.9 [20.2, 99.7]
Sex	Male	5/3609 (0.1)	43/3629 (1.2)	88.2 [70.2, 95.3]
	Female	5/3411 (0.2)	53/3390 (1.6)	91.0 [77.3, 96.4]
Race [a)]	White	8/6625 (0.1)	85/6635 (1.3)	90.7 [80.8, 95.5]
	Non-white	2/302 (0.7)	8/297 (2.7)	75.7 [−21.6, 97.5]
Comorbidity [b)]	Yes	3/3117 (0.1)	33/3143 (1.1)	90.9 [70.4, 97.2]
	No	7/3903 (0.2)	63/3876 (1.6)	89.1 [76.2, 95.0]

n = number of subjects with COVID-19, N = number of subjects analyzed
a) Subjects with no report or with unknown race, etc., were excluded.
b) Subjects with at least one comorbidity or those with BMI>30 kg/m^2 at screening
c) Poisson regression model with explanatory variables of vaccination group, age (18-64, ≥65), and region

(c) Effect in preventing severe COVID-19

In the PP-EFF analysis set of Study 301, the first onset of PCR-confirmed moderate or severe COVID-19 from Day 7 after the second dose was observed in 0 subjects in the Nuvaxovid group and 14 subjects (10 moderate, 4 severe) in the placebo group, with VE [2-sided 95%CI] of 100% [87.0%, 100%].

In the PP-EFF analysis set (final analysis) in Study 302, the first occurrence of PCR-confirmed moderate or severe COVID-19 from Day 7 after the second dose was observed in 9 subjects (all moderate) in the Nuvaxovid group and 68 subjects (63 moderate, 5 severe) in the placebo group, with VE [2-sided 95%CI] of 86.9% [73.7%, 93.5%]. VE [2-sided 95%CI] for severe COVID-19 events was 100% [-8.7%, 100%].

(d) Immunogenicity

Tables 45 and 46 show the neutralizing antibody titer against the original Wuhan strain in subjects who were seronegative at baseline in Study 301 and Study 302, respectively. In subjects receiving Nuvaxovid, the neutralizing antibody titer markedly increased on Day 14 after the second dose in both the entire population and the age-based subpopulations (non-elderly [18 to 64], elderly [≥65]).

Table 45. Neutralizing antibody titer against the original Wuhan strain (Study 301, PP immunogenicity analysis set, subjects seronegative at baseline)

		Entire population		18 to 64 years old		≥65 years old	
		Nuvaxovid	Placebo	Nuvaxovid	Placebo	Nuvaxovid	Placebo
Baseline	No. of subjects	708	331	351	161	357	170
	GMT [a]	**10.5**	**10.1**	**10.6**	**10.0**	**10.4**	**10.1**
	[2-sided 95% CI]	[10.2, 10.9]	[10.0, 10.1]	[10.1, 11.2]	[10.0, 10.0]	[10.0, 10.9]	[10.0, 10.3]
Day 14 after second dose	No. of subjects	703	332	349	163	354	169
	GMT	**1078.2**	**10.7**	**1292.8**	**10.6**	**901.6**	**10.8**
	[2-sided 95% CI]	[968.0, 1200.9]	[10.2, 11.2]	[1128.0, 1481.6]	[9.9, 11.4]	[764.4, 1063.4]	[10.1, 11.6]
	GMFR	**102.8**	**1.1**	**122.7**	**1.1**	**86.4**	**1.1**
	[2-sided 95% CI]	[91.9, 115.1]	[1.0, 1.1]	[106.0, 142.2]	[1.0, 1.1]	[73.0, 102.4]	[1.0, 1.1]
	Seroconversion rate % (n/N)	**96.3 (674/700)**	**2.1 (7/330)**	**98.3 (341/347)**	**1.9 (3/161)**	**94.3 (333/353)**	**2.4 (4/169)**
	[2-sided 95% CI] [b]	[94.6, 97.6]	[0.9, 4.3]	[96.3, 99.4]	[0.4, 5.3]	[91.4, 96.5]	[0.6, 5.9]

a) The lower quantitation limit was 20. Values below the lower quantitation limit were converted to "0.5 × lower quantitation limit."
b) Clopper-Pearson method

Table 46. Neutralizing antibody titer against the original Wuhan strain (Study 302, PP immunogenicity analysis set, subjects seronegative at baseline)

		Entire population		18 to 64 years old		65 to 84 years old	
		Nuvaxovid	Placebo	Nuvaxovid	Placebo	Nuvaxovid	Placebo
Baseline	No. of subjects	381	380	270	284	111	96
	GMT [a]	**10.1**	**10.1**	**10.1**	**10.1**	**10.3**	**10.0**
	[2-sided 95% CI]	[10.0, 10.3]	[10.0, 10.2]	[10.0, 10.1]	[10.0, 10.2]	[9.8, 10.8]	[10.0, 10.0]
Day 14 after second dose	No. of subjects	381	380	270	284	111	96
	GMT	**1133.1**	**10.4**	**1241.2**	**10.5**	**907.9**	**10.0**
	[2-sided 95% CI]	[999.4, 1284.7]	[9.9, 10.8]	[1069.4, 1440.5]	[9.9, 11.1]	[720.1, 1144.8]	[10.0, 10.0]
	GMFR	**112.1**	**1.0**	**123.5**	**1.0**	**88.6**	**1.0**
	[2-sided 95% CI]	[98.7, 127.3]	[1.0, 1.1]	[106.4, 143.3]	[1.0, 1.1]	[69.4, 113.0]	[1.0, 1.0]
	Seroconversion rate % (n/N)	**98.2 (374/381)**	**0.5 (2/380)**	**98.1 (265/270)**	**0.7 (2/284)**	**98.2 (109/111)**	**0.0 (0/96)**
	[2-sided 95% CI] [b]	[96.3, 99.3]	[0.1, 1.9]	[95.7, 99.4]	[0.1, 2.5]	[93.6, 99.8]	[0.0, 3.8]

a) The lower quantitation limit was 20. Values below the lower quantitation limit were converted to "0.5 × lower quantitation limit."
b) Clopper-Pearson method

Although the neutralization titer on Day 14 after the second dose was lower in the elderly subjects than in the non-elderly subjects, there is no clinical problem in the disease-preventive effect of Nuvaxovid in the elderly people, given the following findings:

(a) The antibody titer in elderly people tends to be lower than the titer in non-elderly people with other COVID-19 vaccines as well.

(b) In Study 302 (in which approximately 27% of enrolled subjects were ≥65 years old), VE [2-sided 95% CI] by age group was 89.8% [79.7%, 94.9%] in those 18 to 64 years old and

88.9% [20.2%, 99.7%] in those 64 to 84 years old, showing no tendency of VE decrease in the elderly.

(e) Efficacy in the Japanese population

In the Japanese Study 1501, the neutralizing antibody titer (GMT [2-sided 95% CI]) against the original Wuhan strain on Day 14 after the second dose was 884.4 [749.0, 1044.4], showing a marked increase from baseline. The increase in the neutralizing antibody titer (GMT) on Day 14 after the second dose was observed both in the elderly (≥65 years old) and in the non-elderly (20 to 64 years old), but the antibody titer tended to be lower in the elderly than in the non-elderly subjects (Table 16). Similar tendencies were observed in foreign studies 301 and 302. In addition, in the subpopulation analysis of VE in Study 301, VE [2-sided 95% CI] in the Asian subpopulation, albeit with a limited number of subjects, was 100% [52.8%, 100%], showing no tendency of lower VE in the Asian subpopulation than in other races. These results suggest that Nuvaxovid has similar efficacy in Japanese people as that demonstrated in non-Japanese people in foreign studies.

(f) Efficacy against variants

Efficacy against variants was evaluated based on the results of Study 301 and Study 302. During the period of Study 301, multiple variants of concern (VOC) and variants of interest (VOI) including Alpha variant were dominant in the United States and Mexico. During the period of Study 302, Alpha variant was dominant in the U.K.

Of 77 subjects who developed COVID-19 (the primary endpoint) in Study 301, 6 in the Nuvaxovid group and 38 in the placebo group were infected by viral strains classified as VOC/VOI by WHO. The VE [2-sided 95% CI] against these strains was 93.2% [83.9%, 97.1%]. The most frequently reported viral strain was Alpha variant. The severity of COVID-19 caused by Alpha variant was mild in 6 subjects in the Nuvaxovid group; and mild in 29 subjects, moderate in 7 subjects, and severe in 2 subjects in the placebo group.

In the final analysis of Study 302, 106 developed COVID-19, the primary endpoint. Of the 106 subjects, 8 in the Nuvaxovid group and 58 in the placebo group were infected by Alpha variant, with the VE [2-sided 95% CI] of Nuvaxovid against Alpha variant being 86.3% [71.3%, 93.5%]. COVID-19 was mild in 1 subject and moderate in 7 subjects in the Nuvaxovid group; and mild in 15 subjects, moderate in 39 subjects, and severe in 4 subjects in the placebo group.

According to the preliminary results of the final analysis of the primary endpoint in Study 501, VE [2-sided 95%CI] was 48.6% [28.4%, 63.1%] [see Section 7.2.1], which was lower than the VE in Study 301 and Study 302. In this study, severe COVID-19 was reported in 5 subjects in the entire population, all in the placebo group. Study 501 was conducted in South Africa during the period when Beta variant was the predominant strain. Of 44 subjects who developed COVID-19 in Study 501, the genome of the viral strain was sequenced in 41 subjects (93.2%), and Beta variant was identified in 38 subjects (92.7%). This suggests the possibility that the low VE in Study 501 was due to the infection by Beta variant. Usually, immunocompromised individuals including those with HIV are usually excluded from clinical studies that evaluate the efficacy of a novel vaccine, because the immune

response to vaccines in such individuals may be different from that in the general population. However, HIV-positive people were not excluded from Study 501 conducted in South Africa, because approximately 20% of people 15 to 49 years old are HIV-positive in the country. Both IgG antibody titer and neutralizing antibody titer in HIV-positive subjects were approximately 50% of those in HIV-negative subjects; this suggests that inclusion of HIV-positive subjects affected the results of the primary endpoint. The final analysis of the primary endpoint showed that VE [2-sided 95% CI] in the HIV-negative subpopulation was 55.4% [35.9%, 68.9%], which fulfills the criteria of FDA and WHO guidelines. Thus, the results show that the primary series of Nuvaxovid has acceptable efficacy against Beta variant.

The efficacy against variants other than Beta variant will be assessed based on IgG antibody titer and neutralizing antibody titer determined by validated assay.

PMDA's view on the efficacy of Nuvaxovid:
Results of Studies 301 and 302 demonstrate the COVID-19-preventive effect of Nuvaxovid. Also, the Japanese Study 1501 showed that serum neutralizing antibody titer against SARS-CoV-2 after the second dose of Nuvaxovid was higher than the baseline and the level in the placebo group. In addition, the serum neutralizing antibody titer in Japanese subjects after the second dose of Nuvaxovid in Japanese Study 1501, was not significantly different from the serum neutralizing antibody titer in the PP immunogenicity analysis set in Studies 301 and 302. Nuvaxovid is thus expected to have COVID-19-preventive effect in Japanese people as well.

The submitted study results should be interpreted with care in terms of the effect in preventing severe COVID-19, because neither Study 301 nor 302 was designed to confirm the effect in preventing severe disease. Nevertheless, the results submitted do not raise significant doubt as to the effect of Nuvaxovid in preventing severe COVID-19.

Nuvaxovid is expected to be effective against the variants that were epidemic during the conduct of Studies 301 and 302. In contrast, VE observed in Study 501 was lower than that in Studies 301 and 302, suggesting the possibility that Nuvaxovid may have a lower efficacy against Beta variant. Yet it is difficult to reach this conclusion based only on the results of this study, because (a) the subject characteristics such as "HIV-positive" may have affected the results, (b) the total number of events is limited, and (c) the study design was not intended to evaluate the efficacy against individual variants. After these studies, novel variants have been detected in various countries including Japan, and the efficacy of Nuvaxovid against these variants has not been investigated. The applicant should continue to pay attention to the emergence and prevalence of variants, evaluate the neutralizing activity and clinical efficacy of Nuvaxovid against variants (including non-clinical evaluation), collect relevant information, and take appropriate actions such as disseminating new information as necessary.

7.R.2.3 Duration of efficacy

The applicant's explanation about the duration of efficacy after the primary series of Nuvaxovid:
Currently, no information is available on the long-term disease-preventing effect of Nuvaxovid. In Studies 301 and 302, subjects in the placebo group received Nuvaxovid according to the crossover design; therefore these studies cannot provide data on the long-term disease-preventing effect.

In Part I of Study 101, the subjects in the safety analysis set were included in the PP analysis set and were handled as the primary analysis set for immunogenicity. Table 47 shows the neutralizing antibody titer (>99% inhibitory concentration) against the original Wuhan strain on the day of study vaccination (baseline), Day 21 after the first dose, Day 14 after the second dose, and Day 168 after the second dose in the PP analysis set. Decreased antibody titers were observed on Day 168 after the second dose.

Table 47. Neutralizing antibody titer against original Wuhan strain in Part 1 of Study 101 (PP analysis set)

		Group A	Group B	Group C	Group D	Group E
Baseline	Number of subjects	23	25	29	28	26
	GMT [a)]	**20.0**	**20.0**	**20.0**	**20.0**	**20.0**
	[2-sided 95%CI]	[20.0, 20.0]	[20.0, 20.0]	[20.0, 20.0]	[20.0, 20.0]	[20.0, 20.0]
Day 21 after first dose	Number of subjects	21	25	29	27	26
	GMT [a)]	**20.0**	**21.7**	**103.3**	**126.2**	**117.8**
	[2-sided 95%CI]	[20.0, 20.0]	[19.2, 24.6]	[74.8, 142.6]	[79.5, 200.4]	[74.2, 187.0]
	GMFR	**1.0**	**1.1**	**5.2**	**6.3**	**5.9**
	[2-sided 95%CI]	[1.0, 1.0]	[1.0, 1.2]	[3.7, 7.1]	[4.0, 10.0]	[3.7, 9.3]
	Seroconversion rate % (n)	**0 (0)**	**4.0 (1)**	**72.4 (21)**	**74.1 (20)**	**65.4 (17)**
	[2-sided 95%CI] [b)]	[0, 16.1]	[0.1, 20.4]	[52.8, 87.3]	[53.7, 88.9]	[44.3, 82.8]
Day 14 after second dose	Number of subjects	21	25	29	27	26
	GMT [a)]	**20.0**	**41.4**	**3906.3**	**3305.0**	**127.6**
	[2-sided 95%CI]	[20.0, 20.0]	[27.5, 62.4]	[2555.9, 5970.0]	[2205.3, 4953.2]	[81.8, 199.1]
	GMFR	**1.0**	**2.1**	**195.3**	**165.3**	**6.4**
	[2-sided 95%CI]	[1.0, 1.0]	[1.4, 3.1]	[127.8, 298.5]	[110.3, 247.7]	[4.1, 10.0]
	Seroconversion rate % (n)	**0 (0)**	**28.0 (7)**	**100 (29)**	**100 (27)**	**73.1 (19)**
	[2-sided 95%CI] [b)]	[0, 16.1]	[12.1, 49.4]	[88.1, 100]	[87.2, 100]	[52.2, 88.4]
Day 168 after second dose	Number of subjects	20	23	27	25	26
	GMT [a)]	**20.0**	**21.2**	**121.7**	**110.6**	**26.2**
	[2-sided 95%CI]	[20.0, 20.0]	[18.7, 24.1]	[77.9, 190.1]	[70.3, 174.0]	[21.5, 32.1]
	GMFR	**1.0**	**1.1**	**6.1**	**5.5**	**1.3**
	[2-sided 95%CI]	[1.0, 1.0]	[0.9, 1.2]	[3.9, 9.5]	[3.5, 8.7]	[1.1, 1.6]
	Seroconversion rate % (n)	**0 (0)**	**4.3 (1)**	**77.8 (21)**	**64.0 (16)**	**11.5 (3)**
	[2-sided 95%CI] [b)]	[0, 16.8]	[0.1, 21.9]	[57.7, 91.4]	[42.5, 82.0]	[2.4, 30.2]

a) The lower quantification limit was 20.
b) Clopper-Pearson method

In Part 2 of Study 101 as well, the specific IgG antibody titer against SARS-CoV-2 rS protein and the neutralizing antibody titer against the original Wuhan strain after the second dose of Nuvaxovid, peaked on Day 14 after the second dose, then decreased over time from Day 14 through Day 168 after the second dose. An additional single dose (third dose) of Nuvaxovid was administered on Day 168 after the second dose. The specific Ig antibody titer against SARS-CoV-2 rS protein and the neutralizing antibody titer against the original Wuhan strain on Day 28 after the third dose, were 4.7 and 4.0 times higher, respectively, than their peak levels on Day 14 after the second dose.

Although the correlation between the antibody titer and COVID-19 prevention has not been established, the correlation between the antibody titer and the efficacy of SARS-CoV-2 vaccines has

been suggested: Thus, the higher the antibody titer, the higher the efficacy (*Vaccine.* 2021;39:4423-28, *Nat Med.* 2021;27:1205-11). Accordingly, the decrease over time in the neutralizing antibody titer may cause, or be correlated with, a decrease in the efficacy of the vaccine. The efficacy of approved vaccines against SARS-CoV-2 may be reduced after a certain period of time after the primary series (*N Engl J Med*. 2021;385:1761-73, *MMWR Morb Mortal Wkly Rep*. 2021;70:1150-1155. doi:10.15585/mmwr.mm7034e1., etc.). A booster dose decreases the risk of SARS-CoV-2 infection and the risk of severe COVID-19 (*N Engl J Med*. 2021;385:1393-1400).

The results of neutralizing antibody titer against Beta variant in Part 2 of Study 101:
Group B1 (63 subjects) received 2 doses of Nuvaxovid and the third dose of placebo on Day 168 after the second dose. Group B2 (65 subjects) received 2 doses of Nuvaxovid and the third dose of Nuvaxovid on Day 168 after the second dose. The neutralizing antibody titer (GMT [2-sided 95%CI]) against Beta variant on Day 28 after the third dose was 11.3 [10.4, 12.2] in Group B1 and 660.8 [492.7, 886.2] in Group B2. Using the data on Day 168 after the second dose as the baseline, GMFR [2-sided 95%CI] was 1.0 [0.9, 1.1] in Group B1 and 48.0 [33.8, 68.2] in Group B2, and the seroconversion rate [2-sided 95% CI] was 0% [0.0%, 5.7%] in Group B1 and 92.3% [83.0%, 97.5%] in Group B2. Both parameters markedly increased in subjects who received the third dose of Nuvaxovid. The neutralizing antibody titer against variants other than Beta variant will be evaluated in future, but the following preliminary results have been obtained in Part 2 of Study 101:

> The neutralizing antibody titer (maximum fold dilution that maintains >99% of the neutralizing activity of the undiluted serum) against the original Wuhan strain (wild type), Delta variant, and Omicron variant, was measured by an unvalidated method. The neutralizing antibody titer (GMT [2-sided 95%CI]) in Group B2 (n = 28) on Day 14 after the second dose and on Day 28 after the third dose was 853 [490.2, 1484] and 13123 [7619, 22603], respectively, against the original Wuhan strain, 332 [212, 518.5] and 4629 [2961, 7236], respectively, against Delta variant, and 232 [169.4, 317.7] and 823 [530.8, 1277], respectively, against Omicron variant.

The applicant considers that, in order to keep the efficacy of Nuvaxovid for a long period, a booster dose should be given approximately 6 months after the second dose of the primary series.

PMDA's view:
Part 1 and Part 2 of Study 101 showed a decrease in the neutralizing antibody titer on Day 168 after the second dose. Although the long-term efficacy of Nuvaxovid is unclear at the present moment, findings with approved vaccines indicate the relationship between antibody titer and clinical efficacy and show the necessity of a booster dose administered sometime after the previous vaccination. Study results of Nuvaxovid also suggest that a booster dose may be required sometime after the primary series. The applicant proposed the dosage and administration of a booster dose in the present application. Since there are ongoing clinical studies, the appropriateness of the dosage and the sufficiency of the study results are reviewed in Section 7.R.5.2, based on the data submitted so far.

7.R.3 Safety

7.R.3.1 Incidences of adverse events in clinical studies

The applicant's explanation:

Table 48 shows the incidences of local and solicited systemic adverse events in Studies 301 and 302.

Table 48. Summary of adverse events in Studies 301 and 302
(301, safety analysis set; 302, solicited adverse event analysis set)

	Study 301				Study 302			
	After first dose		After second dose		After first dose		After second dose	
Study vaccine	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)
Number of subjects	18072	8904	17139	8278	1364	1350	1348	1335
Solicited local adverse events	10475 (58.0)	1881 (21.1)	13525 (78.9)	1797 (21.7)	762 (59.3)	266 (20.9)	965 (80.2)	199 (17.01)
Grade ≥3	198 (1.1)	23 (0.3)	1147 (6.7)	26 (0.3)	14 (1.1)	2 (0.2)	63 (5.2)	1 (<0.1)
Solicited systemic adverse events	8614 (47.7)	3562 (40.0)	11906 (69.5)	2969 (35.9)	610 (47.6)	482 (37.9)	774 (64.6)	359 (30.8)
Grade ≥3	439 (2.4)	188 (2.1)	2077 (12.1)	170 (2.1)	19 (1.5)	17 (1.3)	83 (6.9)	16 (1.4)

n = Number of subjects with events
Definition of grade: The standard toxicity grade classification of the U.S. FDA was applied, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."
n (%)

(a) Study 301

In Study 301, solicited adverse events occurred more frequently in the Nuvaxovid group than in the placebo group, and the incidence in the Nuvaxovid group was higher after the second dose than after the first dose. Main solicited local adverse events were tenderness and pain, and main solicited systemic adverse events were headache, fatigue, myalgia, and malaise (Table 34). In the Nuvaxovid group, the median time to onset (range) was 1 day (1 to 7 days) after vaccination for solicited local adverse events and 2 days (1 to 7 days) after vaccination for solicited systemic adverse events.

Most of solicited adverse events were Grade 1 or 2 in severity. Table 49 shows the incidences of Grade ≥3 solicited adverse events. For both local and solicited systemic adverse events, Grade ≥3 events occurred more frequently in the Nuvaxovid group than in the placebo group. The incidence of Grade ≥3 events was higher after the second dose than after the first dose.

The incidence of unsolicited adverse events up to Day 49 after the first dose (up to Day 28 after the second dose) was 12.7% (2,514 of 19,729 subjects) in the Nuvaxovid group and 11.5% (1,137 of 9,853 subjects) in the placebo group. Among them, those considered related to the study vaccination were observed in 782 subjects (4.0%) in the Nuvaxovid group and in 233 subjects (2.4%) in the placebo group. Tables 35 and 36 show main events. Adverse events with a ≥0.2% higher incidence in the Nuvaxovid group than in the placebo group were fatigue (0.9% in the Nuvaxovid group, 0.7% in the placebo group; the same order applies hereinafter), injection site pain (0.7%, 0.4%), pyrexia (0.6%, 0.2%), myalgia (0.53%, 0.28%), and chills (0.3%, 0.1%). Most of unsolicited adverse events were mild or moderate. The incidence of severe unsolicited adverse events was 0.9% (178 of 19,729) in the Nuvaxovid group and 0.6% (63 of 9,853) in the placebo group.

Table 49. Grade ≥3 solicited adverse events (Study 301, safety analysis set)

	All ages		18 to 64 years		≥65 years	
	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)
Local (after first dose)						
	N = 18072	N = 8904	N = 15852	N = 7806	N = 2220	N = 1098
All events	198 (1.1)	23 (0.3)	184 (1.2)	20 (0.3)	14 (0.6)	3 (0.3)
Pain	55 (0.3)	3 (<0.1)	52 (0.3)	2 (<0.1)	3 (0.1)	1 (0.1)
Tenderness	157 (0.9)	19 (0.2)	147 (0.9)	17 (0.2)	10 (0.5)	2 (0.2)
Erythema	3 (<0.1)	0	3 (<0.1)	0	0	0
Swelling/induration	7 (<0.1)	3 (<0.1)	6 (<0.1)	3 (<0.1)	1 (<0.1)	0
Local (after second dose)						
	N = 17139	N = 8278	N = 15119	N = 7314	N = 2020	N = 964
All events	1147 (6.7)	26 (0.3)	1090 (7.2)	23 (0.3)	57 (2.8)	3 (0.3)
Pain	302 (1.8)	8 (0.1)	288 (1.9)	7 (0.1)	14 (0.7)	1 (0.1)
Tenderness	837 (4.9)	18 (0.2)	805 (5.3)	17 (0.2)	32 (1.6)	1 (0.1)
Erythema	143 (0.8)	2 (<0.1)	135 (0.9)	2 (<0.1)	8 (0.4)	0
Swelling/induration	91 (0.5)	2 (<0.1)	82 (0.5)	1 (<0.1)	9 (0.5)	1 (0.1)
Systemic (after first dose)						
	N = 18072	N = 8904	N = 15852	N = 7806	N = 2220	N = 1098
All events	439 (2.4)	188 (2.1)	401 (2.5)	177 (2.3)	38 (1.7)	11 (1.0)
Headache	151 (0.8)	63 (0.7)	138 (0.9)	59 (0.8)	13 (0.6)	4 (0.4)
Fatigue	227 (1.3)	101 (1.1)	206 (1.3)	98 (1.3)	21 (1.0)	3 (0.3)
Malaise	144 (0.8)	55 (0.6)	132 (0.8)	52 (0.7)	12 (0.5)	3 (0.3)
Myalgia	83 (0.5)	37 (0.4)	80 (0.5)	33 (0.4)	3 (0.1)	4 (0.4)
Arthralgia	52 (0.3)	29 (0.3)	48 (0.3)	25 (0.3)	4 (0.2)	4 (0.4)
Pyrexia	14 (0.1)	7 (0.1)	12 (0.1)	7 (0.1)	2 (0.1)	0
Nausea/vomiting	21 (0.1)	10 (0.1)	21 (0.1)	10 (0.1)	0	0
Systemic (after second dose)						
	N = 17139	N = 8278	N = 15119	N = 7314	N = 2020	N = 964
All events	2077 (12.1)	170 (2.1)	1987 (13.1)	155 (2.1)	90 (4.5)	15 (1.6)
Headache	518 (3.0)	38 (0.5)	500 (3.3)	36 (0.5)	18 (0.9)	2 (0.2)
Fatigue	1423 (8.3)	111 (1.3)	1362 (9.0)	100 (1.4)	61 (3.0)	11 (1.1)
Malaise	1082 (6.3)	59 (0.7)	1042 (6.9)	54 (0.7)	40 (2.0)	5 (0.5)
Myalgia	846 (4.9)	33 (0.4)	814 (5.4)	31 (0.4)	32 (1.6)	2 (0.2)
Arthralgia	417 (2.4)	26 (0.3)	400 (2.7)	24 (0.3)	17 (0.8)	2 (0.2)
Pyrexia	64 (0.4)	3 (<0.1)	62 (0.4)	2 (<0.1)	2 (0.1)	1 (0.1)
Nausea/vomiting	36 (0.2)	9 (0.1)	34 (0.2)	9 (0.1)	2 (0.1)	0

N = Number of subjects analyzed, n = number of subjects with events
Definition of grade: The standard toxicity grade classification of the U.S. FDA was applied, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

(b) Study 302

Solicited adverse events occurred more frequently in the Nuvaxovid group than in the placebo group, and the incidence in the Nuvaxovid group was higher after the second dose than after the first dose. Main solicited local adverse events were tenderness and pain, and main solicited systemic adverse events were headache, fatigue, and myalgia (Table 39). The median time (range) to the onset in the Nuvaxovid group was 1 day (1 to 7 days) after vaccination for solicited local adverse events and 2 days (1 to 7 days) for solicited systemic adverse events.

Most of the solicited adverse events were Grade 1 or 2 in severity. Table 50 shows the incidences of Grade ≥3 solicited adverse events. Grade ≥3 events occurred more frequently in the Nuvaxovid group than in the placebo group, and the incidence in the Nuvaxovid group was higher after the second dose than after the first dose.

The incidence of unsolicited adverse events up to Day 49 after the first dose was 37.8% (2,860 of 7,569 subjects) in the Nuvaxovid group and 23.1% (1,748 of 7,570 subjects) in the placebo group.

Among the unsolicited adverse events, those considered related to the study vaccination were observed in 1,936 subjects (25.6%) in the Nuvaxovid group and in 677 subjects (8.9%) in the placebo group. Tables 40 and 41 show the main events. Unsolicited adverse events observed at a ≥1% higher incidence in the Nuvaxovid group than in the placebo group were headache (7.7% in the Nuvaxovid group, 4.2% in the placebo group; the same order applies hereinafter), injection site pain (5.8%, 0.9%), fatigue (5.4%, 2.7%), myalgia (5.2%, 1.1%), pain in extremity (4.8%, 0.7%), pyrexia (2.5%, 0.4%), and chills (1.3%, 0.2%). Most of the unsolicited adverse events were mild in severity. The incidence of severe unsolicited adverse events was 1.2% (93 subjects) in the Nuvaxovid group and 0.8% (63 subjects) in the placebo group.

Table 50. Grade ≥3 solicited adverse events
(Study 302, solicited adverse event analysis set)

	All ages		18 to 64 years		65 to 84 years	
	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)
Local (after first dose)						
	N = 1285	N = 1272	N = 1060	N = 1037	N = 225	N = 235
All events	14 (1.1)	2 (0.2)	14 (1.3)	2 (0.2)	0	0
Pain	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	0
Tenderness	14 (1.1)	1 (<0.1)	14 (1.3)	1 (<0.1)	0	0
Erythema	0	0	0	0	0	0
Swelling/induration	0	0	0	0	0	0
Local (after second dose)						
	N = 1203	N = 1172	N = 981	N = 950	N = 222	N = 222
All events	63 (5.2)	1 (<0.1)	60 (6.1)	1 (0.1)	3 (1.4)	0
Pain	11 (0.9)	0	11 (1.1)	0	0	0
Tenderness	49 (4.1)	1 (<0.1)	47 (4.8)	1 (0.1)	2 (0.9)	0
Erythema	11 (0.9)	0	11 (1.1)	0	0	0
Swelling/induration	5 (0.4)	0	4 (0.4)	0	1 (0.5)	0
Systemic (after first dose)						
	N = 1281[a)]	N = 1273[b)]	N = 1056[c)]	N = 1037[d)]	N = 225[e)]	N = 236[f)]
All events	19 (1.5)	17 (1.3)	18 (1.7)	14 (1.4)	1 (0.4)	3 (1.3)
Nausea/vomiting	1 (<0.1)	0	1 (<0.1)	0	0	0
Headache	7 (0.5)	3 (0.2)	6 (0.6)	3 (0.3)	1 (0.4)	0
Fatigue	7 (0.5)	6 (0.5)	7 (0.7)	4 (0.4)	0	2 (0.8)
Malaise	5 (0.4)	4 (0.3)	5 (0.5)	3 (0.3)	0	1 (0.4)
Myalgia	2 (0.2)	4 (0.3)	2 (0.2)	4 (0.4)	0	0
Arthralgia	1 (<0.1)	2 (0.2)	1 (<0.1)	1 (<0.1)	0	1 (0.4)
Pyrexia	6 (0.5)	2 (0.2)	6 (0.6)	1 (<0.1)	0	1 (0.4)
Systemic (after second dose)						
	N = 1198[g)]	N = 1164[h)]	N = 977[i)]	N = 945[j)]	N = 221[k)]	N = 219[l)]
All events	83 (6.9)	16 (1.4)	80 (8.2)	13 (1.4)	3 (1.4)	3 (1.4)
Nausea/vomiting	1 (<0.1)	0	1 (0.1)	0	0	0
Headache	17 (1.4)	3 (0.3)	17 (1.7)	2 (0.2)	0	1 (0.5)
Fatigue	43 (3.6)	9 (0.8)	42 (4.3)	8 (0.8)	1 (0.5)	1 (0.5)
Malaise	34 (2.8)	7 (0.6)	34 (3.5)	5 (0.5)	0	2 (0.9)
Myalgia	34 (2.8)	3 (0.3)	33 (3.4)	3 (0.3)	1 (0.5)	0
Arthralgia	24 (2.0)	2 (0.2)	23 (2.4)	2 (0.2)	1 (0.5)	0
Pyrexia	8 (0.7)	2 (0.2)	7 (0.7)	1 (0.1)	1 (0.5)	1 (0.5)

N = Number of subjects analyzed, n = number of subjects with events
Definition of grade: The standard toxicity grade classification of the U.S. FDA was applied, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."
a) Headache, N = 1280, Pyrexia, N = 1230; b) Pyrexia, N = 1233; c) Headache, N = 1055, Pyrexia, N = 1014; d) Pyrexia, N = 1006; e) Pyrexia, N = 216; f) Pyrexia, N = 227; g) Pyrexia, N = 1152; h) Pyrexia, N = 1123; i) Pyrexia, N = 942; j) Pyrexia, N = 910; k) Pyrexia, N = 210; l) Pyrexia, N = 213

(c) Study 1501

Table 51 shows the incidences of adverse events. Adverse events in the Nuvaxovid group occurred more frequently after the second dose than after the first dose.

Table 51. Summary of the incidences of adverse events in Japanese Study 1501 (safety analysis set)

	After first dose		After second dose	
Study vaccine	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)
The number of subjects studied	150	50	150	49
Death	0	0	0	0
Serious adverse events	0	0	0	0
Solicited local adverse events	76 (50.7)	3 (6.0)	103 (68.7)	2 (4.1)
Grade ≥3	0	0	15 (10.0)	0
Solicited systemic adverse events	44 (29.3)	6 (12.0)	75 (50.0)	6 (12.2)
Grade ≥3	1 (0.7)	0	8 (5.3)	0
Unsolicited adverse events	15 (10.0)	4 (8.0)	44 (29.3)	6 (12.2)
Grade ≥3	0	0	0	0
Unsolicited adverse reactions	7 (4.7)	2 (4.0)	34 (22.7)	1 (2.0)

n = number of subjects with events
Definition of grade: The standard toxicity grade classification of the U.S. FDA was partially modified, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

In the Nuvaxovid group, the median time (range) to the onset of solicited local adverse events was 0 days (0 to 2 days) after vaccination, and the median duration (range) was 2 days (0 to 9 days) after vaccination. In the Nuvaxovid group, the median time (range) to the onset of solicited systemic adverse events was 1 day (0 to 6 days) after vaccination, and the median duration (range) was 1 day (0 to 12 days) after vaccination.

Grade ≥3 solicited local adverse events were observed in 15 of 150 subjects (10.0%) in the Nuvaxovid group. They were tenderness in 9 subjects, erythema/redness in 3, injection site pain in 2, and induration and swelling in 1 each. All of them occurred after the second dose. Grade ≥3 solicited systemic adverse events were observed in 1 of 150 subjects (0.7%) after the first dose in the Nuvaxovid group. They were fatigue and malaise in 1 subject each. After the second dose, Grade ≥3 solicited systemic adverse events were observed in 8 of 150 subjects (5.3%) in the Nuvaxovid group. They were fatigue and malaise in 6 subjects each, headache in 4, myalgia and arthralgia in 2 each, and pyrexia in 1. No Grade ≥3 events were observed in the placebo group.

Main unsolicited adverse events:

- Injection site pruritus (5 subjects [3.3%]), diarrhoea (3 [2.0%]), injection site swelling (2 [1.3%]), and nasopharyngitis (2 [1.3%]) until Day 21 after the first dose.
- Injection site pruritus (24 subjects [16.0%]), chills (5 [3.3%]), injection site warmth (3 [2.0%]), and nasopharyngitis (3 [2.0%]) until Day 28 after the second dose.

The outcome of all of these events was "resolved." All of the unsolicited adverse events were mild or moderate in severity.

(d) Adverse events in subpopulations

In Studies 301 and 302, the incidences of solicited adverse events and Grade ≥3 solicited adverse events were lower in the elderly subjects than in non-elderly subjects (Tables 52 and 53).

In the Japanese Study 1501, the overall incidence of adverse events tended to be lower in the elderly subjects (≥65 years old) than in non-elderly subjects (20 to 64 years old) (Table 17). In the Nuvaxovid group, solicited adverse events occurring at least twice more frequently in non-elderly subjects than in

elderly subjects were fatigue (35.0% in non-elderly, 8.0% in elderly; the same order applies hereinafter), malaise (42.0%, 16.0%), arthralgia (21.0%, 6.0%), and headache (33.0%, 16.0%). No solicited adverse events occurred at least twice more frequently in elderly subjects than in non-elderly subjects. There was no significant difference either in the types or the incidence of unsolicited adverse events between elderly and non-elderly subjects.

The incidences of solicited adverse events by sex were as follows. In Study 301, the incidence of solicited adverse events and the incidence of Grade ≥3 solicited adverse events were lower in male subjects than in female subjects, both in the Nuvaxovid and placebo groups (Tables 52 and 53). Results of Study 302 showed a similar tendency of sex difference. The observed difference is not considered to suggest sex difference in adverse reactions caused by Nuvaxovid, for the following reasons: (a) A similar tendency was observed in the placebo group as well. (b) Since adverse events were assessed based on spontaneous reports from subjects, they were prone to be affected by both biological and behavioral factors. (c) In clinical studies of vaccines, spontaneous reports of adverse events tend to be submitted more often by women than by men (*Vaccine*. 2017;35:2600-04).

Table 52. Incidences of solicited adverse events by subpopulation

(Study 301, safety analysis set)

		Dose No.	All grades		Grade ≥3	
			Nuvaxovid n/N (%)	Placebo n/N (%)	Nuvaxovid n/N (%)	Placebo n/N (%)
Solicited local adverse events						
Entire population		1	10475/18072 (58.0)	1881/8904 (21.1)	198/18072 (1.1)	23/8904 (0.3)
		2	13525/17139 (78.9)	1797/8278 (21.7)	1147/17139 (6.7)	26/8278 (0.3)
Age	18 to 64	1	9624/15852 (60.7)	1704/7806 (21.8)	184/15852 (1.2)	20/7806 (0.3)
		2	12269/15119 (81.1)	1637/7314 (22.4)	1090/15119 (7.2)	23/7314 (0.3)
	≥65	1	851/2220 (38.3)	177/1098 (16.1)	14/2220 (0.6)	3//1098 (0.3)
		2	1256/2020 (62.2)	160/964 (16.6)	57/2020 (2.8)	3/964 (0.3)
Sex	Male	1	5027/9447 (53.2)	800/4510 (17.7)	59/9447 (0.6)	6/4510 (0.1)
		2	6609/8926 (74.0)	779/4188 (18.6)	405/8926 (4.5)	7/4188 (0.2)
	Female	1	5448/8625 (63.2)	1081/4394 (24.6)	139/8625 (1.6)	17/4394 (0.4)
		2	6916/8213 (84.2)	1018/4090 (24.9)	742/8213 (9.0)	19/4090 (0.5)
Solicited systemic adverse events						
Entire population		1	8614/18072 (47.7)	3562/8904 (40.0)	439/18072 (2.4)	188/8904 (2.1)
		2	11906/17139 (69.5)	2969/8278 (35.9)	2077/17139 (12.1)	170/8278 (2.1)
Age	18 to 64	1	7890/15852 (49.8)	3217/7806 (41.2)	401/15852 (2.5)	177/7806 (2.3)
		2	10923/15119 (72.3)	2701/7314 (36.9)	1987/15119 (13.1)	155/7314 (2.1)
	≥65	1	724/2220 (32.6)	345/1098 (31.4)	38/2220 (1.7)	11/1098 (1.0)
		2	983/2020 (48.7)	268/964 (27.8)	90/2020 (4.5)	15/964 (1.6)
Sex	Male	1	4013/9447 (42.5)	1620/4510 (35.9)	164/9447 (1.7)	54/4510 (1.2)
		2	5818/8926 (65.2)	1295/4188 (30.9)	893/8926 (10.0)	55/4188 (1.3)
	Female	1	4601/8625 (53.3)	1942/4394 (44.2)	275/8625 (3.2)	134/4394 (3.0)
		2	6088/8213 (74.1)	1674/4090 (40.9)	1184/8213 (14.4)	115/4090 (2.8)

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

Definition of grade: The standard toxicity grade classification of the U.S. FDA was applied, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

Table 53. Incidences of solicited adverse events by subpopulation
(Study 302, solicited adverse event analysis set)

		Dose No.	All grades		Grade ≥3	
			Nuvaxovid n/N (%)	Placebo n/N (%)	Nuvaxovid n/N (%)	Placebo n/N (%)
Solicited local adverse events						
Entire population		1	762/1285 (59.3)	266/1272 (20.9)	14/1285 (1.1)	2/1272 (0.2)
		2	965/1203 (80.2)	199/1172 (17.0)	63/1203 (5.2)	1/1172 (<0.1)
Age	18 to 64	1	683/1060 (64.4)	244/1037 (23.5)	14/1060 (1.3)	2/1037 (0.2)
		2	823/981 (83.9)	179/950 (18.8)	60/981 (6.1)	1/950 (0.1)
	65 to 84	1	79/225 (35.1)	22/235 (9.4)	0/225 (0)	0/235 (0)
		2	142/222 (64.0)	20/222 (9.0)	3/222 (1.4)	0/222 (0)
Sex	Male	1	342/624 (54.8)	122/634 (19.2)	5/624 (0.8)	1/634 (0.2)
		2	429/570 (75.3)	77/571 (13.5)	23/570 (4.0)	1/571 (0.2)
	Female	1	420/661 (63.5)	144/638 (22.6)	9/661 (1.4)	1/638 (0.2)
		2	536/633 (84.7)	122/601 (20.3)	40/633 (6.3)	0/601 (0)
Solicited systemic adverse events						
Entire population		1	610/1281 (47.6)	482/1273 (37.9)	19/1281 (1.5)	17/1273 (1.3)
		2	774/1198 (64.6)	359/1164 (30.8)	83/1198 (6.9)	16/1164 (1.4)
Age	18 to 64	1	545/1056 (51.6)	423/1037 (40.8)	18/1056 (1.7)	14/1037 (1.4)
		2	666/977 (68.2)	311/945 (32.9)	80/977 (8.2)	13/945 (1.4)
	65 to 84	1	65/225 (28.9)	59/236 (25.0)	1/225 (0.4)	3/236 (1.3)
		2	108/221 (48.9)	48/219 (21.9)	3/221 (1.4)	3/219 (1.4)
Sex	Male	1	288/622 (46.3)	217/637 (34.1)	8/622 (1.3)	4/637 (0.6)
		2	342/567 (60.3)	157/570 (27.5)	28/567 (4.9)	6/570 (1.1)
	Female	1	322/659 (48.9)	265/636 (41.7)	11/659 (1.7)	13/636 (2.0)
		2	432/631 (68.5)	202/594 (34.0)	55/631 (8.7)	10/594 (1.7)

N = Number of subjects analyzed, n = number of subjects with events
Definition of grade: The standard toxicity grade classification of the U.S. FDA was applied, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

(e) Serious adverse events and adverse reactions

In Study 301, the incidences of deaths, serious adverse events, and adverse events that led to cancellation of the second dose of the study vaccine were as follows:

Before the data cut-off point, death occurred in 9 subjects in the Nuvaxovid group and in 5 subjects in the placebo group. These deaths were considered unrelated to the study vaccination, except the death (caused by myocardial infarction) in 1 subject in the placebo group.

During the period between the first dose and the data cut-off point or the start of blinded crossover period, serious adverse events related to the study vaccination occurred in 5 subjects (<0.1%) in the

Nuvaxovid group and in 5 subjects (0.1%) in the placebo group. Except peroneal nerve palsy, the events in the 5 subjects in the Nuvaxovid group resolved or were resolving before the data cut-off point or the start of blinded cross over period.

During the period between the first dose and the data cut-off point or the start of blinded crossover period, adverse events resulting in discontinuation of the study vaccination occurred in 0.3% (57 of 19,729) of subjects in the Nuvaxovid group and in 0.2% (16 of 9,853) of subjects in the placebo group. Among them, those considered related to the study vaccination were observed in 14 subjects in the Nuvaxovid group (fatigue in 3 subjects, headache in 2, blood pressure increased/dizziness/sinus bradycardia, angioedema/urticaria, diarrhoea, myalgia, chest pain, musculoskeletal stiffness, lymphadenopathy, injection site pruritus, and somnolence in 1 each) and in 2 subjects in the placebo group (myocardial infarction and seizure in 1 subject each). All events were nonserious, except angioedema in the Nuvaxovid group and myocardial infarction in the placebo group. Also, all events resolved, except musculoskeletal stiffness in the Nuvaxovid group and myocardial infarction in the placebo group.

In Study 302, the incidences of deaths, serious adverse events, and adverse events that led to cancellation of the second dose of the study vaccine were as follows:

During the study period, death occurred in 2 subjects in the Nuvaxovid group and in 1 subject in the placebo group. Causal relationship to the study vaccination was ruled out for all deaths.

Myocarditis in 1 subject in the Nuvaxovid group was identified as a study vaccination-related serious adverse event. The subject was a male between 10 and 19 years old with no medical history. On Day 3 after the second dose, he was hospitalized because of severe chest pain, light headedness, breath shortness, and an increased troponin level. He was discharged without treatment on Day 6 after the second dose. The outcome was “resolved.” A causal relationship between this event and the study vaccination was not ruled out by the investigator, but the independent monitoring committee reviewed the case and ruled out the relationship, concluding that the event was probably due to viral infection, as suggested by the clinical course of the subject.

Adverse events leading to discontinuation of the study vaccination occurred in 0.4% (30) of subjects in the Nuvaxovid group and in 0.3% (23) of subjects in the placebo group. Among them, those considered related to the study vaccination were observed in 11 subjects in the Nuvaxovid group (headache/gastroenteritis/insomnia/dizziness, myalgia/pyrexia/headache/injection site pain, chills and pain/injection site pain, myalgia, pelvic pain, paraesthesia, rash pruritic, pain in extremity, vaccination site inflammation, rales, and urticaria in 1 subject each) and in 9 subjects in the placebo group (muscular weakness/arthralgia/back pain, arthropathy, systemic inflammatory response syndrome, limb mass, dyspnoea, rash erythematous, pityriasis rosea, nausea, and polyarthritis in 1 subject each). All of them were mild or moderate in severity. All events resolved, except rales in the Nuvaxovid group and arthropathy and dyspnoea in the placebo group.

In the Japanese Study 1501, no death occurred up to the data cut-off date. There was no serious adverse event for which causal relationship to the study vaccination could not be ruled out. There was an event (tinnitus) leading to the cancellation of the second dose. The event was mild in severity and considered related to the study vaccination, with the outcome of "resolved."

In Study 101, no death occurred during the study period. Serious adverse events considered related to the study vaccination were multiple sclerosis in 1 subject (placebo group) and colitis in 1 subject (single-dose Nuvaxovid group) in Part 2. The outcome at the data cut-off point was "not resolved" for multiple sclerosis and "resolving" for colitis. Adverse events leading to discontinuation of study vaccination occurred in 1 subject in Part 1 and in 13 subjects in Part 2. Among them, those considered related to the study vaccination were multiple sclerosis in 1 subject (placebo group), colitis in 1 subject (single-dose Nuvaxovid group), and pyrexia/myalgia/malaise in 1 subject (SARS-CoV-2 rS 25 μg + Matrix-M group) in Part 2. The subjects who experienced multiple sclerosis and colitis were the same subjects who had serious adverse events for which causal relationship to the study vaccination could not be ruled out. The outcome in 1 subject of the SARS-CoV-2 rS 25 μg + Matrix-M group was "resolved."

In Study 501, death occurred in 4 subjects (2 in the Nuvaxovid group, 2 in the placebo group) at the data cut-off point, including 3 subjects who showed worsening symptoms after SARS-CoV-2 infection. The deaths were considered unrelated to the study vaccination. The cause of death in 1 subject in the Nuvaxovid group was unknown, but its causal relationship with the study vaccination was ruled out because of the long interval between the second dose and the death. There were no serious adverse events for which causal relationship to the study vaccination could not be ruled out or adverse events leading to discontinuation of vaccination.

(f) Adverse events of special interest

As AESIs, potential immune-mediated events (Table 60) and adverse events unique to COVID-19 (Table 61) were evaluated. In Studies 302, 101, and 501, adverse events unique to COVID-19 were classified as "COVID-19-related adverse events of special interest" (Table 62) in the clinical study protocol.

In Study 301, potential immune-mediated events specified in the clinical study protocol were observed in 0.12% of subjects in each group (23 of 19,729 in the Nuvaxovid group, 12 of 9,853 in the placebo group) between the first dose and the data cut-off point or the start of blinded crossover period. The following events occurred more frequently in the Nuvaxovid group than in the placebo group and were experienced by ≥2 subjects in the Nuvaxovid group: Basedow's disease, alopecia areata, and psoriasis (in 2 subjects each). In Study 302, potential immune-mediated events occurred in <0.1% of subjects (5 of 7,569) in the Nuvaxovid group and in 0.1% (8 of 7,570) of subjects in the placebo group, showing a similar incidence between the 2 groups. There were no events experienced by ≥2 subjects. In Study 101, no potential immune-mediated events occurred in the active vaccine groups, but multiple sclerosis occurred in 1 subject in the placebo group. In Study 501, a potential immune-mediated event occurred in 1 subject (COVID-19) in the placebo group by the data cut-off point. No potential immune-mediated event was observed in the Japanese Study 1501.

In Study 301, the incidence of events unique to COVID-19 was <0.1% both in the Nuvaxovid group and in the placebo group. Events with a higher incidence in the Nuvaxovid group than in the placebo group were myocarditis, sinus tachycardia, and Raynaud's phenomenon occurring in 1 subject each of the Nuvaxovid group. In Study 302, events unique to COVID-19 were observed in 0.1% (8 of 7,569) of subjects in the Nuvaxovid group and in 0.3% (23 of 7,570) of subjects in the placebo group. There were no events with a higher incidence in the Nuvaxovid group than in the placebo group. In Study 501, events unique to COVID-19 were observed in 0.5% (11) of subjects in the Nuvaxovid group and in 0.6% (14) of subjects in the placebo group between the first dose and Day 28 after the second dose. The incidence of events observed in ≥2 subjects in both groups (anosmia, ageusia, etc.) was similar between the two groups. No events unique to COVID-19 were observed in the Japanese Study 1501 and in Study 101.

As described in the above (a) through (f), 2-dose vaccination with Nuvaxovid is well-tolerated with no serious safety concerns, as shown by (1) the incidences of adverse events in the Japanese and foreign clinical studies and (2) the low incidence of death and serious adverse events, most of which were considered unrelated to Nuvaxovid.

PMDA's view:
The submitted results of the Japanese and foreign clinical studies showed that solicited local and systemic adverse events were observed in many subjects, particularly after the second dose, but most of them were mild or moderate and resolved. In addition, given the incidences of other adverse events, serious adverse events, and adverse events by age group, etc., there are so far no serious concerns affecting the approval of the primary series of Nuvaxovid.

However, the following findings are important information for recipients of Nuvaxovid, and therefore should be provided to the healthcare professionals and vaccine recipients in an appropriate manner: (a) Grade ≥3 solicited adverse events affecting the daily living were observed. (b) Some events occurred more frequently after the second dose than after the first dose.

Since there are no sufficient data on the long-term safety after vaccination with Nuvaxovid, information should be collected continuously after the market launch.

7.R.3.2 Safety in populations with specific baseline characteristics

7.R.3.2.1 Subjects with underlying disease

Tables 54 and 55 show the incidences of solicited adverse events, classified by underlying disease or condition in Studies 301 and 302.

Table 54. Incidences of solicited adverse events by underlying disease or condition (Study 301, safety analysis set)

	Dose No.	All grades n/N (%)		Grade ≥3 n/N (%)	
		Nuvaxovid	Placebo	Nuvaxovid	Placebo
Solicited local adverse events					
Entire population	1	10475/18072 (58.0)	1881/8904 (21.1)	198/18072 (1.1)	23/8904 (0.3)
	2	13525/17139 (78.9)	1797/8278 (21.7)	1147/17139 (6.7)	26/8278 (0.3)
Obesity (BMI ≥30 kg/m^2)	1	3306/6728 (49.1)	697/3371 (20.7)	70/6728 (1.0)	9/3371 (0.3)
	2	4588/6393 (71.8)	661/3120 (21.2)	303/6393 (4.7)	12/3120 (0.4)
Chronic pulmonary disease	1	1498/2561 (58.5)	317/1330 (23.8)	39/2561 (1.5)	1/1330 (0.1)
	2	1881/2400 (78.4)	311/1225 (25.4)	195/2400 (8.1)	3/1225 (0.2)
Chronic renal disease	1	51/120 (42.5)	15/52 (28.8)	2/120 (1.7)	0/52 (0)
	2	74/113 (65.5)	11/50 (22.0)	4/113 (3.5)	0/50 (0)
Cardiovascular disease	1	82/203 (40.4)	16/112 (14.3)	1/203 (0.5)	0/112 (0)
	2	113/186 (60.8)	15/105 (14.3)	0/186 (0)	0/105 (0)
Type 2 diabetes mellitus	1	583/1369 (42.6)	124/721 (17.2)	8/1369 (0.6)	3/721 (0.4)
	2	754/1279 (59.0)	109/677 (16.1)	38/1279 (3.0)	2/677 (0.3)
Solicited systemic adverse events					
Entire population	1	8614/18072 (47.7)	3562/8904 (40.0)	439/18072 (2.4)	188/8904 (2.1)
	2	11906/17139 (69.5)	2969/8278 (35.9)	2077/17139 (12.1)	170/8278 (2.1)
Obesity (BMI ≥30 kg/m^2)	1	3088/6728 (45.9)	1377/3371 (40.8)	172/6728 (2.6)	84/3371 (2.5)
	2	3922/6393 (61.3)	1093/3120 (35.0)	477/6393 (7.5)	45/1330 (3.4)
Chronic pulmonary disease	1	1368/2561 (53.4)	596/1330 (44.8)	92/2561 (3.6)	45/1330 (3.4)
	2	1670/2400 (69.6)	524/1225 (42.8)	337/2400 (14.0)	43/1225 (3.5)
Chronic renal disease	1	48/120 (40.0)	23/52 (44.2)	4/120 (3.3)	1/52 (1.9)
	2	61/113 (54.0)	14/50 (28.0)	6/113 (5.3)	1/50 (2.0)
Cardiovascular disease	1	69/203 (34.0)	33/112 (29.5)	4/203 (2.0)	3/112 (2.7)
	2	89/186 (47.8)	31/105 (29.5)	8/186 (4.3)	2/105 (1.9)
Type 2 diabetes mellitus	1	503/1369 (36.7)	254/721 (35.2)	33/1369 (2.4)	10/721 (1.4)
	2	586/1279 (45.8)	196/677 (29.0)	54/1279 (4.2)	11/677 (1.6)

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

Definition of grade: The standard toxicity grade classification of the U.S. FDA was applied, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

Table 55. Incidences of solicited adverse events by underlying disease or condition (Study 302, solicited adverse event analysis set)

	Dose No.	All Grades n/N (%)		Grade ≥3 n/N (%)	
		Nuvaxovid	Placebo	Nuvaxovid	Placebo
Solicited local adverse events					
Entire population	1	762/1285 (59.3)	266/1272 (20.9)	14/1285 (1.1)	2/1272 (0.2)
	2	965/1203 (80.2)	199/1172 (17.0)	63/1203 (5.2)	1/1172 (<0.1)
Obesity (BMI ≥30 kg/m^2)	1	175/335 (52.2)	84/312 (26.9)	4/335 (1.2)	0/312 (0)
	2	246/323 (76.2)	59/293 (20.1)	14/323 (4.3)	1/293 (0.3)
Respiratory disease	1	88/156 (56.4)	32/157 (20.4)	0/156 (0)	0/157 (0)
	2	116/142 (81.7)	25/145 (17.2)	7/142 (4.9)	0/145 (0)
Heart disease	1	3/13 (23.1)	0/15 (0)	0/13 (0)	0/15 (0)
	2	6/13 (46.2)	1/15 (6.7)	0/13 (0)	0/15 (0)
Vascular disease	1	68/161 (42.2)	19/147 (12.9)	1/161 (0.6)	0/147 (0)
	2	97/158 (61.4)	22/147 (15.0)	3/158 (1.9)	0/147 (0)
Metabolic disease	1	27/62 (43.5)	9/45 (20.0)	0/62 (0)	0/45 (0)
	2	44/60 (73.3)	5/46 (10.9)	1/60 (1.7)	0/46 (0)
Solicited systemic adverse events					
Entire population	1	610/1281 (47.6)	482/1273 (37.9)	19/1281 (1.5)	17/1273 (1.3)
	2	774/1198 (64.6)	359/1164 (30.8)	83/1198 (6.9)	16/1164 (1.4)
Obesity (BMI ≥30 kg/m^2)	1	176/334 (52.7)	142/314 (45.2)	10/343 (3.0)	10/314 (3.2)
	2	202/323 (62.5)	98/290 (33.8)	16/323 (5.0)	5/290 (1.7)
Respiratory disease	1	82/154 (53.2)	54/157 (34.4)	5/154 (3.2)	3/157 (1.9)
	2	92/141 (65.2)	53/142 (37.3)	12/141 (8.5)	1/142 (0.7)
Heart disease	1	3/13 (23.1)	4/15 (26.7)	0/13 (0)	0/15 (0)
	2	2/13 (15.4)	3/15 (20.0)	0/13 (0)	0/15 (0)
Vascular disease	1	56/161 (34.8)	41/148 (27.7)	2/161 (1.2)	2/148 (1.4)
	2	72/157 (45.9)	39/144 (27.1)	5/157 (3.2)	0/144 (0)
Metabolic disease	1	27/62 (43.5)	16/45 (35.6)	0/62 (0)	1/45 (2.2)
	2	28/60 (46.7)	15/46 (32.6)	2/60 (3.3)	0/46 (0)

N = Number of subjects analyzed, n = number of subjects with events
Definition of grade: The standard toxicity grade classification of the U.S. FDA was applied, using "Department of Health and Human Services Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

The incidences of solicited adverse events and Grade ≥3 solicited adverse events tended to be higher in the population with chronic pulmonary or respiratory disease than in the population with other diseases or conditions. Despite this observation, the incidence observed in subjects with chronic pulmonary or respiratory disease was similar to that observed in the entire population, suggesting that Nuvaxovid does not pose any greater risk on the population with chronic pulmonary or respiratory disease.

PMDA's view:
PMDA confirmed that Nuvaxovid does not pose any particular safety concern for subjects with underlying disease or condition compared with the entire population. Compared with limited range of underlying diseases or conditions in subjects enrolled in clinical studies, however, Nuvaxovid is expected to be used in people with various underlying diseases after the market launch. Accordingly, it is necessary to collect safety information in vaccine recipients with a wide range of underlying diseases and conditions, including the above underlying diseases, and to take appropriate measures.

7.R.3.2.2 Pregnant and lactating women

According to the safety database at the data cut-off date of October 26, 2021, a total of 137 cases (95 in the Nuvaxovid group, 42 in the placebo group) of pregnancy were reported after vaccination with Nuvaxovid in clinical studies (Table 56).

The outcome of 95 pregnant cases reported in the Nuvaxovid group was birth in 8 subjects, pregnancy termination in 11, spontaneous abortion in 16, continued pregnancy in 55, and unknown in 5. No fetal death or stillbirth was reported in the clinical studies of Nuvaxovid. There are no safety data of Nuvaxovid administered to lactating women.

Table 56. Outcome of subjects with reported pregnancy

	Subjects vaccinated with Nuvaxovid [a)]				Subjects receiving only placebo
	Total	Vaccinated >30 days before the last menstrual period	Vaccinated during fertile period ≥30 days before the last menstrual period	Last menstrual period unknown	
Total number of pregnancies	95	48	34	13	42
Outcome of pregnancy, n (%)					
Birth	8 (8.4)	1 (2.1)	6 (17.6)	1 (7.7)	13 (31.0)
Pregnancy termination	11 (11.6)	5 (10.4)	4 (11.8)	2 (15.4)	5 (11.9)
Spontaneous abortion	16 (16.8)	7 (14.6)	7 (20.6)	2 (15.4)	4 (9.5)
Fetal death/abortion	0	0	0	0	0
Ectopic pregnancy	0	0	0	0	1 (2.4)
Continued pregnancy	55 (57.9)	34 (70.8)	15 (44.1)	6 (46.2)	18 (42.9)
Unknown	5 (5.3)	1 (2.1)	2 (5.9)	2 (15.4)	1 (2.4)

n = number of subjects with events
a) Includes subjects receiving Nuvaxovid only and those receiving both Nuvaxovid and placebo.

Neither the reproductive toxicity studies nor clinical studies of Nuvaxovid have revealed any particular safety concerns associated with Nuvaxovid in pregnant or lactating women. When pregnant women are infected with SARS-CoV-2, there is a higher risk of severe COVID-19 and premature delivery (*MMWR Morb Mortal Wkly Rep*. 2020;69:1635-40, *MMWR Morb Mortal Wkly Rep*. 2020;69:1641-47). The package insert should therefore include a precautionary statement that pregnant or possibly pregnant women should receive Nuvaxovid only if its benefits outweigh the risk.

The risk management plan of Nuvaxovid will define the administration to pregnant women and lactating women as important missing information. When information on administration to pregnant women is obtained after the market launch, follow-up study and evaluation will be conducted appropriately, and necessity of additional safety measures will be investigated. An observational study in registered pregnant women and their offspring is planned in Europe.

PMDA accepted the applicant's explanation.

7.R.3.3 Other

7.R.3.3.1 Risk of Nuvaxovid-associated enhanced disease

The applicant's explanation:

Nuvaxovid has been administered to approximately 50,000 people in the clinical studies of Nuvaxovid in Japan and foreign countries, but there have been no cases of vaccine-associated enhanced respiratory disease (VAERD). As a result of the review by the safety monitoring committee in foreign clinical studies, no VAERD-related concerns were raised in any of the studies. Also, no severe COVID-19 was observed in subjects in the Nuvaxovid group at the time of the final efficacy analysis on Studies 301 and 302. In Part 1 and Part 2 of Study 101, cellular immune response of cytokines secreted by Th1 and Th2 cells was evaluated. Results showed Th1-dominant immune response as

observed in nonclinical studies [see Section 3.1.1.2], suggesting that the risk of Nuvaxovid-associated enhanced disease is low.

Thus, it is considered unnecessary to raise caution against VAERD in the package insert, etc. In the risk management plan of Nuvaxovid, vaccine-associated enhanced disease (VAED) including VAERD will be defined as an important potential risk, and necessity of caution will be investigated depending on the incidences of VAED after the market launch. Also, information on the risk of VAED will be provided to healthcare professionals through the guide for proper use for healthcare professionals

PMDA accepted the explanation of the applicant. The applicant should continue to collect information on Nuvaxovid-associated enhanced disease after the market launch. When new information becomes available, the applicant should promptly discuss actions to be taken and disseminate the information.

7.R.3.3.2 Co-administration of Nuvaxovid with a seasonal influenza vaccine

The applicant's explanation:

In Study 302, a substudy was conducted involving approximately the first 400 subjects enrolled to evaluate the safety and immunogenicity of co-administration of Nuvaxovid with a seasonal influenza vaccine. In total, 431 subjects (217 in the Nuvaxovid group, 214 in the placebo group) were randomized in the substudy. For the first dose, Nuvaxovid or placebo was administered to one arm and a seasonal influenza vaccine (approved overseas) to the deltoid muscle of the other arm. (Subjects 18 to 64 years old received a quadrivalent influenza vaccine, and subjects ≥65 years old received an adjuvanted trivalent influenza vaccine.)

In the safety analysis set of the subset population receiving co-administration of Nuvaxovid with a seasonal influenza vaccine, the incidence of solicited local adverse events was 70.1% in the Nuvaxovid group and 39.4% in the placebo group after the first dose and 85.0% in the Nuvaxovid group and 21.6% in the placebo group after the second dose; and the incidence of solicited systemic adverse events was 60.1% in the Nuvaxovid group and 47.2% in the placebo group after the first dose and 69.7% in the Nuvaxovid group and 37.9% in the placebo group after the second dose. In both the Nuvaxovid and placebo groups, adverse events occurred more frequently in subjects receiving the co-administration than in subjects receiving Nuvaxovid alone. Yet the co-administration was well tolerated, and its safety profile was similar to that observed in the main study (Table 57).

The immunogenicity of co-administration of Nuvaxovid with a seasonal influenza vaccine was evaluated in the following subject population:

> Among the subjects in the PP immunogenicity analysis set, 359 subjects (178 in the Nuvaxovid group, 181 in the placebo group) who were measured for specific IgG antibody titer against SARS-CoV-2 rS protein by ELISA before receiving the vaccines and provided a serum sample between Day 14 and 28 after the second dose (handled as "a serum sample on Day 14 after the second dose").

In this subject population, the specific IgG antibody titer (GMT) [2-sided 95%CI] against SARS-CoV-2 rS protein on Day 14 after the second dose was 31,236.1 [26,295.5, 37,104.9] EU/mL in

the Nuvaxovid group and 115.7 [106.1, 126.1] EU/mL in the placebo group. The antibody titer in the Nuvaxovid group was approximately 30% lower than the titer observed in the main study of Study 302 (44,678.3 [40,352.2, 49,468.2] EU/mL in the Nuvaxovid group, 113.2 [106.8, 120.0] EU/mL in the placebo group), but was much higher than the titer in the placebo group. Also, the seroconversion rate [2-sided 95% CI] in the Nuvaxovid group was 97.8% [94.3%, 99.4%], which was similar to that observed in the main study (99.0% [97.5%, 99.7%]. Neutralizing antibody titer against SARS-CoV-2 was not measured in the substudy. The hemagglutinin-inhibiting antibody titer induced by the seasonal influenza vaccine was evaluated on Day 21 after the first dose. Results showed no marked difference between the Nuvaxovid group and the placebo group.

Table 57. Incidences of solicited adverse events in subjects with or without co-administration of a seasonal influenza vaccine (Study 302, solicited adverse event analysis set)

	Without co-administration of influenza virus vaccine		With co-administration of influenza virus vaccine	
	Nuvaxovid n (%)	Placebo n (%)	Nuvaxovid n (%)	Placebo n (%)
Local (after first dose)				
	N = 1111	N = 1092	N = 174	N = 180
All events	640 (57.6)	195 (17.9)	122 (70.1)	71 (39.4)
Injection site pain	325 (29.3)	100 (9.2)	69 (39.7)	30 (16.7)
Tenderness	592 (53.3)	156 (14.3)	113 (64.9)	67 (37.2)
Erythema/redness	23 (2.1)	3 (0.3)	2 (1.1)	2 (1.1)
Swelling/induration	10 (0.9)	6 (0.5)	2 (1.1)	0
Local (after second dose)				
	N = 1070	N = 1047	N = 133	N = 125
All events	852 (79.6)	172 (16.4)	113 (85.0)	27 (21.6)
Injection site pain	548 (51.2)	93 (8.9)	76 (57.1)	14 (11.2)
Tenderness	817 (76.4)	139 (13.3)	105 (78.9)	25 (20.0)
Erythema/redness	85 (7.9)	2 (0.2)	15 (11.3)	0
Swelling/induration	75 (7.0)	4 (0.4)	14 (10.5)	0
Systemic (after first dose)				
	N = 1108 [a)]	N = 1093 [b)]	N = 173 [c)]	N = 180 [d)]
All events	506 (45.7)	397 (36.3)	104 (60.1)	85 (47.2)
Nausea/vomiting	58 (5.2)	57 (5.2)	9 (5.2)	12 (6.7)
Headache	271 (24.5)	235 (21.5)	43 (24.9)	39 (21.7)
Fatigue	215 (19.4)	192 (17.6)	48 (27.7)	52 (28.9)
Malaise	124 (11.2)	93 (8.4)	25 (14.5)	30 (16.7)
Myalgia	237 (21.4)	145 (13.3)	49 (28.3)	36 (20.0)
Arthralgia	71 (6.4)	60 (5.5)	13 (7.5)	3 (1.7)
Pyrexia	21 (2.0)	16 (1.5)	7 (4.3)	3 (1.7)
Systemic (after second dose)				
	N = 1066 [e)]	N = 1040 [f)]	N = 132 [g)]	N = 124 [h)]
All events	682 (64.0)	312 (30.0)	92 (69.7)	47 (37.9)
Nausea/vomiting	114 (10.7)	38 (3.7)	14 (10.6)	6 (4.8)
Headache	426 (40.0)	185 (17.8)	61 (46.2)	23 (18.5)
Fatigue	430 (40.3)	162 (15.6)	61 (46.2)	32 (25.8)
Malaise	321 (30.1)	87 (8.4)	56 (42.4)	20 (16.1)
Myalgia	430 (40.3)	99 (9.5)	62 (47.0)	14 (11.3)
Arthralgia	182 (17.1)	54 (5.2)	23 (17.4)	5 (4.0)
Pyrexia	49 (4.8)	9 (0.9)	10 (8.3)	0

N = Number of subjects analyzed, n = number of subjects with events
a) Headache, N = 1107, Pyrexia, N = 1067; b) Pyrexia, N = 1061; c) Pyrexia, N = 163; d) Pyrexia, N = 172; e) Pyrexia, N = 1031; f) Pyrexia, N = 1003; g) Pyrexia, N = 121; h) Pyrexia, N = 120

At present, co-administration of various vaccines, including inactivated vaccines, is permitted by the "Operating Procedure for Vaccination (https://www.mhlw.go.jp/bunya/kenkou/teiki-yobou/10.html [last accessed on March 8, 2022])," issued by the Ministry of Health, Labour and Welfare. Seasonal influenza is an important disease because it should be differentiated from COVID-19, and the

importance of seasonal influenza vaccination is increasing under the current epidemic of COVID-19. Judging from the currently available information, including data from the substudy of Study 302, it is unnecessary to contraindicate the co-administration of Nuvaxovid and a seasonal influenza vaccine. Thus the recombinant protein vaccine Nuvaxovid can be co-administered with other vaccines according to the principles of the "Operating Procedure for Vaccination."

PMDA's view:
Co-administration of Nuvaxovid with a seasonal influenza vaccine caused a decrease in the specific IgG antibody titer against SARS-CoV-2 rS. The effect of the decreased titer on the clinical efficacy is unclear. No significant safety concerns have been identified about the co-administration of Nuvaxovid and a seasonal influenza vaccine. Therefore the applicant's view that the co-vaccination need not be contraindicated is understandable. At present, however, there are no sufficient data available to recommend the co-administration.

7.R.4 Clinical positioning and indication

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

The applicant's explanation about the clinical positioning of Nuvaxovid:
Multiple COVID-19 vaccines have been approved across the world and vaccination has progressed in many countries including Japan, but there remains a high need worldwide for new vaccines that allow easy storage with excellent stability. Development of multiple COVID-19 preventive vaccines is currently ongoing, and multiple approaches for effective vaccination may be needed to protect the world from SARS-CoV-2 (*Science*. 2020;368:948-50). Also, these is an increasing need for measures against variants that are emerging incessantly and for booster doses to compensate for the decrease in the antibody titer over time after the primary series.

In the 2 phase III studies (Study 301 and Study 302) of Nuvaxovid, VE against PCR-confirmed symptomatic COVID-19 was approximately 90%, and a similar level of efficacy was demonstrated against variants. VE against variants was as follows: 96.4% against variants other than Alpha variant (B.1.1.7) (Study 302); 93.2% against variants classified as VOC/VOI according to the classification by the Centers for Disease Control and Prevention (CDC) of the United States (Study 301); and 86.3% (Study 302) and 93.6% (Study 301) against Alpha variant. No subjects receiving Nuvaxovid experienced severe COVID-19 from Day 7 after the second dose [see Section 7.R.2.2]. As for safety, most events were mild or moderate solicited adverse events of a short duration (median duration: 1 to 2 days). Serious or fatal adverse events were observed in a very few subjects, both in the Nuvaxovid and placebo groups, and these events were similar in the types and incidence between the 2 groups [see Section 7.R.3.1]. In the Japanese Study 1501, the neutralizing antibody titer (immunogenicity) showed a marked increase similar to that observed in foreign studies, and the safety profile was favorable with no significant difference from that in foreign studies.

Nuvaxovid thus prevents COVID-19 with an acceptable safety profile and therefore has a high usefulness. Given the continuing public health emergency caused by SARS-CoV-2 and new variants and the need for effective novel vaccines, Nuvaxovid is considered to have clinical significance.

PMDA's view:
In Japan, multiple drugs are approved for the treatment of COVID-19 as of March 8, 2022, and the following vaccines are approved for the prevention of COVID-19 (preceding 3 vaccines): Comirnaty Intramuscular Injection (Pfizer Japan Inc.), Vaxzevria Intramuscular Injection (AstraZeneca K.K.), and Spikevax Intramuscular Injection (previously COVID-19 Vaccine Moderna Intramuscular Injection, Takeda Pharmaceutical Company Limited). Nuvaxovid is a vaccine with a platform different from that of the preceding 3 vaccines. As reviewed in Sections 7.R.2.1, 7.R.2.2 and 7.R.3, Nuvaxovid has been shown to be effective without any significant safety concerns affecting the decision of approval. Accordingly, Nuvaxovid, a protein vaccine that can be stored under refrigeration, provides a novel option as a COVID-19-preventive vaccine at the current situation where the pandemic is ongoing and effective disease prevention with SARS-CoV-2 vaccines is required.

In Japan, 78% of people have completed the primary series of an approved SARS-CoV-2 vaccine. Yet there are people, albeit in a small number, who experienced adverse reactions after receiving the preceding 3 vaccines, who hesitate to receive these vaccines for various reasons, and who have not completed the primary series. Providing a new vaccine option by approving Nuvaxovid, which is based on a platform different from that of the preceding 3 vaccines, is meaningful.

Based on the above review, the indication of Nuvaxovid should be "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)," as proposed by the applicant.

7.R.5 Dosage and administration

The proposed dosage and administration are as follows:

Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 3 to 4 weeks apart.
Booster dose: A single dose of 0.5 mL is injected intramuscularly usually ≥6 months after the second dose of the primary series.

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

(a) Dosage and the number of doses

The applicant's explanation about the dosage regimen and the number of doses of Nuvaxovid:
The dosage regimen and the number of doses in the 2 phase III studies (Study 301 and Study 302) of Nuvaxovid were determined based on the data from Study 101. In Study 101, subjects receiving "2 doses of SARS-CoV-2 rS 5 μg + Matrix-M 50 μg (Nuvaxovid)" or "2 doses of SARS-CoV-2 rS 25 μg + Matrix-M 50 μg" showed a higher immune response induction than those receiving "1 dose of SARS-CoV-2 rS 25 μg + Matrix-M 50 μg," "2 doses of SARS-CoV-2 rS 25 μg alone," or placebo (Tables 23 and 24; 2 doses were given 21 days apart). The safety assessment showed that all dosage regimens were well tolerated [see Section 7.1.2], but the optimal dosage regimen was considered to be "2 doses of SARS-CoV-2 rS 5 μg + Matrix-M 50 μg, administered 21 days apart" based on the risk-benefit profile. This dosage regimen was used in the subsequent clinical studies in subjects ≥18 years old. The 2 phase III studies (Study 301 and Study 302) showed the efficacy of Nuvaxovid, as demonstrated by VE against symptomatic COVID-19 and VE against severe COVID-19, and suggested similar efficacy against variants, without any significant safety concerns. In these studies,

the acceptable range of interval between the first and second doses was 21 days + ≤7 days. The median dose interval (interquartile range) was 21.0 days (21 to 23 days), with most of the subjects receiving the second dose on Day ≥21 after the first dose.

The Japanese Study 1501 used the same dosage regimen used in Studies 301 and 302. In Japanese Study 1501, Nuvaxovid showed a favorable safety profile without any safety concerns unique to the Japanese population, and immunogenicity results were consistent with those in foreign studies. The acceptable range of interval between the first and second doses was 21 days + ≤3 days.

Thus, the phase III studies showed the efficacy of Nuvaxovid and its acceptable safety, and Nuvaxovid is expected to have similar efficacy and safety in Japanese people as in non-Japanese people. Accordingly, the applicant proposed the following dosage for the primary series:

"Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 3 to 4 weeks apart."

(b) Age eligibility

The precautions concerning dosage and administration state that people ≥18 years old are eligible for vaccination with Nuvaxovid. Currently, Novavax is conducting an expanded part of Study 301 involving subjects ≥12 to <18 years old. Novavax also plans to conduct Study 2019nCoV-503 to evaluate Nuvaxovid in subjects <12 years old.

PMDA's view on the dosage for the primary series:

As a result of the review on the efficacy [see Sections 7.R.2.1 and 7.R.2.2] and safety [see Section 7.R.3], PMDA considers that the following dosage and administration is acceptable based on the dosage regimen used in the 2 confirmatory studies (Studies 301 and 302).

Two doses of Nuvaxovid (0.5 mL [equivalent to SARS-CoV-2 rS 5 μg + Matrix-M 50 μg] each) injected intramuscularly, 3 weeks apart

In the main clinical studies of Nuvaxovid, the interval between the first and second doses was 21 days + ≤3 or ≤7 days, and the actual interval was 21 days plus several days in most of the subjects vaccinated. Accordingly, 2 doses of Nuvaxovid should be administered, usually 3 weeks apart.

As for the age range eligible for vaccination with Nuvaxovid, subjects ≥20 years old were enrolled in the Japanese Study 1501, and no data are available in Japanese subjects 18 to 19 years old. Nevertheless, "the eligible range of ≥18 years old" is acceptable, taking account of the following:

(a) Immune response was observed in Japanese subjects in the Japanese Study 1501 with no significant difference in the safety profile between Japanese and non-Japanese subjects.
(b) The study population of the Japanese studies of approved SARS-CoV-2 vaccines and the approval status of the vaccines.

7.R.5.2 Dosage and administration in booster dose

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

Table 28 shows the results of a booster dose in Part 2 of Study 101. On Day 168 after the second dose, a single booster dose of Nuvaxovid was administered, which resulted in a marked increase in the immune response. The GMT [2-sided 95% CI] of the neutralizing antibody titer against the original

Wuhan strain on Day 28 after the booster dose was higher than that on Day 14 after the primary series in the same population (n = 22) (6185.4 [4640.4, 8244.8] vs. 1546.4 [989.3, 2417.1]).

As for safety, in the safety analysis set (Group B2, n = 97), the incidence of solicited local and systemic adverse events was higher after the booster dose than after the second dose of the primary series, but most of the events occurring after the booster dose were Grade ≤2 in severity. The median duration of each event was 2.0 to 2.5 days after the booster dose for local events and 1.0 day after the booster dose for systemic events, except myalgia (2.0 days after the booster dose). Thus, the booster dose of Nuvaxovid, administered 24 weeks after the 2-dose primary series, was well-tolerated.

Based on the above, the applicant proposed the following dosage and administration of the booster dose:

A single dose of 0.5 mL is injected intramuscularly usually ≥6 months after the second dose of the primary series.

Currently, the following clinical studies are ongoing to evaluate the immunogenicity of the booster dose: An extension study of Study 301 conducted by Novavax and a Japanese booster dose study conducted by the applicant.

PMDA's view:

As described in Section 7.R.2.3, the long-term clinical efficacy of Nuvaxovid is unclear at this moment. The results of the neutralizing antibody titer approximately 6 months after the primary series of Nuvaxovid in Study 101 and other data suggest that a booster dose may be needed at a certain point after the primary series of Nuvaxovid, as with approved COVID-19 vaccines. At present, the immunogenicity and safety data after the booster dose of Nuvaxovid are available only from Part 2 of Study 101. The study showed that the booster dose of Nuvaxovid increased the neutralizing antibody titer [see Section 7.1.2, (c)], but these are only exploratory data because the study did not investigate the efficacy (based on immunogenicity) of a booster dose according to the pre-defined protocol. The correlation between the neutralizing antibody titer and the clinical efficacy of SARS-CoV-2 vaccines has been suggested, but the threshold of the effective neutralizing antibody titer after the primary series or a booster dose has not been established. It is thus difficult to conclude that the efficacy of the booster dose of Nuvaxovid has been demonstrated by the descriptive results of Part 2 of Study 101 because they were not based on adequately designed protocol.

Accordingly, whether to approve the dosage of the booster dose should be judged based on the immunogenicity and safety data from the ongoing clinical studies of a booster dose.

Currently, the dosage of the booster dose of Nuvaxovid is not approved in any countries or regions, including EU where the dosage of the primary series of Nuvaxovid is approved.

PMDA will draw a conclusion regarding the dosage and administration of Nuvaxovid, taking account of comments from the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant's plan about the post-marketing surveillance of Nuvaxovid:

The applicant plans to conduct a specified use-results survey (safety surveillance during the early period of SARS-CoV-2 vaccine administration: planned sample size, 3,000 individuals; follow-up period, 8 months) to investigate the safety during the period from the first dose of Nuvaxovid up to 8 months after the last dose in the following people: (a) those receiving the primary series of Nuvaxovid, (b) those receiving a booster dose of Nuvaxovid after the primary series of Nuvaxovid, and (c) those receiving a booster dose of Nuvaxovid after the primary series of another SARS-CoV-2 vaccine.

PMDA's view on the plan for the post-marketing surveillance:

Limited safety data are available from the clinical studies of Nuvaxovid and limited safety information in Japanese people is available before the marketing approval [see Section 7.R.3]. Therefore, it is appropriate to plan a post-marketing use-results survey to investigate the safety up to 8 months after the last dose of Nuvaxovid. As described in Section 7.R.5.2, appropriateness of the dosage and administration of the booster dose of Nuvaxovid should be assessed based on data from the ongoing studies. Accordingly, the survey should cover only individuals receiving the primary series. However, limiting the survey population to those receiving the primary series of Nuvaxovid may make the survey unfeasible, because many people have received, or will receive, the primary series and a booster dose of other vaccines through the public vaccination program. Accordingly, the post-marketing surveillance of Nuvaxovid should be designed considering how Nuvaxovid is used after the marketing launch in Japan, and the appropriateness of the surveillance plan should be discussed when the dosage and administration for the booster dose is determined.

PMDA will draw a conclusion regarding the post-marketing investigations, taking account of comments raised in the Expert Discussion.

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

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2)

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

On the basis of the data submitted, PMDA has concluded that Nuvaxovid has efficacy in preventing COVID-19 and acceptable safety in view of its benefits. Nuvaxovid is a recombinant protein vaccine manufactured based on a platform different from that of SARS-CoV-2 vaccines already approved in Japan, and thereby provides a novel option for the prevention of COVID-19. Making Nuvaxovid

available in clinical practice is thus clinically meaningful. The dosage and administration and the post-marketing investigations should be further discussed.

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

10. Other

10.1 Definition of severity of COVID-19

Table 58 shows the definition of the severity of COVID-19 in Studies 301, 302, and 501.

Table 58. Definition of the severity of COVID-19

Severity	Definition
Virologically -confirmed [a)]	1 or more COVID-19 symptoms, AND Does not meet criteria for mild, moderate, or severe disease
Mild	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 COVID-19 respiratory/non-respiratory symptoms [b)] **AND** • Does not meet criteria for moderate or severe disease [c)]
Moderate	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) + any 2 COVID-19 symptoms [b)] for ≥ 3 days (need not be contiguous days) • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) • Any evidence of significant lower respiratory tract infection: ・ Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) ・ Tachypnoea: 20 to 29 breaths per minute at rest [d)] ・ SpO_2: 94% to 95% on room air ・ Abnormal chest x-ray or chest CT consistent with pneumonia or lower respiratory tract infection ・ Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor) **AND** • Does not meet criteria for severe disease
Severe	≥ 1 of: • Tachypnoea: ≥30 breaths per minute at rest • Resting heart rate ≥125 beats per minute • SpO_2: ≤ 93% on room air or PaO_2/FiO_2 <300 mmHg • High flow oxygen therapy or NIV/NIPPV (e.g., CPAP or BiPAP) • Mechanical ventilation or extracorporeal membrane oxygenation (ECMO) • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: ・ Acute respiratory distress syndrome (ARDS) [e)] ・ Acute renal failure ・ Acute hepatic failure ・ Acute right or left heart failure ・ Septic or cardiogenic shock (with shock defined as systolic arterial pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg ・ Acute stroke (ischemic or haemorrhagic) ・ Acute thrombotic event: Acute myocardial infarction, deep-vein thrombosis, pulmonary embolism ・ Requirement for vasopressors, systemic corticosteroids, or haemodialysis. • Admission to an intensive care unit (ICU) • Death

a) Only for Study 501
b) Symptoms
Study 301: new onset or worsening of shortness of breath or difficulty breathing compared to baseline; new onset fatigue; new onset generalised muscle or body aches; new onset headache; new onset ageusia or smell loss; acute onset of sore throat; congestion or runny nose; new onset nausea, vomiting, or diarrhoea.
Study 302: fever; new onset cough; new onset or worsening of shortness of breath or difficulty breathing compared to baseline; new onset fatigue; new onset generalised muscle or body aches; new onset headache; new loss of taste or smell; acute onset of sore throat, congestion, and runny nose; new onset nausea, vomiting, or diarrhoea.
Study 501: new onset cough; new onset respiratory distress; new onset of shortness of breath or difficulty breathing; pain pharynx; loss of smell; nasal congestion; runny nose; fever (defined by subjective or objective measurement regardless of the use of anti-pyretic medications; ≥37.8°c); myalgia; chills; ageusia; headache; diarrhoea; fatigue; nausea or vomiting; anorexia.
c) Not specified in Study 301
d) Defined as 20 to 29 breaths per minute in Studies 302 and 501. As it turned out that this criterion was easily met in both studies, the definition of tachypnoea was changed to 24 to 29 breaths per minute in subsequent studies.
e) Acute respiratory failure including ARDS in Study 301

10.2 Definition of symptoms suspected of COVID-19

Table 59 shows the definition of symptoms suspected COVID-19, the primary endpoint in Studies 301 and 302.

Table 59. Definition of symptoms of suspected COVID-19

Study 301	Study 302
• Fever (≥38°C without other symptoms) or chills • New onset or worsening of cough compared to baseline • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalised muscle aches or body aches • New onset headache • New loss of taste or smell • Acute onset of pain pharynx • Acute onset of congestion or runny nose • New onset nausea or vomiting • New onset diarrhoea	• Fever (≥37.8°C or feeling hot) • New onset cough • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalised muscle or body aches • New onset headache • New loss of taste or smell • Acute onset of sore throat, congestion, and runny nose • New onset nausea, vomiting, or diarrhoea

10.3 Adverse events of special interest

In the clinical studies of Nuvaxovid, potential immune-mediated events (Table 60) and adverse events unique to COVID-19 (Table 61) were defined as AESIs. In Studies 302, 101, and 501, adverse events unique to COVID-19 were specified as COVID-19-related AESIs (Table 62) in the clinical study protocol.

Table 60. Potential immune-mediated events (common to all studies)

Classification	Disease (MedDRA preferred terms)
Neuroinflammatory diseases	Acute disseminated encephalomyelitis (including localized lesions such as noninfective encephalitis, encephalomyelitis, myelitis, and spinal radicular myelitis), cranial nerve disorder including paralysis and paresis (e.g., Bell's palsy), convulsions generalized, Guillain-Barre syndrome (including Miller Fisher syndrome), immune-mediated peripheral neuropathy and nerve plexus disorder (including chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, and polyneuropathy associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, myelitis transverse, and uveitis
Musculoskeletal and connective tissue disorders	Antisynthetase syndrome, dermatomyositis, juvenile rheumatoid arthritis (including Still's disease), mixed connective tissue diseases, polymyalgia rheumatica, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic sclerosis and CREST syndrome), spondylarthritis (including ankylosing spondylitis, arthritis reactive [Reiter syndrome], and spondylarthritis unclassifiable), systemic lupus erythematosus, systemic sclerosis, and Sjogren's syndrome
Vasculitis	Large vessel vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium and/or small vessel vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], vasculitis necrotizing, and ANCA-associated vasculitis [type unknown], Henoch-Schonlein purpura, Behcet's syndrome, and leukocytoclastic vasculitis)
Gastrointestinal disorders	Crohn's disease, coeliac disease, colitis ulcerative, proctitis ulcerative
Liver disorders	Autoimmune hepatitis, autoimmune cholangitis, sclerosing cholangitis primary, biliary cirrhosis primary
Renal disorders	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous nephropathy, glomerulonephritis membranoproliferative, and mesangioproliferative glomerulonephritis)
Cardiac disorders	Autoimmune myocarditis/cardiomyopathy
Skin disorders	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune vesicular dermatosis (including pemphigus, pemphigoid, and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome
Hematological disorders	Autoimmune haemolytic anaemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia
Metabolic disorders	Autoimmune thyroiditis, Graves'/Basedow's disease, Hashimoto's disease (new onset only), type 1 diabetes mellitus, Addison's disease
Other disorders	Goodpasture's syndrome, idiopathic pulmonary fibrosis, pernicious anaemia, sarcoidosis

ANCA, Antineutrophil cytoplasmic antibody; IgA, immunoglobulin A

Table 61. Adverse events[a] unique to COVID-19 (Studies 301 and 1501)

Classification	Disease name (MedDRA system organ class/preferred terms)
Respiratory/infectious diseases	Acute respiratory distress syndrome, pneumonitis, septic shock syndrome
Cardiac disorders	Acute cardiac disorder, arrhythmia
Coagulopathy	Deep vein thrombosis, myocardial infarction, stroke
Renal disorders	Acute kidney injury
Hematological disorders	Thrombocytopenia, septic shock syndrome
Inflammatory disorders	Cytokine release syndrome associated with COVID-19,[b] multisystem inflammatory syndrome in children
Neurological disorders	Convulsions generalised

a) COVID-19 symptoms related to severer symptoms and decompensation, taking account of disease enhancement. The list is based on CEPI/Brighton Collaboration Consensus Meeting (*Vaccine*. 2020;38:4783-91) and will be modified with accumulation of data.
b) Disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath

Table 62. COVID-19-related AESIs[a] (Studies 302, 101, and 501)

	Disease name
Immune system	Disease enhancement after vaccination, [b] cytokine release syndrome associated with COVID-19,[c] and multisystem inflammatory syndrome in children
Respiratory	Acute respiratory distress syndrome (ARDS)
Heart	Heart injuries including the following: • Microvascular damage • Cardiac failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Blood	Coagulation disorders • Deep vein thrombosis • Pulmonary embolism • Cerebrovascular accident • Limb ischemia • Haemorrhagic disease • Thrombotic complication
Kidney	Acute kidney injury
Digestive organ	Liver disorder
Nervous system	Guillain-Barre syndrome, anosmia, ageusia, meningoencephalitis
Skin	Chilblains-like lesion, single-organ vasculitis, erythema multiforme

a) AESIs occurring in subjects with PCR-confirmed COVID-19
b) Signs of COVID-19 associated severer symptoms and decompensation suggesting disease enhancement
c) Characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath

Review Report (2)

April 8, 2022

Product Submitted for Approval

Brand Name	Nuvaxovid Intramuscular Injection
Non-proprietary Name	Recombinant Coronavirus (SARS-CoV-2) Vaccine
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	December 16, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Clinical data package and Review Policy

PMDA's conclusion presented in Section "7.R.1 Clinical Data Package and Review Policy" in the Review Report (1) was supported by the expert advisors.

1.2 Efficacy

The expert advisors supported the conclusion by PMDA presented in Section "7.R.2 Efficacy" of the Review Report (1), and made the following comments:

- Nuvaxovid has shown a certain level of efficacy against variants although further evidence should be accumulated.
- Although no sufficient long-term data after Nuvaxovid administration are available, the neutralizing antibody titer decreased gradually and showed a marked decrease on Day 168 after the second dose. A booster dose approximately 6 months after the second dose of Nuvaxovid should be investigated, as with approved vaccines.

1.3 Safety

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

PMDA should provide an explanation regarding anaphylaxis, myocarditis/pericarditis, and thrombosis, which are included in the current reporting criteria for adverse reactions to COVID-19 vaccines, stipulated in "Reporting Suspected Adverse Reactions for Routine Vaccinations, etc." (Joint HSB

Notification No. 0330-3 and PFSB No. 0330-1 dated March 30, 2013, issued by Health Service Bureau and Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare,).

PMDA's explanation:
As of March 17, 2022, Nuvaxovid is approved in European Union (EU) countries and in the following countries: Indonesia, Philippines, United Arab Emirates, India, Korea, Australia, the U.K., Singapore, New Zealand, Canada, and Bangladesh. A total of 18 spontaneous reports from 8 patients were collected between December 20, 2021 and February 28, 2022, including a serious adverse event (seronegative arthritis). Nonserious adverse events with ≥2 reports were headache and pain in extremity (2 events each).

In the Japanese Study 1501 and in the foreign studies (Studies 101, 301, 302, and 501), no shock or anaphylaxis was reported. There have been no reports of these events after the market launch in foreign countries, either. The applicant explained that since anaphylaxis and anaphylactic shock may possibly occur with vaccines in general, they are defined as important potential risks and a precautionary statement will be included in the package insert and guidelines for healthcare professionals and for vaccine recipients.

Myocarditis
Myocarditis was observed in 2 subjects receiving Nuvaxovid (0.03 events/100 person-years) and in 1 subject receiving placebo (0.02 events/100 person-years) in Japanese Study 1501 and in foreign studies (Studies 101, 301, 302, and 501) combined. One of the 2 subjects receiving Nuvaxovid was a 1[redacted]-year-old healthy male who visited a hospital with symptoms of chest pain that developed on Day 3 after the second dose. Myocarditis was confirmed by increased troponin level and by cardiac MRI. The event resolved without treatment on Day 22 after the second dose. The subject did not show symptoms of infection before the onset of myocarditis symptoms but, 11 days after the first occurrence of myocarditis symptoms, showed pharyngitis and swollen cervical lymph nodes. The applicant provided the following explanation:

> The subjects tested negative for infections, but viral and bacteriological tests conducted in the clinical studies covered only a limited range of pathogens. This suggests that myocarditis may have been caused by a pathogen other than SARS-CoV-2.

The investigator did not rule out the causal relationship between myocarditis and the study vaccination, but the independent safety monitoring committee evaluated this case and concluded that the event was viral myocarditis not related to the study vaccination, based on the comparison between the clinical course in this subject and the clinical course of viral respiratory disease in general. The other subject receiving Nuvaxovid was a 6[redacted]-year-old man with obesity and hypertension. Myocarditis was reported on Day 28 after the first dose. Myocarditis was considered to be related to severe COVID-19 that developed on Day 7 after the first dose, and was considered unrelated to the study vaccination.

Thrombosis
Thrombotic, thromboembolic, and neurovascular events were extracted using Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQ) "Embolic and thrombotic events (narrow)" from the Japanese Study 1501 and the foreign studies (Studies 101, 301, 302, and 501

[during the period of primary series]). The incidence of the events was similar in the Nuvaxovid group (0.11% [35 of 30,802 subjects]) and the placebo group (0.10% [19 of 19,941 subjects]). There were no subjects who experienced thrombocytopenia together with these events. In Study 301, cerebrovascular accident, a MedDRA preferred term included in SMQ "Embolic and thrombotic events (narrow)" was observed in 7 subjects (0.04%) in the Nuvaxovid group and in 1 subject (0.01%) in the placebo, showing a higher incidence in the Nuvaxovid group. The 7 subjects in the Nuvaxovid group consisted of 4 men and 3 women, with a median age of 5[redacted] years (4[redacted] to 7[redacted] years). The events occurred between Day 10 and Day 83 after the last dose of study vaccination. All of them had at least 1 risk factor for cerebrovascular accident. None of the events came under the definition of "thrombosis with thrombocytopenia syndrome," and platelet count was normal in all of them except in 1 subject. This subject was a 7[redacted]-year-old woman who experienced cerebrovascular accident with mild thrombocytopenia on Day 48 after the second dose, but thereafter platelet counts were within the reference range. In all of the 7 subjects, causal relationship between cerebrovascular accident and the study vaccination was ruled out.

Based on the above, PMDA explained that no precautionary statements on these events are needed at this moment. This PMDA's conclusion was supported by the expert advisors.

1.4 Clinical positioning and indication

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

- Nuvaxovid is a protein vaccine, which is a familiar type in Japan compared with the existing 3 vaccines (mRNA vaccines, adenovirus vector vaccine), and may become an option for SARS-CoV-2 vaccination. This is meaningful not only in Japan but also globally.
- Nuvaxovid may be an option for those who are hesitant to receive vaccination, those who have not completed the primary series, and those who experienced severe adverse reactions to existing vaccines.

1.5 Dosage and administration

1.5.1 Trend after the Review Report (1) and PMDA's conclusion

The following are the trend after the Review Report (1) and PMDA's conclusion (as of March 14, 2022) regarding Section "7.R.5.2 Dosage and administration in booster dose" of the Review Report (1). At the expert discussion, the expert advisors raised comments (see Section 1.5.2 (b)) on the PMDA's conclusion presented in (c) below.

(a) Trend after the finalization of the Review Report (1)

As of March 11, 2022, the number of newly infected people was decreasing slightly but at a slow rate, and the bed occupancy rate remained high in some areas. While there are concerns about the emergence of novel variants, only less than 30% of people have completed the third dose of vaccination in Japan (https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html). A certain number of people probably hesitate or avoid receiving the booster dose of an mRNA vaccine out of concern for adverse reactions. Meanwhile, after the finalization of the Review Report (1), the applicant submitted data on the booster dose administered during the crossover period of Study 501,

but it will take a long time before the applicant submits data from the clinical study evaluating the immunogenicity of a booster dose of Nuvaxovid. Therefore, from the perspective of public health, the appropriateness of approving the dosage of the booster dose should be discussed based on all data available at present, rather than waiting for the submission of data from the ongoing clinical studies.

Based on the above, PMDA discussed again the appropriateness of approving the dosage and administration for the booster dose.

(b) Foreign phase IIa/b study (CTD 5.3.5.1.5: Study 2019nCoV-501, crossover period (booster dose) [data cut off: [redacted], 20[redacted]]) (reference data)

The following are the summary results of the booster dose of Nuvaxovid administered during the crossover period of Study 501:

In Study 501, the immunogenicity and safety of a booster dose of Nuvaxovid were investigated as a secondary evaluation in some subjects who had received the 2-dose primary series of Nuvaxovid. When statistically significant VE and acceptable safety were observed in the primary analysis after the primary series, a crossover period was to be started under blinded conditions. On Day 180 after the second dose (allowable period: ±15 days), 2 doses of Nuvaxovid or placebo were to be administered intramuscularly as shown in Table 63.

Table 63. Study vaccination and dose interval during the crossover period of Study 501

Group	Cohort	Number of subjects randomized for the primary series	Study vaccine in the crossover period, number of doses	Dose interval
Nuvaxovid booster (Primary series: Nuvaxovid)	HIV-negative	1480-2082	1 dose each of Nuvaxovid and placebo	21 days (+7 days)
	HIV-positive	120		
Placebo-then-Nuvaxovid (Primary series: placebo)	HIV-negative	1480-2082	2 doses of Nuvaxovid	
	HIV-positive	120		

The crossover period started on [redacted], 20[redacted]. A total of 3,791 subjects (1,896 in the Nuvaxovid booster group, 1,895 in the placebo-then-Nuvaxovid group; the same order applies hereinafter) were randomized and included in the ITT analysis set. A total of 3,791 subjects (1,898, 1,893) who actually received at least 1 dose of the study vaccine were included in the safety analysis set. Among them, 3,730 (1,874, 1,856) continued the study. The 3,791 subjects received the third dose (Nuvaxovid in both groups), and 3,702 subjects (1,857, 1,845) received the fourth dose (placebo in the Nuvaxovid booster group, Nuvaxovid in the placebo-then-Nuvaxovid group).

Neutralizing antibody titer was measured in the Nuvaxovid booster group in the PP immunogenicity analysis set in HIV-negative and HIV-positive cohorts (SARS-CoV-2 seronegative at baseline, SARS-CoV-2 seropositive at baseline, regardless of serostatus). Table 64 shows the change over time in the neutralizing antibody titer against the original Wuhan strain on the day of the first dose, Day 14 after the second dose (after the primary series), Day 180 after the second dose (before the booster dose), and Day 215 after the second dose (Day 35 after the third dose).

Table 64. Neutralizing antibody titer against original Wuhan strain
(PP immunogenicity analysis set, Nuvaxovid booster group)

		HIV-negative subjects			HIV-positive subjects		
		Baseline seronegative	Baseline seropositive	Regardless of serostatus	Baseline seronegative	Baseline seropositive	Regardless of serostatus
		N = 1111	N = 591	N = 1704	N = 62	N = 38	N = 100
Day of first dose	Number of subjects	n = 1106	n = 587	n = 1695	n = 62	n = 38	n = 100
	GMT [a)]	**10.2**	**58.0**	**18.6**	**10.5**	**70.4**	**21.6**
	[2-sided 95% CI]	[10.0, 10.3]	[52.3, 64.3]	[17.6, 19.6]	[10.0, 10.9]	[45.8, 108.2]	[16.9, 27.6]
Day 14 after second dose	Number of subjects	n = 1088	n = 568	n = 1658	n = 60	n = 38	n = 98
	GMT [a)]	**724.2**	**3150.2**	**1199.2**	**323.7**	**2655.1**	**732.1**
	[2-sided 95% CI]	[670.6, 782.0]	[2851.1, 3480.7]	[1118.7, 1285.5]	[229.6, 456.3]	[1409.4, 5001.8]	[501.7, 1068.2]
	GMFR [b)]	**71.1**	**53.8**	**64.6**	**30.9**	**37.7**	**33.4**
	[2-sided 95% CI]	[65.8, 76.8]	[48.6, 59.5]	[60.8, 68.8]	[22.1, 43.3]	[20.6, 68.9]	[24.6, 45.3]
	Seroconversion rate [c)] % (n)	**97.3 (1059)**	**97.7 (555)**	**97.5 (1616)**	**98.3 (59)**	**92.1 (35)**	**95.9 (94)**
	[2-sided 95% CI] [d)]	[96.2, 98.2]	[96.1, 98.8]	[96.6, 98.2]	[91.1, 100]	[78.6, 98.3]	[89.9, 98.9]
Day 180 after second dose	Number of subjects	n = 958	n = 514	n = 1474	n = 62	n = 38	n = 100
	GMT [a)]	**69.4**	**575.3**	**145.1**	**56.6**	**688.4**	**146.2**
	[2-sided 95% CI]	[62.8, 76.6]	[505.4, 654.9]	[132.1, 159.4]	[39.1, 81.9]	[419.1, 1130.9]	[100.1, 213.6]
	GMFR [b)]	**6.8**	**9.8**	**7.7**	**5.4**	**9.8**	**6.8**
	[2-sided 95% CI]	[6.2, 7.5]	[8.7, 11.0]	[7.1, 8.3]	[3.8, 7.8]	[6.3, 15.2]	[5.1, 9.0]
	Seroconversion rate [c)] % (n)	**70.6 (676)**	**83.9 (431)**	**75.2 (1109)**	**58.1 (36)**	**84.2 (32)**	**68.0 (68)**
	[2-sided 95% CI] [d)]	[67.6, 73.4]	[80.4, 86.9]	[73.0, 77.4]	[44.8, 70.5]	[68.7, 94.0]	[57.9, 77.0]
Day 215 after second dose (Day 14 after second booster dose = Day 35 after third dose of Nuvaxovid)	Number of subjects	n = 395	n = 237	n = 632	n = 30	n = 28	n = 58
	GMT [a)]	**3687.7**	**4004.8**	**3803.5**	**2619.8**	**3445.5**	**2990.3**
	[2-sided 95% CI]	[3332.0, 4081.5]	[3567.9, 4495.1]	[3522.9, 4106.6]	[1884.6, 3641.9]	[2060.1, 5762.4]	[2229.1, 4011.4]
	GMFR [b)]	**361.4**	**55.3**	**178.8**	**238.9**	**42.0**	**103.2**
	[2-sided 95% CI]	[325.8, 400.8]	[47.0, 64.9]	[159.7, 200.3]	[168.5, 338.6]	[26.4, 66.9]	[71.9, 148.2]
	Seroconversion rate [c)] % (n)	**99.5 (393)**	**99.6 (236)**	**99.5 (629)**	**100 (30)**	**100 (28)**	**100 (58)**
	[2-sided 95% CI] [d)]	[98.2, 99.9]	[97.7, 100]	[98.6, 99.9]	[88.4, 100]	[87.7, 100]	[93.8, 100]

a) The lower quantitation limit was 20. Values below the lower quantitation limit were converted to "0.5 × lower quantitation limit."
b) Geometric mean fold rise from the day of the first dose
c) ≥4-fold increase from the day of the first dose
d) Clopper-Pearson method
N = number of subjects analyzed; n = number of subjects with data on each visit among the PP analysis set on said visit

The safety endpoints and the follow-up period were as follows:

- Study vaccine-related adverse events requiring treatment, serious adverse events, and AESIs were collected until Day 386 after the first dose of the study vaccine.

Neither solicited adverse events nor unsolicited adverse events other than the above were collected during the crossover period.

In the safety analysis set, the combined incidence of "study vaccine-related adverse events requiring treatment," "serious adverse events," and "AESIs" from the third dose up to Day 35 after the third dose was as follows:

- 0.9% (17 of 1,898) in all of the Nuvaxovid booster groups combined, regardless of cohort
- 0.5% (10 of 1,893) in all of the placebo-then-Nuvaxovid groups combined

The incidence of these adverse events for which causal relationship to the study vaccination could not be ruled out was as follows:

- 0.4% in all of the Nuvaxovid booster groups combined (8 of 1,898 subjects: injection site pain and injection site swelling in 3 each; injection site erythema, injection site induration, vaccination site lymphadenopathy, vaccination site nodule, and hypertension in 1 each [some subjects had more than 1 event])

- 0.1% in all of the placebo-then-Nuvaxovid groups combined (2 of 1,893 subjects: injection site induration, procedural headache, and vaccination complication in 1 each [some subjects had more than 1 event])

Before the data cut-off after the third dose, 4 deaths occurred in all of the placebo-then-Nuvaxovid groups combined (unknown cause of death, homicide, gunshot wound, and physical assault in 1 each), all of which were considered unrelated to the study vaccination. During the crossover period, an adverse event leading to discontinuation of vaccination occurred in 1 subject in all of the placebo-then-Nuvaxovid groups combined (abortion spontaneous). Adverse events leading to study discontinuation occurred in 3 subjects in all of the placebo-then-Nuvaxovid groups combined (death in 2, physical assault in 1).

Before the data cut-off after the third dose, the incidence of serious adverse events other than death was as follows:

- 0.3% in all of the Nuvaxovid booster groups combined (6 subjects: bronchitis, dyspepsia, gastroenteritis, abortion spontaneous, depression accompanied by psychosis, and renal failure in 1 each)
- 0.1% in all of the placebo-then-Nuvaxovid groups combined (5 subjects: pneumonia, abortion spontaneous, diabetic ketoacidosis, rotator cuff syndrome, arthralgia/joint swelling in 1 each)

All of the events were considered unrelated to the study vaccination.

(c) PMDA's conclusion

PMDA's view:

Efficacy:

The threshold of the neutralizing antibody titer that ensures the efficacy of a booster dose is unclear, and the neutralization titer has not been established as a surrogate endpoint for efficacy. On the other hand, favorable results were obtained in studies that evaluated the efficacy of the primary series of Nuvaxovid based on clinical events, and neutralizing antibody titer after the primary series did not differ significantly between studies. This suggests that the efficacy of Nuvaxovid can be estimated to a certain extent from changes in the neutralizing antibody titer. In the booster dose part of Study 101, the neutralizing antibody titer on Day 28 after the booster dose was approximately 4 times higher than that on Day 14 after the second dose (the neutralizing antibody titer on Day 14 after the second dose was shown to be associated with the clinical efficacy of the primary series of Nuvaxovid). [Section 7.R.5.2 of the Review Report (1)]. In addition, the neutralizing antibody titer (GMT) after the booster dose tended to increase to a similar extent from baseline both in (a) subjects (n = 22) in whom the day of the first dose (before the primary series of Nuvaxovid) was defined as the baseline and in (b) subjects (n = 84) in whom Day 168 after the second dose (before the booster dose) was defined as the baseline (Table 28 in the Review Report (1)). After the finalization of the Review Report (1), additional data from Study 501 were submitted; VE and the neutralizing antibody titer after the primary series in Study 501 tended to be differ from those in other studies [Section 7.R.2.2 (f) of the Review Report (1)]. However, the neutralizing antibody titer (GMT) on Day 35 after the booster dose of Nuvaxovid was approximately (a) 5.1 and (b) 8.1 times higher than that on Day 14 after the second dose in (a)

HIV-negative subjects who were SARS-CoV-2 seronegative at baseline and (b) HIV-positive subjects who were SARS-CoV-2 seronegative at baseline (Table 64); these data support the efficacy of a booster dose of Nuvaxovid. After reviewing these results comprehensively, PMDA cannot conclude that Studies 101 and 501 showed the efficacy of a booster dose of Nuvaxovid, but considers that a certain level of efficacy of the booster can be expected.

Safety:

PMDA considers that the safety of a booster dose of Nuvaxovid is acceptable based on the following findings:

(a) There were no major safety concerns in the safety assessment population (105 subjects) who received a booster dose in Part 2 of Study 101 [Sections 7.1.2 (c) and 7.R.5.2 of the Review Report (1)].
(b) The safety of the primary series of Nuvaxovid has been confirmed in observer-blinded studies involving >30,000 subjects [Section 7.R.3 of the Review Report (1)].
(c) The booster dose of the approved SARS-CoV-2 vaccines has not raised safety concerns greater than those associated with their primary series.

In Study 501, only limited safety information is available from 1,898 subjects in the safety analysis set who received the booster dose of Nuvaxovid, but there are no significant concerns as far as available data are concerned.

Taking account of the public health usefulness of Nuvaxovid and the above results, PMDA considers that the following dosage and administration of the booster dose of Nuvaxovid is acceptable based on the results of Studies 101 and 501, on the condition that the study results of the booster dose are submitted after the marketing approval.

Dosage and Administration

Booster dose: A single dose of 0.5 mL is injected intramuscularly.

Precautions Concerning Dosage and Administration

Timing of administration: The third dose is administered usually at least 6 months after the second dose of Nuvaxovid.

At present, the immunogenicity and safety of a booster dose of Nuvaxovid in subjects who received the primary series of another vaccine (heterologous booster dose), cannot be evaluated based on the results from subjects who received Nuvaxovid for both the booster dose and the primary series (homologous booster dose). Accordingly, the package insert or other information materials should include a statement to the effect that the efficacy and safety of a heterologous booster dose of Nuvaxovid have not been established. After the marketing approval of the already-approved SARS-CoV-2 vaccines, the Health Sciences Council discussed the appropriateness of heterologous vaccination in the primary series or a booster dose. As a result, a heterologous booster dose of either Comirnaty Intramuscular Injection or Spikevax Intramuscular Injection has been allowed regardless of the vaccine used for the primary series. Accordingly, the appropriateness of a heterologous booster dose of Nuvaxovid may be discussed as well after the marketing approval. The applicant is currently

conducting a clinical study to evaluate the immunogenicity and safety of a heterologous booster dose of Nuvaxovid in Japan.

If the dosage and administration of the booster dose of Nuvaxovid is approved, "safety of booster dose of Nuvaxovid after the primary series of another COVID-19 vaccine" should be included in the post-marketing safety specification, and data regarding adverse reactions should be evaluated periodically and disseminated.

At present, the dosage regimen for a booster dose of Nuvaxovid is not approved in any countries or regions. However, use of Nuvaxovid for a booster dose is allowed in adults ≥18 years old who are ineligible, or do not wish, to receive an mRNA vaccine, in multiple countries and organizations where the primary series of Nuvaxovid is approved or authorized for use.[35)]

1.5.2 Expert discussion on dosage and administration

(a) Primary series

The conclusions of PMDA presented in Section "7.R.5.1 Dosage and administration in the primary series" of the Review Report (1) were supported by the expert advisors at the Expert Discussion.

(b) Booster dose

The expert advisors supported the PMDA's conclusion presented in Section "7.R.5.2 Dosage and administration in the booster dose" of the Review Report (1) and Section 1.5.1 of the Review Report (2). The expert advisors made the following comments:

- A certain percentage of people hesitate to receive a booster dose of an mRNA vaccine. The approval of the booster dose of Nuvaxovid will contribute to increasing the percentage of people receiving the booster dose and to public health benefits.
- Although a heterologous booster dose will be highly needed, there are scanty data on its efficacy or safety. If the heterologous booster dose is allowed, relevant information should be collected in Japan and form other countries and should be disseminated.
- The data on the booster dose in Part 2 of Study 101 and in Study 501 show no problem in the efficacy of a booster dose of Nuvaxovid. However, the incidence of solicited local and systemic adverse events was slightly higher after the booster dose than after the primary series.
- At present, the dosage regimen for the booster dose of Nuvaxovid is not established. Consideration should be given to changes over time in the antibody titer and to the efficacy against variants.
- The dosage regimen for a booster dose is yet to be approved in other countries. PMDA should explain the reason for approving the booster dose of Nuvaxovid in Japan ahead of the rest of the world.

---

35) Australia Technical Advisory Group on Immunization (ATAGI) (https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/atagi-recommends-novavax-for-use-as-a-covid-19-second [last accessed on April 8, 2022]);
Canada National Advisory Committee on Immunization (NACI) Recommendations (https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-novavax-nuvaxovid-covid-19-vaccine.html [last accessed on April 8, 2022]);
Germany Standing Committee on Vaccination (STIKO) Recommendations (https://www.rki.de/DE/Content/Kommissionen/STIKO/Empfehlungen/PM_2022-02-03.html [last accessed on April 8, 2022]);
Sweden Public Health Agency (PHA) Recommendations (https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2022/mars/covid-19-vaccinet-nuvaxovid-rekommenderas-fran-18-ar/ [last accessed on April 8, 2022]), etc.

- PMDA concluded that the booster dose should be approved on the condition that the applicant submits data on the booster dose. This conclusion is appropriate.
- PMDA should provide explanation about the additional clinical study of a booster dose of Nuvaxovid after the primary series of another vaccine already approved.

PMDA provided the following explanation, and its conclusions were supported at the Expert Discussion.

PMDA' explanation:
As for the safety of the booster dose of Nuvaxovid, results obtained in the Nuvaxovid group (105 subjects) in the booster dose part of Study 101 do not rule out the possibility that, in homologous booster dose, the incidence of solicited adverse events increases after the booster dose than after the primary series, but most of the events were mild to moderate in severity and resolved promptly. Also, no significant safety concerns were reported in the COV-BOOST study (CTD 2.7.6.6, *Lancet*. 2021;398:2258-76) in which subjects received a SARS-CoV-2 vaccine including Nuvaxovid approximately 3 months after the completion of the primary series of Vaxzevria Intramuscular Injection or Comirnaty Intramuscular Injection, although the results are reference data because the vaccination conditions, such as dose interval, were different from those to be used in clinical practice.

Currently, the following studies of a booster dose of Nuvaxovid are ongoing:

(a) The extended Study 301 to evaluate the neutralizing antibody titer after a booster dose of Nuvaxovid, mainly involving those who received the primary series of Nuvaxovid in Study 301
(b) Study TAK-019-3001 to evaluate the neutralizing antibody titer after a booster dose of Nuvaxovid, involving 150 subjects who received the primary series of Comirnaty Intramuscular Injection in Japan.

The extended Study 301 is intended mainly to evaluate the homologous booster dose. Study TAK-019-3001 is intended to evaluate the immunogenicity and safety of the heterologous booster dose of Nuvaxovid. Results of both studies will be evaluated and information will be disseminated in an appropriate manner by revising the package insert and other information materials as needed. In addition, the incidences of adverse reactions to Nuvaxovid will be published after the market launch, as with the approved SARS-CoV-2 vaccines.

The dosage regimen for the booster dose has yet to be approved in any country or region, but actually the heterologous booster dose of Nuvaxovid is allowed in many countries, as described above.

In Japan, PMDA considers that the following should be done to benefit the public healthcare before the approval of Nuvaxovid: (a) The dosage and administration of the booster dose of Nuvaxovid should be evaluated, as with Comirnaty Intramuscular Injection and Spikevax Intramuscular Injection; (b) The package insert should state that the homologous booster dose of Nuvaxovid is allowed. Accordingly, PMDA has reached the conclusions presented in Section 7.R.5.2 of the Review Report (1) and Section 1.5.1 of the Review Report (2).

1.6 Post-marketing investigations

Based on the PMDA's conclusions in "7.R.6 Post-marketing investigations" of the Review Report (1) and on the discussions on the booster dose, PMDA concluded that the risk management plan (draft) for Nuvaxovid should include the safety specifications presented in Table 65, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 66 and 67. The PMDA's conclusion was supported by the expert advisors.

Table 65. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• Shock, anaphylaxis • Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	• Safety in pregnant and lactating women receiving the vaccination • Safety of booster dose of Nuvaxovid after primary series of another COVID-19 vaccine
Efficacy specification		
None		

Table 66. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey • Post-marketing clinical study [Japanese Study TAK-019-1501] • Foreign phase III study (Study 2019nCoV-301) • Foreign phase III study (Study 2019nCoV-302) • Foreign phase I/II study (Study 2019nCoV-101) • Foreign phase II study (Study 2019nCoV-501) • Post-marketing clinical study (Japanese booster dose study [Study TAK-019-3001])	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information for healthcare professionals (a proper use guide for Nuvaxovid) • Organize and disseminate information for vaccine recipients (for those who receive Nuvaxovid Intramuscular Injection) • Periodical publication of the occurrence of adverse reactions

Table 67. Outline of use-results survey (draft)

Objective	To confirm the safety and efficacy of Nuvaxovid after the primary series (1st and 2nd doses) and after the booster dose (3rd dose: homologous or heterologous vaccination*)
Survey method	Central registry system
Population	Recipients of the primary series (1st, 2nd) and recipients of the booster dose (homologous or heterologous vaccination*)
Observation period	From the first dose through 8 months (32 weeks) after the last dose of Nuvaxovid
Planned sample size	3,000 vaccine recipients (The number of recipients of the primary series will fall within the possible range.)
Main survey items	• Characteristics of vaccine recipients (past history [government-specified underlying diseases in the COVID-19 vaccination program], other comorbidities and past illness) • Prior COVID-19 vaccination other than Nuvaxovid (yes/no, name of the vaccine, date of vaccination) • Prior vaccination other than COVID-19 vaccination (yes/no, name of the vaccine [within 2 weeks before the first dose of Nuvaxovid]) • Allergy (yes/no, type, allergens) • Pregnancy/lactation (females only) • Adverse events • Information on COVID-19 ([a] test for SARS-CoV-2; [b] symptoms [yes/no], date of diagnosis, treated/untreated, outcome, date of outcome in those testing positive for SARS-CoV-2) • Other information

* In the draft proposed by the applicant, the term "alternate vaccination" is used instead of "heterologous vaccination."

1.7 Quality

1.7.1 Shelf-life of active substance and vaccine product

The applicant submitted results of the safety studies of the active substance and the vaccine product (Process e and Process E), which were ongoing during the preparation of the Review Report (1) (see Tables 68 and 69). Results confirmed that there were no significant changes in the quality of either the active substance or the vaccine product throughout the study period.

Table 68. Summary of major stability studies for the active substance

	Manufacturing process for active substance	Number of batches	Storage conditions	Study period*	Storage form
Long-term	Process d	2	−70 ± 10°C	9 months	[redacted]
	Process e	3	≤−60°C	1 to 3 months	

*: The stability studies are ongoing up to 36 months

Table 69. Summary of major stability studies for the vaccine product

	Manufacturing process for active substance	Manufacturing process for vaccine product	Number of batches	Storage conditions	Study period*	Storage form
Long-term	Process d	Process C	2	2°C to 8°C (upright and inverted)	9 months	Glass vial with [redacted] rubber stopper
	Process e	Process E	3		0 to 1 month	

*: The stability studies are ongoing up to 24 months.

Based on the stability studies of the active substance and the vaccine product manufactured outside Japan, the applicant proposed the shelf-life of 9 months for the active substance stored at ≤−60°C and the shelf-life of 9 months for the vaccine product stored at 2°C to 8°C.

The applicant's rationale for the shelf-lives:

The proposed shelf-life of 9 months for the active substance is appropriate for the following reasons:

(a) Process e of the active substance employs the same manufacturing technology used in Process d. The important raw materials (e.g., WCB, culture media components, and the container for the storage of active substance) used in Processes e and d are the same.

(b) With each change of the manufacturing process, the pre-change and post-change active substances were shown to be comparable by batch analysis and characterization.

A long-term test (≤−60°C) of the active substance manufactured by Process d and Process e is currently ongoing, and no stability concerns have been identified regarding the active substance manufactured by Process d up to 9 months or the active substance manufactured by Process e up to 3 months.

The proposed shelf-life of 9 months for the vaccine product is appropriate for the following reasons:

(a) The long-term test (2°C to 8°C) of the vaccine product manufactured by Process C did not show any significant changes in the stability up to 9 months.

(b) The vaccine products manufactured by Process C and Process E were shown to be comparable by batch analysis.

A long-term test (2°C to 8°C) of the vaccine product manufactured by Process E is currently ongoing, and no safety concerns have been identified up to 1 month.

PMDA's conclusion:

On the basis of the applicant's explanation, PMDA accepted the proposed shelf-lives: 9 months for the active substance stored at ≤−60°C and 9 months for the vaccine product stored at 2°C to 8°C. Results of the ongoing long-term tests (3 batches of the active substance manufactured by Process e and 3 batches of the vaccine product manufactured by Process E) should be submitted to PMDA as soon as possible after obtaining 9-month data.

1.7.2 New excipients

The control methods (i.e., specifications and stability studies) for adjuvants Matrix-A and Matrix-C (novel excipients), described in the Review Report (1), are described in Supplement.

PMDA confirmed that the adjuvants were controlled appropriately, based on the submitted data.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Overall, the application documents were collected and prepared in accordance with the GLP/GCP compliance standards. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding requiring corrective action in CTD 5.3.5.1-2. Although it had no significant impact on the review of the overall clinical studies, PMDA notified the applicant of the finding.

Finding requiring corrective action:

<u>Sponsor</u>

- The sponsor assessed eligibility of subjects for the primary efficacy analysis set without knowing information necessary for eligibility assessment and, without correcting this error, conducted the primary efficacy analysis using the population.

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review on the submitted data, PMDA has concluded that the product may be approved for the following indication and dosage and administration, with approval conditions shown below. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is 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

Primary series: Two doses (0.5 mL each) are injected intramuscularly, usually 3 weeks apart.

Booster dose: A single dose of 0.5 mL is injected intramuscularly.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only limited information is available on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed 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. Results of the ongoing clinical studies to confirm the immunogenicity and safety of the booster dose of the product, should be submitted promptly to PMDA. Also, the applicant is required to take actions necessary to ensure that the updated efficacy and safety information on the product is easily accessible to healthcare professionals.
4. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to give physicians appropriate instructions to ensure that they administer the product to vaccine recipients who, or whose legally acceptable representatives, have been provided with the most updated efficacy and safety information of the product in written form, and have provided written informed consent through the vaccine screening questionnaire in advance.

Appendix

List of Abbreviations

ACE2	Angiotensin-converting enzyme 2
AESIs	Adverse events of special interest
Antibody response rate	Percentage of subjects who had, at each measurement point, an antibody titer exceeding the 95 percentile of the antibody titer in all subjects at baseline
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
Original Wuhan strain	Strain Wuhan-Hu-1
COVID-19	Disease caused by SARS-CoV-2 infection (coronavirus disease)
CPE	Cytopathic effect
Day X after vaccination	Day X from the vaccination day counted as Day 1
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immune absorbent spot
EMA	European Medicines Agency
EOPCB	End-of-Production Cell Bank
EU	European Union
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
hACE2	Human angiotensin-converting enzyme 2
HCP	Host cell protein
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
ICU	Intensive Care Unit
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IL	Interleukin
IMRC	Independent Medical Review Committee
ITT	Intent-to-treat
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger RNA
MVS	Master Virus Seed
N-protein	Nucleocapsid protein
Original Wuhan strain	Strain Wuhan-Hu-1
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PMDA	Pharmaceuticals and Medical Devices Agency
PO_2	Partial pressure of oxygen
PP	Per Protocol
PP-EFF	Per-protocol Efficacy
qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic acid

RT-PCR	Reverse transcription PCR
S1	Amino-terminal region of S-protein containing RBD
S2	Carboxyl-terminal region of S-protein containing the membrane-spanning region
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
SARS-CoV-2 rS + Matrix-M	SARS-CoV-2 rS adjuvanted with Matrix-M
SEC	Size exclusion liquid chromatography
Seroconversion rate	Subjects who were seronegative at baseline and showed a ≥4-fold increase in antibody titer Japanese Study 1501: Percentage of subjects who were seronegative at baseline and showed a ≥4-fold increase in antibody titer or subjects who were seropositive at baseline and showed a ≥2-fold increase in antibody titer. Booster dose in Part 2 of Study 101: Among all subjects, the percentage of subjects who showed a ≥4-fold increase in antibody titer from baseline is defined as seroconversion
Sf9 cells	Cell line derived from the ovary of *Spodoptera frugiperda*
Sf-RV	Sf Rhabdovirus
SMQ	Standardised MedDRA queries
SpO_2	Saturation of percutaneous oxygen
S-protein	Spike protein
Study 101	Study 2019nCoV-101
Study 1501	Study TAK-019-1501
Study 301	Study 2019nCoV-301
Study 302	Study 2019nCoV-302
Study 501	Study 2019nCoV-501
Th1/2	Type 1/2 T helper
The product	Nuvaxovid Intramuscular injection, recombinant corona virus (SARS-CoV-2) vaccine, TAK-019, SARS-CoV-2 rS 5 μg + Matrix-M 50 μg
TNF-α	Tumor necrosis factor-alpha
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine efficacy
VOC	Variants of concern
VOI	Variants of interest
WCB	Working cell bank
WHO	World Health Organization
WVB	Working Virus Bank
Day X (after the first dose, second dose, etc.)	The day of vaccine administration is regarded as Day 1